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**OPP OFFICIAL RECORD  
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SCIENTIFIC DATA REVIEWS  
EPA SERIES 361**

OFFICE OF PREVENTION,  
PESTICIDES AND  
TOXIC SUBSTANCES

March 14, 2002

Memorandum

SUBJECT: Review of "*Occupational Exposure Monitoring of Mixing/Loading Activities for Aerial Application of PENNCAP M<sup>®</sup> Microencapsulated Insecticide Utilizing Biological Monitoring*" (MRID #455130-01)

FROM: Renee Sandvig, Environmental Protection Specialist  
Reregistration Branch II  
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*Renee Sandvig 3/14/02*

THROUGH: Al Nielsen, Branch Senior Scientist  
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*Al Nielsen 3/14/02*

TO: Laura Parsons, Chemical Review Manager  
Reregistration Branch I  
Special Review and Reregistration Division (7508C)

DP Barcode: D278646 and D280203

Pesticide Chemical Codes: 053501

EPA MRID Numbers: 455130-01 and 455526-01

Attached is a review of the handler biomonitoring data submitted by Cerexagri, Inc. (formerly Elf Atochem North America, Inc.). This review was completed by Versar, Inc. on December 7, 2001, under supervision of HED. It has undergone secondary review in the HED and has been revised to reflect Agency policies.

## Executive Summary

The data collected reflecting the workers exposure to methyl parathion meet most of the criteria specified in the U.S. Environmental Protection Agency OPPTS Guidelines, Group A, Group A: 875.1500, Biological Monitoring. The data will be considered in future methyl parathion REDs.

## Summary

The purpose of this study was to quantify potential exposure of mixer/loader to the restricted use organophosphate insecticide, methyl parathion, formulated as a 20.9% product in PENNCAP-M<sup>®</sup> Microencapsulated Insecticide. Ten aerial applications were made to a variety of crops (including cotton, corn, soybeans, grain sorghum, and rice) in two geographical locations (Newport, Arkansas and Washington, Louisiana). PENNCAP-M<sup>®</sup> (a flowable aqueous suspension containing packaged in 2.5 gallon containers) was applied using an airplane at the maximum application rate of 1.0 lbs ai/A.

Ten volunteer mixer/loaders were monitored via urinary analyses. Methyl parathion exposure was quantified by measuring total 4-nitrophenol (4-NP) in urine samples. The samples were also analyzed for creatinine content. Twenty-four hour urine samples were collected for 48 hours prior, through 96 hours after, exposure. The workers were sequestered in a hotel during this period, leaving only to perform application activities.

Versar corrected 4-NP field data for Arkansas using a correction factor of 75.0% and for Louisiana using a correction factor of 73.2% (the average field fortification recoveries for each location not corrected for laboratory recovery). Since the raw data were not corrected for laboratory recoveries, the field recoveries used to correct the raw data were also not corrected for laboratory recoveries. In Arkansas, the geometric mean net urinary 4-NP values rose from a baseline of 0.067  $\mu\text{g/kg}$  to 1.07  $\mu\text{g/kg}$  after one day of exposure and then declined to 0.12  $\mu\text{g/kg}$  two days after exposure. Thereafter, net urinary excretion of 4-NP declined to below baseline levels by 72 hours after exposure. Total adjusted net normalized 4-NP excreted (expressed as  $\mu\text{g}/70$  kg body weight) from Day 0 through 96 hours after exposure ranged from 29.58 to 557.46  $\mu\text{g/kg}$ . In Louisiana, the geometric mean net urinary 4-NP value decreased from a baseline of 0.19 to 0  $\mu\text{g/kg}$  after the first day of exposure. Average baseline (0-49 hours prior to exposure) 4-NP levels in Louisiana therefore exceeded on the first day after application (0-24 hours after exposure) levels.

Statistical analysis of the residue data included arithmetic and geometric means, median, standard deviation, and the range of values. Residue data sets were analyzed by the Registrant using SYSTAT Version 8.0 software.

The study was in compliance with most of the OPPT Series 875 Occupational and Residential Exposure Test Guidelines. The following issues of potential concern were identified:

- Baseline 4-NP levels at the Louisiana site were higher than the measured 4-NP values after the first day of exposure (24+ hours).
- The storage stability results presented in this Study Report (31 days from Study No. KP-2000-02) do not support the period of frozen storage pertinent to this study (48 days for 13 samples from the Louisiana test site).
- The exposure period was variable, ranging from 39 to 100 minutes for mixing/loading (based on worker observations on pages 64-70 of the Study Report).
- The only meteorological information presented was the temperature and percent relative humidity for the day of mixing/loading. The source of these weather data was not reported.

