

*In vivo* Dermal Absorption Studies of Methamidophos in Rats, Monkeys, and Human Volunteers

By

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HS – 1830

October 18, 2001

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Department of Pesticide Regulation  
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This technical report contains three memoranda with the following titles:

1. The Percutaneous Absorption of Methamidophos (SX-1757) in Male Rats (pages 2-5).
2. A Dermal/Intravenous Cross Over Study to Determine the Dermal Absorption of [<sup>14</sup>C]-Methamidophos in Male Rhesus Monkeys (pages 6-12).
3. Absorption, Excretion, Balance and Pharmacokinetics of <sup>14</sup>C Radioactivity after Single Dose Dermal Application of One Dose Level of <sup>14</sup>C Labeled Methamidophos from a Taron 600 SL Formulation Administered to Healthy Volunteers (pages 13-19).



# Department of Pesticide Regulation



Paul E. Helliker  
Director

Gray Davis  
Governor  
Winston H. Hickox  
Secretary, California  
Environmental  
Protection Agency

TO: John Inouye  
Registration specialist  
Pesticide Registration Branch

HSM-01006

FROM: Thomas Thongsinthusak  
Staff Toxicologist (Specialist)  
(916) 445-4267

DATE: July 3, 2001

SUBJECT: BRAND NAME: Monitor  
ACTIVE INGREDIENT: Methamidophos  
COMPANY NAME: Mobay Chemical Corporation  
TRACKING I.D. NUMBER: 128195 - E  
RECORD NUMBER (RN): 92476  
DATA PACKAGE NUMBER (DPN): 315-123  
EPA REGISTRATION NUMBER: 3125-0-  
TITLE: The Percutaneous Absorption of Methamidophos (SX-1757) in Male  
Rats

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Chevron Environmental Health Center, Inc. conducted a dermal absorption study of methamidophos in male Sprague-Dawley<sup>®</sup> rats. This study was initiated on June 16, 1987. Sample analyses were completed on July 16, 1987 and the study was completed on January 18, 1991. The study was performed in compliance with the U.S. EPA FIFRA Good Laboratory Practice Standards (40 CFR Part 160), except inspection of the in-life portion of the study was not conducted by the Quality Assurance Unit of Chevron. A summary of this dermal absorption study and the evaluation of the results are presented below.

## **A. Preparation of Animals**

Thirty six male Sprague-Dawley<sup>®</sup> rats (CrI:CD (SD)<sup>®</sup>BR) were used in this study. The animals were approximately 50 days old and the weights ranged from 241 - 317 grams. After receiving, animals were quarantined for 13 days. The rats were randomly allocated to 3 dose groups and within each dose group the animals were further subdivided into 3 exposure time groups consisting of 4 rats each. Food and water was available ad libitum during the course of the study. All rats were housed in individual stainless steel cages with wire-mesh floors prior to dosing. The room conditions were: 12-hour light/dark cycle, temperature ranged from 68 – 71 °F and humidity ranged from 62 to 66%. The application site (dorsal trunk) was clipped on the day prior to dosing. Approximately one hour before dosing, the application site was shaved free of hair with disposable razor and washed with mild soap and water to remove sebaceous gland secretions. A neoprene rubber template was glued to the back of each rat with cyano-acrylate glue, defining a 2.5 x 4-cm application site. After dermal application of the test material, rats

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were placed individually in Metrap<sup>®</sup> restraining metabolism chambers for their respective exposure times. Air from the metabolic cages was exhausted through a CO<sub>2</sub> trap (~150 ml 0.5N NaOH) and a volatile trap (activated charcoal).

### **B. Preparation and Administration of the Doses**

[S-methyl-<sup>14</sup>C]-Methamidophos was obtained from Mobay Chemical Corporation and purified by thin-layer chromatography to 99.8%. Appropriate amounts of Monitor<sup>®</sup> technical (SX-1757, 81.4% methamidophos) was added to [S-methyl-<sup>14</sup>C]-methamidophos to get concentrations of 40, 4 and 0.4 µCi/mg methamidophos. Deionized water was added to obtain final concentrations of approximately 1, 10 and 100 mg/mL dosing solution. Homogeneity of the dosing solution was verified before dosing. The three groups of rats were dosed as follows: Group I = 0.05 mg/rat (average 5 µg/cm<sup>2</sup>), Group II = 0.5 mg/rat (average 49 µg/cm<sup>2</sup>), and Group III = 5.0 mg/rat (average 486 µg/cm<sup>2</sup>). The test material was vortexed immediately before dosing each animal. Approximately, 50 µL of the dosing solution was applied to the application site of each animal with a VWR Digital Microdispenser. The exposure times were 2, 10 and 24 hours.

