2-12-91

008265

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

2/12/91

MEMORANDUM

SUBJECT: Maneb, Review of a Dermal Absorption Study in the Rat

TO: Kathy Martin PM-60
Special Review Branch
Special Review and Reregistration Division (H7508C)

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THROUGH: Albin Kocialski Ph.D. 2/12/91
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Registration Standards and Special Review Section

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Science Analysis and Coordination Branch

Compound; Maneb | Tox Chem #539

Registration #014505 | Registrant; Atochem

MRID #416693-01 | Tox Project #1-0232

Action Requested

Review the following study:

[illegible]
WIL Research Laboratories, WIL-[illegible], Oct, 12, 19[illegible], MRID
416693-01

Conclusions

BEST AVAILABLE COPY

The study is acceptable.

Dermal [illegible] 'binding' [illegible] are relatively
small. [illegible]

Mean Dose (ug/rat)	Time of Exposure (hours)	Time of Sacrifice (hours)	Absorbed (%)	Absorbed (ug)	On/in Washed Skin (%)	On/in Washed Skin (ug)
77.2*	10.0	10.0	<0.9	<0.7	6.8	5.2
	24.0	72.0	3.0	2.3	5.3	4.1
707	10.0	10.0	<0.2	<1.4	1.8	12.7
	24.0	72.0	1.0	7.8	1.1	7.8
8909	10.0	10.0	<0.2	<17.8	[illegible]	[illegible]
	24.0	72.0	2.0	142.5	1.6	142.5
75.3†	10.0	10.0	1.6	1.2	26.4	19.9
	24.0	72.0	5.1	3.8	24.4	18.4

*in formulation vehicle suspended in water. † suspended in water.

Recommendation

The Registrant has advised OPP that the report is being revised to better reflect the actual quantities of radiolabel present 'at the limit of detection'. This will enable us to better assess the pattern of absorption and present a more realistic estimate of comparative body load by dermal and oral routes. At this time one can realistically consider that 24 hour dermal absorption of Maneb would not exceed one percent of the applied dose. Approximately 12% of the absorbed Maneb is converted to ETU.

In contrast, following an oral dose of Maneb at least 50% of the dose is absorbed within a few hours and approximately 12% of the total oral dose is converted into ETU.

Discussion

The toxicological risk associated with Maneb exposure is attributed to its metabolite ethylene thiourea (ETU). ETU has been found to be oncogenic in rodent studies but no acceptable oncogenic studies exist on Maneb. Thus, we must not only determine the dermal absorption of Maneb but also what portion of that absorption is represented as ETU. In this [illegible] Maneb, ETU [illegible] the metabolism of Maneb.

The ETU [illegible] feeding study. Typically, a rodent feeds heavily shortly after lights out and then feeds again shortly before the end of the dark period. Because of the relatively rapid absorption by the oral route, this pattern results in two peaks of systemic exposure daily. In contrast the dermal dose is absorbed over a relatively long period of time at a [illegible] rate. A very moderate, perhaps undetectable, systemic peak [illegible] and the systemic [illegible] is extended over a significant period of time.

Ideally, we would compare a parameter such as the maximum blood concentration following oral and dermal dosing as a indicator of the relative potential for systemic effect. In this case we do not have such data and will base our comparison on the portion of administered dose absorbed in a 24 hour period.

An oral metabolism study of Maneb in the rat is available which provides data on its oral absorption, excretion and quantitative metabolism into ETU. The study also provides tissue residue data (=25969% & 263913). No significant sex related differences were observed in the study. The male data will be used to help interpert the male dermal absorption data. Excretion data are presented in Table 1.

Table 1, Excretion of radio label by male rats following a single oral dose of ^{14}C-Maneb. Values are the means of five animals.