## M E M O R A N D U M

**TO:** Renee Sandvig cc: 110082.2000.001.01 File  
Linda Phillips

**FROM:** Nica Mostaghim/Marit Espevik

**DATE:** December 7, 2001

**SUBJECT:** Review of "*Occupational Exposure Monitoring of Mixing/Loading Activities for Aerial Application of PENNCAP M<sup>®</sup> Microencapsulated Insecticide Utilizing Biological Monitoring*" (MRID #455130-01)

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Versar reviewed the study entitled "*Occupational Exposure Monitoring of Mixing/Loading Activities for Aerial Application of PENNCAP M<sup>®</sup> Microencapsulated Insecticide Utilizing Biological Monitoring*," submitted to US-EPA in support of the reregistration requirements for *PENNCAP M<sup>®</sup>*. Study requirements were specified by the U.S. Environmental Protection Agency under OPPTS Guidelines, Group A: 875.1500, Biological Monitoring - Handler.

The following information may be used to identify the study:

Title:	" <i>Occupational Exposure Monitoring of Mixing/Loading Activities for Aerial Application of Penncap-M<sup>®</sup> Microencapsulated Insecticide Utilizing Biological Monitoring</i> " 764 pages (2 volumes)
Sponsor:	Rodney M. Bennett (Author) Cerexagri, Inc. 630 Freedom Business Center, Suite 402 King of Prussia, PA 19406
Analytical Laboratory:	Richard L. Reed Morse Laboratories, Inc. 1525 Fulton Avenue Sacramento, CA 95825
Author/Study Director and Testing Facility:	Tommy R. Willard American Agricultural Services, Inc. 404 E. Chatham Street Cary, NC 27512
Report Date:	October 3, 2001
Identifying Codes:	MRID # 455130-01; Cerexagri Study No. KP-2001-03; Morse Project No. ML01-0919-CRX

## EXECUTIVE SUMMARY

The purpose of this study was to quantify potential exposure of mixer/loader to the restricted use organophosphate insecticide, methyl parathion, formulated as a 20.9% product in PENNCAP-M<sup>®</sup> Microencapsulated Insecticide. Ten aerial applications were made to a variety of crops (including cotton, corn, soybeans, grain sorghum, and rice) in two geographical locations (Newport, Arkansas and Washington, Louisiana). PENNCAP-M<sup>®</sup> (a flowable aqueous suspension containing packaged in 2.5 gallon containers) was applied using an airplane at the maximum application rate of 1.0 lbs ai/A.

Ten volunteer mixer/loaders were monitored via urinary analyses. Methyl parathion exposure was quantified by measuring total 4-nitrophenol (4-NP) in urine samples. The samples were also analyzed for creatinine content. Twenty-four hour urine samples were collected for 48 hours prior, through 96 hours after, exposure. The workers were sequestered in a hotel during this period, leaving only to perform application activities.

Versar corrected 4-NP field data for Arkansas using a correction factor of 75.0% and for Louisiana using a correction factor of 73.2% (the average field fortification recoveries for each location not corrected for laboratory recoveries). In Arkansas, the geometric mean net urinary 4-NP values rose from a baseline of 0.067  $\mu\text{g/kg}$  to 1.07  $\mu\text{g/kg}$  after one day of exposure and then declined to 0.12  $\mu\text{g/kg}$  two days after exposure. Thereafter, net urinary excretion of 4-NP declined to below baseline levels by 72 hours after exposure. Total adjusted net normalized 4-NP excreted (expressed as  $\mu\text{g}/70$  kg body weight) from Day 0 through 96 hours after exposure ranged from 29.58 to 557.46  $\mu\text{g/kg}$ . In Louisiana, the geometric mean net urinary 4-NP value decreased from a baseline of 0.19 to 0  $\mu\text{g/kg}$  after the first day of exposure. Average baseline (0-49 hours prior to exposure) 4-NP levels in Louisiana therefore exceeded on the first day after application (0-24 hours after exposure) levels.

Statistical analysis of the residue data included arithmetic and geometric means, median, standard deviation, and the range of values. Residue data sets were analyzed by the Registrant using SYSTAT Version 8.0 software.

