MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 499-GIL
PT-230 Tri-Die

FROM: William S. Woodrow WSW 3-30-93
Precautionary Review Section
Registration Support Branch
Registration Division (H75-05C)

TO: R. Mountfort / Daphne Wald (PM 10)
Insecticide - Rodenticide Branch
Registration Division (H75-05C)

APPLICANT: Whitmire Research Labs., Inc.
3568 Tree Court Ind. Blvd.
St. Louis, MO 63122

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Pyrethrins	0.6
Piperonyl Butoxide, Technical	4.8
Inert Ingredient(s):	94.6
Total	100.0%

BACKGROUND

Whitmire Research Labs. submitted six acute Toxicity studies to support registration of PT-230 Tri-Die Insecticide. (EPA Reg. NO. 499-GIL The MRID NOS. used were 426137-02 through 426137-07. This product is contained in a pressurized spray can; and was tested for eye irritation using the pressurized spray. The remaining five acute tox. studies were evaluated using the product-less the propellent.

RECOMMENDATION

1) The six acute toxicity studies submitted by Whitmire Research Labs. are acceptable. The acute oral, acute dermal, acute inhalation and the eye irritation study were graded Core Guideline Data.

The skin irritation study was graded Core Minimum data; as was the dermal sensitization study:

a. skin irritation - All animals showed irritation throughout the observation

period - which was terminated at 7 days post treatment. Two animals showed eschar within 24 hours after treatment, and continued to show eschar through the 7 day observation period. The animals should have been observed for at least 21 days.

b. sensitization - The Draize scoring scale was was used, instead of the Buehler scale.

2) An acute toxicity data profile for NO. 499-GIL follows:

study	Classification	Tox. Category
acute oral (LD_{50} > 5.0 g/kg	Guideline	IV
acute dermal (LD_{50} > 2.0 g/kg	Guideline	III
acute inhalation (LC_{50} > 4.8 mg/l	Guideline	III
eye irritation 3 EI. 0 scores 14 d.	Guideline	II
skin irritation 2 animals eschar → 7 d. terminated at 7 days	Minimum	I
skin sensitization did sensitize g.p.	Minimum	—

3) No additional acute toxicity studies are required for NO. 499-GIL.

LABELING

1) Change the product signal word from WARNING to read "DANGER".

2) Change the Precautionary Statements to read as follows:

"Corrosive. Causes burns. Causes substantial but temporary eye injury. Do not get in eyes, on skin, or on clothing. Harmful if absorbed through skin. Harmful if inhaled. [redacted] Wear protective clothing and rubber gloves. Avoid breathing dust (vapor or mist). Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse."

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3) Under Statement of Practical Treatment

a. Add "Get medical attention" to the IF INHALED statement."

b. Add "Get medical attention" to the if on SKIN statement.

4) Add the following under Precautionary Statements -

"Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals."

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5) HITS CRP TRIGGER DUE TO SKIN IRRITATION. HITS RESTRICTED USE TRIGGER FOR SAME REASON. PM TEAM MUST DECIDE IF ALTERNATIVE LABELING IS SUFFICIENT TO OFFSET HAZARD AND THE NEED FOR RESTRICTED USE CLASSIFICATION.

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DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§81-1)

Product Manager: (10) 10-16-92
Reviewer: (Woodrow) ~~M. Waller~~
MRID No.: 426137-02
Report Date: 3-25-93
Testing Facility: Biosearch, Inc.
Report No. 92-7607A
Author(s): D. Gabriel
Species: Rat, Sprague Dawley
Age: not given
Weight: 201-224 g
Observation ~~Days~~ (Post Exposure): (14); other ( )
Source: Buckshire Corp. Perkasie, PA.
Test Material: PT-230 Tri-Die Insecticide (less propellent), liquid
Quality Assurance (40 CFR §160.12): both G.L.P. & Q.A.

Conclusion:

1. LD50 (mg/kg): Males = ~~—~~; Females = ~~—~~; Combined = ~~—~~
2. The estimated LD50 is > 5.0 g/kg
3. Tox. Category: IV. Classification: Guideline

Procedure (~~Deviations From §81-1~~): Animals acclimated at least 5 days pre-test. One group of 5 M & F rats were deprived of food overnight. These animals were dosed by gavage with 5.0 g/kg. Animals observed frequently day of dosing, and daily

~~Results~~: Reported Mortality

DOSAGE (g /kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
5.0 g/kg	0/5	0/5	0/10

Symptomology & Gross Necropsy Findings:

for 14 days for toxic signs and mortality. All animals were subjected to gross necropsy examinations. Body wts. recorded on weekly basis.