Collection Period (hours)	Dose	Urine Excretion 25	Urine Excretion 250	Urine Excretion 2235	Fecal Excretion 25	Fecal Excretion 250	Fecal Excretion 2235	mg/kg
0 - 24		46.61	36.63	11.78	24.99	18.51	10.12	
24 - 48		2.37	11.49	15.48	3.21	10.35	9.61	
40 - 72		0.35	1.21	2.59	0.59	1.30	9.85	
72 - 96		0.13	0.23	1.00	0.25	0.30	6.19	
96 -120		0.08	0.17	0.44	0.17	0.12	0.95	
120 -144			0.09	0.10		0.08	0.44	
144 -168			0.05	0.04		0.06	0.13	
Totals		49.54	49.87	31.43	29.21	30.72	37.29	

Examining the data one can see that significant differences in the pattern of excretion occur with increasing doses. These differences can be simply explained as due to decreased intestional motility due to increasing dose resulting in a more extended period for absorption or, in a greater degree of complexity, as due to the existance of rate limiting metabolic/tissue storage changes with increasing systemic dose. [illegible] most indicative of [illegible] those following dermal absorption.

At the dose of 25 mg/kg maximum urinary and fecal excretion occur during the first 24 hours and decrease exponentially with a half time of 11 hours (Figure 1). Excretion by both routes appears to be monophasic. 21.3% of the ^{14}C in the urine was identified as [illegible] of the total dose. The study indicates rapid absorption by the oral route and can be used to help quantitation of the gastrointestinal absorption rate.

It is very likely that the ETU detected in the feces represents absorbed maneb. The ETU dermal absorption study included groups of male rats dosed by IV, Oral and dermal routes with a dose of 2.6 ug/rat. The excretion data are summarized in Table 2. Fecal excretion was observed from all routes of administration clearly showing bile excretion. The percent of total excreted by the fecal route is essentially the same by the IV and oral route but the dermal doses showed a higher relative percent of total dose excreted in the feces.

Table 2. Excretion follow a single ^{14}C labaled dose of 2.6 ug/rat ETU by the routes noted.

Route	Urine	Feces	Urine/Feces	Total Excreted	% of Total Excreted	
					Urine	Feces
IV	90.23	6.01	15.01	96.24	93.76	6.24
Oral	81.78	3.46	23.57	85.24	95.94	4.06
Dermal 10 hr	16.89	4.81	3.51	21.7	77.83	22.17
Dermal 7 day	36.85	12.49	2.95	49.34	74.69	25.31

The metablism study also generated data on the tissue concentrations of label as ug equivalents of Maneb (Table 3).

Table 3. Tissue concentrations of ^{14}C, as ug equivalents of maneb, in rats 5 days after a single oral dose of 25 mg/kg.

Tissue	Male	Female
Bone	1.14	0.62
gonads	0.47	0.88
Spleen	1.07	0.72
Liver	2.67	1.59
Heart	0.74	0.52
Brain	0.29	0.19
Fat	0.58	0.47
Lung	1.07	0.73
Muscle	0.62	0.35
Kidneys	2.03	1.96
Thyroid	9.01	11.00
Carcass	0.69	0.45

The relatively high concentration remaining in the thyroid five days after dosing is considered indicative of bioaccumulation. The [illegible] dermal absorption study did not determine tissue distribution but a dermal absorption study of ETU did. (Table 4). In the latter study a threshold for

appearance of label in the thyroid and bioaccumulation when the threshold was exceeded were demonstrated. The threshold was located between blood concentrations of 0.006 and 0.0020 ug/ml and bioaccumulation was in the order of ten times the highest concentration in other organs or tissues. The relative tissue concentration is very similar to that in the Maneb oral metabolism study.

For Maneb, neither the metabolism study nor the dermal absorption study generated data on blood concentrations. However, the ETU dermal absorption study did produce blood concentration data from groups of male rats which received a single intravenous or a single oral dose of 2.6 ug ^{14}C-ETU (equivilant to 10.4 ug/kg) The blood concentration with time is presented in Table 5 and is shown in Figures 7 and 8 from the study report (403120-01). By either route plasma concentration drops rapidly (t1/2 = 6.2 hr) to below the limit of detection by 24 hours while whole blood concentration remains relatively constant for the entire 7 day blood collection period. This is a clear indication of erythrocyte binding of ETU. This data also provide some indication of the rapidity of oral absorption of ETU, maximum plasma concentration is observed one hour after the oral dose. Table 5 also presents blood concentrations following the same dose dermally with exposures of 10 hours and 7 days (Figures 9 & 10). Plasma concentrations are essentially undetectable dispite readily detectable whole blood concentrations. Clearly erythrocyte binding is strong and could represent an active process.