The study was in compliance with most of the OPPT Series 875 Occupational and Residential Exposure Test Guidelines. The following issues of potential concern were identified:

- Baseline 4-NP levels at the Louisiana site were higher than the measured 4-NP values after the first day of exposure (24+ hours).
- The storage stability results presented in this Study Report (31 days from Study No. KP-2000-02) do not support the period of frozen storage pertinent to this study (48 days for 13 samples from the Louisiana test site).

- The exposure period was variable, ranging from 39 to 100 minutes for mixing/loading (based on worker observations on pages 64-70 of the Study Report).
- The specific gravity of the samples were not reported.
- The only meteorological information presented was the temperature and percent relative humidity for the day of mixing/loading. The source of these weather data was not reported.
- A brief history from each participant in relation to known prior exposures to pesticides for at least 2 weeks was not provided. It is only reported that test subjects were prescreened one to two weeks prior to exposure monitoring.

## STUDY REVIEW

### Study Background

The purpose of this study was to monitor urinary excretion of methyl parathion (o,o-dimethyl o-p-nitrophenylphosphorothioate, CAS No. 298-00-0) in mixers and loaders. It was a follow-up study to another mixer/loader study using the PENNCAP-M<sup>®</sup> Microencapsulated Insecticide at sites in Mississippi and Arizona. (MRID # 45327101). Methyl parathion was formulated as a 20.9% product in PENNCAP-M<sup>®</sup> Microencapsulated Insecticide. In this study, 4-nitrophenol (4-NP), a urinary metabolite of methyl parathion, was used to quantify methyl parathion exposure. Exposure was determined by analysis of 4-NP in 24-hour composite urine samples collected before, during, and after exposure to PENNCAP-M<sup>®</sup>. In addition, creatinine levels in the urine were measured as a qualitative measure of the completeness of the urine samples.

This study took place from April 24, 2001 through May 27, 2001 in Washington, Louisiana and from June 24, 2001 through July 15, 2001 in Newport, Arkansas. The field phase of the study was directed by American Agricultural Services, Inc., of Cary, North Carolina. Sample analysis was conducted between April 27, 2001 and August 31, 2001 by Morse Laboratories, Inc., of Sacramento, California.

The final report concludes the work presented in an interim report (MRID 45327101). The interim report, which discusses the biomonitoring at test sites located in Greenville, MS; Gila Bend, AZ, and Harquahala Valley, AZ, has already been reviewed by Versar. This review, therefore, focuses on the Louisiana and Arkansas replicates.

### Attestations

The study sponsor waived claims of confidentiality within the scope of FIFRA Section 10 (d)(1)(A), (B), or (C). The study sponsor and author attested that the study was conducted and reported in compliance with EPA Good Laboratory Practice Standards (40 CFR Part 160), with certain exceptions. These were: (1) the test substance was characterized concurrently with the study rather than prior to study initiation, (2) test substance containers will not be retained (however, this exception has been authorized by the USEPA), (3) weather data collected by NOAA were not reported, (4) calibration and maintenance records for the aerial sprayer were not collected, (5) test substance containers were not labeled with expiration dates, and (6) inclusion in the report of photographs from a previously submitted study is an exception to 40 CFR Part 160.

### Study Subjects

Ten workers (five at the Louisiana test sites and five at the Arkansas test site) were monitored for exposure for a total of 10 replicates. Five of these replicates were monitored at the Louisiana test site and five were monitored at the Arkansas test site. Study participants were

nine healthy males and one healthy female. Some workers had previous experience, while others were given training on pesticide mixing/loading at their specific test site. The workers ranged in age from 21 to 66 years, in weight from 134 to 236 lbs, and in height from 63 to 74 inches. All participants read and signed informed consent forms.

All workers were required to stay at a hotel from two days prior to the exposure monitoring period until three days after the exposure period.

### **Personal Protective Clothing and Equipment**

During the application, participants wore personal protective equipment (PPE) similar to that prescribed on the product label. The following PPE was worn by the participants:

- cotton coveralls over long-sleeved shirt, undershirt, and long pants;
- chemical resistant boots;
- long nitrile gloves;
- fullface shield;
- overhead exposure;
- dust/mist filtering half-face respirator (OSHA/NIOSH approval number prefix TC-21C);
- chemical resistant nitrile apron; and
- Tyvek® hat.

### **Test Sites**

This study follow-up was conducted at two test sites:

- (1) R&D Research Farms, Inc., Washington, LA; and
- (2) Shoffner Farms, Inc., Newport, AR.