### **C. Sample Collection and Analysis**

At the end of the exposure period, the animals were anesthetized with an intraperitoneal injection with sodium pentobarbital. The application site was vigorously scrubbed three cycles (times) with a two-inch square, 12-ply gauze pad, which was immersed in 0.5% soap solution and squeezed before scrubbing, followed by one scrubbing with deionized water alone. The skin of each rat was excised around the template. The skin was separated from the template and each was analyzed separately. A small strip of skin around the periphery of the template was also excised. Samples collected for the analysis were soap/water scrubs, acetone skin rinse, methanol template rinse, treated-skin residues, blood, urine, feces, carcass, methanol cage rinse, CO<sub>2</sub> trap (NaOH solution) and volatile trap (activated charcoal). The radioactivity in the prepared samples was analyzed using a Beckman LS-9800 or LS-5801 liquid scintillation counter.

### **D. Results**

The mean recoveries of radioactivity as percent of administered dose for the three dose groups and exposure/sacrifice times are shown in Tables 1, 2 and 3. The treated-skin residue is considered absorbed unless bioavailability of the residue can be determined using the exponential saturation model (Thongsinthusak *et al.*, 1999). The estimated dermal absorption was calculated as percent of the applied dose found in the treated skin, blood, urine, feces, carcass, cage rinse, carbon dioxide trap and volatile trap. The estimated dermal absorption values are shown in those Tables. The mass balance, especially for 10- and 24-hour exposures for the low dose (5 µg/cm<sup>2</sup>), is too low and is not acceptable. The low recovery was likely due to poor trapping efficiency of volatile <sup>14</sup>CO<sub>2</sub> or other metabolites. Also, improper handling and analysis of samples could possibly result in low recovery.

Table 1. Mean recoveries of radioactivity (% dose) in rats topically administered with 14C-methamidophos at 0.05 mg/rat (average 5 ug/cm2).

Exposure time (h)	Soap/water scrubs	Acetone skin rinse	Template rinse	Skin residue	Blood**	Urine	Feces**	Carcass	Cage rinse	CO2 trap	Volatile trap	Total
2	60.0	10.2	0.9	13.7	0.1	0.5	0.1	1.9	0.2	1.1	0.1	88.8
	<i>Dermal absorption* = 17.7</i>											
10	37.3	12.8	1.4	6.2	0.1	1.2	0.1	2.8	0.3	1.2	0.4	63.8
	<i>Dermal absorption* = 12.3</i>											
24	33.3	11.2	1.6	14.1	0.0	1.2	0.2	2.5	0.4	0.5	0.8	65.8
	<i>Dermal absorption* = 19.7</i>											

\* Unadjusted (% administered dose in skin residue+blood+urine+feces+cacass+cage rinse+co2 trap+volatile trap) \*\*0.1 is used instead of <0.1 shown in the report for three values

Table 2. Mean recoveries of radioactivity (% dose) in rats topically administered with 14C-methamidophos at 0.5 mg/rat (average 49 ug/cm2).

Exposure time (h)	Soap/water scrubs	Acetone skin rinse	Template rinse	Skin residue	Blood	Urine	Feces**	Carcass	Cage rinse	CO2 trap	Volatile trap	Total
2	62.8	11.2	1.4	5.8	0.1	0.3	0.1	2.9	0.2	1.1	0.1	86.0
	<i>Dermal absorption* = 10.6</i>											
10	35.3	14.3	1.4	13.4	0.2	2.0	0.2	4.6	0.4	1.5	0.4	73.7
	<i>Dermal absorption* = 22.7</i>											
24	22.3	14.0	2.1	18.7	0.1	3.2	0.3	4.9	0.3	0.8	0.7	67.4
	<i>Dermal absorption* = 29.0</i>											

\* Unadjusted (% administered dose in skin residue+blood+urine+feces+cacass+cage rinse+co2 trap+volatile trap) \*\*0.1 is used instead of <0.1 shown in the report for one value

Table 3. Mean recoveries of radioactivity (% dose) in rats topically administered with 14C-methamidophos at 5 mg/rat (average 486 ug/cm2).

Exposure time (h)	Soap/water scrubs	Acetone skin rinse	Template rinse	Skin residue	Blood	Urine	Feces**	Carcass	Cage rinse	CO2 trap	Volatile trap	Total
2	69.0	6.5	0.8	3.4	0.2	1.8	0.1	4.5	0.3	1.3	0.0	87.9
	<i>Dermal absorption* = 11.6</i>											
10	39.8	11.6	0.8	9.4	0.1	9.8	0.4	6.0	0.7	2.7	0.1	81.4
	<i>Dermal absorption* = 29.2</i>											
24	29.1	13.1	1.5	12.2	0.1	8.4	0.5	5.8	0.7	1.0	0.5	72.9
	<i>Dermal absorption* = 29.2</i>											

\* Unadjusted (% administered dose in skin residue+blood+urine+feces+cacass+cage rinse+co2 trap+volatile trap) \*\*0.1 is used instead of <0.1 shown in the report for one value

### **E. Discussion and Recommendation**

Recoveries of the administered doses for different exposure times ranged from 63.8% to 88.8%. Generally, the recovery should be on the order of 85% or greater. An important factor that could cause the low recovery was because [S-methyl-<sup>14</sup>C]-methamidophos was used instead of [<sup>32</sup>P]-methamidophos. A significant portion of volatile compounds might have not been accounted for. Some other factors could also contribute to a low recovery.

