

**Dermal Absorption Of Cyromazine, Diclofop-Methyl,
Fenpropathrin, Fipronil, And MB 46513 In Rats**

By

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This technical report contains five memoranda with the following titles:

1. Hazard and risk evaluation for cyromazine used as Larvadex 2SL: Dermal absorption of cyromazine in rats (Special metabolism study) (pages 2-8)
2. Diclofop-methyl: Dermal absorption in rats (pages 9-14)
3. Dermal absorption of ¹⁴C-fenpropathrin in Danitol[®] using male Sprague-Dawley rats (pages 15-18)
4. Dermal absorption of ¹⁴C-fipronil Regent 80 WDG in male rats (pages 19-24)
5. Dermal absorption of ¹⁴C-MB 46513 in male rats (pages 25-30)

Phil Anderson, Registration Specialist
Pesticide Registration Branch

November 21, 1991

Sacramento

Via: John Ross, Senior Toxicologist
Worker Health and Safety Branch

4-0455

-Tian Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch

PRODUCT NAME: Larvadex 2SL

ACTIVE INGREDIENT: cyromazine

COMPANY NAME: Ciba-Geigy Corp., Agricultural Div.

I.D. NUMBER: 129530-E

DOCUMENT NUMBER: 414-084 (2 of 2 memos)

EPA REGISTRATION NUMBER: 100-0-

TITLE: Hazard and Risk Evaluation for Cyromazine Used as Larvadex 2SL: Dermal Absorption of Cyromazine in Rats (Special Metabolism Study)

Two dermal absorption studies of ^{14}C -cyromazine in male rats were conducted. The first was done using three dose levels: 0.1, 1.0, and 100 mg per rat equivalent to 10, 100, and 10,000 $\mu\text{g}/\text{cm}^2$, respectively (Murphy and Simoneux, 1985). The exposure times were 1, 2, 4, and 10 hours. Animals were sacrificed at the end of the exposure. Percent of dose recovered in the treated skin was: 29-35% for low dose, 19-27% for mid dose, and 8-15% for high dose. Systemic absorption (percent of dose recovered in urine, feces, carcass, plasma, and RBC) were 4.5-11%, 3.5-11.4%, and 2.2-7.1% for low, mid and high doses, respectively. Because of the short sample collection period and the high amount of bound skin residues, this study was not considered for the determination of dermal absorption.

The second study was conducted using three dose levels: 0.1, 1.0, and 10 mg/rat equivalent to 0.01, 0.1, and 1 mg/cm^2 , respectively (Murphy, 1987). Labeled cyromazine (for low and mid doses) and labeled cyromazine plus non-labeled cyromazine (for high dose) were mixed with formulation blank prior to application to the shaved backs of male rats. Four rats were used for each sacrifice time. The treated skin was covered with a non-occlusive protective appliance. At the conclusion of the exposure, the treated skin was washed with 2% Dove solution in water. Short- and long-term sample collections were made in two groups. For the short-term sample collection, the exposure times were 2, 4, and 10 hours and the animals were sacrificed at the end of the exposure. For the long-term study, the exposure times were 10 and 24 hours and the animals were sacrificed 48 hours after the exposure. Samples collected for the analyses included blood, carcass, skin washes, cage washes, treated skin and the skin around the treated area, urine, feces, and rinses of the protective appliance.

The results revealed cyromazine was rapidly absorbed into the skin and absorption was saturated in a short period of time. Bound skin residues, total dose recovery and dose absorbed are shown in Table 1.

Dermal absorption of cyromazine is apparently time and dose dependent. Absorption for low doses is greater than the higher doses; percent of dose absorbed is also greater with longer exposure time. Because of a substantial amount of dose bound to the treated skin, the determination of bioavailability of bound skin residues (further absorption and excretion of bound skin residues) as part of the absorbed dose was necessary. Percent of dose recovered in excreta for 58- and 72-hour sacrifice times (Table 2) was used to estimate the bioavailability of the skin residues.

Asymptotic extrapolation of percent of dose recovered in the excreta as a function of time was conducted using an exponential saturation with lag time model. Examples of the plot and output (performed by Steve Saiz, Worker Health and Safety Branch) are shown in Figure 1 and Attachment 1. The estimated bioavailability of skin residues is the difference of the percent of dose at asymptote and in excreta collected at the termination of the study. Bound skin residues that are determined to be bioavailable are shown in Table 3.

The low dose in this rat dermal absorption study most closely approximates the estimated human dermal dose. Dermal absorption of the three dose groups for the 58-hour sacrifice time (Table 3) appeared atypical because the mid dose showed the lowest absorption. Linear plots of percent dermal absorption versus dose levels gave a dermal absorption of 16.6% for the low dose with a low regression correlation. This percent dermal absorption was similar to dermal absorption of the low dose for the 72-hour sacrifice time (17.3%). Plots of percent dermal absorption and dose for the 72-hour sacrifice time showed a high regression correlation ($R^2 = 0.941$). Considering the results obtained from these two sacrifice times, a dermal absorption of 17% will be used for worker exposure estimates.

There was no inhalation absorption study of this chemical in animals. Thus, inhalation absorption was based on the study of several chemicals in humans (Raabe, 1988). For the purpose of inhalation exposure estimates, a 50% inhalation uptake and 100% absorption will be used.

Table 1. Percent of administered dose absorbed and remaining in the treated skin.

	Exposure time (hours)				Exposure time (hours)	
	2	4	10	24	10	24
Sacrifice time (hours) ^{a/}	2	4	10	24	58	72
<u>Low dose (0.01 mg/cm²)</u>						
Total recovery	100.8	88.7	95.5	92.2	110.4	101.6
Skin residues	22.6	19.0	18.6	23.9	14.8	7.2
% Dose absorbed ^b	3.3	7.3	7.6	6.9	20.3 ^c	16.1
<u>Mid dose (0.1 mg/cm²)</u>						
Total recovery	100.4	102.3	97.9	99.1	102.0	103.3
Skin residues	9.9	13.6	12.0	21.3	8.4	11.5
% Dose absorbed ^b	6.6	3.5	5.1	2.8	8.8	12.5
<u>High dose (1.0 mg/cm²)</u>						
Total recovery	87.3	77.5	76.8	89.0	94.9	101.1
Skin residues	4.5	6.3	8.6	9.3	3.2	5.9
% Dose absorbed ^b	2.1	0.8	0.8	2.6	11.6	9.1

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^a Hours after treatment

^b Percent dose in blood, urine, feces, carcass, and cage wash.

^c Cage wash for rat # 3816 was not included due to abnormally high value compared to other animals.

Table 2. Percent of administered dose excreted in urine and feces following 10- and 24-hour exposures.

<u>A. 10-hour exposure</u>		Sample collection time (hours) ^a		
Dose	Sample	10	34	58
0.01 mg/cm ²	Urine (non-cum.)	2.48	4.26	2.27
	Feces (non-cum.)	0.07	0.11	0.24
	Urine + feces (cum.)	2.55	6.92	9.43
0.1 mg/cm ²	Urine (non-cum.)	2.66	1.99	2.39
	Feces (non-cum.)	0.23	0.05	0.08
	Urine + feces (cum.)	2.89	4.93	7.40
1.0 mg/cm ²	Urine (non-cum.)	3.16	2.33	0.66
	Feces (non-cum.)	0.01	0.08	0.05
	Urine + feces (cum.)	3.17	5.58	6.29
<u>B. 24-hour exposure</u>		Sample collection time (hours) ^a		
Dose	Sample	24	48	72
0.01 mg/cm ²	Urine (non-cum.)	5.64	3.53	1.54
	Feces (non-cum.)	0.16	0.13	0.11
	Urine + feces (cum.)	5.80	9.46	11.11
0.1 mg/cm ²	Urine (non-cum.)	3.31	3.37	1.96
	Feces (non-cum.)	0.09	0.08	0.08
	Urine + feces (cum.)	3.40	6.85	8.89
1.0 mg/cm ²	Urine (non-cum.)	0.45	4.37	1.78
	Feces (non-cum.)	0.01	0.22	0.09
	Urine + feces (cum.)	0.46	5.05	6.92

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^a Hours post treatment
(cum. = cumulative)

Table 3. Dermal absorption of cyromazine in rats when bound skin residues were taken into consideration.

