

# **Dermal Absorption of Propargite, Bensulfuron-Methyl, Captan, and Maneb in Rats**

By

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This technical report contains four memoranda with the following titles:

1. Summary and dermal absorption for Omite technical, Omite 30W, Omite 6E, and Comite (pages 2-6)
2. Dermal absorption of <sup>14</sup>C-bensulfuron-methyl (pages 7-9)
3. Dermal absorption of captan (pages 10-16)
4. Dermal absorption of radiolabeled manebe in male rats (pages 17-18)

## Memorandum

To : Kathy A. Wynn, Registration Specialist  
Pesticide Registration Branch

Date : May 30, 1990  
Place : Sacramento

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

Phone: 5-8474

From : **Department of Food and Agriculture** - Tian Thongsinthusak, Staff Toxicologist  
Worker Health and Safety Branch

Subject: PRODUCT NAME: Omite technical, Omite 30W, Omite 6E, and Comite  
ACTIVE INGREDIENT: Propargite  
COMPANY NAME: Uniroyal Chemical Co., Inc.  
I.D. NUMBER: 122609-ER (One of two memoranda)  
DOCUMENT NUMBER: 259-113  
EPA REGISTRATION NUMBER: 400-0-  
TITLE: Summary and dermal absorption for Omite technical, Omite 30W, Omite 6E, and Comite. April 17, 1990.

Uniroyal Chemical Company has submitted the results of a second complete rat dermal absorption study for Omite technical, Omite 30W, Omite 6E, and Comite (Doc. No. 259-113). The first study was previously submitted and the results contained in Document Number 259-094, -095 and 259-014 (1). The second study was conducted by the Department of Toxicology and Animal Metabolism, Ricerca, Inc. The study protocol had been reviewed and commented on by the Worker Health and Safety Branch (WH&S), California Department of Food and Agriculture on August 16, 1989 (2). Part of the protocol was further amended and agreed upon by the WH&S reviewer according to a Uniroyal letter dated September 27, 1989 (3). Upon reviewing the submitted final report, minor modifications were made during the study, such as the storage temperature and method of anesthetizing rats before killing. However, the study was well executed as evidenced from good recoveries of all administered doses.

Three dose levels were used in the second study: 0.05, 0.5 and 5.0 mg/kg approximately equivalent to 1.1, 11.1, and 111.8  $\mu\text{g}/\text{cm}^2$  respectively. Radiolabeled  $^{14}\text{C}$ -Omite with purity of 99% was used for low and mid dose by mixing with formulation blank in HPLC grade water before administration. For high doses the  $^{14}\text{C}$ -Omite was mixed with  $^{12}\text{C}$ -Omite and formulation blank in HPLC grade water. For Omite technical the dose was diluted in isopropanol:water in the ratio of 1 to 4 (v/v).

Four male rats (200-249 grams) were used for each exposure period. The dose of Omite was administered to 4 x 2.5  $\text{cm}^2$  skin on the back and shoulder. Treated skin area was lightly clipped with electric clippers and demarcated before dose application. The exposed areas were covered with non-occlusive patches to prevent loss of chemical. At the end of the 0 (5 mg/kg only), 2, 4 hour exposure, the treated site was washed with 5% Liquid Ivory soap/water and rinsed with

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water. A total of five washes and rinses were performed. One wash consisted of one soap wash with a single cotton ball and one water rinse with three separate cotton balls soaked in water. At the end of each observation, rats were anesthetized with ether and killed by exsanguination. All samples necessary for the analysis were collected and kept at  $-10^{\circ}\text{C}$  or lower for analysis. At the end of the 8 and 24 hour exposure, the treated site was also washed and rinsed the same way. These rats were maintained in metabolism cages for 5 days (Omite 6E and Comite) and 21 days (Omite technical and Omite 30W).

Samples for analyses were appropriately prepared, such as dilution or combustion, and radioactivity was analyzed using liquid scintillation counting. Total radioactivity recovered was the sum of the radioactivity recovered from the protective device, non-occlusive patch, skin washes, urine, feces, blood, skin, hair from rat maintained for 5 days or longer, carcass and cage washes; whereas, percent dermal absorption (as percent of administered dose) was the sum of the radioactivity recovered in the carcass, blood, skin, urine, feces, and cage washes (plus hair if rats were maintained for 5 days or longer).

