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

TXR 0002254

2-NOV-1982

002254

MEMORANDUM

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)

SUBJECT: Ectrin™ Insecticide Livestock and Premise Spray. A 10% Water Dispersible Liquid (WDL). EPA File No. 677-UUT (EPA Reg. No. 677-447).
TOX Chem No. 77A

Diammond Shamrock Corporation is seeking to register this product for use as a direct animal spray and for use in animal premises.

Toxicology Branch (TB) objects to the registration of this product. TB is not able to evaluate the potential hazard resulting from the use of this product until:

- The RCB problems are resolved (see RCB review by A. Rathman dated July 26, 1982).

- The following two acute studies are submitted on the formulation:

  i. Acute Dermal LD50
  ii. Primary skin irritation

The same objections were raised in our previous review of this product.

The petitioner has also asked for the deletion of the sentence "Do not treat animals intended for slaughter." which appears in the remarks column for horses. TB believes this deletion at this time would be objectionable to RCB and therefore suggests that Registration Division obtain an RCB opinion with respect to this request by Diamond Shamrock.

The TB has reviewed, classified and categorized for purpose of toxicity the submitted 4.0 hour AILC50 study.

The confidential formula for this product is as follows:

CONFIDENTIAL

CONFIDENTIAL

Chemical	Percent (%)
Technical fenvalerate	11.15

CBI removed

The inerts are cleared under Section 180.1001(e).

Subject: Acute Inhalation Toxicity Study in Rats with Ectrin™ 10% WDL Formulation.

Test Compound: Ectrin™ - 10% WDL Formulation (active ingredient is fenvalerate)

Accession Number: Not given, EPA File Symbol No 677-UUT

Testing Facility: Hazleton Laboratories America Inc.

Study Number: Project No. 200-252

Testing Period: March 18, 1982 - April 9, 1982

Report Submitted to Sponsor: July 22, 1982

Materials and Methods:

Sprague-Dawley descended CD-Crl rats obtained from the Charles River Breeding Laboratories (Kingston, New York) were quarantined for 7 days under environmentally controlled conditions. Fifteen males and 15 females in good health were divided into 3 groups of 5 males and 5 females per group. One group (Group 1) served as the control group and received air alone. Groups 2 and 3 received a total actual concentration of between 2.3 to 4.7 of* aerosolized test material. All groups were exposed for a period of 4 hours in 100-L exposure chambers. Airflow was maintained at 16.7 liters/minute. Chamber environment was monitored every 30 minutes during exposure and closely resembled conditions of the quarantine period.

The actual total concentration of exposure for each group was calculated. Gravimetric chamber concentrations were also determined. Samples were collected at approximate hourly intervals during exposures. Four particle size distribution samples were also obtained during exposure approximately every 60 minutes.

The behavior and appearance of all animals were observed at 30 minute intervals during the exposures, hourly for 4 hours following the exposures and twice daily during the remainder of the 14 day post-exposure period.

* mg/L

Animals were weighed 5 times prior to termination and at termination. Body weights were analyzed statistically.

Animals were exsanguinated at termination and necropsied. Lungs, liver, kidneys and any organ exhibiting gross changes were preserved in 10% neutral buffered formalin for possible future examination.

Results:

The total actual concentration for groups 2 and 3 was between 2.3 to 4.7 mg/L. The gravimetric concentration data for groups 2 and 3 was 32.6 and 93.7 ug/L respectively. The mean aerodynamic diameter and geometric S.D. for Group 2 was 3.59 u and 1.48 respectively. The mean aerodynamic diameter for Group 3 could not be determined because the MMAD was greater than 4.7 u. However, at least 43% of the respirable aerosal was less than 4.7 u.

No animals died during the study.

Exposure - related observations noted in the treatment groups during and/or immediately following the exposure included rapid respiration, clear discharge from the nose and mouth, lacrimation, reddish-brown discharge from the nose and sluggishness of movement and labored respiration. All group 2 and 3 animals appeared normal by Day 1 and throughout the 14-day post-exposure period.

Statistically significant and possibly exposure related reductions of mean body weight gains were apparent only in Group 3 males and females.

No consistent exposure-related trend was apparent in any of the gross pathology observations.