The total acreage treated in Arkansas was approximately 1,800 acres (or 120 acres per plane load x 3 plane loads per worker x 5 workers). The total acreage treated at the Louisiana site was 1,725 acres (or 115 acres per plane load x 3 plane loads per workers x 5 workers). Descriptions of neither the test plots nor the governing counties were provided for this study by the submitter.

### **Materials and Work Practices Monitored**

The product label for PENNCAP-M® Microencapsulated Insecticide [EPA Reg. No. 4581-293] was provided with the Study Report. PENNCAP-M® is a flowable formulation consisting of a water suspension of polymeric-type microcapsules containing 20.9% methyl parathion at 2 lbs ai/gallon. The formulation is packaged in 2.5 gallon containers. PENNCAP-M® was applied to a variety of crops including cotton, corn, soybeans, grain sorghum, and rice



for control of insect pests. In this study, PENNCAP-M<sup>®</sup> was used at the maximum application rate of 1.0 lb ai/acre.

The maximum application rate for corn, cotton and soybeans is reported to be 4 pints/acre (or 1.0 lb ai/acre), while the maximum application rate for grain sorghum and rice is reported to be 3 pints/acre (or 0.75 lb ai/acre).

At the Arkansas site, each worker performed applications with three plane loads of spray mixture and each worker handled 180 gallons of PENNCAP-M<sup>®</sup> to treat 360 acres of crop. Each worker emptied and rinsed 24 containers (2.5 gallons of PENNCAP-M<sup>®</sup>) into a large stainless steel vat (~ 100g). A transfer hose was used to pump the PENNCAP-M<sup>®</sup> from the vat, into an Air Tractor Model 502B aircraft. The exposure duration for each of the five subjects monitored at the Arkansas site was approximately 39 to 85 minutes while mixing and loading the three plane loads of spray mixture.

At the Louisiana site, each worker performed applications with three plane loads of spray mixture and handled 172.5 gallons of PENNCAP-M<sup>®</sup> to treat 345 acres of crop. Each worker emptied and rinsed 23 2.5-gallon containers into a large cylindrical vat (~75 gallons). Each worker used a transfer hose to pump the PENNCAP-M<sup>®</sup> to an Air Tractor Model 502B aircraft. The exposure duration for each of the five subjects monitored was approximately 80-100 minutes while mixing and loading the three plane loads of spray mixture.

### **Meteorology**

The meteorological information for each site is provided on pages 66 and 70 in the study report. The source of the data is not reported. No rainfall was reported for either the Arkansas or Louisiana sites. In Arkansas, air temperatures ranged from 77-89°F and the relative humidity ranged from 63-84%. In Louisiana, air temperatures ranged from 54-84°F, the relative humidity ranged from 15-84%, and the windspeed was reported to range from 0-7 miles per hour.

### **Sampling**

Sampling consisted of biological monitoring (urine analysis for the metabolite 4-NP). Amendments and deviations from the protocol were reported (see Appendix E, page 227 of the study report).

At both sites, twenty-four hour urine samples were collected from 48 hours prior to and 96 hours after exposure. Baseline urine samples were collected from each applicator between 48 hours prior to and on the day of exposure. Urine samples were also collected from the inception of application activities (Day 0) up to 96 hours following exposure activities. All urine was collected from each worker during the exposure monitoring period. The workers collected their urine in pre-weighted and coded UriSafe<sup>®</sup> Urine collection containers (3-Liter) for each 24-hour time period. Samples were stored in ice chests with blue ice packs during the sampling period. After urine samples were collected from workers, the entire sample weights and total volumes

were determined. The urine was acidified with a small amount of HCL. The amount was not identified by the Registrant. Samples were then subsampled into duplicate 50 mL samples for laboratory analyses. All subsamples were stored frozen until shipment.

## QA/QC

### *Sample History*

The Registrant provided a comprehensive history of all samples analyzed. All sample analyses were conducted between May 2 and August 29, 2001 by Morse Laboratories, Inc., of Sacramento, CA. Worker exposure samples from the Arkansas test site were received at Morse Laboratories on July 25, 2001. Worker exposure samples from the Louisiana test site were received on May 30, 2001. All worker exposure samples from Arkansas and Louisiana were analyzed within 31 days of sampling, except thirteen exposure samples from the Louisiana site that were stored up to 48 days prior to analysis. Field fortified samples from both sites were analyzed within 35 days of generation.

