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M E M O R A N D U M

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Worker Health and Safety Branch

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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 ^{14}C-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 ^{o}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 ^{14}C-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 $\mu g/cm^2$. 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 SigmaPlot™ (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 $\mu g/cm^2$ are shown in Table 5. Dermal absorption values for other dermal exposures can also be calculated or determined from Figure 1.

<u>Recommendations</u>:

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 ug/cm2) to male rats.

	Percentage of applied dose												
Sacrifice time (h)	Nonoccl. cover	Enclosure rinse	Skin wash	Treated skin site	Blood	Carcass	Cage wash	Cage wipe	Urine	Feces	Total recovery	Dermal absorption 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 ug/cm2) to male rats.

	Percentage of applied dose												
Sacrifice time (h)	Nonoccl. cover	Enclosure rinse	Skin wash	Treated skin site	Blood	Carcass	Cage wash	Cage wipe	Urine	Feces	Total recovery	Dermal absorption 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 ug/cm2) to male rats.

	Percentage of applied dose												
Sacrifice time (h)	Nonoccl. cover	Enclosure rinse	Skin wash	Treated skin site	Blood	Carcass	Cage wash	Cage wipe	Urine	Feces	Total recovery	Dermal absorption 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

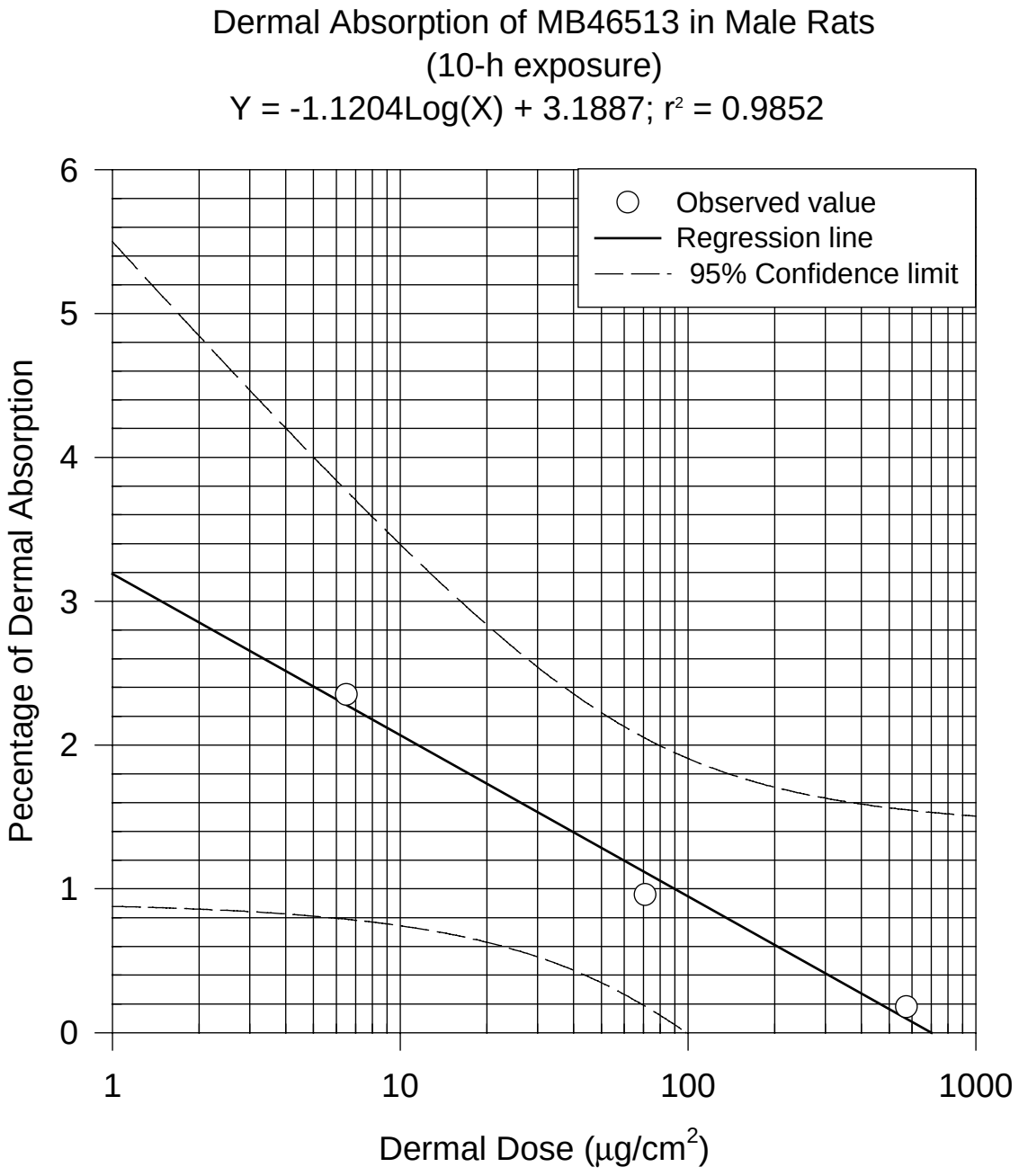
Table 5. Estimated percentage of dermal absorption of MB 46513 based upon different dermal exposures*

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/cm2)	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)



(TCSG/MB46513a.SPW)

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).

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(TCW/Dermal/HSM-99006)