Conclusions re oral and dermal absorptions of Maneb/ETU

With the information available we can make the following general conclusions;

1. Orally ^{14}C-Maneb is rapidly absorbed and the label is excreted in urine and feces.

2. Dermally absorption of ^{14}C-Maneb is small and slow and the label is excreted in the urine and feces.

3. Dermally absorption of ^{14}C-ETU is greater and faster than that of Maneb [illegible]

4. Therefore excretion of Maneb following an oral dose includes bile excretion and a measure of this excretion is necessary in order to quantitate absorption by the oral route.

5. ^{14}C-Maneb by the oral route shows excretion of ETU in urine and feces.

6. ^{14}C-Maneb [illegible] (bioaccumulation [illegible] thyroid.

7. ETU by the dermal route shows a threshold for and and concentration (bioaccumlation) in the rat thyroid.

8. Therefore the label in the rat thyroid following oral ^{14}C-Maneb most likely represents ETU.

9. Following IV or oral ^{14}C-ETU plasma concentrations of label fall rapidly to indetectable within hours while whole blood concentrations stay relatively constant for the whole sampling period of 7 days.

10. Therefore, ETU concentrates in the rat erythrocyte.

References

Metabolism of Radiolabeled Maneb in Rats, P.J. Giesler, K.M. MacKenzie, A. Bosch, R.J. Puhl and R.J. Daun, Study No.: 6181-101, Hazleton Laboratories America, Dec 3, 1985, 259890

Metabolism of Radiolabeled Maneb in Rats (Amendment No. 2 to Study No.: 6181-101, Hazleton Laboratories America, Sept 8, 1985, 263913

Ethylene Thiourea: Dermal/Oral Absorption Study in Male Rats. L.J. Didonatoi & S.L. Longacre, Toxicology Dept. Rophm & Haas Co. Protocol No. 85P-419, Report No. 85R-206, July 31, 1987. MRID 403120-01