Dose	Sacrifice time (hours)/	Exposure time (hours)	
		10	24
		58	72
0.01 mg/cm ²	% Dose absorbed	20.30	16.10
	% Dose bioavailable ^a	4.42	1.24
	% Dermal absorption	24.72	17.34
	% Dermal absorption ^b	22.39	17.07
0.1 mg/cm ²	% Dose absorbed	8.80	12.50
	% Dose bioavailable ^a	1.14	2.94
	% Dermal absorption	9.94	15.44
	% Dermal absorption ^b	9.75	14.95
1.0 mg/cm ²	% Dose absorbed	11.60	9.10
	% Dose bioavailable ^a	0.30	1.28
	% Dermal absorption	11.90	10.38
	% Dermal absorption ^b	12.54	10.27

Thongsinthusak, WH&S, 1991

^a From asymptotic extrapolation (% dose at asymptote minus % cumulative dose excreted).

^b Corrected percent dermal absorption for total dose recovery.

REFERENCES:

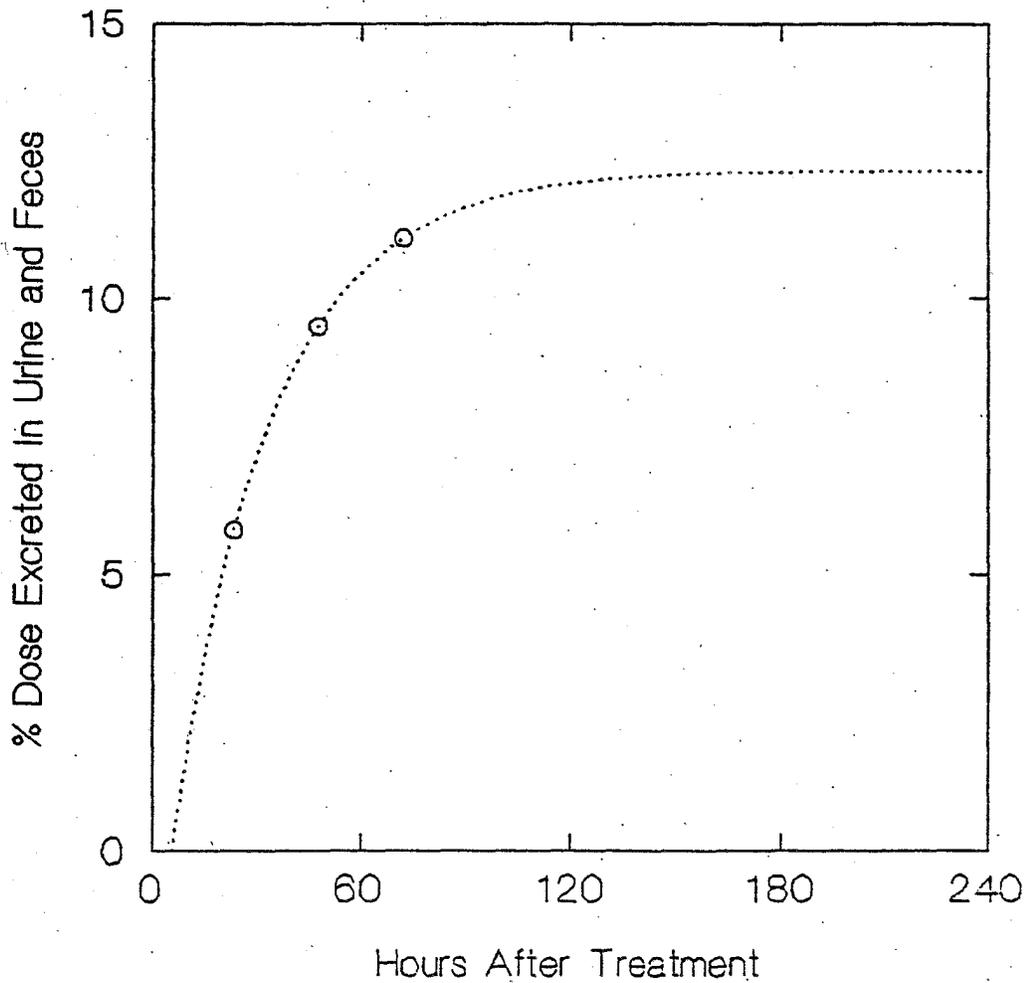
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cc: Joshua Johnson (1 original, 5 copies)
David Haskell
Steven G. Saiz
Robert I. Krieger

FIGURE 1

Determination of Bioavailability of Bound Skin Residues
(Cyromazine: 10 ug/cm²; 24-hour exposure; 72-hour sacrifice time)

$$Y=12.35*(1 - \text{EXP}(- 0.0347*(X - 5.709)))$$



Steven G. Saiz WH&S 10/29/91

ATTACHMENT 1

Determination of bioavailability of bound skin residues.
 (Cyromazine: 10 ug/cm²; 24-hour exposure with 72-hour sacrifice times)

ITERATION	LOSS	PARAMETER VALUES		
0	.2392410D+02	.1200D+02	.1000D+00	.6600D+01
1	.4959226D+01	.1115D+02	.9617D-01	.1711D+02
2	.5954550D+00	.1107D+02	.6458D-01	.1367D+02
3	.27283560+00	.1114D+02	.5773D-01	.1164D+02
4	.9913226D-01	.1152D+02	.4768D-01	.9841D+01
5	.5349085D-01	.1172D+02	.4358D-01	.8474D+01
6	.9792697D-02	.1217D+02	.36850-01	.6342D+01
7	.6128211D-03	.12310+02	.3493D-01	.5787D+01
8	.4619081D-04	.1234D+02	.3478D-01	.5732D+01
9	.6634240D-05	.1234D+02	.3474D-01	.5739D+01
10	.3240568D-06	.1235D+02	.3467D-01	.5708D-01
11	.4919159D-08	.1235D+02	.34.67D-01	.5709D+01
12	.2468737D-09	.12MD+02	.3467D-01	.5709D+01
13	.7611229D-11	.1235D+02	.3467D-01	.5709D+01

DEPENDENT VARIABLE IS: % Dose excreted = 5.8, 9.5, and 11.1 for 24, 48, and 72 hours after treatment, respectively.

PARAMETER	ESTIMATE
A	12.3502
B	0.0347
C	5.7087

Bioavailability of bound skin residues = 12.35-11.11 = 1.24%

Fely Frank, Registration Specialist
Pesticide Registration Branch

March 25, 1996

Sacramento

445-4267

-Tom Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch

PRODUCT NAME: Hoelon[®] 3 EC, Hoelon[®] 3 EW
ACTIVE INGREDIENT: Diclofop-methyl
COMPANY NAME: AgrEvo USA Company
DOCUMENT NUMBER: 385-090, -091, -092
I.D. NUMBER: SBDR-159922-E (1 of 2 memos)
EPA REGISTRATION NUMBER: 45639-0-
TITLE: Diclofop-methyl: Dermal Absorption in Rats

A dermal absorption study of (Ring-U-¹⁴C)-diclofop-methyl in male rats was conducted by Hoechst Pharmaceutical Research Laboratories, UK. The submitted report claimed that the study was conducted in compliance with (unspecified) Good Laboratory Practice principles. However, there was no QA record in this report. The second study was an *in vitro* study on rates of penetration of diclofop-methyl through human and rat skin preparations. This study was performed by Hazleton Europe and was in compliance with UK Principles of Good Laboratory Practice. The Head of the Quality Assurance Section signed the QA report. A summary of dermal absorption and rate of penetration, and the evaluation of the results are presented below.

I. In vivo Study in Male Rats

A. Preparation of Animals

Adult male Wistar strain rats obtained from Olac 1976 Ltd. were used in the dermal absorption study. Body weights of these rats ranged from 225 to 255 grams. These animals were inspected and acclimatized for about one week prior to the study. The room temperature was maintained at 20 to 22 °C and at a relative humidity of 40 to 60%. The photoperiod was 12 hours of light/12 hours of dark cycle. Prior to dosing, the back and shoulders of each animal were clipped free of hair. An area of 10 cm² was washed with water and then dried. A raised non-occlusive plastic cover was applied over the shaved area and strapped into place using Sleek adhesive dressing.