The report revealed that Monitor<sup>®</sup> technical (SX-1757, 81.4% methamidophos) was mixed with [S-methyl-<sup>14</sup>C]-methamidophos in deionized water to prepare the dosing solution. If in fact, SX-1757 is the technical material (no other surface active agents), the dosing solution is not appropriate. Typically, a formulation blank should be added to the dosing solution (Zendzian, 1994). The report did not disclose other compositions of SX-1757 since it contains 81.4% methamidophos.

The report indicates that Bayer Corporation discussed with and endorsed by the U.S. EPA to add the percent unrecovered dose (presumably untrapped volatile metabolites) to the percent systemic absorption (not include the treated-skin residue) to obtain a conservative estimate of percent dermal absorption. This method of estimation of the dermal absorption is not scientifically defensible because an unrecovered dose may be due to the handling or analytical process. In order to obtain an acceptable recovery, methamidophos must be labeled at the core of the molecule, i.e. using [<sup>32</sup>P]-methamidophos instead of [S-methyl-<sup>14</sup>C]-methamidophos.

Results from this study will not be used to estimate the dermal absorption of methamidophos for the pesticide exposure assessment process.

### **References:**

- Thongsinthusak, T., Ross, J. H., Saiz, S. G., and Krieger, R. I. 1999. Estimation of dermal absorption using the exponential saturation model. *Reg. Toxicol. Pharmacol.* 29:37-43.
- Zendzian, R. P. 1994. Dermal Absorption of Pesticides. Pesticide Assessment Guidelines. Subdivision F, Hazard Evaluation: Human and Domestic Animals. Series 85-3. Health Effect Division, Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C.

cc: Wendy Zhao  
Joseph P. Frank  
James Goodbrod

(Dermal/Tamaron-Rats; HSM-01006)



# Department of Pesticide Regulation



Paul E. Helliker  
Director

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TO: Denise Webster  
Pesticide Registration Specialist  
Pesticide Registration Branch

HSM-01007

FROM: Thomas Thongsinthusak  
Staff Toxicologist (Specialist)  
(916) 445-4267

DATE: July 12, 2001

SUBJECT: BRAND NAME: Tamaron  
ACTIVE INGREDIENT: Methamidophos  
COMPANY NAME: Bayer Corporation  
TRACKING I.D. NUMBER: 189659  
RECORD NUMBER (RN): 181706  
DATA PACKAGE NUMBER (DPN): 315-165  
EPA REGISTRATION NUMBER: 3125---  
TITLE: A Dermal/Intravenous Cross Over Study to Determine the Dermal Absorption of [<sup>14</sup>C]-Methamidophos in Male Rhesus Monkeys  
(Revised the July 3, 2001 memo by adding the tracking I.D., RN and DPN. There are no other changes)

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Sierra Biomedical, Incorporated (SBI) conducted a dermal absorption study of methamidophos in four male rhesus monkeys (Fuller, 2000). This study was completed on August 12, 2000. All aspects of this study performed at the SBI were conducted in accordance with the U.S. EPA FIFRA Good Laboratory Practice Standards (40 CFR Part 160), except for a few protocol deviations. For example, urine containers did not contain dry ice when checked at approximately 18 hours following the intravenous (IV) administration and the apparatus used to protect the dermal-dose area of the back of two of the animals became dislodged within 1 and 2 hours after dosing. These deviations could affect the results of the study. A summary of this dermal absorption study and the evaluation of the results are presented below.

## **A. Preparation of Test Subjects**

Basically, the method of the study was based on the principle used by Feldmann and Maibach (1974) or Wester and Maibach (1985). Four male rhesus monkeys, experimentally naive and weighing 4.6 to 5.5 kg (average 5.1 kg) at the outset of the study, were used in this study. Prior to the dermal or intravenous administration, the animals were placed in restraint chairs and were kept in the chairs for 8 hours following dosing. The animals were then transferred to metabolism cages. The same four monkeys were used for the dermal administration of the dose. Fourteen days after the initiation of the IV dosing phase and on the day prior to the dermal administration, an area on the back of the animals, large enough to accommodate a Duoderm<sup>®</sup> patch and a protective dome, was shaved. The shaved area was cleaned with Ivory soap solution (1:100, v/v, with distilled water) and patted dry. On the day of the dermal dose administration, a Duoderm<sup>®</sup> patch was placed around the dosing site to expose a 4 x 6-cm area.

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### **B. Preparation and Administration of the Dose**

[<sup>14</sup>CH<sub>3</sub>S]-Methamidophos was prepared in 0.9% saline for IV dosing and [<sup>14</sup>CH<sub>3</sub>S]-Tamaron 600 SL for dermal dose administration. For the IV dose administration, four male monkeys received a mean dose of  $239 \pm 2$  µg of [<sup>14</sup>CH<sub>3</sub>S]-methamidophos in 1 mL of 0.9% saline via an IV bolus injection through a catheter in a cephalic vein. The mean dose was 46.9 µg/kg body weight.

