5-25-89

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 59-EGR
EXSPOT for DOGS

FROM: William S. Woodrow WSW 5-25-89
Precautionary Review Section
Registration Support Branch
Registration Division (H75-05C)
E 5/25/89

TO: George LaRocca (PM 15)
Insecticide-Rodenticide Branch
Registration Division (TS-767C)

APPLICANT: Coopers Animal Health, Inc.
2000 South 11th St.
Kansas City, KS 66103

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Permethrin (3-phenoxyphenyl) methyl (±) - cis, trans 3-3(2,2-dichloroethenyl-2,2-dimethyl-cyclopropanecarboxylate	65.0
Inert Ingredient(s):	35.0
Total	100.0%

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BACKGROUND:

Coopers Animal Health, Inc. submitted Acute oral, dermal, Primary eye and dermal irritation, and Dermal sensitization studies to support Registration of Exspot for Dogs. MRID NOS. used were: 410569-01 through 410569-05

RECOMMENDATION:

1) The acute toxicity studies submitted by Coopers animal health are acceptable to RSB/PRS.
2) The Registrant must submit an acute inhalation toxicity evaluation of EXSPOT for Dogs.

~~LABELING:~~

LABELING:

1) Change the label signal word from CAUTION, to read, "WARNING".
2) Change Precautionary Statements as follows; after "..... or absorbed through skin", add, "causes substantial but temporary eye injury. Avoid contact with skin, eyes or clothing. Wear goggles, face shield, or safety glasses. Wash thoroughly with soap and water after handling. Remove contaminated clothing and

wash before reuse.

3) Change Statements of Ptactical treatment as follows; add, " Get medical attention" to the " IF on skin", statement.

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

Product Manager: (15)
MRID No.: 410569-01
Testing Facility: T.P.S. Inc. IN
Author(s): E.P. Miller, J.E. Dyer
Species: Rat, Sprague Dawley
Age: Young adult
Weight: M 128-305-4, F 123-194-6
Source: Charles River, Michigan
Test Material: 65% Permethrin liquid
Quality Assurance (40 CFR §160.12): Satisfactory

Reviewer: Woodrow ~~M Waller~~
Report Date: 5-24-89
Report No. 36A-101-010-88

Observation Days (Post Exposure): (14); other ( )

Conclusion:

1. LD_{50} (mg/kg): Males = > 5.5 g/kg; Females = 4.8 (3.5-6.6) g/kg; Combined =
2. The estimated LD_{50} is 4.8 g/kg.
3. Tox. Category: III. Classification: Guidelines

Procedure (~~Deviations From §81-1~~): Doses by gavage to groups of 5 m + 5 f Fasted (rats). Observed 4x day of dosing, 2x Daily Wkt Days + necropsy

Results:

Reported Mortality

DOSAGE (g /kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
5.5 g/kg	2/5	0/5	2/10
8.25 g/kg	0/5	1/5	1/10
5.5 g/kg	0/5	3/5	3/10
4.125 g/kg	—	2/5	2/5
6.6 g/kg	—	4/5	4/5

Symptomology & Gross Necropsy Findings:

Clinical signs included tremors, diarrhea, severe tremors. Surviving rats did not display ~~Gross~~ gross abnormalities at necropsy. Dead ~~rats~~ rats showed sanguineous discharge mouth & cerebral vessels. Surviving rats gained weight

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager: (15)
Reviewer:- ~~M. Waller~~ Woodruff
MRID No.: 410569-02
Report Date: 5-24-89
Testing Laboratory: T-P.S., Inc.
Report No. 360C-301-2/0-88
Author(s): E. P. Miller & J. E. Dyer
Species: Rabbit
Sex : 5M + 5F Wt.: —
Test Material: Permethrin Technical 65%
Quality Assurance (40 CFR §160.12): Satisfactory

Summary:

1. LD_{50} (mg/kg): Males = —; Females = —; Combined = —;
2. The estimated LD_{50} is > 2.2 g/kg
3. Tox. Category: III. Classification: Guidelines

Procedure (~~Deviations From §81-2~~): 2.2 g/kg to backs of 5M & 5F rabbits (moistened, clipped). Sites occluded 24 hrs, cleaned. Animals observed 2x daily to 14 days for mortality, topic effects. Terminal necropsies.