B. Administration of the Doses

Three dose levels of each diclofop-methyl formulation were used in this study. The nominal doses were 0.1, 1.0 and 10 mg of diclofop-methyl per animal equivalent approximately to 10, 100 and 1,000 µg/cm², respectively. For the low dose the radiolabeled test substance was used to prepared the dosing solution. For the medium and high doses the test substance was prepared by mixing the appropriate amount of radiolabeled diclofop-methyl (>98% pure) and non-labeled diclofop-methyl (98.5% pure). The test substance was then suspended in formulation A (Hoelon[®] 3 EW, oil in water) or formulation B (Hoelon[®] 3 EC, emulsifiable concentrate). These formulations were diluted with water to give an appropriate dosing solution. The dosing solution was applied at a nominal dose volume of 200 µL per animal. Each animal was thereafter placed in an individual restraining cage with the collection device

for urine and feces until the time of sacrifice. Four animals were used per sacrifice time at each dose.

C. Sample Collection and Analysis

The exposure and sacrifice times for all dose groups were: 0.5, 1, 2, 4, 10 and 24 hours. The animals were sacrificed at the end of each exposure period. The non-occlusive cover and adhesive dressing was removed from the application site. The dosed area was washed with a mild soap solution and then rinsed five times with distilled water using an alginate swab. Samples collected for analysis were: non-occlusive cover and adhesive dressing, skin washings, treated skin, cagewash, blood, carcass, urine and feces.

D. Results of the Study

Recovery of administered doses of diclofop-methyl for the 0.5, 1, 2, 4, 10 and 24-hour sacrifice times are shown in Tables 1 and 2. The dose recoveries are generally greater than 80%, except for animals from one sacrifice time where the recovery was 50 percent. The results of the study indicated that percent of the dose recovered in excreta and carcass is time dependent, i.e., the recovered dose is increased with increasing exposure time. This trend was also observed for blood concentration of radioactivity as shown in the submitted report. The treated skin sites of animals for both formulations contained high concentration of skin residues, ranging from 22 to 74 percent.

II. In vitro Absorption Study in Rat and Human Skin Preparations

A. Preparation of Skin

Animal skin samples were obtained from 3-5 week old female, Crl:CD(SD)BR strain rats. Rat skin was excised from the dorso-lumbar region previously clipped free of hair and washed with acetone. Human skin was obtained from suppliers in UK and USA and stored at ca -20 °C. In order not to compromise the integrity of the study, human skin was obtained from donors who had not received medical treatment. Pieces of excised skin (rat and human) were partially thawed and cut to a uniformed thickness (ca 0.4 mm) using a dermatome. The resulting section consisted of intact epidermis and a portion of dermis. Skin sections were stored flat at ca -20 °C until use. On the day of the study, the skin sections were thawed and mounted in a "Franz type" static *in vitro* dermal penetration cell. Membrane integrity was checked by measuring its permeability to tritiated water (μL of $^3\text{H}_2\text{O}/\text{cm}^2$ penetrating in two hours); deionized water was used as the receptor fluid. Rat skin preparations with values greater than $9 \mu\text{L}/\text{cm}^2$ were considered damaged and were not suitable for the study. All human skin preparations had values less than $5 \mu\text{L}/\text{cm}^2$ and were considered to be suitable for use.

B. Dose Application

The test article was prepared from (Ring- ^{14}C)-diclofop-methyl (purity >97.5%) and non-labeled material (purity 98.5%) in the formulation vehicle. The test article was diluted in deionized water to form an emulsion and provide an application volume of $25 \mu\text{L}/\text{cm}^2$. The nominal doses used in the penetration study were 10, 100 and $1,000 \mu\text{g}/\text{cm}^2$. The receptor fluid was ethanol:water (1:1, v/v); it was maintained at 32 ± 2 °C and stirred constantly on a magnetic stirrer.

Duplicate aliquots (0.05 mL) of receptor fluid were taken at the following time points after dose application: 1, 2, 4, 8, 10, 16-18, 24, 48 and 72 hours. Additional skin preparations were also washed at 10 hours post application to simulate a 10-hour occupational exposure. Samples collected for analysis were receptor fluid, membrane washings and solubilized skin.

C. Results of the Study

The rates of ¹⁴C-diclofop-methyl penetration through isolated rat and human skin preparations are shown in Table 3. The rates for rat skin range from 0.857 to 14.46 µg/cm²/hr and that for human skin range from 0.26 to 3.228 µg/cm²/hr. Overall recoveries of administered doses range from 92 to 104%. The penetration rates for rat skin are 3 to 6 fold higher than that for human skin.

III. Evaluation of the Results

The submitted report mentioned that the rat dermal absorption study was performed according to the 1985 U.S. EPA guideline. The results from both formulations clearly show a high level of bound skin residues, which range from 22 to 74%. An additional study was not conducted as suggested in the guideline. This guideline suggests an extended sample collection period for up to two weeks. For the evaluation of dermal absorption of diclofop-methyl, percent of the dose recovered in treated skin was assumed to be absorbed because bioavailability of bound skin residues could not be determined. The estimated dermal absorption values are shown in Tables 1 and 2. These values were adjusted to reflect a 100 percent recovery.

Based on the *in vivo* and *in vitro* studies, human dermal absorption values were extrapolated using an equation shown in Table 4. The extrapolation was performed for the low and medium doses of both formulations. The high dose used in the study was rather high and does not reflect a realistic level of occupational exposure. The extrapolated *in vivo* human dermal absorption values are shown in Table 4. Within the same dose level, formulation A exhibits consistently higher dermal absorption rates than that from formulation B. It is anticipated that occupational exposure to diclofop-methyl is low. In this case a dermal absorption rate obtained from the low dose was considered. Furthermore, a dermal absorption value to be used for regulatory purposes should be from formulation B (Hoelon[®] 3 EC) because this is the formulation the registrant has requested for exemption from the required health effect studies. Also, the maximum exposure time as required by the California Department of Pesticide Regulation is 10 hours. Therefore, a dermal absorption value of 16 percent is appropriate for use in the calculation of absorbed dosages for diclofop-methyl.

The Department will reevaluate the dermal absorption value based on new information on registered formulations, levels of occupational exposures, and any additional dermal absorption studies.

cc: John Ross
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Karen Flethcer
Rich Bireley

(TCW/dermal/Hoelon1)

Table 1. In vivo dermal absorption study in male rats: recovery of administered diclofop-methyl (Formulation A - Hoelon 3 EW).

Mean dose (a.i.)	Exposure/ sacrifice time (hr)	Percent of applied dose							Dose considered absorbed*	Adjusted absorbed dose**
		Skin washings	Cover washings	Exposed skin	Urine and cagewash	Feces	Carcass	Recovery		
10 µg/cm ² (actual 10.7 µg)	0.5	33.86	2.2	74.18	0.05	0.01	2.5	113	77	68
	1	24.87	3.43	61.77	0.1	0.01	2.37	93	64	69
	2	27.39	3.22	59.71	0.21	0.012	2.99	94	63	67
	4	21.35	4.84	51.9	0.93	0.024	9.08	88	62	70
	10	24.14	2.86	59.52	0.43	0.08	8.54	96	69	72
	24	17.56	4.8	47.04	0.87	1.77	19.5	92	69	76
100 µg/cm ² (actual 107 µg)	0.5	24.7	2.59	57	0.07	0.01	3.06	87	60	69
	1	20.04	10.19	58.25	0.07	0.01	2.92	91	61	67
	2	26.65	4.36	43.68	0.08	0.01	6.1	81	50	62
	4	18.07	8.91	51.81	0.39	0.01	6.37	86	59	68
	10	22.52	8.81	43.95	0.6	0.22	13.93	90	59	65
	24	10.66	12.91	42.69	0.86	0.87	16.65	85	61	72
1,000 µg/cm ² (actual 984 µg)	0.5	39.65	5.79	42.84	0.02	0.01	4.32	93	47	51
	1	28.5	9.38	37.11	0.27	0.01	5.43	81	43	53
	2	42.88	4.43	41.58	0.05	0.01	2.72	92	44	48
	4	34.49	5.24	39.09	0.05	0.01	4.72	84	44	52
	10	35.18	6.52	38.24	0.3	0.04	7.44	88	46	52
	24	38.74	4.17	37.44	0.09	0.49	10.3	91	48	53

Notes:

Application site = 10 cm².

* percent dose recovered in exposed skin + urine and cagewash + feces + carcass. Percent dose in blood is minimal compared to other samples.

