State California

Memorandum

HSM-93003

[HSM # assigned after issuance of original memo]

To: Kathy Wynn, Registration Specialist
Pesticide Registration Branch

Dale: July 26, 1993

Place: Sacramento
4-0455

From: **Department of Pesticide Regulation** –Tian Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch

Subject: PRODUCT NAME: Metam-Sodium
ACTIVE INGREDIENT: Sodium N-methyldithiocarbamate
COMPANY NAME: Metam-Sodium Task Force c/o ICI Americas Inc.
I.D. NUMBER: SBC-1 39037-E
DOCUMENT NUMBER: 50150-095
EPA REGISTRATION NUMBER: 1051005-0
TITLE: Metam Sodium: *In vivo* Dermal Absorption in the Rat and Stability Determination of Aqueous Solutions

There are two separate studies in this submitted document. The first study is on **stability** determination of aqueous solutions which was conducted by Zeneca Central Toxicology Laboratory and the second study is on in vivo dermal absorption in the rat. The latter was performed by Hazleton UK. The first study was conducted to determine the appropriate dose levels prior to the dermal absorption study of metam-sodium in rats. Both studies were performed in compliance with Good Laboratory Practice standards. Summary of the two studies and the evaluation of dermal absorption values are presented below.

A. Metam-Sodium: Stability Determination of Aqueous Solutions

Stability of metam-sodium in water was conducted prior to the dermal absorption study in the rat. A mixture of high purity 14C-metann sodium (between 94.4 and 97.4%) and nonlabeled metam-sodium (99.4%) were used in this and the dermal absorption study. The labeled position of [14C] was the carbonyl carbon. 14C-Metam sodium (7.66 ma) was mixed with nonlabeled metam-sodium (193.85 mg), evacuated, and dissolved in degassed HPLC grade water at about 200 mL to make a solution of 200 mg/mL. Dilutions were also done to prepare concentrations of 20, 2, and 0.2 mg/mL. All of the solutions were stored under nitrogen environment at room temperature in the dark. At different time intervals after the preparation of the solutions, samples were analyzed by HPLC using UV absorption at 241 nm with on-line radioactivity for [14C] analysis.

The results showed that the 0.2 mg/mL solution is not stable because less than 63% of its initial analyzed concentration remained after three hours. For the 2 mg/mL solution, more than 93% of its initial concentration remained one hour after its preparation and 86% three hours after its preparation. Solutions of 200 and 20 mg/mL appeared to be stable for at least 20 hours. Due to the instability of the lowest concentration solution of 0.2 mg/mL, this concentration was not used in the dermal absorption study in rats.

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B. **Metam-Sodium:** ***In vivo*** **Dermal Absorption in the Rat**

B.1 Preparation of Animals

Six to ten-week old Charles River Crl:CD(SD)BR strain rats were used in the dermal absorption study. Body weights of these rats ranged from 178-274 grams. These animals were acclimatized 4-12 days prior to the study. An area of the dorso-lumbar skin was clipped free of hair using veterinary clippers, without abrading the skin. The shaved skin sites were washed with acetone. The treated skin site with an area of 11.6 cm2 was enclosed with a glass saddle. The animals were placed in individual all glass metabolism cages that allowed the separate collection of urine, feces, and expired air.

B.2 Administration of the Doses

The test material was prepared as an aqueous solution in degassed HPLC grade water to give a nominal volume of 0.05 mL per animal. Three dose levels at nominal concentrations of 0.1, 1, and 10 mg/animal (equivalent to 8.6, 86.2, and 862 ug/cm2) were applied dermally. After administration of the dosing solution, an activated charcoal filter, resting between two glass sinters, was placed in the saddle. The charcoal and sinters were secured by a foam disc, cotton -gauze and an elastic band.

B.3 Sample Collection and Analysis

The sacrifice times were 1, 2, 10, 24, and 72 hours which corresponded to the exposure times 1, 2, 10, 24, and 10 hours, respectively. For the 72-hour sacrifice time, the treated skin sites and the inside of the glass saddles were swabbed thoroughly with liquid Ivory® soap solution and water and the animals were returned to the metabolism cages. Urine, feces and cage washings of animals for the 72-hour sacrifice time were collected at 10, 24, 48, and 72 hours. Samples collected for analysis were: nonocclusive cover (charcoal, charcoal washings and sinter washings), treated and untreated skin sites, cage washings, carcass, urine, feces, blood, air traps, and cage debris.