Clinical: All animals appeared normal and gained weight during 14 day observation period.

Necropsy examination: No gross abnormalities observed.

Product Manager: 101 (046942) Reviewer: [redacted]
MRID No.: 426137-03 Report Date: 3-25-93
Testing Laboratory: Biosearch, Inc. Report No. 92-7607A
Author(s): D. Gabriel
Species: Rabbit, N.Z. White
Sex: 5M+5F Wt.: 2.63 – 2.98
Test Material: PT-230 THI-Die Insecticide (Less Propellent)
Quality Assurance (40 CFR §160.12): both G.L.P. + Q.A.

Summary:

1. LD_{50} (mg/kg): Males = ~~[redacted]~~; Females = ~~[redacted]~~; Combined = ~~[redacted]~~;
2. The estimated LD_{50} is > 2.0 g/kg
3. Tox. Category: III. Classification: Guideline

Procedure ~~(Deviations From §81-2):~~ Animals acclimated at least 5 days prior to test. Approx 24 hrs prior to dosing, fur was clipped from backs of 5M+5F Rabbits. 2.0 g/kg was applied to clipped backs of each animal, to cover approx 10% of body surface – dose applied to

~~Results:~~

Reported Mortality

DOSAGE (g /kg)	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
2.0 g / kg	0/5	0/5	0/10

Symptomology & Gross Necropsy Findings:

Large, porous gauze patches which were placed on test sites. Treated area was wrapped with occlusive material & secured with elastic tape. 24 hours skin contact & sites wiped. Animals observed for toxic signs and mortality to 14 days. Dermal irritation scored according to the Draize System. Body weights recorded at weekly intervals.

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Clinical: Well defined erythema - mod. to severe edema, 2 animals, necrotic skin for 3 animals at 24 hours. Eschar + slight to mod. edema day 2, for 5 animals. Eschar noted throughout 14 day observation period. Animals systemically healthy by appearance for 14 days (appeared normal).

Necropsy:

one male - green colored liquid in stomach, fecal staining, light green liquid & gas in stomach of 2nd male.

one female exhibited gas in stomach.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: (16) 10-14-92 Reviewer: W. Woodrow
MRID No.: 426137-04 Report Date: 3-25-92
Testing Laboratory: Biosearch, Inc. Report No. 92-7607A
Author(s): R.J. Hetschman
Species: Rat Sprague Dawley
Sex: 5M/5F Weight: 209-239 g
Source: Buckshire Corp., Perkasie PA.
Test Material: PT-230 Tri-Die Insecticide (Less Propellent)
Quality Assurance (40 CFR §160.12): both G.L.P. & Q.A.

Summary:

1. LC_{50} (mg/kg): Males = —; Females = —; Combined = —
2. The estimated LC_{50} is > 4.78 mg/L
3. Mean Concentration: —
4. Tox. Category: III. Classification: Guideline

Procedure ~~(Deviations From §81-3)~~: 5M/5F rats were placed in restraining cages to hold animals separately, and then the group placed into 230 L for 4 hours while being exposed to aerosol of test material.

Results:

Exposure Concentration (mg/L)	Reported Mortality (NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
4.78 mg/L	0/5	0/5	0/10

Symptomology & Gross Necropsy Findings:

Exposed animals observed daily to 14 days for signs of toxicity and/or mortality. Body weights recorded weekly. All animals subjected to gross necropsy examinations.

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The cosol was generated by a 1/8 JCO-55 plus SUIA-55 spray nozzel (spraying 4 gpm) fed by syring pump. Air was passed through dessicant prior to passing through nozzel. Temp. & humidity recorded every 30 min.

The chamber concentration was measured 4 times during exposure by pulling chamber air through pre-weighed glass fiber filters - increased wt. ÷ L air sampled = mg/L air. Four sets of tandem midget impinger samples collected at 4 periods during exposure for analytical chemical determination.

Particle size distribution was determined by pulling chamber air samples (4) through a Cascade Impactor. Material collected on each plate (pre-weighed) determined gravimetrically. MMAD & GSD calculated.