** adjusted to reflect a 100 percent recovery.

(TXL/Dermal/Hoelon)

Table 2. In vivo dermal absorption study in male rats: recovery of administered diclofop-methyl (Formulation B - Hoelon 3 EC).

Mean dose (a.i.)	Exposure/ sacrifice time (hr)	Percent of applied dose							Dose considered absorbed*	Adjusted dose absorbed**
		Skin washings	Cover washings	Exposed skin	Urine and cagewash	Feces	Carcass	Recovery		
10 ug/cm ² (actual 9.2 µg)	0.5	31.35	2.09	33.94	0.02	0.011	3.25	71	37	53
	1	36.04	2.98	44.8	0.03	0.01	3.29	87	48	55
	2	22.47	2.63	22.2	0.07	0.016	2.22	50	25	49
	4	37.74	6.1	38.1	0.36	0.05	7.62	90	46	51
	10	23.64	4.11	22.08	0.15	0.04	6.87	57	29	51
	24	24.43	6.48	27.28	1.33	0.76	27.07	87	56	65
100 ug/cm ² (actual 96.9 µg)	0.5	49.4	3.61	35.21	0.04	0.01	5.99	94	41	44
	1	42.16	1.29	29.58	0.01	0.01	6.99	80	37	46
	2	45.61	1.62	40.61	0.09	0.01	7.29	95	48	50
	4	35.55	1.69	40.25	0.07	0.014	7.2	85	48	56
	10	43.42	3.52	33.57	0.28	0.06	15.12	96	49	51
	24	25.14	4.72	25.3	0.81	0.86	21.35	78	48	62
1,000 ug/cm ² (actual 944 µg)	0.5	44.78	3.24	29.37	0.03	0.01	6.96	84	36	43
	1	44.24	4.09	30.07	0.04	0.01	8.18	87	38	44
	2	52.99	5.42	23.28	0.03	0.01	6.82	89	30	34
	4	47.15	4.31	27.53	0.15	0.01	9.42	89	37	42
	10	37.04	7.54	25.59	0.25	0.1	8.47	79	34	44
	24	43.09	4.34	29.09	0.46	0.56	13.65	91	44	48

Notes:

Application site = 10 cm².

* percent dose recovered in exposed skin + urine and cagewash + feces + carcass. Percent dose in blood is minimal compared to other samples.

** adjusted to reflect a 100 percent recovery.

Table 3. In vitro absorption study in rat and human skin preparations.

Formulation	Skin preparations	Mean penetration rate (ug/cm ² /hr)		
		10 ug/cm ²	100 ug/cm ²	1,000 ug/cm ²
Emulsion*	Rat (n = 8)	0.857	5.494	14.46
	Human (n = 8)	0.26	0.946	3.228
	Ratio: rat/human	3	6	4

* (14C)-diclofop-methyl emulsion

Table 4. Extrapolation of percent dermal absorption of diclofop-methyl in humans.

$$\text{Equation:}^* \quad \frac{\text{Rats}}{\text{Humans}} \frac{\text{Absorption rate}}{\text{Absorption rate}} = \frac{\text{In vitro}}{\text{In vivo}} \frac{\text{Dermal absorption}}{\text{Dermal absorption}}$$

DPR. 1993. Guidance for the Preparation of Human Pesticide Exposure Assessment Documents. Worker Health and Safety Branch, Department of Pesticide Regulation. HS-1612 (May 4, 1993).
(Authors: T. Thongsinthusak, J. H. Ross, D. Meinders).

A. Rats: 10
µg/cm²

Time (hr)	Adjusted dermal absorption (%)	
	Formulation A	Formulation B
0.5	68	53
1	69	55
2	67	49
4	70	51
10	72	51
24	76	65

B. Rats: 100 µg/cm²

Time (hr)	Adjusted dermal absorption (%)	
	Formulation A	Formulation B
0.5	69	44
1	67	46
2	62	50
4	68	56
10	65	51
24	72	62

A1. Humans: 10 µg/cm²

Time (hr)	Extrapolated dermal absorption (%)		
	Formulation A	Formulation B	
In vitro	0.5	21	16
Penetration	1	21	17
rate (µg/cm ² /hr)	2	20	15
<u>Rats 0.857</u>	4	21	16
Humans 0.26	10	22	16
	24	23	20

B1. Humans: 100 µg/cm²

Time (hr)	Extrapolated dermal absorption (%)		
	Formulation A	Formulation B	
In vitro	0.5	12	8
Penetration	1	12	8
rate (µg/cm ² /hr)	2	11	9
<u>Rats 5.494</u>	4	12	10
Humans 0.946	10	11	9
	24	12	11

Terry Schmer, Registration Specialist
Pesticide Registration Branch

May 13, 1994

Sacramento

4-0455

-Tom Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch

PRODUCT NAME: Danitol[®] (2.4 EC)
ACTIVE INGREDIENT: Fenpropathrin
COMPANY NAME: Valent U.S.A. Corporation
I.D. NUMBER: SBRA-138380-N, -138381-N
DOCUMENT NUMBER: 50489-098
EPA REGISTRATION NUMBER: 59639-77
TITLE: Dermal Absorption of ¹⁴C-Fenpropathrin in Danitol[®] Using Male Sprague-Dawley Rats.

A dermal absorption study of fenpropathrin (Danitol[®]) in adult male Sprague-Dawley (CD/BR) rats was conducted by the Toxicology and Pharmacology Department of the Battelle Columbus Division for Valent U.S.A. Corporation. This study was performed in compliance with Good Laboratory Practice standards as mentioned in 40 CFR, part 160, 1989 and 1987 U.S. EPA's Procedure for Studying Dermal Absorption. However, inspection statements by a Quality Assurance officer were not included in the final report. A summary of this dermal absorption study and the evaluation of the results are presented below.

A. Preparation of Animals

Six to seven week old adult male Sprague-Dawley rats were used in this dermal absorption study. Body weights of these animals ranged from 211 to 287 grams. These animals were inspected and acclimatized prior to the study. The room temperature was 65 to 75 °F with 41 to 64% relative humidity. The photo period was 12 hours of fluorescent light/12 hours of dark cycle. The test facilities were ventilated with a minimum of ten air changes per hour. One day prior to the study, the dorsal surface and sides of animals were clipped free of fur using animal clippers. Animals that had abraded skin were not used in the study. The clipped dorsal surface area was wiped with a piece of acetone-soaked cotton. Prior to dosing, the treated skin site (4 x 6 cm) was delineated using a felt tip marking pen to demarcate the border of the application site. A piece of Reston[®] foam spacer with an approximately 5 x 7 cm window cut in the center was attached and secured to the animal with Holister[®] medical adhesive. Five animals were used per sacrifice time of each dose.

B. Administration of the Doses

Three dose levels of fenpropathrin were used in this dermal absorption study. Radiolabeled and non radiolabeled materials were used in the preparation of high and medium dosing solution. ¹⁴C was labeled at the benzylic carbon position of fenpropathrin. For the highest dose level (30% dose group or 1,250 ug/cm²) and the medium dose level (1.5% dose group or 62.5 ug/cm²), appropriate amounts of non labeled fenpropathrin (>99% pure) in 2.4 EC Danitol[®] and Danitol[®] 2.4 EC blank formulation were added to the ¹⁴C-fenpropathrin (>99% pure) and suspended in water. The low dose level (0.03% dose group or 1.25 ug/cm²) was prepared by adding Danitol[®] 2.4 EC blank formulation to ¹⁴C-fenpropathrin and suspended in water. The dose solution of 100 uL was spread over a clipped skin area of 24 cm² (4 x 6 cm). The treated skin site was then allowed to air dry and a non occlusive protective appliance was attached.

The window of the foam spacer was later covered with a section of wire mesh screen and a piece of filter paper. The entire protective appliance was secured with an adhesive bandage (Elastikone[®]) cut open in the center about the size of the window of a foam spacer. The animals were individually housed in 320 cm² polycarbonate (Nalgene[®]) metabolism cages during the study that allowed collection of urine and feces samples.

C. Sample Collection and Analysis

The sacrifice times for various groups of animals were: 0.5, 1, 2, 4, 10, or 24 hours after exposure. Before sacrifice, the animals were given an intraperitoneal injection of sodium pentobarbital. The protective appliance was removed and the treated skin site was vigorously scrubbed and washed with a mild soap (Ivory[®]) and water solution, rinsed with water, and dried. Urine and feces samples were collected and analyzed separately. Samples collected for analysis were: non occlusive protective appliance, skin washes, treated and non-treated skin site, blood, carcasses, feces, and urine (plus cage rinses).