Before the dermal dose administration, the four animals were placed in the restraint chairs and received a dermal application of 0.1 mL of [<sup>14</sup>CH<sub>3</sub>S]-Tamaron 600 SL. The mean dose was  $239 \pm 2$  µg of test substance equivalent approximately to 10 µg/cm<sup>2</sup>. The application site was covered with a nonocclusive dome and secured. Approximately 8 hours after dosing, the animals were removed from the chairs and the protective dome and Duoderm<sup>®</sup> patch were removed. The surface of the treated site was swabbed with a series of 16 soap-water soaked cotton-tipped swabs (1% Ivory liquid soap in water) followed by two isopropyl alcohol (IPA)-wetted swabs. Approximately 24 and 48 hours after dose administration, the entire dose site was swabbed with two IPA-wetted swabs. After swabbing, an area of the dose site (approx. 4 x 1.5-cm), representing ¼ of the dose site) was tape stripped 16 times. A separate area of the dose site was used for the tape stripping each day. On study day 19, a final series of two IPA-wetted swabs was used to swab the dose site.

### **C. Sample Collection and Analysis**

Urine and feces (including feed biscuits) were collected at 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours after the IV dosing. Blood samples were collected at 5 min., 15 min., and 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours post dosing. Other samples collected for analysis were IV dose catheters, dosing syringes and needles, excreta, plasma, and red blood cells.

For the dermal dose administration, urine, feces and feed biscuits were collected at 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours. Blood samples were collected at 15 min., and 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours post dosing. Other samples collected for analysis were dermal application pipettes, swabs, tape strips, Duoderm<sup>®</sup> patches, protective (dermal) domes, excreta, plasma and red blood cells.

### **D. Results**

For IV dosing, an average of 11.35% of the administered dose was recovered in the urine and 0.51% was recovered in the feces, indicating that the main route of excretion was through the urine. Results of cumulative urinary excretion are shown in Table 1.

Table 1. Cumulative urinary excretion of the applied dose in rhesus monkeys following the intravenous bolus dose of [<sup>14</sup>CH<sub>3</sub>S]-methamidophos at 46.9 µg/kg body weight.

Post dose interval (hour)	Mean value (%)	Cumulative mean value (%)
0-4	8.22	8.22
4-8	1.84	10.06
8-12	0.28	10.34
12-24	0.38	10.72
24-48	0.22	10.94
48-72	0.19	11.13
72-96	0.12	11.25
96-120	0.10	11.35

For dermal administration, the majority of the applied dose (57.3%) was recovered in the skin swabs with soap and water. Alcohol swabs contained 4.10% and tape strips contained 0.15% of the administered dose. Other dose recoveries were: Duoderm<sup>®</sup> 2.76%, dermal dome 1.33% and feed biscuits 0.11%. The mean total recovery of unabsorbed dose was 65.75%. The mean recovery in the urine was 1.20% and that in the feces was 0.06%. Results of urinary excretion are shown in Table 2.

Table 2. Cumulative urinary excretion of the applied dose in rhesus monkeys after the dermal administration of [<sup>14</sup>CH<sub>3</sub>S]-methamidophos at 10 µg/cm<sup>2</sup>.

Post dose interval (hour)	Mean value (%)	Cumulative mean value (%)
0-4	0.04	0.04
4-8	0.08	0.12
8-12	0.09	0.21
12-24	0.33	0.54
24-48	0.29	0.83
48-72	0.17	1.00
72-96	0.11	1.11
96-120	0.09	1.20

Determination of the dermal absorption of methamidophos is based on the principle used by Feldmann and Maibach (1974) or Wester and Maibach (1985). The method employs the percentage of the applied dose excreted in the urine or feces or both obtained from topical administration and IV dosing. Since the majority of the administered dose was excreted in the urine, only the dose recovered in the urine is used for estimation of the dermal absorption.

The estimated maximum urinary excretion following both routes of administration was used so that there was no discrepancy for the length of sample collection times. The estimated maximum excretion of the dose in the urine was performed by using the exponential saturation model with lag time (Thongsinthusak *et al.*, 1999). The scientific software Systat<sup>®</sup>, version 8.0 (SPSS, 1998) was utilized for the statistical analysis and plotting a graph. The estimated maximum excretion post IV dosing was determined to be 11.09% and that for post dermal dosing was determined to be 1.25% (Figure 1).

The dermal absorption was calculated using the equation shown below.

$$\% \text{ Dermal absorption} = \frac{(\text{Topical}) \text{ } ^{14}\text{C in urine (\% dose)}}{(\text{IV}) \text{ } ^{14}\text{C in urine (\% dose)}} \times 100$$