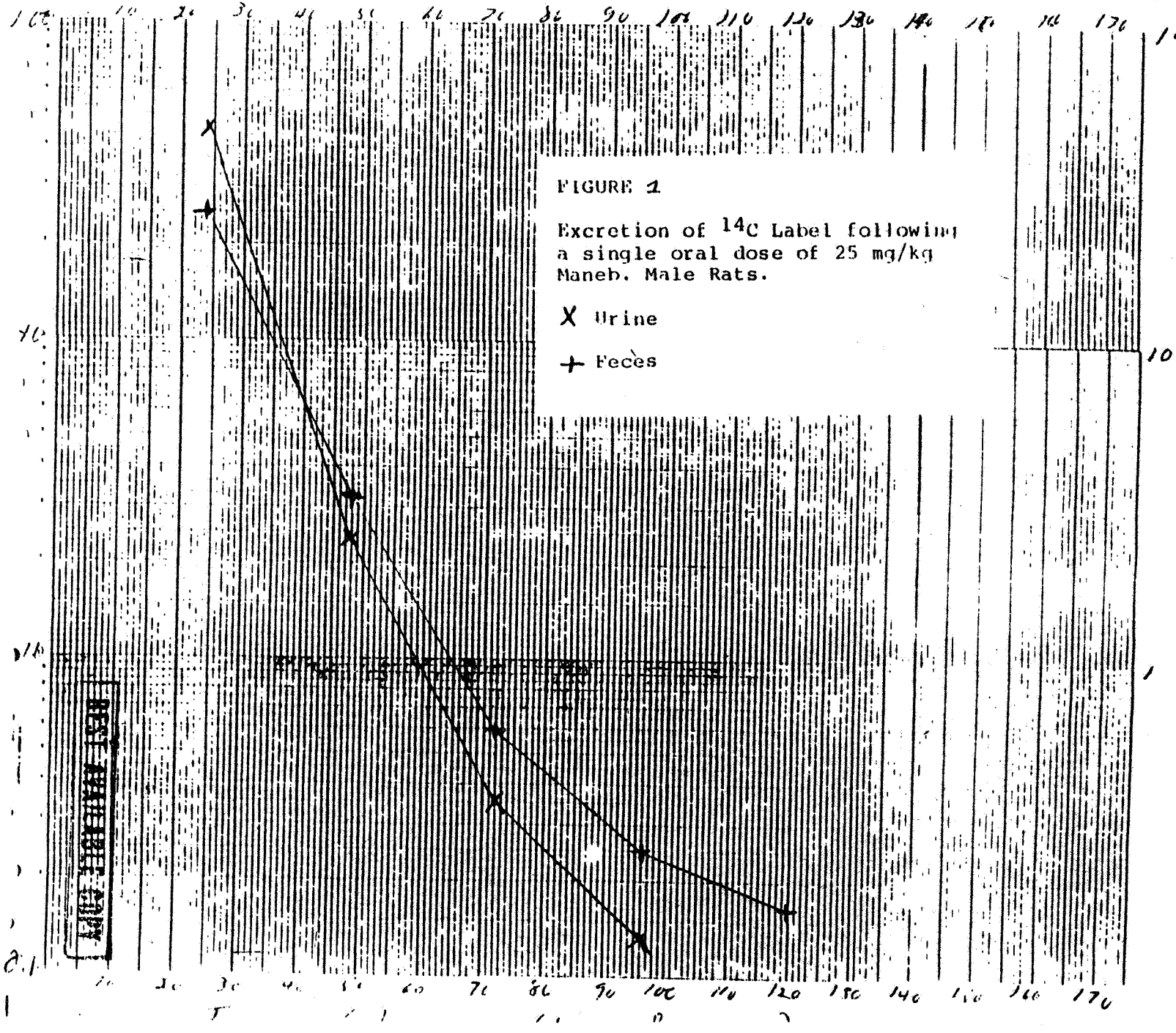

FIGURE 1

Excretion of ^{14}C Label following a single oral dose of 25 mg/kg Maneb. Male Rats.

X Urine

+ Feces

Table 4. Mean ETU in tissues after application of ^{14}C ETU dermally for 10 hours. Data from tables IV and V of the report. Concentration in ppm and % of dose applied.

Group (mg/kg)	Blood	Liver	Thyroid	Kidney	Brain	Fat	Heart	Testes	Lung	Muscle	Spleen	Skin	Carcass
G 12													
ppm	0.005	0.001	0.000	0.001	0.001	0.002	0.001	0.002	0.000	0.001	0.002	0.000	0.002
%	3.0	0.4	0	0.07	0.07	1	0	0.09	0	5	0.03	0	11
H 112													
ppm	0.003	0.002	0.000	0.013	0.003	0.000	0.003	0.001	0.003	0.011	0.020	0.002	0.003
%	0.2	0.09	0	0.1	0.02	0	0.01	0.01	0.02	5	0.01	1	2
I 1176													
ppm	0.003	0.024	0.432	0.026	0.009	0.024	0.011	0.018	0.015	0.044	0.012	0.022	0.040
%	0.1	0.07	0.01	0.02	0	0.1	0	0.02	0.01	2	0.01	2	2

Table 5. Mean (4 animals) whole blood and plasma concentrations of ^{14}C as ETU(ug/ml) following a single dose of 2.6 mg/kg by the routes given.