Percent dermal absorption of Omite for different dose levels and formulations are shown in Table 1. Data for a rat (# 111736) exposed to Omite 30W at 0.05 mg/kg for 24 hours was not used toward the determination of dermal absorption. These data were determined as outliers by the contractor according to procedure by W.J. Dixon (Biometrics, 9:74-89, 1953). However, data for a rat (# 112554) exposed to Comite at 0.05 mg/kg for 24 hours was not excluded from the estimation of dermal absorption as suggested by the contractor. Exclusion of this rat data was not justifiable because there was more variation in the radioactivity recovered among 4 rats in this dose group.

Table 1. Twenty-four hour dermal absorption of propargite (Omite technical, Omite 30W, Omite 6E, and Comite) in male rats<sup>a</sup>

Formulation	Dosage <sup>b</sup>		Reported dermal absorption <sup>c</sup>	% Administered dose recovered	% Corrected dermal absorption <sup>d</sup>	% Dermal absorption first study <sup>e</sup>
	mg/kg	µg/cm <sup>2</sup>				
Omite tech.	0.05	1.1	20.1 ± 3.6	99.0 ± 3.8	20	NS
	0.5	11.1	12.6 ± 4.1	92.0 ± 1.6	15	NS
	5.0	111.8	5.6 ± 1.1	80.4 ± 1.5	7	NS
Omite 30W	0.05	1.1	17.2 ± 0.6	92.9 ± 2.2	19	9
	0.5	11.1	7.0 ± 1.0	88.4 ± 6.8	8	8
	5.0	111.8	8.7 ± 3.5	89.5 ± 7.6	10	3
Omite 6E	0.05	1.1	10.7 ± 2.9	94.8 ± 1.5	11	9
	0.5	11.1	10.6 ± 2.9	97.3 ± 2.3	11	NS
	5.0	111.8	5.9 ± 1.5	94.7 ± 0.3	6	NS
Comite	0.05	1.1	9.1 ± 7.2	93.6 ± 7.0	10	17
	0.5	11.1	5.1 ± 1.0	89.0 ± 2.8	6	16
	5.0	111.8	8.7 ± 1.1	92.8 ± 2.1	9	14

<sup>a</sup> n=4 for each dose group, except for Omite 30W at 0.05 mg/kg where n=3.

<sup>b</sup> Dosage (µg/cm<sup>2</sup>) was calculated based on the average dosage applied to 10 CM<sup>2</sup>.

<sup>c</sup> According to final results submitted (CDFA Pest. Reg. Doc. 259-113).

<sup>d</sup> Corrected dermal absorption = (c x 100)/% administered dose recovered.

<sup>e</sup> Dermal absorption (1) determined by Worker Health and Safety Branch, CDFFA.

NS = No Study

Results shown in Table 1 are grouped according to dosages from all formulations and the results are shown in Table 2.

Table 2. Summary: 24-hour dermal absorption ranges of propargite in male rats for all formulations

mg/kg	Dosage		Percent dermal absorption (range of means)	
	mg/kg	$\mu\text{g}/\text{cm}^2$	second study <sup>a</sup>	first study <sup>b</sup>
0.05	1.1		10 - 20	9 -17
0.5	11.1		6 - 15	8 -16
5.0,	111.8		6 - 10	3 -14

<sup>a</sup> CDFA Pesticide Registration Document No. 259-113.

<sup>b</sup> CDFA Pesticide Registration Document No. 259-094, -095 and 259-014.

There were some differences among percent dermal absorption reported in the first study and in this study. For example, percent dermal absorption at 0.05 mg/kg in the first study for Comite II and Omite 30W were 15 and 10, respectively; however, they were 9 (Comite) and 17 (Omite) percent for the second study, respectively. Due to the range of results of the two studies, a higher percent dermal absorption of Omite technical material (20 percent), and the general trend of worker exposure in the proximity of 1-10  $\mu\text{g}/\text{cm}^2$  the Worker Health and Safety Branch has determined that 24-hour dermal absorption of 17 percent as had been previously calculated is appropriate for estimation of absorbed dosages for workers. Dermal absorption studies by nature have inherent variability. These results between studies are remarkably consistent.

