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001425

Chemical:	**Fipronil**
PC Code:	**129121**
HED File Code	**13000 Tox Reviews**
Memo Date:	**10/17/95**
File *ID*:	**TX011697**
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

129121

OCT 17 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Fipronil, Dermal Absorption in rats

TO: Barbara Madden PM 10
RCAB
Registration Division (7505C)

10/11/95

FROM: Robert P. Zendzian Ph.D.
Senior Pharmacologist
Toxicology Branch I
Health Effects Division (7509C)

THROUGH: Karl Baetcke Ph.D.
Chief
Toxicology Branch I
Health Effects Division (7509C)

10/16/95

Compound; Fipronil Tox Chem #N/A Registration #; 000264

Registrant; Rhone Poulenc MRID 437373-08 DP Barcode; D218898

Action Requested

Review the following study;

Citation

Dermal absorption of ^{14}C-Fipronil Reagent 80 WDG in male rats (preliminary and definitive phases). T. Cheng. Hazleton Wisconsin. HWI 6224-210. Feb 10, 1995. MRID 437373-08

Core Classification Acceptable

Conclusions

Male rats dosed at 0.071, 0.688 & 3.88 mg/cm^2 for exposures of 0.5, 1, 2, 4, 10 and 24 hours. Quantity in washed skin 1.14-2.45%, 0.60-3.29% and 0.35-0.80% of respective doses and quantity absorbed <1% all doses. Absorption saturated at 3.88 mg/cm^2. See review for detailed absorption data.

Attachment
DER

Data Evaluation Report

Compound Fipronil

Study Demal Absorption Guideline 85-2

Citation

Dermal absorption of ^{14}C-Fipronil Reagent 80 WDG in male rats (preliminary and definitive phases). T. Cheng. Hazleton Wisconsin. HWI 6224-210. Feb 10, 1995. MRID 437373-08

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Reviewed by Robert P. Zendzian PhD
Senior Pharmacologist

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Materials

Fipronil
AS 120068-37-3
5-Amino-1[2,6-Dichloro-4-Triflouromethylphenyl]-3-cyano-4-Triflouromethanesulphinylpyrazxole
$C_{12}H_4Cl_2F_6OS$
Mole weight 437
off white solid powder

Regent 80 WDG, 79% active ingredient (fipronil)

	Radiolabeled (Fipronil)	Nonlabeled (Regent 80 WDG)
Lot #	GHS-826	OP930794
Chemical Purity	NA	789g/kg
Radiopurity	98%	NA
Specific Activity	19.8 mCi/mM	NA
Expiration date	Dec 9, 1995	Dec 9, 1995

Male Charles River Crl:CD®BR rats from Charles River Portage Michigan

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Experimental Design

Phase	Group	Number of Animals	Dose Level	Dose ai (mg/rat)
Preliminary	1	4	1:99 dilution	0.8
	2	4	Concentrate[a]	40
Definitive	3	2	vehicle only	0
	4	24	1:99 dilution	0.8
	5	24	1:9 dilution	8.0
	6	24	Concentrate[a]	40.0

a. 1:1 dilution of formulation with 1.0% CMC solution

Preliminary phase (1 & 2) animals were used to test application and collection procedures. Group 3 (control animals) were maintained for 24 hours. Group 4, 5 and 6 animals were exposed, in groups of four animals, for 0.5, 1, 2, 4, 10 and 24 hours.

Dose preparation and verification

"Dose suspensions were prepared by combining known amounts of ^{14}C-fipronil, nonlabeled Regent 80 WDG and 1.0% carboxymethylcellulose (CMC). The carrier, 1.0% CMC, was used for the Group 3 (control). The group 6 dose suspension was prepared a second time when it became apparent that the amount of suspension from the first preparation was insufficient. The actual measurements are listed below. Components were mixed with magnetic stir bars, by vortex mixing and sonication. The dose suspensions were prepared and stored (with constant stirring) refrigerated for 1 or 2 days prior to dosing. Radioactivity levels and homogeneity were determined before dosing."

"Aliquots collected predose and postdose were analyzed to confirm radioactivity levels, homogeneity and radiochemical and chemical purities."

"Group	^{14}-Fipronil (mg)[b]	Formulation (mg)[c]	1.0% CMC (mg)	Dose Suspension (% Fipronil)
1	3.297	30.0	3461.3	0.77
2	3.297	1500	1721.8	37.0
4	5.535	50.0	4950	0.90
5	5.363	500	4500	8.0
6	5.363	2500	2500	39.0
6[a]	5.875	2500	2500	39.0

a. second preparation
b. calculated value
c. contains 79% fipronil"

Dosing

"At least one day before dosing (preliminary and definitive) the back and shoulders of each animal were shaved and the shaved area was washed with water. Care was taken not to abrade the skin. The site for application of the test material was defined by a plastic enclosure (approximately 12.5 cm^2) which was affixed to the back with cyanoacrylate-based glue. Medical silicone adhesive Type A was applied on the outside of the enclosure for sealing purposes."