Route / Tissue	Sample taken at hours after dosing													
	0.08	0.16	0.33	0.50	1	3	10	24	48	72	96	120	144	168
Intravenous														
whole blood	0.040	0.048	0.053	0.075	0.063	0.104	0.061	0.053	0.054	0.067	0.083	0.040	0.054	0.053
plasma	0.019	0.017	0.017	0.016	0.016	0.015	0.007	0.002	0.000	0.000	0.000	0.000	0.000	0.000
Oral														
whole blood				0.041	0.039	0.067	0.048	0.079	0.048	0.067	0.056	0.045	0.066	0.055
plasma				0.012	0.014	0.011	0.005	0.000	0.001	0.000	0.000	0.000	0.000	0.000
Dermal (10h)														
whole blood					0.018	0.034	0.037	0.037	0.037	0.041	0.035	0.035	0.039	0.049
plasma					0.003	0.000	0.000	0.001	0.001	0.000	0.000	0.000	0.001	0.000
Dermal (7d)														
whole blood				0.027	0.028	0.034	0.043	0.037	0.042	0.050	0.049	0.023	0.050	0.047
plasma				0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

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Data Evaluation Report

165

Compound Maneb

Citation
A dermal absorption study in rats with ^{14}C-Maneb, E.M. Craine, WIL Research Laboratories, WIL-134010, Oct, 12, 1990, MRID 416693-01

Reviewed by Robert P. Zendzian PhD
Senior Pharmacologist

Core Classification Acceptable

Conclusions

Dermal absorption and skin 'binding' of maneb are relatively small. Representative values are;

Mean Dose (ug/rat)	Time of Exposure (hours)	Time of Sacrifice (hours)	Absorbed (%)	Absorbed (ug)	On/in Washed Skin (%)	On/in Washed Skin (ug)
77.2*	10.0	10.0	<0.9	<0.7	6.8	5.2
	24.0	72.0	3.0	2.3	5.3	4.1
707*	10.0	10.0	<0.2	<1.4	1.8	12.7
	24.0	72.0	1.0	7.8	1.1	7.8
8909*	10.0	10.0	<0.2	<17.8	3.8	338.5
	24.0	72.0	2.0	142.5	1.6	142.5
75.3†	10.0	10.0	1.6	1.2	26.4	19.9
	24.0	72.0	5.1	3.8	24.4	18.4

*in formulation vehicle suspended in water. † suspended in water.

Materials

^{14}C-Maneb labeled in the ethylene position
Sigma Chemical Co.
Lot #118F9217
91% pure
32.7 mCi/m mol or 123 uCi/mg

Inert ingredients for MANEB PLUS ZINC F4 (the vehicle) from Penwalt Agchem
Sample 134010-3 from Batch No. B35-6-1, 9/18/89
Sample 134010-127 from Batch No. B-35-81, 10/16/89

Experimental Design

Four animals per subgroup were dosed as follows;

Animal Group Number	Planned Dose (mg/rat)	Dosage Formulation	Subgroup	Time of Exposure (hours)	Time of Sacrifice (hours)
1	0.1	Practical (F4 vehicle)	1	0.5	0.5
			2	1.0	1.0
			3	2.0	2.0
			4	4.0	4.0
			5	10.0	10.0
			6	24.0	24.0
			7	24.0	48.0
			8	24.0	72.0
2	1.0	Practical (F4 vehicle)	1	0.5	0.5
			2	1.0	1.0
			3	2.0	2.0
			4	4.0	4.0
			5	10.0	10.0
			6	24.0	24.0
			7	24.0	48.0
			8	24.0	72.0
3	10.0	Practical (F4 vehicle)	1	0.5	0.5
			2	1.0	1.0
			3	2.0	2.0
			4	4.0	4.0
			5	10.0	10.0
			6	24.0	24.0
			7	24.0	48.0
			8	24.0	72.0
4	0.1	Aqueous Solution	1	0.5	0.5
			2	1.0	1.0
			3	2.0	2.0
			4	4.0	4.0
			5	10.0	10.0
			6	24.0	24.0
			7	24.0	48.0
			8	24.0	72.0

Dosing preparations

Dosing preparations for groups 1, 2 and 3 were prepared as suspensions in the "Inert Ingredients for MANEB PLUS ZINC F4" by addition of sufficient ^{14}C-Maneb for radiotracer purposes and sufficient unlabeled Maneb to make up the dose concentration. The dosing preparation for group 4 consisted of ^{14}C-Maneb suspended in deionized water. All dosing preparations were analyzed extensively for stability and for radiolabel and Manab concentrations.