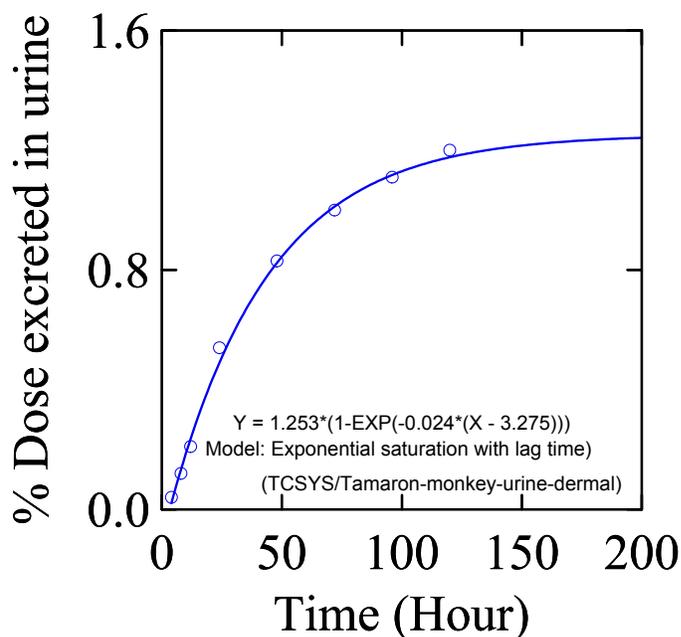
$$\% \text{ Dermal absorption of methamidophos in monkeys} = \frac{1.25}{11.09} \times 100 = 11.3\%$$

#### **E. Discussion and Conclusion**

[<sup>32</sup>P]-Methamidophos is ideal for use in a dermal absorption study in animals because it is radiolabeled at the core of the molecule. Loss of radioactivity due to volatilization of its metabolites is expected to be minimal. However, [<sup>14</sup>CH<sub>3</sub>S]-methamidophos was used in this study. The dermal dose used in this study was higher than anticipated. The low end of the dermal dose should range from 1 to 6 µg/cm<sup>2</sup>. The dermal absorption of 11.3% was estimated based upon the conditions of this study. However, this dermal absorption value is not recommended for the exposure assessment of methamidophos because the mean recovery following the IV administration was very low, indicating the loss due to volatile metabolites.

DPR recommends a new dermal absorption study be conducted by using <sup>32</sup>P-methamidophos in animals, such as nonhuman primates. In a dermal absorption study, it is essential that a compound be radiolabeled at a position, which is part of the core of the molecule. An appropriate dermal dose should be prepared in an aqueous suspension with the addition of formulation blank (ingredients used in the methamidophos formulation minus methamidophos). A probe study is recommended. A dermal absorption study protocol should be submitted to DPR for review prior to the study.

Figure 1. Asymptotic plot of cumulative urinary excretion of [<sup>14</sup>CH<sub>3</sub>S]-methamidophos after dermal administration of 10 µg/cm<sup>2</sup> to rhesus monkey skin.



SYSTAT Rectangular file D:\DATA\TCSYS\Tamaron-monkey-urine-Dermal.SYD, created Mon Jun 25, 2001 at 16:09:17, contains variables:					Dependent variable is RECOV																												
Iteration No. Loss MAX RATE LAG					<table border="1"> <thead> <tr> <th>Source</th> <th>Sum-of-Squares</th> <th>df</th> <th>Mean-Square</th> </tr> </thead> <tbody> <tr> <td>Regression</td> <td>4.708</td> <td>3</td> <td>1.569</td> </tr> <tr> <td>Residual</td> <td>0.004</td> <td>5</td> <td>0.001</td> </tr> <tr> <td>Total</td> <td>4.713</td> <td>8</td> <td></td> </tr> <tr> <td>Mean corrected</td> <td>1.525</td> <td>7</td> <td></td> </tr> </tbody> </table>					Source	Sum-of-Squares	df	Mean-Square	Regression	4.708	3	1.569	Residual	0.004	5	0.001	Total	4.713	8		Mean corrected	1.525	7					
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					Raw R-square (1-Residual/Total) = 0.999 Mean corrected R-square (1-Residual/Corrected) = 0.997 R(observed vs predicted) square = 0.997																												

Denise Webster  
July 12, 2001  
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**References:**

Feldmann, R. J., and Maibach, H. I. 1974. Percutaneous penetration of some pesticides and herbicides in man. *Toxicol. Appl. Pharmacol.* 28:126-132.

Fuller B. 2000. A dermal/intravenous cross over study to determine the dermal absorption of [<sup>14</sup>C]-methamidophos in male rhesus monkeys. Bayer Report No. 109812.

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Thongsinthusak, T., Ross, J. H., Saiz, S. G., and Krieger, R. I. 1999. Estimation of dermal absorption using the exponential saturation model. *Reg. Toxicol. Pharmacol.* 29:37-43.

Wester, R. C., and Maibach, H. I. 1985. *In vivo* percutaneous absorption and decontamination of pesticides in humans. *J. Toxicol. Environ. Hlth.* 16:25-37.