RESULTS

1) Chamber concentration, particle size info (averages)

particle size	Gravimetric conc.			
AV. of 4 (μ)	Andersen	Filter	analytical	
2.93μ	2.48 mg/L	2.34 mg/L	4.78 mg/L	

MMAD = 2.93μ ± 0.15

Note that the analytical (chemical) measurement of chamber concentration was approximately 2 x that of the two gravimetric measurements: the testers states that very small particulates or volatile vapor material would not be impinged onto the gravimetric glass fiber filter media; which would account for the difference.

Clinical observations & gross necropsy exams:

All animals appeared normal.

All animals gained weight.

MRID No.: 426137-05 Report Date: 3-25-93
Testing Laboratory: Biosearch, Inc. Report No. 92-7607A
Author(s): G. E. Moore
Species: Rabbit, N Z White
Sex: 3M + 3 female Weight: not Given
Source: Davidson Mill Farm, Jamesburg NJ
Dosage: 1 sec. spray from 10 cm
Test Material: PT 1230 Tri-Die Insecticide (Pressurized Product)
Quality Assurance (40 CFR §160.12): both G.C.P. + Q.A.

Summary:

Tox. Category: II Classification: Guideline

Procedure ~~(Deviation From §81-4)~~: ~~Animals acclimated at least 5 days pre-test. Within 24 hours pre-test, both eyes 6 rabbits examined for defects using fluorescein dye. One eye each rabbit: Spray can shaken and test~~ sults: sprayed. A one-second spray to each test eye

Observations
(number "positive"/number tested)

	Hour	Days					
	1	1	2	3	4	7	14	21
Cornea Opacity	0/6	1/6 2	1/6 1	1/6 1	0/6	0/6	0/6	0/6
Iris	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
Conjunctivae Redness	6/6 1-3	6/6 1-3	4/6 1-3	2/6 1-3	1/6 3	1/6 1	1/6 1	0/6
Chemosis	6/6 1-3	6/6 1-3	3/6 1-4	2/6 1-3	1/6 3	1/6 3	1/6 1	0/6
Discharge	6/6 2-3	5/6 1-3	2/6 1-3	1/6 3	1/6 3	1/6 3	1/6 1	0/6

Comments: ~~(6 eyes sprayed), at a distance of 4 inches, or 10 cm. Lids held together following spray one second. Eyes examined at 1, 24, 48, 72 hours and at 4 and 7 days following instillation of test material. All eyes examined also at 14 and 21 days, using Draize system.~~
NOTE: Clearing in 8-21 days for Cat. III, but did not (14d+)

MRID NO.: 426131-02
Testing Laboratory: Biosearch, Inc. Report No. 92-7607A
Author(s): G.E. Moore
Species: Rabbit, NZ White
Age: Not given
Sex: 3M & 3F
Weight: (approx) M = 2 kg, female 2.75 kg
Dosage: 0.5 ml
Test Material: PT-230 Tri-Pre Insecticide (Less Propellent), liquid
Quality Assurance (40 CFR §160.12): both G.L.P. & Q.A.

Summary: observations suspended after 7 days - two animals exhibited eschar at 7 days - scores of 4.0 (in depth injury) should have gone to 21 days

The Primary Irritation Index = _____

Toxicity Category: I

Classification: Core Minimum

Procedure ~~(Deviations From §81-5)~~: Animals acclimated at least 5 days pre-test. A group of six rabbits ~~were~~ was clipped and a wide area on backs approx. 24 hrs before dosing. 0.5 ml of test material applied to each test site (6 animals); approx. 6 cm^2. Gauze patches on tape placed over treated and adjacent control areas. Semi-occlusive dressing wrapped around trunks & secured w/ elastic tape. 4 hr skin contact. Wrapping removed, sites wiped. Treated areas examined for erythema and edema, using Draize scoring @ 30-60 min post patch removal, at 24, 48, 72, and at 7 days.

Results:

NOTE: Scoring was suspended after recording on (at) 1, 24, 48 & 72 hours and at 7 days

~~Special Comments~~: Edema: One animal showed 1.0 scores thru 72 hrs, 3 more animals showed 1 or 2 readings at 1 hr, Erythema 1 animal 1.0 scores thru 72 hrs, another two animals showed 1.0 scores @ 24, 48 & 72 hrs. However 12 two animals exhibited eschar beginning (1 at 24 and 1 at 1 hr), and continuing thru 7 days, when scoring was suspended.