Dose administration

"The anterior dorsal hair of each rat was shaved with an electric shaver 24 hours prior to treatment with care not to abrade or damage the skin. The shaved area of skin was washed with acetone to remove oily secretions. Before application of the test material, a small linked stainless steel jewelers chain was attached to shackle the rear legs of each rat to prevent scratching of the treated area. The skin dose area was defined and enclosed with a nonocclusive covering or "protective appliance", which consisted of a piece of Stomahesive, filter paper and an aluminum bridge (See figure 1 and Figure 2). ----- The Stomahesive was adhered to the skin with Skin-Bond cement to form a "well" surrounding the area of skin to be treated. The treated area was covered with the filter paper elevated by the foil bridge to prevent contact with the applied dose. The application site, within the "well" was 10.0 sq. cm."

"An aliquot of the test material was taken up with a positive displacement glass pipet and was applied to the appliction site, using the pipet to spread the test material evenly over the site. The pipet was washed internally and externally with 1% sodium EDTA. ^{14}C in the pipet wash was determined. The actual dose applied was calculated as the amount in the glass pipet minus the amount in the pipet wash. The protective appliance was assembled and the rat was placed individually in a Nalgene plastic metabolism unit."

"A single urine collection and a single fecal collection were made for each animal of sub-groups 1 through 6 from the time of dosing to the time of sacrifice. Urine and feces were collected in 24-hour periods for the rats of sub-groups 7 and 8."

"After an interval of either 0.5, 1.0, 2.0, 4.0, 10 or 24 hours after application of the dose, each rat of sub-groups 1 through 6 was euthanized by carbon dioxide inhalation. The paper cover and the aluminum bridge were removed from the protective device. The bridge was washed with 1% EDTA. The abdominal cavity of the rat was opened and a sample of blod (5 to 7 ml) was removed from the inferior vena cava. The application site was washed vigorously four times to remove recoverable ^{14}C-Manab using sterile cotton gauze squares. The first two washes were with Dove liquid detergent in deionized water (20:1000) and the second two washes were with deionized water."

"The piece of Stomahesive was removed from the carcass and was washed with 1% EDTA. The skin of the application site (skin 1) and the skin which was underneath the Stomahesive (skin 2) were dissected from the carcass separately. Urine in the bladder was removed by syringe and was added to the urine

collection. The remaining carcass was frozen and retained in the frozen state."

"The rats of sub-groups 7 and 8 were exposed to the test material for a 24-hour period. Twenty four hours after applicaton of the dose, the paper and aluminum bridge were removed from the protective appliance of a rat." The application site was washed as above and the rat placed back in the metaboism unit and urine and feces collected for 24 hour durations. After either 48 or 72 hours after application, the rat was euthanized and the remaining terminal samples collected as above.

Samples analyzed

The following samples from each rat were analyzed for radioactivity and results were presented as cpm and converted to quantity of parent compound and percent of dose applied.

pipet wash

paper digest
Stomatohesive wash
Soap wash
Water Wash
Skin 1 digest (application site)
Skin 2 digest (underneath Stomatohesive)
Cage wash
Urine total 0.5 to 24 hour
Urine 24-48 hr where applicable
Urine 48-72 hr where applicable
Blood
Whole carcass
Feces total 0.5 to 24 hour
Feces 24-48 hr where applicable
Feces 48-72 hr where applicable

Results

Actual dose applied is presented in table 1. All derived values are based on the actual dose.

Stability determinations showed that the concentrated stock solutions for doses preparations for groups 1 through 3 were chemically stable but dilutions suitable for groups 1 and 2 were unstable. Therefore, individual dilutions were prepared directly as needed and used to dose the individual rats in these groups. The dose preparation for group four was determined to be chemically unstable. Therefore, dose suspensions were prepared for this group and applied as rapidly as possible after preparation.

Table 1. Actual dose applied. Mean of four per subgroup.