Results:

Reported Mortality

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

Symptomology & Gross Necropsy Findings:

No skin reactions at end of product contact, & at 72 hrs. No mortality, or clinical observations, no gross lesions at necropsy.

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DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4)

Product Manager: (15)
MRID No.: 410569-03
Testing Laboratory: T.P.S., Inc, IN
Author(s): E.P. Miller & J.P. Dyet
Species: Rabbit, NZ White
Sex: _____ Weight: 2.70–2.97 kg
Source: Lesser's Rabbitry, Wisconsin
Dosage: 0.1 ml undiluted.
Test Material: 65% Permethrin liquid
Quality Assurance (40 CFR §160.12): Satisfactory

Reviewer: ~~M. Waller~~ Woodrow
Report Date: 5-24-89
Report No. 360E-303-912-88

Summary:

Tox. Category: II Classification: Guidelines

Procedure ~~(Deviation From §81-4)~~: 0.1 ml instilled into 1 eye, each of 6 rabbits. Examinations & scoring according to Draize at 1 hr, 24, 48, 72 hrs, Days 4, 7 & 10. Eyelids held gently ~~not~~ shut 1 sec. Body weights.

Results:

	Observations (number "positive"/number tested)							
	Hour	Days						
	1	1	2	3	4	7	~~14~~ 10	21
Cornea Opacity	0/6	0/6	0/6	0/6	0/6	0/6	0/6	
Iris	0/6	0/6	0/6	0/6	0/6	0/6	0/6	
Conjunctivae Redness	6/6	4/6	3/6	1/6	1/6	1/6	0/6	
Chemosis	6/6	4/6	2/6	1/6	0/6	0/6	0/6	
Discharge	6/6	0/6	0/6	0/6	0/6	0/6	0/6	

Comments: No iris or corneal involvement. Redness, irritation present through day 7 (1 animal), absent by day 10.

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5)

Product Manager: (15)
MRID No.: 410569-04
Testing Laboratory: T.P.S., Inc. IN
Author(s): E. P. Miller & V. E. Dyer
Species: Rabbit, NZ white
Age: young
Sex: 3M & 3F
Weight: 2.81 — 3.24 kg
Dosage: 0.5ml, undiluted
Test Material: (EX spot) → 65% Permethrin
Quality Assurance (40 CFR §160.12): satisfactory

Reviewer: ~~M. Waller~~ Woodrow
Report Date: 5-25-89
Report No. 360D-302-211-88

Summary:

The Primary Irritation Index = 0.1

Toxicity Category: IV

Classification: Guidelines.

Procedure ~~(Deviations From §81-5):~~ 0.5ml to clipped backs of 3M & 3F rabbits (undiluted) 1" sq gauze patch secured ⊂ tape over site/ covered ⊂ dental dam. Entire Trunk wrapped ⊂ Coban self-adhesive wrap. 4hr contact, sites wiped. Scoring for irritation according to Draize @ 30-60 minutes, 24, 48 & 72 hrs.