We currently do not know enough about the kinetics or peculiarities of foliar transfer to say that one formulation (or the technical) is more representative of the nature of foliar residue.

Kathy A. Wynn  
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References:

1. Uniroyal Chemical Co., Inc. Study on dermal absorption of different <sup>14</sup>C-Omite formulations by male rats. California Department of Food and Agriculture, Pesticide Registration Document Number 259-095, -095 and 259-014.
2. Thongsinthusak, Tian. Review and comments on dermal absorption protocol of Omite in rats, Project No. 8920B. A letter to W. F. Cummings (Uniroyal Chemical), WH&S, CDFA, August 16, 1989.
3. Parkins, M.D. Study on the dermal absorption of Omite in rats, Project No. 8920B. A letter to Tian Thongsinthusak. September 27, 1989.

cc: Joshua Johnson (1 original, 5 copies)  
Robert I. Krieger

## Memorandum

To : Bruce Bly, Registration Specialist  
Pesticide Registration Branch

Date : October 23, 1990

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

Place : Sacramento

Phone : 5-8474

From : **Department of Food and Agriculture** - Tian Thongsinthusak, Staff Toxicologist  
Worker Health and Safety Branch

Subject: PRODUCT NAME: Londax  
ACTIVE INGREDIENT: Bensulfuron-methyl  
COMPANY NAME: E.I. du Pont de Nemours & CO.  
I.D. NUMBER: 124886-E  
DOCUMENT NUMBER: 50670-040  
EPA REGISTRATION NUMBER: 312-506  
TITLE: Dermal Absorption of <sup>14</sup>C-Bensulfuron-methyl

The registrant has submitted a final audited report on the dermal absorption study of bensulfuron-methyl in rats as part of California registration for Londax. This document has been reviewed and evaluated by the Worker Health and Safety Branch concerning the percent dermal absorption and acceptability of the study.

Four CrI:CD BR male rats (223-289 grams) were used for each sacrifice time. All rats were quarantined and properly inspected by the performing laboratory. Prior to dose administration, hair on the application site was clipped using mechanical clippers. The clipped area was gently rubbed with an acetone soaked gauze pad. Only healthy rats with normal dose site surfaces were used in the study. The protective appliance constructed from a Reston 1560 self-adhering foam pad was attached to the dose site. A non-occlusive gauze pad attached to a perforated metal screen was affixed to the protective appliance after dose administration.

Doses of bensulfuron-methyl used in this study were 0.08, 0.8, and 8.0 mg per rat or equivalent to 6.7, 66.7, and 667 ug/cm<sup>2</sup>. Non-labeled (purity 90+%) and labeled <sup>14</sup>C-bensulfuron-methyl (purity 93+% with a specific activity of 57.5 uCi/mg) were mixed and formulated as a 60% (w/1w) dry flowable formulation. The dosing suspension was prepared in 50 nM aqueous potassium phosphate buffer solution (pH was approximately 8). Two hundred microliters of the dose suspension was administered using a positive displacement pipetor to the 12 cm<sup>2</sup> area of the clipped back of the rats. All treated rats were individually housed in a "Roth" -type glass metabolism unit which allows separate collection of urine and feces. Each rat was supplied with tap water and Certified Laboratory Chow #5002 ad libitum.

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The exposure times were 1, 2, 4, 10, and 24 hours. At the conclusion of the exposure period rats were anesthetized with Metofane. The protective appliance was removed and the treated site was washed with a gauze pad soaked in 10% soap solution and then with a gauze pad soaked in water. Rats were killed by exsanguination. Samples collected for the analysis were: urine (+ cage wash), feces, blood, carcass, protective appliance, skin wash, and dosed skin.

All samples were prepared for analysis by liquid scintillation counter. Results were reported as percent of dose as shown in Table 1.

Table 1. Summary: Percent dose recovered in various samples.