C. Determination of the Results

Results of the dermal absorption study are shown in Table 1. Radioactivity in the blood calculated as percent dose are shown in Table 2. The results indicated that metam-sodium and/or its degradates are absorbed rapidly into the skin. Absorption in one hour after exposure is similar to that with longer exposure time. There is no obvious indication that absorption is dose or time dependent. This may be due to metam-sodium being rapidly degraded and the degradate(s) volatilized and are trapped in the charcoal or limited absorption of a radiolabeled impurity. Percent dose absorbed for 1, 2, 10, and 24-hour sacrifice times are presented in Table 1 as the sum of percent dose in treated skin, urine, feces, carcass, cage washings, air traps, and blood. These dermal absorption values were not used for worker exposure estimates because bioavailability of bound skin residues can be estimated from the 72-hour sacrifice time group.

In order to resolve the issue of bound skin residues, cumulative percent doses in urine, feces, and cage washings for different time intervals over 72 hours (Table 3) were used for estimating the asymptote by employing an exponential saturation model with lag time. An equation representing

this model is: Y = A*(1-EXP(-B*(X+C))) or Recov = Max*(1-EXP(-Rate*(Time+Lag))). Example of the plots for the lowest dose and the outputs are shown in Figure 1. The dermal absorption value is the sum of percent dose at asymptote (maximum or "A" term) and percent of dose recovered in carcass, blood, air traps, and cage washings. Table 4 summarizes the dermal absorption values for low, medium and high doses used in this study. Percent doses excreted in three doses are similar, ranging from 0.89 to 1.18 percent. The obvious difference is percent dose in carcass for high and percent dose in air traps for medium dose. The corrected dermal absorption value of 2.5% for the lowest dose (8.6 ug/cm2) is appropriate to be used in the worker exposure estimates because this dose should be representative of exposure experienced by the agricultural workers.

D. **Recommendations**

1. The dermal absorption study of metam-sodium in male rats as reported in this document is acceptable.

2. Dermal absorption of 2.5 percent will be used to estimate absorbed dosages of worker exposure to this pesticide. It is assumed that this percent dermal absorption is the combined absorption value of metam-sodium and its degradate(s), such as MITC.

3. It is assumed that the nature of exposure the workers will experience would resemble the manner in which this pesticide was administered to animals in the dermal absorption study. Nonocclusive patch used in the study would resemble the clothing the workers wear in their routine handling of this chemical.

cc: Joshua Johnson (1 original, 5 copies)
John Ross

Table 1. Percent recovery of administered dose of metam-sodium.

		Percent dose (mean)									
Dose	Sacrifice time (h)	Unab-sorbed*a	Cage debris	Treated skin*b	Urine	Feces	Carcass	CW	Air traps*c	Blood*d	Total recovery
0.1 mg/rat (8.6 ug/cm2)	1	92.8	0	2.738	0	0	0	0	1.791	0	97.329
				*(1-h) Absorbed dose (% dose)*e=*			*4.529*				
	2	87.61	0	3.575	0.018	0	0	0	2.161	0	93.364
				*(2-h) Absorbed dose (% dose)*e=*			*5.754*				
	10	91.73	0	7.741	0.451	0	0	0.081	0.824	0	100.827
				*(10-h) Absorbed dose (% dose)*e=*			*9.097*				
	24	71.29	0	8.423	1.002	0.035	0	0.015	1.93	0	82.695
				*(24-h) Absorbed dose (% dose)*e=*			*11.405*				
	72	92.95	0	2.794	1.049	0.006	0	0.1	1.276	0	98.175
1.0 mg/rat (86.2 ug/cm2)	1	82.71	0	3.623	0.011	0	0.144	0.022	1.707	0.06	88.277
				*(1-h) Absorbed dose (% dose)*e=*			*5.567*				
	2	78.22	0	6.777	0.044	0	0.266	0	2.777	0.07	88.154
				*(2-h) Absorbed dose (% dose)*e=*			*9.934*				
	10	90.16	0	4.31	0.749	0.026	0	0.087	2.823	0.02	98.175
				*(10-h) Absorbed dose (% dose)*e=*			*8.015*				
	24	76.37	0	4.107	1.321	0.701	0.815	0.161	1.725	0.02	85.22
				*(24-h) Absorbed dose (% dose)*e=*			*8.85*				
	72	87.65	0	1.633	0.697	0.016	0	0.129	2.325	0	92.45
10 mg/rat (862 ug/cm2)	1	64.11	0	14.88	0	0	0	0.064	0.324	0.05	79.428
				*(1-h) Absorbed dose (% dose)*e=*			*15.318*				
	2	79.34	0.03	1.754	0.079	0.044	0.432	0.062	0.682	0.04	82.463
				*(2-h) Absorbed dose (% dose)*e=*			*3.093*				
	10	80.82	0	1.31	0.489	0.021	0.342	0.106	0.556	0.03	83.674
				*(10-h) Absorbed dose (% dose)*e=*			*2.854*				
	24	80.1	0	2.472	0.753	0.459	0.541	0.157	0.325	0.02	84.827
				*(24-h) Absorbed dose (% dose)*e=*			*4.727*				
	72	79.07	0	0.7	0.942	0.109	1.217	0.145	1.101	0	83.284