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(Dermal/Tamaron-Monkeys; HSM-01007)



# Department of Pesticide Regulation



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TO: Kathy Wynn  
Pesticide Registration Specialist  
Pesticide Registration Branch

HSM-01008

FROM: Thomas Thongsinthusak  
Staff Toxicologist (Specialist)  
(916) 445-4267

DATE: July 3, 2001

SUBJECT: BRAND NAME: Tamaron 600 SL  
ACTIVE INGREDIENT: Methamidophos  
COMPANY NAME: Bayer Corporation  
TRACKING I.D. NUMBER: 184857  
RECORD NUMBER (RN): 176927  
DATA PACKAGE NUMBER (DPN): 315-164  
EPA REGISTRATION NUMBER: 3125---  
TITLE: Absorption, Excretion, Balance and Pharmacokinetics of <sup>14</sup>C  
Radioactivity after Single Dose Dermal Application of One Dose Level of  
<sup>14</sup>C Labeled Methamidophos from a Tamaron 600 SL Formulation Administered  
to Healthy Volunteers

A dermal absorption study of methamidophos in six healthy male volunteers was conducted by Pharma Bio-Research Clinics, B.V (PBR) of The Netherlands (Clinical phase) and XenoBiotic Laboratories, Inc (XBL) of the United States (Analytical phase). This study was initiated on November 20, 1998 and was completed on July 11, 2000. All aspects of this study, which were performed at Pharma Bio-Research Clinics, were conducted in accordance with Good Clinical Practice Regulations. The conditions were in compliance with the Declaration of Helsinki (with subsequent revisions) and other guidelines on the use of human subjects. All aspects of this study, which were performed at XenoBiotic Laboratories, Inc., were conducted in accordance with the U.S. EPA FIFRA Good Laboratory Practice Standards (40 CFR Part 160). The quality assurance officer inspected various aspects of the study. A summary of this dermal absorption study and the evaluation of the results are presented below.

## **A. Preparation of Test Subjects**

Human volunteers were recruited into the study through the advertisement in English and Dutch. The eligibility screening of the volunteers was conducted within three weeks before initiation of the study. Six healthy male volunteers were selected from a pool of applicants. Consent forms were voluntarily signed by each participant and all were thoroughly instructed as to the nature and objectives of the study. An attending physician and other staff provided the care to volunteers throughout the study. All subjects were housed within the Pharma Bio-Research

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Clinical Research Center for the duration of the study. The mean body weight of the volunteers was  $80.9 \pm 6.6$  kg.

Preliminary baseline urinalysis, hematology and blood chemistry were evaluated. The application site was outlined with ink on the day of dosing and surrounded by an adhesive template (Duoderm<sup>®</sup>, Squibb B.V., The Netherlands) from which a 4 x 6-cm section had been removed. An indwelling intravenous (IV) catheter was placed in both arms for simultaneous collection of blood samples for the first 8 hours of the study.

### **B. Preparation and Administration of the Dose**

An appropriate amount of [<sup>14</sup>CH<sub>3</sub>S]-methamidophos was mixed with Tamaron 600 SL blank formulation. The formulation was diluted with water to obtain a concentration of 72 µg/100 µL. The six volunteers were administered a single 100 µL dose of [<sup>14</sup>CH<sub>3</sub>S]-methamidophos in the Tamaron 600 SL formulation. The mean dose of 71 µg of radiolabeled methamidophos was applied topically to an area of 24 cm<sup>2</sup> equivalent approximately to 3 µg a.i./cm<sup>2</sup>. The applied area was the non-dominant volar (palmar) aspect of the antebrachium of each subject. This dose was selected because it represented the approximate exposure experienced by agricultural workers. After administration of the dose, the site was covered with a porous aluminum dome secured with an adhesive bandage. This allowed air to circulate but avoided loss of test article due to physical contact. Normal daily activity was allowed inside the research center and standard meals were provided at regular hours. Bathing and showering were not allowed until after the tape stripping on day 3 in order to avoid any loss of radioactivity from the stratum corneum. Volunteers were released from the study when radioactivity in the isopropyl alcohol (IPA) swabs of the application area was <5,000 dpm, urine radioactivity was <50 dpm/mL, and fecal radioactivity was <75 dpm/400 mg of homogenized fecal sample. If any of these conditions were not met, the stay of the volunteer was prolonged, and the appropriate test repeated.

### **C. Sample Collection and Analysis**

The dome and bandage were removed after 8 hours of exposure and saved separately for later analysis. The application sites were cleaned with 16 cotton swabs dipped in a 2% solution of Unicura<sup>®</sup> liquid soap in water. Each swab was saved individually in a glass liquid scintillation vial. The site was then rinsed with a steady stream of soapy water. The volume of the rinse was recorded and 2 aliquots saved in scintillation vials for analysis. After rinsing, the site was dried with two more cotton swabs and then wiped with two cotton swabs soaked in IPA. The application area was then covered with a dry gauze pad until tape stripping. Eighteen hours after cleaning, a 1 x 4-cm section (1/6 of the dose site) was “stripped” with adhesive cellophane tape (3 M Company Scotch<sup>®</sup> Magic<sup>®</sup>, 9 mm) and swabbed with IPA to determine the amount of residual radioactivity that was associated with the surface layer of the skin. This process was repeated on another 1 x 4-cm section at 45 hours post application. Sixteen strips were used on

each section. Each strip was applied evenly to the same area of skin and stripped off in a few seconds. On days 5, 6, and 7 the entire application site was swabbed with 2 cotton swabs soaked in IPA. The site was swabbed daily until the radioactivity was <5,000 dpm. Blood samples were taken from both arms simultaneously, ipsilateral (treated) and contralateral (untreated), at 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 120 hours. Total urine volume was collected before dosing and at the intervals 0-4, 4-8, 8-12, 12-24, 24-36, 36-48 hours, and every 24 hours post exposure for 120 hours. Urine was collected after 120 hours only until radioactivity was <50 dpm/mL. One pre-dose fecal sample was collected and all post-dose fecal samples were collected for 120 hours. Samples continued to be collected after 120 hours only until radioactivity was <75 dpm. All samples (urine, blood, feces, swabs, skin rinses, tape strips, the dome, template and gauze) were processed accordingly and analyzed for radioactivity using a Beckman liquid scintillation spectrometer.