Two animals exhibiting eschar to and through observation period (7 days).
The eschar is considered a Draize score of 4.0. Since it (scoring) was discontinued after 7 days, these 4.0 scores are considered toxicity Category I. the recipient should have continued observation of treated sites through 21 days.

Product Manager: (10) 10-14-92 Reviewer: ~~M. Hatter~~ W. Dykstra
MRID No.: 426137-07 Report Date: 3-30-93
Testing Laboratory: Biosearch, Inc. Report No. 97-7607A
Author(s): G. E. Moore
Species: Guinea pig, Hartley
Sex: Male Weight: 410-524 g (less propellant).
Source: Davidson Mill Farm, NJ
Test Material: PT-230 Tri-Die Insecticide Concentrate
Positive Control Material: 2,4 dinitrochlorobenzene DNCB
Quality Assurance (40 CFR §160.12): both G.L.P. & Q.A.

Method: "Modified" Buehler
Draize scoring scale used, instead of using the Buehler scale

Summary:
1. This product [is] / is not a dermal sensitizer.
2. Classification: Core minimum Data

Procedure (~~Deviation From §81-6~~): Animals acclimated at least 7 days prior to test.
Pilot study To determine "minimally irritating threshold concentration and the highest non-irritating
~~Results~~: Concentration" Concentrations of 100% 75%, 50%, 25%, 5% and 10%, diluted v/v in mineral oil. Doses remained in skin contact for 24 hours. Based on the pilot study, test animals were induced using 50% v/v in white mineral oil. A 25% v/v dilution in white mineral was used for challenge.

Induction - A group of 10 M G. pigs. ~~Was~~ Was clipped free of hair on right sides prior to study start & repeated as necessary. 0.4 ml of test material applied to gauze patch, which had been placed onto impervious plastic. Patch was applied to skin, and was wrapped snugly around trunk - secured with tape.

24 hour skin contact for application #1, and 6 hour contact for applications 2 thru 9. Induction applications 3 x weekly, to total 9. Patches removed and sites wiped ε water. After 9th application, animals rested for two-week period.

Challenge - A challenge application was applied to left flank of induced animals (naive also). A group of 5 naive animals were also treated at time of challenge + naive control animals). Challenge applications remained in contact for 24 hours.

Results

Average NO. 1 induction score was 1.2. The average 24 hour challenge score was 1.8 1 - 48 hour challenge animals exhibited a score of 1.0 + one 24 hr. challenge score showed a 3.0 score, and 7 24 hour challenge scores were 2.06 for erythema).

Naive control animals (5) 24 hour contact. One animal exhibited a 2.0 score, one animal showed a 1.0 score for edema.

The results indicate that the test material did sensitize guinea pigs.

The positive control study did result in sensitizing guinea pigs with DNCB.

Tox Chem. No.
069001 Pyrethrins
067501 Piperonyl butoxide

File Last Updated

Current date
3-30-93

Study/Species/Lab/Study# Date	Material	MRID No.	Results	Tox. Cat.	Comments
Acute oral LD50, Rat Biosearch, Inc 92-7607A 10-16-92	PT-230 Tri-Die Insecticide (less propellent).	426137 -02	LD50 > 5.0 g/kg	IV	Guid lim-
Acute dermal LD50, Rabbit Biosearch, Inc 92-7607A 10-16-92	"	426137 -03	LD50 > 2.0 g/kg	III	Gui lim
Acute inhalation LC50, Rat Biosearch, Inc 92-7607A 10-14-92	"	426137 -04	LC50 > 4.78 mg/L	III	Gui lim-
Eye irritation, Rabbit Biosearch, Inc. 92-7607A 10-14-92	PT-230 Tri-Die Insecticide (Pressurized)	426137 -05	3 animals showed 1.0 scores at 14 days	II	Gui lim-
Skin irritation, Rabbit Biosearch, Inc. 92-7607A 10-21-92	PT-230 Tri-Die Insecticide (less propellent)	426137 -06	observations stopped at 7 days - 2 an. showed eschar - Draize 4.0	I	Corr mim
Skin sensitization, Guinea Pigs Biosearch, Inc. 97-7607A 10-14-92	"	426137 -07	Test material did sensitize Guinea Pigs	-	min mu

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