*a Application site washings + charcoal + charcoal washings + sinter washings.

Table 1. (cont.) Percent recovery of administered dose of metam-sodium.

*b Includes untreated skin around treated skin site.
*c Trap (1) 2-ethoxyethanol to trap MITC + trap (2) ethanolamine:2-ethoxyethanol (91:3, v/v) to trap CO2 + trap (3) ethanol: diethylamine:triethanolamine (1000:1:20, v/v) to trap CS2. Due to unusually high percent dose recovered in trap (2) for 24-hour (0.1 mg/animal) and 2-hour (10 mg/animal) sacifice times, an average of % dose from trap (2) of other four sacrifice times of the same group was used.
*d Percent dose in blood was calculated based upon the assumption that one animal has 15 grams of whole blood.
*e When bioavailability of bound skin residues cannot be determined, dermal absorption value = % dose recovered from treated skin site + urine + feces + carcass + cage washings + air traps + blood.

(Note: "ND" shown in the submitted report is assumed = 0, CW = Cage washings)

Table 2. Percent dose of metam sodium in blood of experimental animals.

14C-metam sodium in blood

Sacrifice time	0.1 mg/animal			1 mg/animal			10 mg/animal		
(hour)	ug equiv./g	ug/animal	% dose	ug equiv./g	ug/animal	% dose	ug equiv./g	ug/animal	% dose
1	0	0	0	0.038	0.57	0.06	0.341	5.12	0.05
2	0	0	0	0.044	0.66	0.07	0.28	4.2	0.04
10	0	0	0	0.014	0.21	0.02	0.187	2.81	0.03
24	0	0	0	0.012	0.18	0.02	0.125	1.88	0.02
72	0	0	0	0	0	0	0	0	0

Notes:
1. Assume 15 grams of whole blood/animal.
2. Values were calculated from data in Tables 9.19-9.21 of Reg. Doc. No. 50150-095.

Table 3. Percent dose of metam-sodium excreted following 10-hour exposure.

A. 0.1 mg/animal or 8.6 ug/cm2) (Actual dose: 0.085 mg/animal or 7.3 ug/cm2)

	% Dose				
Time (h)	Urine	Feces	CW		Cumulative
10	0.351	0.006	0.094		0.451
24	0.591	0	0.007		1.049
48	0.082	0	0		1.131
72	0.025	0	0		1.156
Sub-total	1.049	0.006	0.101	Total 1.156	

B. 1 mg/animal or 86.2 ug/cm2) (Actual dose: 0.97 mg/animal or 83.8 ug/cm2)

	% Dose				
Time (h)	Urine	Feces	CW		Cumulative
10	0.356	0	0.112		0.468
24	0.154	0	0.011		0.633
48	0.145	0.016	0.006		0.8
72	0.043	0	0		0.843
Sub-total	0.698	0.016	0.129	Total 0.843	

C. 10 mg/animal or 862 ug/cm2) (Actual dose: 10.01 mg/animal or 863 ug/cm2)

	% Dose				
Time (h)	Urine	Feces	CW		Cumulative
10	0.342	0.011	0.094		0.447
24	0.379	0.05	0.042		0.918
48	0.13	0.024	0.009		1.081
72	0.092	0.024	0		1.197
Sub-total	0.943	0.109	0.145	Total 1.197	