Animal Group Number	Time of Exposure (hours)	Time of Sacrifice (hours)	Actual Dose Applied (ug/rat)	Animal Group Number	Time of Exposure (hours)	Time of Sacrifice (hours)	Actual Dose Applied (ug/rat)
1	0.5	0.5	77.4	3	0.5	0.5	8967
	1.0	1.0	76.2		1.0	1.0	8943
	2.0	2.0	78.2		2.0	2.0	8815
	4.0	4.0	78.0		4.0	4.0	8867
	10.0	10.0	76.0		10.0	10.0	8931
	24.0	24.0	76.6		24.0	24.0	8886
	24.0	48.0	77.8		24.0	48.0	8929
	24.0	72.0	77.2		24.0	72.0	8943
2	0.5	0.5	709	4	0.5	0.5	78.4
	1.0	1.0	702		1.0	1.0	71.5
	2.0	2.0	709		2.0	2.0	73.8
	4.0	4.0	701		4.0	4.0	62.2
	10.0	10.0	710		10.0	10.0	78.0
	24.0	24.0	699		24.0	24.0	79.0
	24.0	48.0	713		24.0	48.0	76.7
	24.0	72.0	711		24.0	72.0	82.5

Mean blood concentrations are presented in Table 2 from the report. With the exception of group 4, the values are below the respective limits of detection.

Representative carcasses were analyzed and in all cases radioactivity was below the limit of detection.

Dose distribution is summarized in Table 2.

Discussion

The dose preparation and application methodology used appear to have compensated for the problems associated with making a suspension and the instability of Mancozeb in water solution. In no case was the planned dose administered, however, the actual doses were relatively consistant within the animal groups. In a dermal absorption study consistancy of dose applied and determination of that dose are more important than 'hitting' a projected dose.

The absorption data (Table 2) show a clear difference between the material prepared with the vehicle for MANEB PLUS ZINC F4 (Groups 1, 2 & 3) and that suspended in water (Group 4). Comparing groups 1 and 4, the water suspension clearly increased the residue on/in the skin after washing and the proportional

and absolute quantity absorbed. Since we have only one dose for comparison it would not be wise to consider that this percise quantitative relationship persists at the higher doses.

Considering only groups 1, 2 and 3, we can make the following observations;

1. Total recovery was greater than 100% in all cases suggesting that the determination of actual dose applied may have been an underestimate. However, since an essentially complete material balance was performed, one may consider the proportional quantities as indicative of the portions, of the applied dose, remaining on/in the skin and absorbed.

2. Measurable quanties of the dose remained on the skin following soap and water wash and increased with increasing dose. The percent of dose remaining on the skin decreased from group 1 to group 2 but was similar or showed a small increase from group 2 to group 3. Usually the percent remaining on/in the skin after wash decreases with increasing dose. The group 2 to 3 relationship may be an effect of the higher concentration of vehicle in group 3 being sufficient to increase the skin 'binding' of the Maneb.

3. Dermal absorption, as percent of dose, was below the limit of detection for the first 10 hours for these groups (and 24 hours for group 1). A total exposure of 72 hours, including a wash, were required to produce measurable absorption. Note, we have extensive data to show that washing the application site, with any solvent system, will produce transient but significant increases in dermal penetration.

The following comments can be made for group 4;

1. Total recovery is less than groups 1-3 and is more in line with that usually seen in these types of studies. Considering that the dosing form is unique to this group, it is possible that dose quantitation is more accurate in the group.

2. Four to five times as much test material remains on/in the skin after washing as found with the comparably dosed group 1. This emphasises the importance of the vehicle in skin 'binding'.

3. Time-related dermal absorption is obviously greater with this group than with the comparably dosed group 1. Again an important effect of the vehicle.

MANEB 014505

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Table 2. Dose distribution of Dermally applied ^{14}C-Maneb. Values are means of four animals. Dose preparations for groups 1, 2 and 3 were formulated in the vehicle for MANEB PLUS ZINC F4. Dose preparation for group 4 was as a suspension in dionized water. Values for blood and carcass are not included as these were generally below the limit of detection. Dosing area 10 cm^2.

