



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 E 5/25/89
Registration Division (H75-05C)

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.
<u>Permethrin (3-phenoxyphenyl) methyl (+) - cis,</u>	<u> </u>
<u>trans 3-(2,2-dichloroethyl)-2,2-dimethyl-</u>	<u> </u>
<u>cyclopropanecarboxylate</u>	<u>65.0</u>
<u>Inert Ingredient(s):</u>	<u>35.0</u>
Total	100.0%

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:

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- 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 Practical 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)

Reviewer: Woodrow
M. Waller

MRID No.: 410569-01

Report Date: 5-24-89

Testing Facility: T.P.S. INC. INC.

Report No. 360A-101-010-88

Author(s): E.P. Miller, J.E. Dyer

Species: Rat, Sprague Dawley

Age: young adult

Observation Days (Post

Weight: M128-305-4, F123-194-6

Exposure): (14); other ()

Source: Charles River, Michigan

Test Material: 65% Permethrin liquid

Quality Assurance (40 CFR §160.12): Satisfactory

Conclusion:

- LD₅₀ (mg/kg): Males = 75.5 g/kg; Females = 4.8 (3.5-6.6) g/kg; Combined = 4.8 g/kg
- The estimated LD₅₀ is 4.8 g/kg
- Tox. Category: III. Classification: Guidelines

Procedure (~~Deviations From §81-1~~): Doses by group to groups of 5m & 5f
Feed (rats) - Observed 4x day of dosing, 2x daily Tolt Day &
measuring

Results:

Reported Mortality

DOSAGE (g /kg)	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
5.5 g/kg	3/5	0/5	3/10
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 abnormalities
at necropsy. Dead rats showed petechial hemorrhages
discharge mouth & cerebral vessels. Surviving rats gained
weight

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

Product Manager: (15)

MRID No.: 410569-02

Testing Laboratory: T.P.S., Inc.

Author(s): E.P. Miller & J.E. Oyer

Species: Rabbit

Sex: 5M & 5F

Wt.: _____

Test Material: Permethrin Technical 65%

Quality Assurance (40 CFR §160.12): Satisfactory

Reviewer: ^{Woodrow} H. Waller

Report Date: 5-24-89

Report No. 360C-301-210-88

Summary:

- LD₅₀ (mg/kg): Males = _____; Females = _____; Combined = _____
- The estimated LD₅₀ is > 2.2 g/kg
- Tox. Category: III. Classification: Guidelines

Procedure (~~Deviations From §91-2~~): 2.2 g/kg to backs of 5M & 5F

rabbits (unshaved, clipped). Sites occluded 24 hrs, cleaned. Animals observed 2x daily to 14 days for mortality, toxic 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. Dyer

Species: Rabbit, N 2 white

Sex:

Weight: 2.70-2.97 kg

Source: Lesser's Rabbitry, Wisconsin

Dosage: 0.1 ml undiluted.

Test Material: 65% Petmethrin liquid

Quality Assurance (40 CFR §160.12): Satisfactory

Reviewer: ^{Woodrow} M. Waller

Report Date: 5-24-89

Report No. 360E-303-912-88

Summary:

Tox. Category: 11 Classification: Guidelines

Procedure (~~Deviation From §81-4~~): 0.1 ml instilled into 1 eye, each of 6 rabbits. Examination & scoring according to Draize at 1 hr, 24, 48, 72 hrs, Days 4, 7 & 10. Eyelids held gently next shut 1-sec. Body weights.

Results:

	Observations (number "positive"/number tested)							
	Hour	Days						
	1	1	2	3	4	7	¹⁰ 14	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 irritative present through day 7 (1 animal), absent by day 10.

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

Product Manager: (15)

Reviewer: Woodrow ~~M. Waller~~MRID No.: 410569-04Report Date: 5-25-89Testing Laboratory: T.P.S., Inc. INReport No. 360D-302-211-88Author(s): E. P. Millet & J. E. DyerSpecies: Rabbit, NZ whiteAge: youngSex: 3m & 3FWeight: 2.81 - 3.24 kgDosage: 0.5ml, undilutedTest Material: (EX spot) → 659, PermethrinQuality Assurance (40 CFR §160.12): satisfactory

Summary:

The Primary Irritation Index = 0.1Toxicity Category: IVClassification: Guide Lines

Procedure (~~Deviations From §81-5~~): 0.5ml to dipped backs of 3m & 3F rabbits (undiluted). 1" sq gauge patch secured & tape over site / covered & dental dam. Entire trunk wrapped & Coban self-adhesive wrap. 4 hr 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:

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. Oyer

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

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 of 0.3% DNCB-80% ethanol (3 inductive applications) 0.4 ml 0.2% DNCB in acetone (1 challenge and 1 rechallenge application)

All induction and challenge applications scored according to Design @ 24 & 48 hrs after application. Application 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 (scored 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 No score 24 hrs (challenge). 6/10 scored 1.0
material at 48 hrs (erythema). Re challenge; 1 animals
(induced) 1.0 at 24 hrs (erythema).

AJL4 DNCB Total score of 19/16 for erythema, and a total score
(induced) 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~~ 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 scoring, therefore
Test material did not sensitize guinea pig. (9)

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD50, LC50, PIS, NOEL, LEL	TOX. Cat.	COKE 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	Guide - lines
Acute dermal LD50, Rabbit. T.P.S., Inc. # 360C-301-210-88 (2-21-88)	"	410569-02	LD50 > 2.2 g/kg	III	Guide - lines
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, about by day 10	II	Guide - lines
Primary dermal irritation, Rabbit. T.P.S., Inc. # 360D-302-211-88 (2-21-88)	"	410569-04	Primary irritation severe = 0.1 At 24 hrs, 448 hrs, a score of 0.2 for erythema recorded	IV	Guide - lines
Dermal sensitization, Guinea Pigs. T.P.S., Inc. # 360B-201-215-88 - 1-3-89	"	410569-05	EXSPOT (65% Permethrin) Red not sensitizing guinea pigs	-	Guide - lines