Treated skin site =11.6 cm2

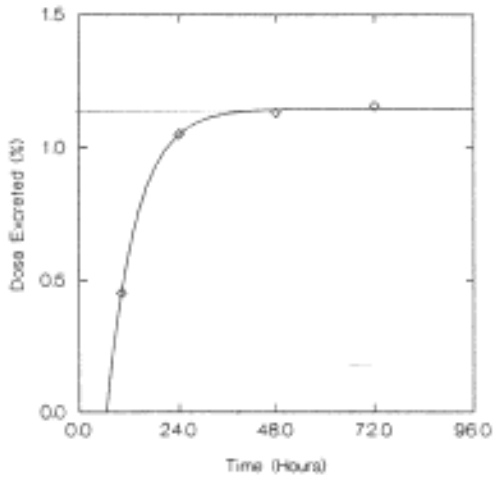
Table 4. Summary Dermal absorption of metam-sodium in male rate

Dose	Percent of dose recovered						
mg/animal (ug/cm2)	Excreted	Blood	Carcass	Expired air	Sub-total	Recovery	Total
0.1 (8.6)	1.15	0	0	1.28	2.43	98.18	2.48
1 (86.2)	0.89	0	0	2.33	3.22	92.45	3.48
10 (862)	1.18	0	1.22	1.1	3.5	83.28	4.20

flXIJDermallMetamOI)

Figure 1. Metam-sodium: Asymptotic plot of cumulative excretion of dose excreted in urine and feces at different time intervals for 0.1 mg/animal (8.6 ug/cm2).

$$Y = 1.1457*(1-EXP(-0.1401*(X-6.4279)))$$



Statistics:

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>MODEL RECOV=Max*(1-EXP(-Rate*(Time+Lag)))
>ESTIMATE/ SIMPLEX

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ITERATION     LOSS      PARAMETER VALUES
   0     .3247758D+01 .1000D+00 .1000D+00 .1000D+00
   1     .3886383D+00 .8715D+00 .2561D+00-.4200D+00
   2     .5451171D-01 .1167D+01 .6549D-01-.5273D+00
   3     .2375178D-01 .1200D+01 .6319D-01-.5593D+00
   4     .2329867D-01 .1200D+01 .6507D-01-.5711D+00
   5     .2322394D-01 .1200D+01 .6498D-01-.6019D+00
   6     .2199541D-01 .1187D+01 .7630D-01-.2021D+01
   7     .6108829D-02 .1178D+01 .9316D-01-.4637D+01
   8     .4324411D-02 .1158D+01 .1081D+00-.5498D+01
   9     .8641067D-03 .1141D+01 .1537D+00-.6789D+01
  10     .2488689D-03 .1145D+01 .1405D+00-.6439D+01
  11     .2377677D-03 .1146D+01 .1399D+00-.6422D+01
  12     .2375677D-03 .1146D+01 .1401D+00-.6428D+01
  13     .2375526D-03 .1146D+01 .1401D+00-.6428D+01
  14     .2375521D-03 .1146D+01 .1401D+00-.6428D+01

DEPENDENT VARIABLE IS   RECOV

  SOURCE   SUM-OF-SQUARES   DF  MEAN-SQUARE

 REGRESSION      3.9191    3     1.3064
  RESIDUAL       0.0002    1     0.0002

   TOTAL         3.9193    4
 CORRECTED       0.3340    3

   RAW R-SQUARED (1-RESIDUAL/TOTAL)    =     0.9999
CORRECTED R-SQUARED (1-RESIDUAL/CORRECTED) =     0.9993


PARAMETER  ESTIMATE  A.S.E.  LOWER <95%> UPPER
   MAX       1.1457   0.0115    0.9999    1.2915
  RATE       0.1401   0.0140   -0.0378    0.3180
   LAG      -6.4279   0.3857  -11.3293   -1.5265


ASYMPTOTIC CORRELATION MATRIX OF PARAMETERS

            MAX      RATE      LAG

   MAX      1.0000
  RATE     -0.5788   1.0000
   LAG      0.4184  -0.9045   1.0000
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(TCW\Dermal\Metam02)