"The radiolabeled dosing suspensions were constantly stirred and mixed using a vortex mixer before aliquots were taken. At dosing, approximately 100 ul of the dosing suspension was applied within the enclosure along the midline of the skin site. The weight of the dosing syringe was recorded before and after dosing. The test material was spread across the surface of the skin site using a glass stirring rod (spreader). The spreader was then rinsed with approximately 5 ml of methanol and wiped with a gauze pad; the rinse and wipe were collected for analysis. Duplicate predose and postdose aliquots were taken for dose verification."

"After administration of the test material, the application site was covered with a nonocclusive (filter paper) cover. The animals had Elizabethan collars put on to protect the dose application site."

Samples collected

Following dosing, the animals were placed in individual metabolism cages and total urine and feces collected for the duration of exposure.

At the end of the exposure period, individual animals were anesthetized with ketamine im. The Elizabethan collar was removed and the nonocclusive cover collected. The application site with swabbed with liquid Ivory and water solution. Animals were further anesthatized with halothane, exsanguinated by cardiac puncture and the blood collected. Residural bladder urine was collected and added to the urine sample. Rectal feces were collected and added to the fecal sample. The skin at the appliction site with the enclosure was excised and collected. The residual carcass was collected and the cage washed and wiped.

The following samples were analyzed for all animals of the control (group 5) the definitive phase (groups 4, 5, and 6);

urine	blood
feces	cage wash and wipe
nonocclusive cover	skin at application site
enclosure	carcass
skin wash	

Results

Material balance for groups 4, 5 and 6 (definitive phase) are presented in Table A.

Discussion

Only a small portion of the dose entered the skin and a much smaller portion was absorbed. Because of these small quantities, at or around the limit of detection, it is impossible to be certain of dose related trends. However, it appears that the percent entering the skin and the percent absorbed decreased with increasing doses. Absorption appears to be saturated at the high dose (3.8 mg/cm^2).

Table A. Fipronil dermal absorption in male rats. Percent dose distribution. Each value is the mean of four rats. Data from tables 6, 7 and 8 from the report.

Exposure (hrs)	Cover & Rinse %	Skin Wash %	Dosed Skin %	Blood %	Carcass %	Cage Wash Wipe %	Urine %	Feces %	Absorbed[a] %	Absorbed[a] ug/cm^2	Total Recovery %
Group 4, 0.876 mg/rat (0.071 mg/cm^2)											
0.5	0.30	98.8	1.14	ND	ND	ND	<0.005	ND	<0.005	<0.0035	100
1	0.22	98.7	1.51	ND	0.07	ND	ND	ND	0.07	0.049	100
2	0.17	97.9	2.45	ND	0.46	ND	ND	ND	0.46	0.327	101
4	0.11	97.8	1.86	ND	ND	ND	<0.005	ND	<0.005	<0.0035	99.7
10	0.29	96.2	1.87	ND	0.65	ND	<0.005	ND	0.65	0.462	99.0
24	0.09	96.8	1.82	ND	0.36	ND	ND	ND	0.36	0.256	99.1
Group 5, 8.35 mg/rat (0.668 mg/cm^2)											
0.5	0.20	101	0.60	ND	ND	ND	ND	ND	ND	ND	101
1	0.36	95.4	5.75[b]	ND	0.06	ND	ND	ND	0.06	0.401	101
2	0.21	101	0.85[b]	ND	0.05	ND	<0.005	ND	0.05	0.334	102
4	0.10	100	1.58	ND	ND	ND	ND	0.01	0.10	0.668	101
10	0.20	101	1.57	ND	ND	0.01	<0.005	0.01	0.02	0.200	103
24	0.12	97.1	3.29	ND	0.38	ND	0.01	0.01	0.40	2.672	100
Group 6, 48.5 mg/rat (3.88 mg/cm^2)											
0.5	0.07	105	0.35	ND	ND	ND	ND	ND	ND	ND	105
1	0.15	101	0.80	ND	0.64	ND	ND	ND	0.64	24.83	103
2	0.08	103	0.35	ND	0.05[c]	ND	ND	ND	0.05	1.94	104
4	0.12	101	0.76	ND	0.07	ND	ND	ND	0.07	2.72	102
10	0.17	103	0.69	ND	0.18	ND	<0.005	<0.005	0.18	6.98	104
24	0.12	103	0.49	ND	0 07	ND	<0.005	ND	0.07	2.72	104

a. Absorbed. Sum of blood, carcass, cage wash/wipe urine and feces.
b. Outliers, individual values 0.99, 3.91, 0.91 & 17.1
c. Outliers, individual values 0.27, ND, 0.22 & 2.09.