D. Determination of the Results

Recovery of administered doses of ¹⁴C-fenproprathrin for the 0.5, 1, 2, 4, 10, and 24-hour sacrifice times are shown in Table 1. The results of the study indicated that dermal absorption of fenproprathrin is dose dependent, i.e. percent dose absorbed for the low dose is higher than that for the medium and high doses. Furthermore, percent dose absorbed is greater for the longer exposure and sacrifice times for the same dose level. There were significant levels of applied doses remaining in the treated skin sites for all dose groups. The highest percent dose in the treated skin site was 24.7% at 4-hour sacrifice time for the low dose, whereas, for medium and high doses were 14.7 and 15.3% at 10 hours after dosing, respectively. The results also showed that most of the dose was not absorbed and the dose was removed by washing the treated skin site with soap and water solution.

Excretion kinetics of fenproprathrin in urine and feces following 10-hour exposure were not conducted. Therefore, bioavailability of bound skin residues cannot be determined by asymptotic plots using an exponential saturation model with lag time (Thongsinthusak, 1993; Thongsinthusak and Ross, 1994). Therefore, percent of dose in the treated skin site following washing is considered absorbed and bioavailable. Dermal absorption values shown in Table 1 were obtained by addition of percent doses found in application site, blood, carcass, urine (plus cage rinses), and feces. These values were then adjusted to reflect 100 percent recovery. Ranges of adjusted dermal absorption values (%) are: 16 to 49 (0.03% dose group), 9 to 28 (1.5% dose group), and 8 to 17 (30% dose group). A dose of 1.25 ug/cm² (0.03% dose group) is similar to dermal exposure of workers to fenproprathrin. The dermal absorption value of 32%, which was obtained from the 10-hour exposure dose group, is appropriate to be used in the estimation of absorbed dosages in humans.

Recommendations:

1. The dermal absorption study of fenproprathrin in male Sprague-Dawley rats as reported in document number 50489-098 is acceptable.
2. Dermal absorption of 32 percent may be used to estimate absorbed dosages of persons exposed to fenproprathrin.

Terry Schmer
Page 3
May 13, 1994

References:

Thongsinthusak, T., Ross, J. R., and Meinders, D. 1993. *Guidance for the Preparation of Human Pesticide Exposure Assessment Documents*. HS-1612. Worker Health and Safety Branch, Department of Pesticide Regulation. (May 4, 1993).

Thongsinthusak, T., and Ross, J. 1994. Determination of dermal absorption of pesticides in animals. A memorandum dated April 7, 1994. Worker Health and Safety Branch, Department of Pesticide Regulation.

cc: Michael Dong
John Ross

(TCW/dml-abs/Danit01)

Table 1. Dermal absorption of fenpropathrin (Danitol) in young adult male Sprague-Dawley rats.

A. 0.03% dose group (1.25 µg/cm²)

Sacrifice time (hour)	Protec. Appl.	Skin washes	Appl. Site	Percent dose (mean)					
				Blood	Carcass*	Urine	Feces	Recovery	Dermal Absorption**
0.5	1.6	89.1	14.6	0.3	2.3	0	0	107.9	17.2
1	0.2	81	15.2	0.1	1.2	0.1	0	97.8	16.6
2	0.2	83.1	17.2	0.3	2.4	0.4	0	103.6	20.3
4	0.3	75.2	24.7	0.2	2.2	0.7	0	103.3	27.8
10	1.1	68.9	19.9	0.5	7.2	5.3	0.4	103.3	33.3
24	1.3	54.7	21.2	0.4	9.1	18.2	5.8	110.7	54.7

B. 1.5% dose group (62.5 µg/cm²)

Sacrifice time (hour)	Protec. Appl.	Skin washes	Appl. Site	Percent dose (mean)					
				Blood	Carcass*	Urine	Feces	Recovery	Dermal Absorption**
0.5	0.1	95.7	8.5	0.1	0.3	0	0	104.7	8.9
1	0.3	90.3	10.2	0.1	0.6	0	0	101.5	10.9
2	0.1	87.7	11.8	0.2	0.8	0.2	0	100.8	13
4	0.5	84.2	11.2	0.2	1.3	0.6	0	98	13.3
10	0.3	80.6	14.7	0.2	2.7	2.5	0	101	20.1
24	0.4	74.2	15	0.2	3.7	8.2	1.8	103.5	28.9

C. 30% dose group (1,250 µg/cm²)

Sacrifice time (hour)	Protec. Appl.	Skin washes	Appl. Site	Percent dose (mean)					
				Blood	Carcass*	Urine	Feces	Recovery	Dermal Absorption**
0.5	0.9	99.6	9	0	0	0	0	109.5	9
1	0.8	100.8	6.7	0	0	0	0	108.3	6.7
2	0.8	98.7	9	0.1	0.5	0.1	0	109.2	9.7
4	3.1	93.3	11.4	0.1	0.6	0.3	0	108.8	12.4
10	1.7	88.8	15.3	0.1	1	1.2	0	108.1	17.6
24	6.1	77.3	11.6	0.1	1.3	4.1	0.4	100.9	17.5

* included nontreated skin site.

** % dose (mean) from application site, blood, carcass, urine (plus cage rinses), and feces.

*** adjusted to reflect 100% recovery.

(TXL/Dermal/Danotol1)

TO: John Ross, Senior Toxicologist HSM-99005
Worker Health and Safety Branch

FROM: Tom Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch
(916) 445-4267

DATE: March 11, 1999

SUBJECT: BRAND NAME: Regent 80 WDG
ACTIVE INGREDIENT: Fipronil
COMPANY NAME: Rhone-Poulenc Ag Company
I.D. NUMBER: 161974-E
RECORD NUMBER (RN): 148578
DATA PACKAGE NUMBER (DPN): 52062-056
EPA REGISTRATION NUMBER: 264-0-
TITLE: DERMAL ABSORPTION OF ¹⁴C-FIPRONIL REGENT
80 WDG IN MALE RATS (HWI 6224-210)

The above report (DPN 52062-056, RN 148578) indicated that the dermal absorption study of Fipronil Regent 80 WDG in male rats was conducted in accordance with the U.S. Environmental Protection Agency Good Laboratory Practice (GLP) Standards, 40 CFR 160.35 (b) (6) (7). The Quality Assurance Statement was also attached in the submitted report. However, it appears that the quality assurance representative did not inspect each study at intervals adequate to ensure the integrity of the study and maintain written and properly signed records according to the GLP standards, 40 CFR 160.35 (b) (3).

Prior to conducting this study, all animals were acclimatized to the environment of the testing facilities, e.g., a temperature range of 19 to 25 °C, a relative humidity of 50 ± 20%, and a 12-h light/12-h dark cycle. Two groups of animals were used for the preliminary phase. This phase was used to evaluate study procedures and to determine the recovery of radioactivity. A control group was also used for the definitive phase of the study, where animals were administered with 1.0% carboxymethylcellulose (CMC). Samples from the control group were used for

radioanalysis validation procedures and background check. Three groups of animals were employed for the definitive phase of the study. The details of test conditions for the definitive phase are shown in Table 1.

Table 1. Details of the test conditions employed in the dermal absorption study of ¹⁴C-Fipronil Regent 80 WDG in male rats.

Test conditions	Details
Fipronil: labeled	([Phenyl-U- ¹⁴ C]Fipronil). Radiopurity – 98%, specific activity 19.8 mCi/mmol.
Fipronil: nonlabeled	Regent 80 WDG: Chemical purity – 789 g/kg
Animals	Male Charles River Crl:CD [®] BR rats. Age upon arrival - approximately 7 weeks old, body weight upon arrival - 332-381g (low dose), 237-280 g (moderate dose), 215-283 g (high dose). Four rats/timepoint.
Dose levels (ratio - labeled: nonlabeled)	¹⁴ C-Fipronil:nonlabeled Regent 80 WDG at 70 (5.54:50), 668 (5.36:500), and 3,880 (5.37:2500) µg a.i./cm ²
Dose: carrier	1.0% CMC, 100 µL dosing suspension/animal.
Skin: preparation and protection	Used shaved back/shoulders of animals (approximately 12.5 cm ²), washed with water prior to dosing, protected the treated skin with a nonocclusive cover (filter paper) and Elizabethan collars.
Exposure time (h)	0.5, 1, 2, 4, 10, 24.
Sacrifice time (h)	0.5, 1, 2, 4, 10, 24. Animals were anesthetized with ketamine injectable via an intramuscular injection in the thigh.
Skin wash	The treated skin was washed using 25 gauze pads and 4 cotton-tipped applicators soaked in 2% Ivory solution).
Samples collected for analysis	Nonocclusive cover, enclosure, skin wash, blood, cage wash, cage wipe, urine, feces, treated skin site, carcass.
Analysis of samples	Prepared samples were analyzed by using a Tri-Carb Liquid Scintillation Analyzer (Packard Instrument Co.).