### *Sample Storage and Shipping*

Urine samples were kept in ice chests with blue ice during the exposure monitoring period. After weighing and acidification, the aliquot samples (i.e., subsamples) were collected and stored frozen until shipment to the analytical laboratory. Freezer temperatures were not provided for either of the two sites. Aliquot samples were shipped on dry ice via Federal Express for overnight delivery to Morse Laboratories, Inc., in Sacramento, CA, and stored in a freezer until analysis. Upon receipt at Morse Laboratories, Inc., frozen urine samples were transferred to a limited-access freezer for storage, where they remained until thawed for further subsampling and extraction. Freezer storage temperatures were monitored daily and remained at  $-20 \pm 5^{\circ}\text{C}$ .

### *Formulation Sample and Tank Mix Analyses*

Formulation samples were analyzed to confirm product purity and concentration. The certified ai content of PENNCAP-M® was 20.8% (May 16, 2001). Tank mix samples were not collected or analyzed.

### *Analytical Methodologies*

#### 1. 4-NP in Urine Analyses

The analytical method referenced in the Study Report for the analysis of 4-NP in urine samples was:

- Morse Laboratories, Inc., Analytical Method No. Meth-120, Revision #4, dated April 18, 2001, entitled "Determination of 4-nitrophenol in Urine;"

4-nitrophenol is a urinary metabolite of methyl parathion. 4-NP was isolated from urine by treating it with sodium bisulfite and subjecting it to acid hydrolysis to free any conjugated residues. An aliquot of the resulting hydrolysate was then extracted with toluene. MTBSTFA [N(tert-Butyldimethylsilyl)-N-methyltrifluoroacetamide] was added to a concentrated form of the toluene extract to convert any 4-NP present to a more volatile tert-butyldimethylsilyl derivative. Detection and quantitation of 4-NP was conducted using a gas chromatograph equipped with a mass selective detector. The retention time was approximately 13.5 minutes.

## 2. Creatinine (urine) analysis:

Creatinine levels were measured in the urine samples as a qualitative measure of the completeness of the urine samples. The analytical method used for the analysis of creatinine was *Morse Laboratories, Inc., Analytical Method No. Meth-111, Revision #2, dated November 9, 2000, entitled "Quantitative Determination of Creatinine in Urine."* In this analytical method, creatinine was reacted with alkaline picrate reagent in sodium borate to form an amber-colored creatinine picrate complex. The concentration of creatinine in the urine sample was calculated against a known standard creatinine concentration based on absorbance of the resulting creatinine picrate complex at 520 nm.

### *Limits of Detection (LOD) and Limits of Quantitation (LOQ)*

1. Urine Samples: For 4-NP and its conjugates in urine samples, the target limit of quantitation (LOQ) was 1.0  $\mu\text{g/L}$  and the target limit of detection (LOD) was 0.3  $\mu\text{g/L}$  4-NP or equivalent.
2. Creatinine in Urine: Method sensitivity was 0.6 mg/dL based on instrument resolution of 0.01 absorbance units.

### *Calibration*

A four point calibration curve was generated by injecting constant volumes of derivatized 4-nitrophenol standard solutions. Sample responses greater than those produced by the highest concentration of applicable standard curve required dilution and reinjection. In order to maintain consistent chromatography, dilutions were made with 1.5% 1-decanol in toluene. A curve check standard was injected every 4-5 sample injections. Details of the instrument parameters were reported on pages 101-103 of the report.

### *Control Samples*

Control urine samples were derived from the laboratory personnel. Urine samples from Morse Laboratory personnel and workers were screened for use in the study as control samples for procedural quality control (concurrently analyzed controls and fortified controls). According to the Registrant "urine for laboratory control use was considered acceptable for this if its

endogenous content of 4-NP (corrected for reagent blank) was less than approximately 1.0-1.5  $\mu\text{g/L}$ .”

Of the 21 control samples used in this study, all but three samples were found to contain less than 1.5  $\mu\text{g/L}$  4-NP. The remaining samples had concentrations of 4-NP ranging between 1.53 and 1.75  $\mu\text{g/L}$ .

#### *Concurrent Laboratory Recovery*

Overall 4-NP procedural recoveries (including fresh fortifications for field fortification runs) yielded a mean and standard deviation of  $87\% \pm 14$  ( $n=41$ ) and ranged from 63 to 117%.

#### *Field Fortification Recovery*

##### 1. Urine Samples

Urine field fortification samples were prepared at three fortification levels for 4-NP analysis. Samples were fortified at 2, 10 and 50  $\mu\text{g/L}$ , representing 2X, 10X, and 50X the LOQ, respectively. The fortification levels chosen corresponded well with the 4-nitrophenol levels measured in the field samples. At both sites, field fortifications were prepared two days prior to exposure and on the first day after treatment. At the Louisiana site, field fortifications were also prepared on the second day after treatment. Field fortification samples were prepared using a stock solution of 4-NP and stabilized (acidified) urine provided by Morse Laboratories. The urine field fortification samples were stored and shipped with the actual field samples.