Animal Group Number	Time of Exposure (hours)	Time of Sacrifice (hours)	Skin Wash (%)	In Urine (%)	In Feces (%)	Absorbed (Urine + Feces) (%)	Absorbed (Urine + Feces) (ug)	On/in Skin (%)	On/in Skin (ug)	Total Recovered (%)
1	0.5	0.5	100.5	†	<0.1	<0.1	<0.07	6.9	5.3	107.4
77.2	1.0	1.0	97.9	<0.8	<0.1	<0.9	<0.7	7.8	6.0	105.7
ug/rat*	2.0	2.0	99.9	<0.8	0.1	0.1	0.07	7.3	5.6	107.2
	4.0	4.0	97.8	0.7	<0.1	0.7	0.5	6.9	5.3	104.9
	10.0	10.0	102.2	<0.8	<0.1	<0.9	<0.7	6.8	5.2	109.0
	24.0	24.0	98.3	<0.8	<0.4	<1.2	<0.9	7.0	5.4	105.3
	24.0	48.0	98.8	<1.6	0.8	0.8	0.6	5.6	4.3	104.8
	24.0	72.0	97.1	<2.5	3.0	3.0	2.3	5.3	4.1	105.1
2	0.5	0.5	103.6	<0.1	<0.1	<0.2	<1.4	3.6	25.5	107.7
707	1.0	1.0	103.6	<0.1	<0.1	<0.2	<1.4	2.5	17.7	106.2
ug/rat	2.0	2.0	101.7	<0.1	<0.1	<0.2	<1.4	1.8	12.7	103.5
	4.0	4.0	103.5	<0.1	<0.1	<0.2	<1.4	1.8	12.7	105.7
	10.0	10.0	103.1	<0.1	<0.1	<0.2	<1.4	1.8	12.7	104.9
	24.0	24.0	100.7	0.2	<0.1	0.2	1.4	2.7	19.1	103.6
	24.0*	48.0	96.1	1.6	3.0	4.6	32.5	1.7	12.0	103.4
	24.0	72.0	102.2	0.4	0.6	1.0	7.8	1.1	7.8	104.3
3	0.5	0.5	98.8	<0.1	<0.1	<0.2	<17.8	3.8	338.5	102.6
8909	1.0	1.0	98.4	<0.1	<0.1	<0.2	<17.8	3.3	294.0	101.8
ug/rat	2.0	2.0	99.1	<0.1	<0.1	<0.2	<17.8	2.6	231.6	100.7
	4.0	4.0	100.4	<0.1	<0.1	<0.2	<17.8	2.2	196.0	102.6
	10.0	10.0	100.9	<0.1	<0.1	<0.2	<17.8	3.8	338.5	104.7
	24.0	24.0	98.3	0.1	<0.1	0.1	8.9	2.8	249.5	101.2
	24.0	48.0	98.3	0.2	0.5	0.7	62.4	2.0	178.2	101.5
	24.0	72.0	97.0	0.4	1.6	2.0	142.5	1.6	142.5	101.2
4	0.5	0.5	77.0	†	<0.1	<0.1	<0.08	22.8	17.2	100.0
75.3	1.0	1.0	69.9	0.4	<0.1	0.4	0.3	34.5	26.0	105.3
ug/rat	2.0	2.0	68.9	1.5	<0.1	1.5	1.1	30.0	22.5	101.7
	4.0	4.0	67.3	1.0	<0.1	1.0	0.8	33.2	25.0	102.3
	10.0	10.0	70.3	1.6	<0.1	1.6	1.2	26.4	19.9	99.0
	24.0	24.0	61.6	3.5	0.67	4.2	3.2	26.8	20.2	94.9
	24.0	48.0	66.6	3.2	1.03	4.2	3.2	28.1	21.2	99.5
	24.0	72.0	64.3	3.9	1.21	5.1	3.8	24.4	18.4	94.1

* Mean dose applied to the groups. * All animals in this group had apparently eaten portions of the protective appliance and test compound. Data is not indicative of dermal absorption. † No sample.