Results from the definitive phase are shown in Tables 2, 3, and 4. The percentage of dermal absorption was calculated as the sum of the percentage of the administered dose found in the treated skin, blood, carcass, cage wash, cage wipe,

urine, and feces. The treated skin residues were included because bioavailability of the residues could not be determined according to the method suggested by Thongsinthusak *et al.* (1998).

Results show that the dermal absorption of Fipronil, especially for the low and moderate doses, is time and dose dependent. In other words, the dermal absorption is higher for the low than the high dose, and higher for the long than the short exposure time. The three dose levels used in this study were relatively high compared to the range of normal occupational exposures, e.g., 1-10 $\mu\text{g}/\text{cm}^2$.

The dermal absorption for low exposure levels may be extrapolated based upon data shown in Tables 2-4. To accomplish this purpose, a log-linear regression line was constructed using the scientific graphing software SigmaPlotTM (Jandel Scientific, 1994). Figure 1 shows the dermal absorption profile of Fipronil in rats after 10-h exposure for the three dose levels. The 10-h exposure period is typically recommended by the Department of Pesticide Regulation for a dermal absorption study because this exposure period is representative of a typical 8-h workday. The dermal absorption profile for a shorter exposure period can also be constructed if there is conclusive evidence to show that the actual exposure time is shorter than a typical workday. This figure also shows the 95% confidence limit (CL). Generally, the mean percentage of the dermal absorption is used to estimate absorbed doses because occupational exposures normally have a wide range of variability. A standard deviation is normally calculated from exposure replicates.

The regression equation, $Y = -0.9464\text{Log}(X) + 4.2753$, was used to estimate the dermal absorption for lower doses. Extrapolated dermal absorption values for dermal exposures ranging from 1 to 500 $\mu\text{g}/\text{cm}^2$ are shown in Table 5. Dermal absorption values for other dermal exposures can also be calculated or determined from Figure 1.

Recommendations:

1. A dermal absorption value of Fipronil should be selected from Table 5 or Figure 1 for the calculation of absorbed doses based upon the similarity of exposure levels.
2. Dermal absorption values for shorter exposure periods may be extrapolated by using the results shown in Tables 2-4.

Table 2. Mean percentage of radioactivity in each matrix at specified time post dose after dermal application of 14C-fipronil (70 µg/cm²) to male rats.

Sacrifice time (h)	Percentage of applied dose											Dermal absorption	
	Nonoccl. cover	Enclosure rinse	Skin wash	Treated skin site	Blood	Carcass	Cage wash	Cage wipe	Urine	Feces recovery	Total	Mean	SD*
	0.5	ND	0.3	98.8	1.14	ND	ND	ND	ND	0.005	ND	100	1.15
1	ND	0.22	98.7	1.51	ND	0.07	ND	ND	ND	ND	101	1.58	0.57
2	ND	0.17	97.9	2.45	ND	0.46	ND	ND	ND	ND	101	2.91	0.95
4	ND	0.11	97.8	1.86	ND	ND	ND	ND	0.005	ND	100	1.87	1.16
10	ND	0.29	96.2	1.87	ND	0.65	ND	ND	0.005	ND	99	2.53	0.53
24	ND	0.09	96.8	1.82	ND	0.36	ND	ND	0.01	ND	99	2.19	0.1

* SD values were taken from the submitted report

ND is "Not detectable."

Table 3. Mean percentage of radioactivity in each matrix at specified time post dose after dermal application of 14C-fipronil (668 µg/cm²) to male rats.

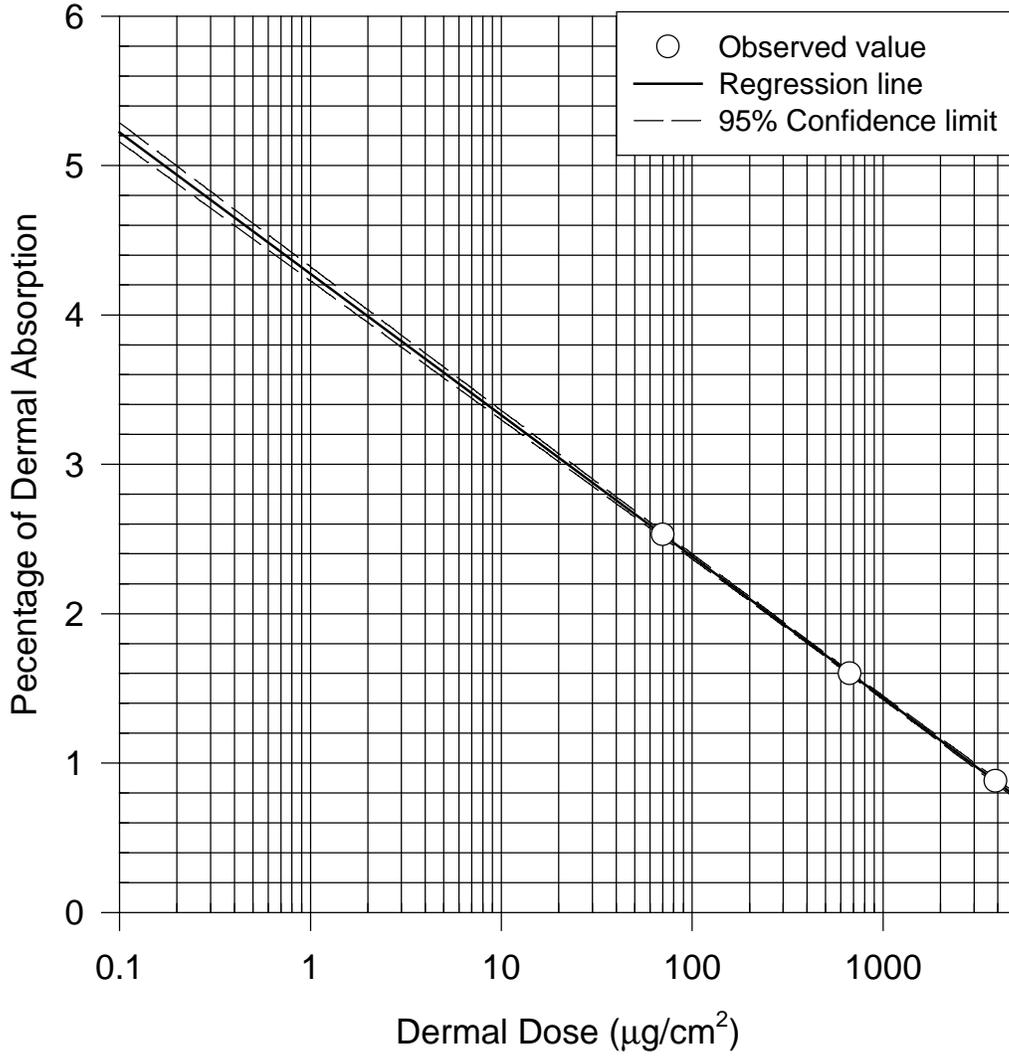
Sacrifice time (h)	Percentage of applied dose											Dermal absorption	
	Nonoccl. cover	Enclosure rinse	Skin wash	Treated skin site	Blood	Carcass	Cage wash	Cage wipe	Urine	Feces recovery	Total	Mean	SD*
	0.5	0.01	0.19	101	0.6	ND	ND	ND	ND	ND	ND	102	0.60
1	0.09	0.27	95.4	5.75	ND	0.06	ND	ND	ND	ND	102	5.81	7.74
2	0.005	0.21	101	0.85	ND	0.05	ND	ND	0.005	ND	102	0.91	0.12
4	0.01	0.09	100	1.58	ND	ND	ND	ND	ND	0.1	102	1.68	1.36
10	0.01	0.19	101	1.57	ND	ND	ND	0.01	0.005	0.01	103	1.60	0.54
24	0.01	0.18	97.1	3.29	ND	0.38	ND	ND	0.01	0.01	101	3.69	1.04

Table 4. Mean percentage of radioactivity in each matrix at specified time post dose after dermal application of 14C-fipronil (3880 µg/cm²) to male rats.