Conclusion:

Exposure to the 10% WDL formulation at a total actual concentration of between 2.3 to 4.7 mg/L for 4 hours produced transitory effects manifested by irritation to the mucous membranes, lethargy, respiratory distress and weight gain fluctuation. No deaths were observed.

The 4 hour AILC50 for the 10% WDL is greater than 2.3 mg/L (total actual concentration).

Conclusion: Core-Guideline

Category of Toxicity: III

NOTE:

See also AILC50 study with Ectrin™ 15% Wettable Powder. Accession No. 247363. Hazleton Project No. 200-238. The results of this study (10% WDL) generally confirm the signs observed in the study conducted on the 15% WP as well as the AILC50 for 4 hours.

Albin B. Kocialski

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

OPP:HED:TOX:A.KOCIALSKI:sb 10/29/82 X77395 Rm. 820 #ml8

UNITED STATES ENVIRONMENTAL PROTECTION
WASHINGTON, D.C. 20460

002254

JUL 26 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Registration No. 667-UUT. Pydrin* direct animal use. Evaluation of analytical methods and residue data

FROM: A. Rathman, Chemist
Residue Chemistry Branch
Hazard Evaluation Division

R.J. Hummel for

THRU: Charles Trichilo, Chief
Residue Chemsitry Branch

TO: Franklin D. R. Gee
Product Manager (17)

and

Toxicology Branch

Diamond Shamrock Corporation is seeking to register their product Ectrin (continuing 10% fenvalerate as a water dispersible liquid) for use as a direct animal spray and for use in animal premises.

Currently there are tolerances for residues of fenvalerate in the meat, fat, and meat byproducts of cattle, hogs, horses and, sheep at 1 ppm and in milk fat at 2 ppm. These tolerances have been established to cover secondary residues which may result from use of the chemical on r.a.c.s that are animal feed items.

Conclusions

1. The manufacturing process (and impurities in the technical material) is different than the process Shell states they are using. However, the technical material is the Shell

*The names fenvalerate, SD 43775, Pydrin, and Ectrin are used throughout this review and are synonymous.

product according to the confidential formula. We need to know which process Shell is actually using.

2. We do not consider the fate of fenvalerate in animals adequately defined when considering direct dermal uses. We need a metabolism study reflecting dermal treatment with residue characterization in meat and milk. We also need a letter of authorization from Shell to use the oral metabolism data that are available.

3. An adequate method for fenvalerate per se is available for enforcement purposes. Depending upon the results of the metabolism study requested in 2 above, additional methodology may be needed.

4a. We can make no final conclusion on the level of residues that are likely to result in milk and beef tissues until 2 above is resolved. However, the submitted residue studies are deficient in that no plateau was ever reached and the studies do not reflect residues likely to result when the animal is both treated dermally and exposed to treated premises.

4b. We can make no final conclusion on the level of residues likely to result in swine tissues until 2 above is resolved and until we know the exact application rate in terms of amount of ai/animal/treatment.

4c. Since, in general, it is not practical to remove poultry when premise treatments are made, this use should either be removed from the label or data to support such a use should be submitted.

4d. Since use on Angora goats raised for mohair production and horses not intended for salughter would not result in residues in food for consumption by man or animal, we have no objections to these uses.

Recommendation

We recommend against the proposed uses on beef and dairy cattle and swine as well as the premise uses because of Conclusions 2, 3, 4(a), 4(b), and 4(c). We have no objections to the proposed uses on Angora goats and horses. The Company should be requested to obtain the correct manufacturing process from Shell since the process included in this submission is different than what we understand Shell's process to be.

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Detailed Considerations

Formulation

The Company notes in the Confidential Statement of Formula that the technical material is obtained from Shell. However, the manufacturing process (and impurities in the technical product) is different than the process detailed in PP# 7F2013. Shell's petition, PP# 7G1926, listed two different manufacturing processes (including the one presented in this submission) and the impurities listed are the same as appear in this submission. It is not clear which process is actually being used and this information should be obtained from Shell.