#### **D. Results**

The majority of the dose (60.23%) was found in the skin swab with soapy water and IPA in day 1. The recovery from day 2 to day 7 averaged 0.49%, indicating the removal of the dose after the 8-hour exposure period was effective. The average recoveries of radioactivity as percent of applied dose were 70.54% (swab, skin rinsate, dome, Duoderm<sup>®</sup>, and gauze pads), 0.89% (tape stripping), 0.0% (feces), and 0.55% (urine). The total average recovery was 71.98%.

The dermal absorption of methamidophos was determined based on the principle used by Feldmann and Maibach (1974) or Wester and Maibach (1985). The method employs the percentage of excreted dose in the urine or feces or both from topical administration and IV dosing. Since there was no recovery of the administered dose in the feces, only the percent of the dose recovered in the urine is used for the estimation of the dermal absorption. Cumulative percentages of the administered dose excreted in the urine are shown in Table 1.

Table 1. Cumulative percentages of dose excreted in the urine after topical administration of methamidophos at 3 µg/cm<sup>2</sup> in human volunteers.

Post dose interval (hour)	Mean value (%)	Cumulative mean value (%)
0-4	0.01	0.01
4-8	0.03	0.04
8-12	0.03	0.07
12-24	0.08	0.15
24-36	0.09	0.24
36-48	0.06	0.30
48-72	0.11	0.41
72-96	0.07	0.48
96-120	0.06	0.54

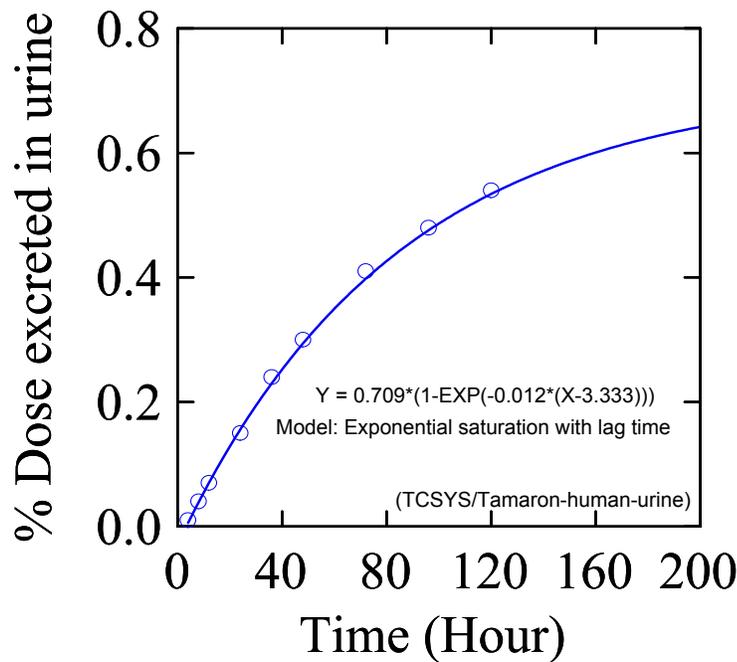
The results indicated that urinary excretion of the administered dose has not reached the plateau at 120 hours post administration. This shows that the excretion of radioactivity was continued after the end of the collection period. The sample collection period should have been longer than 120 hours. Consequently, the maximum excretion of the dose in urine was performed using the exponential saturation model with lag time (Thongsinthusak *et al.*, 1999). The scientific software Systat<sup>®</sup>, version 8.0 (SPSS, 1998) was utilized for the statistical analysis and plotting a graph. Results in Figure 1 shows the estimated maximum urinary excretion was 0.709%. This percentage of the urinary excretion was used to estimate the dermal absorption.

A study using IV dosing of methamidophos in human volunteers was not conducted. Previously, a study in monkeys using IV dosing was performed (Fuller, 2000). Bayer Corporation noted in the report that it is unacceptable to administer [<sup>14</sup>CH<sub>3</sub>S]-methamidophos intravenously to human volunteers. A surrogate study using IV dosing is needed to estimate the dermal absorption of this compound in humans. Wester and Maibach (1993) revealed that dermal absorption values of several chemicals in monkeys and humans are similar. It is assumed that excretion of radioactivity following IV dosing in humans and monkeys would also be similar. Results of the urinary excretion of the dose in monkeys after IV dosing are shown in Table 2.

Table 2. Cumulative urinary excretion of the dose in monkeys following the intravenous bolus dose of methamidophos (46.9 µg/kg body weight).