Sacrifice time (h)	Percentage of applied dose											Dermal absorption	
	Nonoccl. cover	Enclosure rinse	Skin wash	Treated skin site	Blood	Carcass	Cage wash	Cage wipe	Urine	Feces recovery	Total	Mean	SD*
	0.5	0.01	0.06	105	0.35	ND	ND	ND	ND	ND	ND	105	0.35
1	ND	0.15	101	0.8	ND	0.64	ND	ND	ND	ND	103	1.44	0.87
2	0.01	0.07	103	0.35	ND	0.05	ND	ND	ND	ND	103	0.40	0.24
4	0.01	0.11	101	0.76	ND	0.07	ND	ND	ND	ND	102	0.83	0.45
10	0.01	0.16	103	0.69	ND	0.18	ND	ND	0.005	0.005	104	0.88	0.34
24	0.01	0.11	103	0.49	ND	0.07	ND	ND	0.005	ND	104	0.57	0.26

Figure 1. Dermal Absorption of Fipronil in Male Rats Using Regent 80 WDG
(10-h exposure)

$$Y = -0.9464\text{Log}(X) + 4.2753; r^2 = 0.9999$$



(TCSG/Fipron1.SPW)

John Ross
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March 11, 1999

Table 5. Estimated percentage of dermal absorption of fipronil based upon different dermal exposures

Regression equation: $Y = -0.9464\text{Log}(X) + 4.2753$

Y = Mean dermal absorption %
m = -0.9464 Slope
b = 4.2753 Y-Intercept
X = Dermal dose $\mu\text{g}/\text{cm}^2$

Dermal dose ($\mu\text{g}/\text{cm}^2$)	Dermal absorption (%)
1	4.3
2	4.0
5	3.6
10	3.3
25	3.0
50	2.7
100	2.4
500	1.7

References:

Jandel Scientific. 1994. SigmaPlot™ for Windows: Scientific Graphing Software.
P.O. Box 7005, San Rafael, California.

Thongsinthusak, T., Ross, J. H., Saiz, S., and Krieger, R. I. 1998. Estimation of dermal absorption using the exponential saturation model. *Regul. Toxicol. Pharmacol.* 28: (in press).

cc: Joshua Johnson
Gary Sprock
Steve Rhodes

(TCW/Dermal/HSM-99005)



Winston H. Hickox
Secretary for
Environmental
Protection

Department of Pesticide Regulation

James W. Wells, Director
830 K Street • Sacramento, California 95814-3510 • www.cdpr.ca.gov

MEMORANDUM



Gray Davis
Governor

TO: John Ross, Senior Toxicologist
Worker Health and Safety Branch **HSM-99006**

FROM: Tom Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch
(916) 445-4267

DATE: March 11, 1999

SUBJECT: BRAND NAME: N/A
ACTIVE INGREDIENT: MB 46513
COMPANY NAME: Rhone-Poulenc Ag Company
I.D. NUMBER: 169043-45
RECORD NUMBER (RN): 157350
DATA PACKAGE NUMBER (DPN): 52062-150
EPA REGISTRATION NUMBER: N/A
TITLE: DERMAL ABSORPTION OF ¹⁴C-MB 46513 IN MALE
RATS (CHW 6224-230)

The above report (DPN 52062-150, RN 157350) indicated that the dermal absorption study of MB 46513, a photodegradate of the active ingredient Fipronil (MB 46,030), in male rats was conducted in accordance with the U.S. Environmental Protection Agency Good Laboratory Practice (GLP) Standards, 40 CFR 160.35 (b) (6) (7). The Quality Assurance Statement was also attached in the submitted report. However, it appears that the quality assurance representative did not inspect each study at intervals adequate to ensure the integrity of the study and maintain written and properly signed records according to the GLP standards, 40 CFR 160.35 (b) (3).

Prior to conducting this study, all animals were acclimatized to the environment of the testing facilities, e.g., a temperature range of 19 to 25 °C, a relative humidity of 50 ± 20%, and a 12-h light/12-h dark cycle. Two groups of animals were used for the preliminary phase. This phase was used to evaluate and establish test material application and skin washing techniques. A control group was also used for the definitive phase of the study, where animals were administered with 1.0%

carboxymethylcellulose (CMC). Samples from the control group were used for radioanalysis validation procedure and background check. Three groups of animals were employed for the definitive phase of the study. The details of test conditions for the definitive phase are shown in Table 1.

Table 1. Details of the test conditions employed in the dermal absorption study of ¹⁴C-MB 46513 in male rats.

Test conditions	Details
MB 46513: labeled	([Phenyl-U- ¹⁴ C]MB 46513). Radiopurity – 95.9%, specific activity - 22.6 mCi/mmol.
MB 46513: nonlabeled	Chemical purity – 99.2%
Animals	Male Charles River Crl:CD [®] BR rats. Age upon arrival – approx. 7 weeks old, body weight upon arrival 163-183 g (preliminary) and 162-190 g (definitive), 4 rats/timepoint.
Dose levels (ratio – labeled:nonlabeled)	¹⁴ C-MB 46513:nonlabeled MB 46513 (w:w) at 6.5 (labeled), 71 (7.3:53.1), and 574 (7.5:313.7) µg a.i./cm ²
Dose: carrier	1.0% CMC, 100 µL dosing suspension/animal.
Skin: preparation and protection	Used shaved back/shoulders of animals (approx. 12.5 cm ²), washed with water prior to dosing, protected the treated skin with a nonocclusive cover (filter paper) and Elizabethan collars.
Exposure time (h)	0.5, 1, 2, 4, 10, 24
Sacrifice time (h)	0.5, 1, 2, 4, 10, 24. Animals were anesthetized with halothane.
Skin wash	The treated skin was washed using 25 gauze pads and 4 cotton-tipped applicators soaked in 2% Ivory solution).
Samples collected for analysis	Nonocclusive cover, enclosure, skin wash, blood, cage wash, cage wipe, urine, feces, treated skin site, carcass.
Analysis of samples	Prepared samples were analyzed by using a Tri-Carb Liquid Scintillation Analyzer (Packard Instrument Co.).

Results of the definitive phase of the study are shown in Tables 2, 3, and 4. The percentage of dermal absorption was calculated as the sum of the percentage of the administered dose found in the treated skin, blood, carcass, cage wash, cage wipe, urine, and feces. The treated skin residues were included because bioavailability of

the residues could not be determined according to the method suggested by Thongsinthusak *et al.* (1998).

Results show that the dermal absorption of MB 46513 is time and dose dependent. In other words, the dermal absorption is higher for the low than the high dose, and higher for the long than the short exposure time. The lowest dose used in this study was similar to typical occupational exposures, e.g., 1-10 $\mu\text{g}/\text{cm}^2$. Since MB 46513 is a photodegradation product of Fipronil, the exposure level may be generally low compared to the parent chemical, Fipronil.

The dermal absorption for other doses may be extrapolated based upon data shown in Tables 2-4. To accomplish this purpose, a log-linear regression line was constructed using the scientific graphing software SigmaPlotTM (Jandel Scientific, 1994). Figure 1 shows the dermal absorption profile of MB 46513 after 10-h exposure for the three dose levels. The 10-h exposure period is typically recommended by the Department of Pesticide Regulation for a dermal absorption study in animals because this exposure period is representative of a typical 8-h workday. The dermal absorption profile for a shorter exposure period can also be constructed if there is conclusive evidence to show that the actual exposure time is shorter than a typical workday. This figure also shows the 95% confidence limit (CL). Generally, the mean percentage of the dermal absorption is used to estimate absorbed doses because occupational exposures normally have a wide range of variability. A standard deviation is normally calculated from exposure replicates.

The regression equation, $Y = -1.1204\text{Log}(X) + 3.1887$, was used to estimate the percentage of dermal absorption for lower doses. Extrapolated dermal absorption values for dermal exposures ranging from 1 to 500 $\mu\text{g}/\text{cm}^2$ are shown in Table 5. Dermal absorption values for other dermal exposures can also be calculated or determined from Figure 1.