CBI removed

Proposed Uses

The product is used to control various insects and ectoparasites. Spray concentrations range from 0.01-0.25%, applications are to be made by conventional power or low pressure knapsack sprayers or power misters. No pre-slaughter intervals are proposed. The table below lists the direct animal uses with minimum repeat treatment intervals where specified.

Livestock Uses:

Animal	Spray Concentration	Remarks
Beef and Non-Lactating Cattle	0.05%	Use up to 1/2 gal spray/animal (1 gm a.i.). Treatments may be made every 2 weeks.
	0.01%	Use up to 1/2 gal spray/animal (0.2 gm a.i.). No restriction on repeat treatments.
	0.1%	Use 4 fl ozs/animal (0.11 gm a.i.) as a pour-on down mid line of back. No restriction on repeat treatments.

Dairy Cattle	0.25%	2-3 fl oz/animal (0.2 gm a.i.). Repeat applications at weekly intervals.
	0.05%	1-2 pts/animal (0.5 gram a.i.). Repeat applications at weekly intervals.
Swine	0.05%	1 pt/animal (0.25 gram a.i.). Repeat in 30 days if necessary.

Premise Use: A 0.25% solution is to be applied at the rate of 1 gal/500 sq. ft. (or at 1/2 gal./1000 sq. ft. to non-absorptive surfaces) to livestock confinement areas including horse stalls, poultry houses, beef, and dairy barns, calf pens, sheep sheds, swine buildings, animal hospital pens and kennels. Animals are to be removed prior to spraying and returned when surfaces have dried. Repeat applications are not to be made re frequently than every three weeks. Additionally, feed lots (exposed area), exterior walls of farm buildings, feed storage areas, feeders, corrals, and paddocks may be treated with the 0.25% solution at the rate of 1 gal/500 sq. ft.

Other Uses

There are treatments recommended for lice and fly control on horses and Angora goats; these uses are not considered in this review, since only horses not intended for slaughter and goats raised for mohair production are included.

It should be noted that the removal of poultry from poultry houses before premise treatment would be impractical on most farms.

Nature of the Residue

No animal metabolism data have been included in this submission. While the Company states that it can rely on Shell's data, we have no letter of authorization from Shell. In addition to authorization from Shell, we will also need metabolism data reflecting dermal use so that we can determine if the metabolic route is the same from oral and dermal exposure.

Analytical Methods

The method proposed for enforcement purposes is Shell's method MMS-R-447-2 entitled "Determination of SD 43775 Residues in Animal Tissues, Milk, Milk Fat, Cream, Hair, Eggs, and Gauze Patches."

For tissues, fenvolerate is extracted with hexane, partitioned into acetonitrile. The acetonitrile is exchanged to hexane and cleaned-up on a Florisil column. The residue is determined by ECGC.

Data were obtained using either the above method or methods similar to the above method. Samples of milk, milk fat and various tissues were fortified with fenvalerate at levels ranging from 0.001-0.1 ppm with recoveries ranging overall from 54-135% with most in the range of 80-120%. Blanks were <0.01-0.02 ppm with the exception of two samples, one of cream at 0.36 ppm and one of meat fat at 0.38 ppm.

The method was subjected to a method trial with milk samples fortified at 0.02 and 0.04 ppm and found acceptable (J. Onley, memo of 7/24/78; PP# 7F2013). We consider this method suitable for obtaining data and for enforcement purposes.

Residue Data

A total of six studies reflecting dermal treatments were submitted (five on cattle and one on swine).

In considering the maximum level of residues that may result in meat and milk, three combined avenues must be considered: (1) the dietary burden possible from crops that are feed items that currently have fenvalerate tolerances, (2) additional dietary burden from animals licking treated premises or other treated animals and (3) direct application.

CATTLE: None of the available data reflect the maximum possible combined exposure from these avenues, although a number of the studies reflect exaggerated dermal treatment rates both with regard to amount applied and frequency.

A study was conducted utilizing 10 lactating Holsteins, which were treated 3 times at weekly intevals with an EC formulation at the rate of 2 grams a.i./animal/treatment. Only a single animal was available for control purposes. This study was designed to reveal the time required for residues of the parent compound to reach a maximum, and the levels involved. The sampling intervals were 1, 7, 14, 28, and 56 days after the last treatment.