Exposure time (hours)	Samples	Mean % administered dose		
		-----mg/rat-----		
		0.08	0.8	8.0
1	Penetrated dose <sup>a</sup>	0.95	0.59	0.32
	Dosed skin	3.54	11.17	3.87
	Unpenetrated dose <sup>b</sup>	91.07	88.17	92.19
	Total	95.56	99.93	96.38
2	Penetrated dose <sup>a</sup>	0.77	1.23	0.69
	Dosed skin	2.10	5.42	3.79
	Unpenetrated dose <sup>b</sup>	93.24	91.23	91.61
	Total	96.11	97.88	96.09
4	Penetrated dose <sup>a</sup>	0.79	0.71	0.25
	Dosed skin	0.97	4.69	3.21
	Unpenetrated dose <sup>b</sup>	93.49	90.30	94.05
	Total	95.25	95.70	97.51
10	Penetrated dose <sup>a</sup>	0.96	1.40	0.65
	Dosed skin	0.70	9.94	4.03
	Unpenetrated dose <sup>b</sup>	93.97	83.83	91.95
	Total	95.63	95.17	96.63
24	Penetrated dose <sup>a</sup>	1.79	0.72	0.61
	Dosed skin	5.39	7.24	5.28
	Unpenetrated dose <sup>b</sup>	90.97	90.12	90.65
	Total	98.15	98.08	96.54

<sup>a</sup> blood, carcass, urine (+ cage wash), feces

<sup>b</sup> appliance, skin wash

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From the results shown in the Table, penetrated dose of the 0.08 mg dose group has apparently increased for the 24-h exposure time over that of the shorter exposure times. This trend was also shown in the graph presented in the submitted registration document. Within the same dose group, low percent dose recovery in the dosed skin was observed in the 4- and 10-h exposure. The percent dose in the dosed skin for 0.8 and 8.0 mg dose groups is fairly consistent, i.e., the percent dose increased with increasing exposure time. The 8.0 mg dose group may not be representative of actual worker exposure because the recommended application rate for Londax per season is very low (28 g a.i. per acre).

Bioavailability of bound skin residues of all dose groups can not be determined because of short observation times. The desirable observation time should be up to 1 week in order to evaluate the bioavailability of bound residues. Further, a lower dose group of 0.01 mg per rat should have been used in the study because lower levels of worker exposure are anticipated. From the available data, it is appropriate to determine the mean percent dermal absorption by addition of percent penetrated dose and percent dose remaining in washed skin in 0.08 and 0.8 mg dose groups from 24-h exposure. The mean percent dermal absorption was determined to be 7.6 percent.

**Recommendations:**

1. This study is acceptable provided that calculation of dermal absorption is done by addition of percent penetrated dose and percent dose remaining in washed skin.
2. Dermal absorption of 7.6 percent will be used in the Department's worker exposure estimates.
3. Dermal absorption may be reevaluated if the registrant elects to do a new dermal absorption study, but the study protocol must be approved by the Department.

cc: Robert I. Krieger  
Joshua Johnson (1 original, 5 copies)

John Ross, Senior Toxicologist  
Worker Health and Safety Branch

May 30, 1997

Sacramento

445-4267

- Tom Thongsinthusak, Staff Toxicologist  
Worker Health and Safety Branch

## Dermal Absorption of Captan

I have reviewed available *in vivo* and *in vitro* dermal absorption studies and two biological monitoring studies of strawberry harvesters to captan for the purpose of estimating dermal absorption of captan. Brief descriptions of procedures and evaluation of results of each study are given in this memo.

### A. *In vitro* dermal absorption studies

#### A.1 *In vitro* dermal absorption studies in rat and human epidermal membranes

*In vitro* captan dermal absorption studies using human and rat epidermal membranes were conducted by ICI Americas Inc. (ICI Americas Inc., 1989a and 1989b). Epidermal membranes were obtained *post mortem* from the abdomen of predominantly female human subjects of various ages. Integrity of these membranes was tested using tritiated water. The membranes were discarded if the permeability coefficients were  $>1.5 \times 10^{-3} \text{ cm hr}^{-1}$  for human and  $>2.5 \times 10^{-3} \text{ cm hr}^{-1}$  for rat.

The epidermal sheet was mounted on a support screen between the donor and the receptor chambers. The dermal absorption of six dose levels of captan ( $\mu\text{g}/\text{cm}^2$ ) was tested. The application sites were occluded, except for the  $72 \mu\text{g}/\text{cm}^2$  dose and a dose which used acetone as a vehicle. The receptor fluid was 50% v/v ethanol:0.01M hydrochloric acid. Results of the study and the absorption ratio between rat and human epidermal membranes are summarized in Table 1.

Table 1. *In vitro* dermal absorption of captan in rat and human epidermal membranes.