Recommendations:

1. A dermal absorption value of MB 46513 should be selected from Table 5 or Figure 1 for the calculation of absorbed doses based upon similar dose or exposure levels.
2. Dermal absorption values for shorter exposure periods may be extrapolated by using the results shown in Tables 2-4.

Table 2. Mean percentage of radioactivity in each matrix at specified time post dose after dermal application of 14C-MB 46513 (6.5 µg/cm²) to male rats.

Sacrifice time (h)	Nonoccl. cover	Enclosure rinse	Skin wash	Treated skin site	Percentage of applied dose						Total recovery	Dermal absorption	
					Blood	Carcass	Cage wash	Cage wipe	Urine	Feces		Mean	SD*
0.5	NC	0.08	94.1	0.74	NC	NC	NC	NC	NC	NC	95	0.74	0.22
1	0.04	0.27	91.1	0.78	NC	NC	NC	NC	NC	NC	92	0.78	0.96
2	0.03	0.09	92.4	1.39	NC	NC	NC	NC	NC	NC	94	1.39	0.64
4	0.19	0.07	91.4	2.56	NC	NC	NC	NC	NC	NC	94	2.64	1.21
10	0.06	0.19	91.4	1.68	NC	0.67	NC	NC	NC	NC	94	2.35	0.74
24	0.16	0.24	89.8	3.97	NC	2.54	NC	NC	0.03	0.07	97	6.61	1.81

* SD values were taken from the submitted report NC is "Not calculated" because individual values were not detectable.

Table 3. Mean percentage of radioactivity in each matrix at specified time post dose after dermal application of 14C-MB 46513 (71 µg/cm²) to male rats.

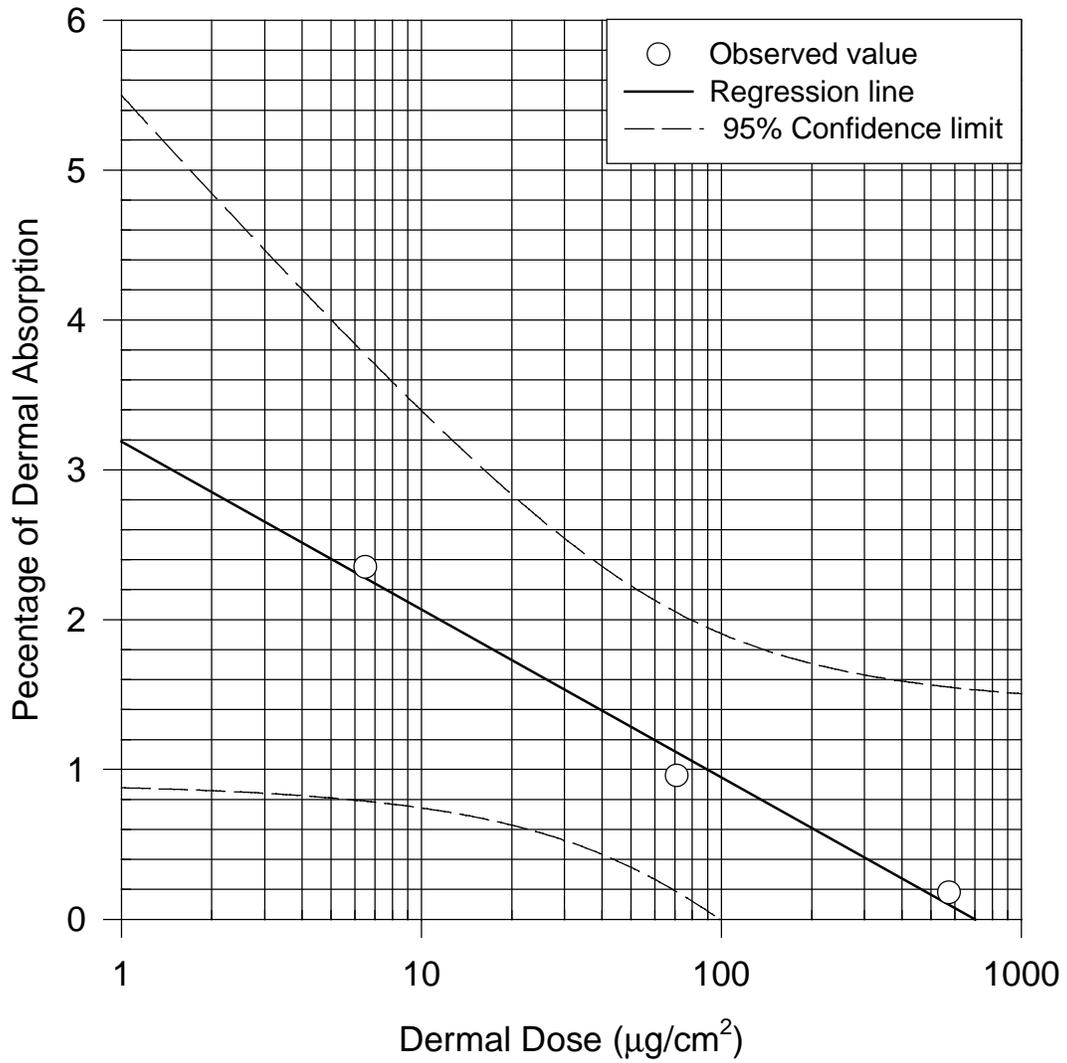
Sacrifice time (h)	Nonoccl. cover	Enclosure rinse	Skin wash	Treated skin site	Percentage of applied dose						Total recovery	Dermal absorption	
					Blood	Carcass	Cage wash	Cage wipe	Urine	Feces		Mean	SD*
0.5	NC	0.17	97.1	0.28	NC	NC	NC	NC	NC	NC	98	0.28	0.32
1	NC	0.26	92.9	0.37	NC	0.58	NC	NC	NC	NC	94	0.95	0.84
2	1.37	0.05	97.8	0.75	NC	NC	NC	NC	NC	NC	100	0.75	0.46
4	2.09	0.11	99.2	1.04	NC	ND	NC	NC	NC	NC	102	1.04	0.45
10	2.05	0.08	98.8	0.83	NC	0.13	NC	NC	NC	NC	102	0.96	0.19
24	0.03	0.08	98.1	1.05	NC	0.31	NC	NC	0.01	0.03	100	1.40	0.4

Table 4. Mean percentage of radioactivity in each matrix at specified time post dose after dermal application of 14C-MB 46513 (574 µg/cm²) to male rats.

Sacrifice time (h)	Nonoccl. cover	Enclosure rinse	Skin wash	Treated skin site	Percentage of applied dose						Total recovery	Dermal absorption	
					Blood	Carcass	Cage wash	Cage wipe	Urine	Feces		Mean	SD*
0.5	NC	0.05	102	0.13	NC	0.14	NC	NC	NC	NC	102	0.27	0.16
1	NC	0.3	99.3	0.27	NC	NC	NC	NC	NC	NC	100	0.27	0.25
2	0.18	0.08	102	0.41	NC	NC	NC	NC	NC	NC	103	0.41	0.26
4	0.03	0.14	100	0.61	NC	NC	NC	NC	NC	NC	101	0.61	0.73
10	0.01	0.04	101	0.18	NC	NC	NC	NC	NC	NC	101	0.18	0.06
24	0.74	0.06	95.3	0.34	NC	NC	NC	NC	NC	NC	96	0.34	0.26

Dermal Absorption of MB46513 in Male Rats
(10-h exposure)

$$Y = -1.1204\text{Log}(X) + 3.1887; r^2 = 0.9852$$



(TCSG/MB46513a.SPW)

Table 5. Estimated percentage of dermal absorption of MB 46513 based upon different dermal exposures*

Regression equation: $Y = -1.1204\text{Log}(X) + 3.1887$

Y = Mean dermal absorption %
m = -1.1204 Slope
b = 3.1887 Y-Intercept
X = Dermal dose ug/cm²

Dermal dose (ug/cm ²)	Dermal absorption (%)
1	3.2
2	2.9
5	2.4
10	2.1
25	1.6
50	1.3
100	0.9
500	0.2

* MB 46513 is a photodegradate of the active ingredient Fipronil (MB 46,030)

References:

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