The data indicate that residues of SD 43775 per se in brain, kidney and liver were all non-detectable (<0.01 ppm). Muscle samples all showed <0.01 or 0.01 ppm (including the control), regardless of sampling interval. Residues appeared to predominate in the fat; unfortunately, the data are of litte value, since the single control animal had an apparent SD 43775 residue of 0.38 ppm in renal fat. This compares with residues ranging from 0.07-0.42 ppm in the treated animals. The 0.42 ppm high value reflects sacrifice 7 days subsequent to the last treatment. At the 56 day post-treat interval, residues of 0.10-0.12 ppm were reported. Subcutaneous fat analyses showed residues of 0.09 ppm for the control animal, and a 0.03-0.22 ppm range for the treated animals. Again, the high values were noted in the animals sampled 7 days after the last treatment. At the 56 day int rval, SD 43775 residues had declined to the 0.04-0.05 ppm level in subcutaneous fat.

Milk and cream analyses for these same animals showed SD 43775 residues reaching a maximum 3 days after the last treatment. The residues ranged from 0.02-0.04 ppm in milk and from 0.06-0.23 ppm in cream. Twenty-eight days post-treatment all samples were reported at <0.01 ppm. As in tissues, the residue levels reported for the control milk and cream of 0.02 and 0.36 ppm, respectively, cast doubt on the validity of the study and render the study valueless. (The control cream value is reported at a level >0.1 ppm higher than the maximum value seen in the treated animals).

Additional tissue, milk, and cream analyses were conducted on a Holstein administered 200 mg SD 43775 orally (ca. 10 ppm dietary) each day for a total of 7 days. The treated and control animal were sacrificed after the morning milking on the last day of the treatment period. All tissues showed <0.01 ppm SD 43775 in the control, and all save fat in the treated animal. Renal and subcutaneous fat are reported at the 0.14 and 0.02 ppm levels, respectively. The daily milk and cream analysis indicate that a residue plateau was not reached in the 7 days of feeding; the final cream samples showed a range of 0.18-0.3? ppm SD 43775 residues. This study has some utility in assesssing the possible burden of SD 43775 per se in tissues from animals licking treated premises or other treated animals, although the fact that a residue plateau was not attained reduces its value. It is noteworthy that the observed range of SD 43775 residues in the cream of the dermally-treated cows discussed above. The showing of up to ca. 80 mg/sq. ft. SD 43775 (acetone extraction) in the hair (thoracic region-4 sites) one day after the third treatment suggests that "lickers" could possibly ingest a substantial portion of the 200 mg/day that is representative of the 10 ppm dietary level. (The study below shows up to ca. 120 mg/sq. ft. hair surface).

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In another study utilizing an emulsifiable concentrate, three lactating cows were treated with ca. 2 grams a.i. three times at weekly intervals. Milk was sampled daily throughout the treatment period and up to one week after the last treatment; all samples (whole milk basis) showed no detectable residues (<0.01 ppm) of SD 43775. Tissues were sampled at sacrifice, which was 1, 3 and 7 days after the last treatment. Unlike the previously described study, the control animal showed no detectable residues (<0.01 ppm) of SD 43775 in fat or any of the tissues sampled. The treated animals also showed <0.01 ppm in muscle, liver, kidney, and brain and up to 0.20 ppm in renal fat 7 days after the last treatment. The various fat samples (subcutaneous, renal, and back) show an increase with time; the study was terminated before a plateau was reached.

In the third study, employing a water dispersible liquid, a single treatment at 2 grams a.i. was administered to each of two lactating cows. Unlike the previously described study, the control animal was housed in a separate pasture, and thus yielded all tissue and milk (fat basis) values at <0.01 ppm. Milk was sampled for 24 days post treatment; the animals were then sacrificed. Residues of SD 43775 peaked in milk fat 6 days post-treatment at 0.64 ppm in one animal and at 3 days and 1.1 ppm in the other. By the 24th day, the 0.01 ppm level was attained in the milk fat of both animals. Tissue residues for both animals at the 24 hour sacrifice interval were 0.02 and 0.03 ppm for renal subcutaneous fat, respectively; all other tissues were reported at <0.01 ppm.