	Dose		n	Dermal absorption (% dose)		Absorp. ratio
	( $\mu\text{g}/\text{cm}^2$ )			Rat	Human	Rat/human
Spray dilution	72	Not occluded	6	19.1	0.3	64
	720	Occluded	6	3.3	1.19	3
	13,050	Occluded	6	2.1	0.67	3
Concentrate	100,000	Occluded	6	0.2	0.02	10
Neat technical	200,000	Occluded	6	0.05	0.004	13
Acetone deposit	40	Not occluded	6	44.0	0.42	105

The results of *in vitro* dermal absorption studies showed that rat epidermal membranes are more permeable to captan than that of human. This finding is consistent with published literature which shows that *in vivo* rats have greater dermal absorption than humans (Wester and Maibach, 1993). It is our policy that *in vitro* dermal absorption alone cannot be used for exposure assessment at this time.

## **B. *In vivo* dermal absorption studies**

### **B.1 *In vivo* dermal absorption studies in rats**

A dermal absorption study of captan in rats was conducted by Stauffer Chemical Company (Stauffer Chemical Company, 1981). Five animals were used for each of the two studies: recovery and plasma profile. Labeled and non-labeled captan in a 50-WP formulation were dissolved in propylene glycol. A dosing solution of 0.1 mL was administered to the shaved back and shoulders of the animals. The mean administered dose was  $761 \mu\text{g}/\text{cm}^2$  (18.8 mg/kg) for the recovery study and that for the plasma profile study was  $753 \mu\text{g}/\text{cm}^2$  (18.4 mg/kg). The treated skin was not washed off after dose administration or at sacrifice. Samples of urine, feces, and expired air were collected at 6, 12, 24, 36, 48, 72, 96, and 120 hours after application; whereas, for the plasma profile study, blood samples were collected from animal tails at 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours post application. Animals were sacrificed at the end of the study. Samples collected for analysis were urine, feces, expired air, carcass, dosed skin, collar, cage washes and blood.

The dermal absorption for a 10-hour exposure could not be derived from this study due to long and continuous exposure. There was no interim sacrifice of the test animals. Furthermore, the dose used in the study was very high relative to human exposure. Propylene glycol is not a suitable vehicle for a dermal absorption study because it is not a constituent of the formulation used in agriculture and because of its persistent nature due to low vapor pressure and highly solvating properties. The mean 54% dermal absorption (% dose found in urine + feces + expired air + carcass) for the 5-day exposure period as concluded in the report was unreasonably high and inappropriate for use in the captan exposure assessment.

### **B.2 *In vivo* dermal absorption studies in rats**

This dermal absorption study was conducted by Stauffer Chemical using male Sprague-Dawley derived rats, which weighed 240-280 g (9-10 weeks old) (Stauffer Chemical, 1982). The two dose levels of captan employed in the study were 0.5 and 5.0 mg/kg equivalent to  $19.4 \mu\text{g}/\text{cm}^2$  and  $194 \mu\text{g}/\text{cm}^2$ , respectively. The dosing solution contained non-labeled (captan 50-WP);  $^{14}\text{C}$ -captan was prepared in water. A 0.2 mL dosing solution was administered to 4 in<sup>2</sup> of shaved back and shoulders. The treated skin was not occluded. The exposure times were 1, 2, 4, and 8 hours. At the end of each exposure period, the animals were anesthetized and sacrificed. The treated skin was not washed off prior to or after the animals were sacrificed. Samples collected for analysis were urine, feces, carcass, blood, cage wash, and treated skin. Total  $^{14}\text{C}$ -captan equivalent ( $\mu\text{g}$  equivalent) and percent of administered dose (% dose) are shown in Table 2.

Table 2. Results of a dermal absorption studies of captan in rats.