Post dose interval (hour)	Mean value (%)	Cumulative mean value (%)
0-4	8.22	8.22
4-8	1.84	10.06
8-12	0.28	10.34
12-24	0.38	10.72
24-48	0.22	10.94
48-72	0.19	11.13
72-96	0.12	11.25
96-120	0.10	11.35

Figure 1. Asymptotic plot of cumulative urinary excretion of [<sup>14</sup>CH<sub>3</sub>S]-methamidophos after topical administration of 3 μg/cm<sup>2</sup> to human skin.



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The exponential saturation model with lag time (Thongsinthusak *et al.*, 1999) was used to estimate the maximum urinary excretion after the IV administration as it was used to estimate the maximum urinary excretion of the dose after the dermal administration in the volunteers. The estimated maximum urinary excretion of the dose in monkeys after IV dosing was 11.09%. The dermal absorption of methamidophos can be calculated using the equation shown below.

$$\% \text{ Dermal absorption} = \frac{(\text{Topical})^{14}\text{C in urine (\% dose)}}{(\text{IV})^{14}\text{C in urine (\% dose)}} \times 100$$

$$\% \text{ Dermal absorption of methamidophos in humans} = \frac{0.709}{11.09} \times 100 = 6.4\%$$

#### **E. Discussion and Conclusion**

Bayer Corporation did not formally request scientists at Department of Pesticide Regulation (DPR) to review the dermal absorption study protocol. Upon contact by the representatives of Bayer Corporation about the labeled compound and the low recovery of radioactivity in the urine, the author of this memorandum recommended that <sup>32</sup>P-methamidophos should be used (Bayer Corporation, 1998). In 1999, the author was informed that Bayer could not find a lab to synthesize <sup>32</sup>P-methamidophos. Later, a lab (person) was found in Russia to synthesize <sup>32</sup>P-methamidophos, but that was unreliable. Typically, scientists at DPR recommend a compound that is radiolabeled at the core of the molecule.

Gray *et al.* (1982) conducted a study to determine the distribution and excretion of [<sup>14</sup>CH<sub>3</sub>S]-methamidophos in female Sprague-Dawley<sup>®</sup> rats. The animals were given IV dosing of a non-lethal dose at 8 µg/kg body weight. Within 24 hours of dosing, 47% of the radioactivity was recovered in the urine and 34% as CO<sub>2</sub> with less than 5% in the feces over 7 days. The results indicated that [<sup>14</sup>CH<sub>3</sub>S]-methamidophos could be used to study the distribution of this compound in animals because the majority of the dose is excreted in urine. Based on this evidence, it is assumed that the majority of the absorbed dose in humans or monkeys would be excreted in urine and a lower percentage would be converted to CO<sub>2</sub> or volatile components. [<sup>14</sup>CH<sub>3</sub>S]-methamidophos was used in dermal absorption studies in monkeys and humans. However, the estimated maximum urinary excretion after IV dosing in monkeys was very low (11.08%) compared to that observed in rats (47%). The average recovery of unabsorbed dose in the dermal absorption study in humans was 70.54%. Approximately, 29% of the administered dermal dose could have been absorbed (indirect estimate). Even though it is more realistic to use a dermal absorption value obtained from a study in humans for exposure assessment, the dermal absorption of 6.4% was estimated based on some assumptions. The dermal absorption of methamidophos could possibly range from 6.4% to 29%. Because of uncertainty for some assumptions, a human dermal absorption value of 6.4% is not recommended for the exposure assessment.

In 1987, a study was conducted to determine the dermal absorption of [<sup>14</sup>CH<sub>3</sub>S]-methamidophos in rats. However, this study was unacceptable because the total dose recoveries for several exposure times of the dermal doses were very low (Thongsinthusak, 2001a).

The dermal absorption study of [<sup>14</sup>CH<sub>3</sub>S]-methamidophos was conducted in monkeys and completed in 2000. Based on the conditions of this study, the dermal absorption was estimated to be 11.3% (Thongsinthusak, 2001b). This dermal absorption is not recommended for the exposure assessment because the recovery of radioactivity after the IV administration in monkeys was very low, accounting for 11.09%.

The estimated dermal absorption of methamidophos in the human volunteers was 6.4%. This estimate was based on a few assumptions, which may not be accurate. The indirect estimate of the dermal absorption (administered dose – unabsorbed dose) in humans was 29%. This dermal absorption value represents an extreme case scenario. DPR recommends a conservative dermal absorption value of 29% because of uncertainty related to the dermal absorption studies in rats, monkeys and human volunteers.

DPR recommends a new dermal absorption study be conducted by using <sup>32</sup>P-methamidophos in animals, such as nonhuman primates. In a dermal absorption study, it is essential that a compound be radiolabeled at a position, which is part of the core of the molecule in order to prevent loss of metabolite(s) due to volatilization. An appropriate dermal dose should be prepared in an aqueous suspension with addition of formulation blank (ingredients used in the methamidophos formulation minus methamidophos). A probe study is recommended. A dermal absorption study protocol should be submitted to DPR for review before the study.

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(Dermal/Tamaron-humans; HSM-01008)