Results:

Av. irritation scores

Time	erythema/eschar	edema
30-60 min.	0	0
24 hrs	0.2	0
48 hrs	0.2	0
72 hrs	0	0

Primary irritation index = 0.1 (Practically not an irritant)

Special Comments:

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DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager: (15)
MRID No.: 410569-05
Testing Laboratory: T.P.S., Inc IN
Author(s): E.P. Miller, J.E. Dyer
Species: guinea pigs, Hartley
Sex: female Weight: 306-393g
Source: Charles River Labs, Michigan
Test Material: Exspot (65% Permethrin
Positive Control Material: 1-chloro, 2,4-dinitrobenzene (DNCB)
Quality Assurance (40 CFR §160.12): satisfactory

Reviewer: ~~M. Waller~~ Woodrow
Report Date: 5-25-89
Report No. 360B-201-215-88

Method: Modified Buehler

Summary:
1. This product is / (is not a dermal sensitizer.)
2. Classification: Guidelines

Procedure (Deviation From §81-6):

Group	# Animals	Treatment
AJL1 Controls for test material	10	0.4ml 65% Permethrin (1-challenge & 1 rechallenge application
AJL2 Controls for DNCB	4	0.4ml 0.2% DNCB in acetone (1 challenge app., & 1 rechallenge application).
AJL3 Test Material	10	0.4ml 65% Permethrin (3-inductive [1 wk intervals], 1 challenge & 1 re-challenge application (2 wks after induction)
AJL4 DNCB	4	0.4ml d/0.3% DNCB-80% ethanol (3 inductive applications) 0.4 ml 0.2% DNCB in acetone (1 challenge and 1 rechallenge application)

~~Results:~~

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All induction and challenge applications scored according to Draize @ 24 & 48 hrs after application. Applications absorbed on 2.5 cm plastic chamber / dental dam.

Results:

AJL1 Controls - 0.0 at challenge, 2 animals showed 1.0 score for Test material at 48 hrs (2/10).

AJL2 Controls - 24 hrs 0.00 score (challenge), at re-challenge: for DNCB 1 animal (score 2.0), 2 animals (score of 3.0 each) (total of 8.0 of possible 16.0 score - erythema) 2 animals showed 1.0 scores for edema. 48 hrs - 2 animals showed 1.0 for erythema.

AJL3 Test material (induced) No score 24 hrs (challenge). 6/10 scored 1.0 at 48 hrs (erythema). Re-challenge; 1 animals 1.0 at 24 hrs (erythema).

AJL4 DNCB (induced) Total score of 10/16 for erythema, and a total score of 5/16 for edema - at 24 hrs (challenge); at 48 hrs, total scored 6/16 for erythema, 4/16 for edema.

Re-challenge - 24 hrs; Total scored 7/16 for erythema, 3/16 for edema - 48 hrs scores of ~~2/16~~ 2/16, for both erythema & edema

Conclusions: A. DNCB (+ control) did sensitize guinea pigs

B. 65% Permethrin test material, and appropriate controls ~~were~~ showed similar scorings, therefore Test material did not sensitize guinea pigs. (9)

Tox Chem No. 652BB Permethrin File Last Updated _____ Current Date 5-25-89

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX. Cat.	CORE Grade/ Doc. No.
Acute oral LD50, Rat. T.P.S., Inc. # 360A-101-010-88 2-24-89	EXSPOT (65% permethrin)	410569 -01	LD50 > 4.8 g/kg	III	Guidelines
Acute dermal LD50, Rabbit. T.P.S., Inc # 360C-301-210-88 12-21-88	"	410569 -02	LD50 > 2.2 g/kg	III	Guidelines
Primary eye irritation, Rabbit. T.P.S., Inc. # 360E-303-912-88 (12-23-88)	"	410569 -03	No corneal or iris involvement. Redness irritation through day 7, absent by day 10	II	Guidelines
Primary dermal irritation, Rabbit. T.P.S., Inc. # 360D-302-211-88 12-21-88	"	410569 -04	Primary irritation score = 0.1 At 24 hrs, & 48 hrs, a score of 0.2 for ery/thema recorded	IV	Guidelines
Dermal sensitization, Guinea pigs. T.P.S., Inc. # 360B-201-215-88 - 1-3-89	"	410569 -05	EXSpot (65% Permethrin) did not sensitize guinea pigs.	-	Guidelines

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