**A. Dose: 19.4 µg/cm<sup>2</sup> (0.5 mg/4 in<sup>2</sup>)**

Exposure time (hr)*		Applied dose	Mean values					Total recovery
			Urine	Feces	Carcass	Cage wash	Dosed skin	
1	µg equiv.	480	0.3	0.008	4.1	2.7	439	446
	% dose	100	0.063	0.002	0.854	0.563	91.458	93
	% absorption**		1.5					
2	µg equiv.	500	1.3	0.18	19.6	8.3	474	503
	% dose	100	0.26	0.036	3.92	1.66	94.8	101
	% absorption**		5.9					
4	µg equiv.	506	4.4	1.47	33.3	5.5	467	512
	% dose	100	0.9	0.3	6.6	1.1	92.3	101
	% absorption**		8.8					
8	µg equiv.	496	4.9	0.72	8.8	5.3	472	492
	% dose	100	1.0	0.1	1.8	1.1	95.2	99
	% absorption**		4.0					

\* same as sacrifice time

\*\* sum of % dose in urine, feces, carcass, and cage wash (included the amounts recovered from the collars)

**B. Dose: 194 µg/cm<sup>2</sup> (5 mg/4 in<sup>2</sup>)**

Exposure time (hr)*		Applied dose	Mean values					Total recovery
			Urine	Feces	Carcass	Cage wash	Dosed skin	
1	µg equiv	4937	2.8	0.4	62.5	71.6	4750	4887
	% dose	100	0.057	0.008	1.266	1.450	96.212	99
	% absorption**		2.8					
2	µg equiv.	4928	21	1.8	274.6	200.9	4310	4808
	% dose	100	0.4	0.0	5.6	4.1	87.5	98
	% absorption**		10.1					
4	µg equiv.	4939	42.3	10.4	183.4	125	4435	4796
	% dose	100	0.9	0.2	3.7	2.5	89.8	97
	% absorption**		7.3					
8	µg equiv.	4901	131.6	14.8	211.8	105.5	4193	4657
	% dose	100	2.7	0.3	4.3	2.2	85.6	95
	% absorption**		9.5					

\* same as sacrifice time

\*\* sum of % dose in urine, feces, carcass, and cage wash (included the amounts recovered from the collars)

Data were taken from Reg. Doc. No. 103-044 or 103-066  
(TDXL/Dermal/Captan1a)

This rat dermal absorption study was conducted poorly at a time before there were guidelines for this type of study conduct. In the submitted report, bioavailability of bound skin residues could not be determined because of lack of necessary excretion data from exposure times beyond 24 hours. Dermal absorption values for the low dose group ( $19.4 \mu\text{g}/\text{cm}^2$ ), as determined by summing the dose recovered in urine, feces, carcasses, and cage washes for animals in the 1, 2, 4, and 8 hour exposure periods, are 1.5, 5.9, 8.8, and 4.0%, respectively. The trend of dermal absorption for the first three exposure periods was increasing for longer exposure time. The dermal absorption rate for the 8-hour exposure group was unrealistically reduced to about half of the value observed for animals in the 4-hour exposure group. Normally we would use dermal absorption data from the dermal dose closest to the human exposure which would be the  $19.4 \mu\text{g}/\text{cm}^2$  data.

Dermal absorption rates for the 4-hour exposure time of the two dose groups are similar. The dermal absorption rate for the 8-hour exposure time is 9.5% for the high dose group ( $194 \mu\text{g}/\text{cm}^2$ ); whereas, it is 4.0% for the low dose group. The trend of the dermal absorption rates for various exposure times of the high dose group is more realistic than the low dose group. For this reason, the dermal absorption rate for the 8-hour exposure time is more appropriate for use in the exposure assessment of captan. However, the absorption rate did not account for percent dose found in cage washes. It is assumed that the majority of the dose found in cage washes was from captan residues of urine and feces, not from collars. The total dermal absorption value of captan was estimated to be 11.7% ( $9.5\% + 2.2\%$ ).

The captan *in vitro* absorption study showed that the ratio of *in vitro* captan absorption of rat and human epidermal membranes ranged from 3 to 105 (Table 1) depending on the concentration of captan and the vehicle used in the dosing solution. Dermal absorption of several other pesticides has been shown to be greater in animals, including rats, than in humans (Bartek and LaBudde, 1975; Wester and Maibach, 1993, Formoli, 1990). The estimated dermal absorption value was not adjusted for the difference in the permeability of the rat skin obtained from *in vitro* studies. This should compensate for unaccounted bound skin residues. The estimated dermal absorption rate of 11.7% should not underestimate the dermal absorption of captan in humans.