Given the limitation of the above study, the results substantiate those discussed previously, considering that cream averages ca. 20% milk fat. The 1.1 ppm figure above could thus be 0.22 ppm expressed on the cream basis. This compares to 0.36 ppm maximum in cream from the 3 treatment 2 gram a.i. dose study. Since the proposed use indicates biweekly treatments, this study is of value to demonstrate the additive residue effects of multiple treatments; more than 3 weeks between treatments would be required for residues of SD 43775 per se to fully dissipate. The study also serves to demonstrate that oral or dermal contact between treated cows is probably a significant source of residues that is, the "segregated" control animal of this study displayed no detectable residues, while the control animal of the 10 cow/3 treatment study showed residues approximating those of the treated animals.

In the fourth study, two cows were treated once with an E.C. at the rate of 2 gm a.i./animal. The study also contained a control animal. Each animal was housed in one of the three separate pastures; the two treated cows were fitted with

restraining straps so that animals could not lick themselves but could still browse and get up and down without difficulty.

Samples of milk were taken for 14 days after the treatment. Maximum residues of SD 43775 were seen after two or 3 days post-treatment at a level of 0.17 ppm. At 14 days post-treatment milk fat from one animal contained 0.02 ppm and the other animal contained no detectable residues (<0.02 ppm). The animals were sacrificed 14 days post-treatment with residues detected only in the fat (0.03 ppm in renal fat). All other tissues contained <0.01 ppm apparent SD 43775.

In the fifth study, a total of 20 beef cattle were used (16 treated and 4 controls). The animals were treated with two quarts of either a WP or a water dispersible liquid made up to concentrations of 0.05% (1 gm a.i./animal). The cattle were given either one treatment with sacrifice at 3 and 7 days post-treatment or two treatments at a 21-day interval with sacrifice either 3 or 7 days after the second treatment. Maximum residues resulted in the fat at 7 days post-treatment (regardless of the number of treatments made). After one treatment the maximum SD 43775 residue in fat was 0.055 ppm, after two treatments, the maximum detected residues was 0.094 ppm.

No final conclusion can be made until the animal metabolism question is resolved. However, these studes are all deficient in that no plateau was ever reached and the studies do not reflect the residues likely to result when the animal is treated dermally and exposed to treated premises (exposure through feeding can be determined by data submitted by Shell). Therefore, we are unable to determine if the established fenvalerate meat and milk tolerances are adequate to allow for these added uses.

SWINE: A single study was submitted reflecting application to swine. In this study a total of twenty pigs were used. The pigs were treated with either on EC or a water dispersible liquid at the rate of 50 mg/sq. ft. (we have no way of calculating the total amount of a.i. applied per animal per treatment). The pigs were treated either 1, 2, or 3 times with biopsy samples taken at 1 and 2 week intervals after each treatment (or at 1, 2, 3, and 4 week intervals after the last treatment). Applications were made at 2-week intervals with some animals sacrificed at 2 weeks post-treatment from a single treatment, from 2 treatments or from all three treatments. Some animals were sacrificed 5 weeks after the third treatment.

It should be noted that residues of SD 43775 were only detectable in fat with other tissues containing no detectable

(<0.01 ppm) residues. Residues in the fat increased with the number of treatments and showed a maximum of 0.2 ppm after three treatments (2 week post-treatment interval). With the 5-week interval (after three applications), residues in fat had declined to 0.05 ppm.

We can make no final conclusion until the metabolism question is resolved and until we know the exact application rate in terms of amount of a.i./animal/treatment.

POULTRY: No data have been submitted for poultry. The label for premise use in poultry houses directs to remove "livestock" from the area prior to spraying. This, in general, is not practical with poultry. Therefore, either the poultry house use most be removed or we must have data to support such a use.

GOATS and HORSES: Since the uses direct application to goats for mohair production only and horses not intended for slaughter, we have no objections to these uses.

TS-769:RCB:ARRATHMAN:X77324:CM#2,RM810:07/26/82
cc:R.F., Circu, Reviewer, S.F. Amended Use File
RDI:R.J.Hummel, 7/23/82;R.D.Schmitt, 7/23/82