### B.3 Dermal absorption of captan in mice

Grissom *et al.* (1985) conducted a dermal absorption study of several pesticides in mice. The dosing solution used in the study was prepared by mixing labeled and non labeled captan in acetone. At present, acetone is not recommended for use as a vehicle in a dermal absorption study because it tends to exaggerate the absorption. The captan dosing solution was applied to  $1.2 \text{ cm}^2$  of shaved upper back at a rate of  $1 \text{ mg}/\text{kg}$  equivalent to approximately  $40 \mu\text{g}/\text{cm}^2$ . The exposure/sacrifice times were 1, 6, and 24 hours. The published report did not mention how many animals were used per exposure/sacrifice time. Penetration of captan was determined from disappearance of captan from the site of application. However, there were neither data for skin residues nor explanation how the percentage of dermal penetration was derived. The geometric mean percentage dermal penetration for captan were reported to be 3.6, 3.8, and 7.8% for 1, 6,

and 24 hour exposure, respectively. The majority of the penetrated dose was found in excreta and carcasses. The distribution profile of the penetrated dose indicated that bound skin residues were not factored in for the determination of dermal absorption. I believe that results from this study should be excluded from the present determination of captan dermal exposure due to uncertainty outlined above.

### **C. Other studies**

#### **C.1 Dermal and oral administration of captan in humans**

In two preliminary dermal tests in human subjects, captan in chloroform solution was administered to ventral and dorsal surfaces of the right and left forearms and hands (Krieger and Thongsinthusak, 1993). Urine samples were collected for five days. Results indicated that absorption may be less than 0.3% for 24 hours in humans. However, there were not enough replicates to adequately estimate dermal absorption. This study emphasized oral instead of dermal administration of captan.

#### **C.2 Biological monitoring studies of strawberry harvesters**

There are two biological monitoring studies that may be used to estimate potential dermal absorption of captan. In the first study, a dermal absorption may be estimated from urinary tetrahydrophthalimide (THPI) and dermal exposure of strawberry harvesters to captan (Maddy *et al.*, 1989). The dermal absorption value was tentatively estimated to be about 2% (0.2 mg urinary captan equivalent x 100/10 mg dermal captan exposure). Under this estimation, several factors were not considered because of insufficient information. Urinary collection periods for harvesters may not be complete to adequately estimate the total output of THPI. Analysis for thiazolidine-2-thione-4-carboxylic acid (TTCA) was not conducted. TTCA is a major metabolite of captan of greater magnitude than THPI according to the study conducted by Krieger and Thongsinthusak (1993). In addition, not all of the estimated dermal dose of captan would be available for dermal absorption because it was tied up in/on dosimeters. These factors would have a good potential to increase the estimated dermal absorption from 2%.

The second biological monitoring study was also conducted in strawberry harvesters (Blewett, 1989). The dermal absorption was estimated to be 5.8% from urinary THPI and the dermal dose of captan (Fong and Krieger, 1992). Many factors mentioned in reviewing the first study were not included in the estimation of dermal absorption. In other words, the dermal absorption could be greater than 5.8% if these factors were considered. Therefore, dermal absorption values estimated from both biological monitoring studies were not considered for inclusion in the final determination of captan dermal absorption.

### **D. Summary and Recommendations**

1. There was no *in vivo* dermal absorption study of captan that was conducted according to guidelines given by the U.S. EPA (Zendzian, 1994) or the Department (Thongsinthusak *et al.*, 1993).

2. The estimated dermal absorption value of 11.7% can be used for the exposure assessment as an interim basis until an acceptable *in vivo* dermal absorption study is available. This dermal absorption value should supersede all previous determinations.
3. The Department encourages the registrant to do a new *in vivo* dermal absorption study based on guidelines given by the U.S. EPA or the Department preferably in human volunteers conducted with an appropriately reviewed human subject protocol. Scientists of the Department are available to assist in protocol development and/or review of a study protocol upon request.

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cc: Michael Dong

(TDW/Memos/Captan1)

**State of California**

**M e m o r a n d u m**

**To :** John Inouye, Registration Specialist  
Pesticide Registration Branch

**Date :** October 11, 1991

**Via :** Tian Thongsinthusak, Staff Toxicologist  
Worker Health and Safety Branch

**Place :** Sacramento

**Phone :** 4-0663

**From :** **Department of Pesticide Regulation**

David Haskell, Associate Environmental  
- Research Scientist  
Worker Health and Safety Branch

**Subject :** PRODUCT NAME: Dithane M-22  
ACTIVE INGREDIENT: Maneb  
COMPANY NAME: Rohm. and Haas Company  
I.D. NUMBER: SBRA 108559E  
DOCUMENT NUMBER: 110-041  
EPA REGISTRATION NUMBER: 707-48-AA  
TITLE: Dermal Absorption of Radiolabeled Maneb in Male Rats  
(February 17, 1988).

In 1985, the Rohm and Haas Company conducted a dermal absorption study with male rats. The back and shoulders of each rat were shaved and washed with acetone and a 4.9 cm<sup>2</sup> circular area was treated. The <sup>14</sup>C-labeled maneb (80% W.P.) was applied as an aqueous suspension at 0.18, 1.8, 17 and 122 mg/rat which is equivalent, respectively, to 0.036, 0.36, 3.47 and 24.9 mg/cm<sup>2</sup> (Group 1 to 4). Twenty male rats were used for each dosage rate and four rats from each dosage rate were sacrificed after 0.5, 1, 2, 4 and 10 hours of exposure. Following exposure, the application site was flooded with deionized water and the skin was carefully scraped with a spatula. This water was then decanted for analysis. Urine and feces were collected 0.5, 1, 2, 4 and 10 hours after application and blood samples were collected after sacrifice.

The accumulation of the <sup>14</sup>C-labeled material in the urine, feces and blood accounted for less than one percent of each applied dose for all exposure periods. Less than 1% of the dose at all dosages was excreted in 10 hours. Rats in Group 1 (0.18 mg/rat) had the greatest excretion of radioactivity with an average of 0.79% of the dose. Blood levels were all less than 0.004% of the dose. Residues in most of the feces samples were below the detection limits (less than twice the background counts). There did appear to be a slight increase with time in the amount of <sup>14</sup>C-residues in urine for each treatment level.

The lower range of the doses was adequate to estimate the potential dermal absorption of maneb for workers although the two highest doses were too high to provide meaningful results. The 10 hour exposure time for the dose is sufficient but excreta collection should normally be extended to 24 hours or longer, depending on the percent of bound skin residues (Zendzian, 1987, 1989). The rate of total recovery was 94.6, 91.4, 99.5 and 105 percent for Groups 1 through 4, respectively. The average percent of the dose remaining' in/on the application site after rinsing was 31.1, 12.6, 2.1, and 0.8 percent for Groups 1 through 4, respectively.

**SURNAME**

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The study authors assume the dose bound to the application site, after rinsing, was not available for absorption. . However, the plotted urine excretion curves for the 0.036 and 0.36 mg/cm<sup>2</sup> doses have not plateaued after 10 hours of exposure. This condition indicates the material bound to the skin is still being absorbed and excreted. Furthermore, another dermal absorption study performed with mancozeb, a closely related chemical, showed that significant urinary excretion was still occurring at 24 hours, following washing of the application site at six hours. Therefore, the amount of the dose bound to the skin, will be considered bioavailable.

The percent of dermal absorption shall include the percent excreted and the percent residues bound to the skin after washing. The low dose rate of 0.036 mg/cm<sup>2</sup> approximates the exposure for mixer/loaders and applicators spraying orchards, according to the worker exposure studies for mancozeb (Hickey, et al., 1987). At this dose rate an average of 31.1% of the dose was bound to the skin after washing and 0.79% of the dose was excreted. The dermal absorption rate for maneb on rats is 32% of the applied dose. Likewise, the dermal absorption rate is 13% if the level of exposure is close to 0.36 mg/cm<sup>2</sup>.

To resolve the question on the bound skin residues, the registrant may elect to conduct a new dermal absorption study using <sup>14</sup>C-labeled maneb in formulation blank at 10 and .30 ug a.i./cm<sup>2</sup>. The treated site should be approximately 10 cm<sup>2</sup>. After the treated site is washed with soap solution (e.g. 2-4% liquid Ivory soap in water, v/v) at the end of 10-hour exposure, the collection of urine and feces should be made at 24-hour intervals and be extended to at least seven days (per Robert Zendzian, EPA, 1987, 1989). Worker Health & Safety will be available to review the protocol prior to the study.

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