Table 1 summarizes field-fortified recovery values before they were corrected by the Registrant. Uncorrected field fortification recoveries for both sites averaged  $73.9\% \pm 10.6\%$ . The Registrant corrected all urine field fortification recovery values with the mean recovery of concurrently analyzed 4-NP in freshly fortified control samples. In Arkansas, uncorrected field recoveries for 4-nitrophenol averaged  $75.0\% \pm 11.8$ . For Louisiana, uncorrected field recoveries averaged  $73.2\% \pm 10.3$ . Individual recovery values were presented in Table 5a and 5b (Pages 135-137) of the report. The Registrant noted that one 2  $\mu\text{g/L}$  field fortifications sample from two days prior to exposure event in Louisiana was unacceptable (with uncorrected percent recovery of 40%), and that it was not used in the statistical evaluation of the recovery results. Recoveries for two Arkansas field fortifications (one at 10  $\mu\text{g/L}$  and another at 50  $\mu\text{g/L}$ ) for the first day after application (24+ hours) mixing/loading events were also found to be unacceptable (with uncorrected percent recoveries of 477% and 17% respectively). The data were not used in the statistical evaluation of the recovery results.

#### *Storage Stability Recovery*

Stability of 4-NP in urine (conducted on urine contained in Urisafe collection containers, stored on wet ice) during the 24-hour collection period of each sampling interval up to 48 hours

(to allow for sample volume measurement and subsampling, prior to freezing) was determined in another study (Study No. KP-99-17, MRID 45200101). The stability results reported in that study (up to 48 hours) support the period of cold storage pertinent to this study.

**Table 1. Field Fortified Recovery Values for 4-Nitrophenol in Urine Samples, Not corrected for Concurrent Laboratory Recovery**

Test Site	4-Nitrophenol Fortification Level	Percent Recovery
Arkansas	2 $\mu\text{g/L}$ (N=3)	85.7 $\pm$ 14.1
	10 $\mu\text{g/L}$ (N=2)	69.0 $\pm$ 2.8
	50 $\mu\text{g/L}$ (N=2)	65.0 $\pm$ 2.8
	<b>TOTAL (N=7)</b>	<b>75.0 <math>\pm</math> 11.8</b>
Louisiana	2 $\mu\text{g/L}$ (N=3)	74.3 $\pm$ 18
	10 $\mu\text{g/L}$ (N=4)	75.8 $\pm$ 3.8
	50 $\mu\text{g/L}$ (N=4)	69.8 $\pm$ 9.9
	<b>TOTAL (N=11)</b>	<b>73.2 <math>\pm</math> 10.3</b>
All Sites Together	<b>GRAND TOTAL (N=18)</b>	<b>73.9 <math>\pm</math> 10.6</b>

Residues of 4-NP were found to be stable in urine during frozen storage for up to 31 days as determined in study No. KP-2000-02, MRID 45204701. The Registrant noted that 13 exposure samples from the Louisiana site were stored frozen for 48 days prior to analysis. Analysis of field fortified samples, stored frozen for 73 days prior to analysis, provided only acceptable results after they were corrected for laboratory recovery, but the Registrant concluded that 4-NP residues were stable in frozen urine for up to 73 days.

### Calculations

The arithmetic and geometric means, median, standard deviation, and range of values were calculated with SYSTAT version 8.0 software. Versar's calculations included converting the gross residue (total  $\mu\text{g}$  4-NP/sample) to net residue by first averaging each worker's 4-NP residues from samples collected pre-exposure (-48 to -24 and -24 to 0 hours) and then subtracting that average from 4-NP found in samples collected post-exposure. The daily net post-exposure 4-NP values was then added together to derive the total 4-NP. Total net 4-NP was then normalized to  $\mu\text{g}$  4-NP per kg bodyweight (by dividing the net 4-NP residue by the worker's weight), and to  $\mu\text{g}$  4-NP /70 kg bodyweight by multiplying the total net 4-NP residue/kg bodyweight by 70 (see tables 2a-c).

## Results

Versar corrected 4-NP field data for Arkansas using a correction factor of 75.0% and for Louisiana using a correction factor of 73.2% (the average uncorrected field fortification recoveries for each location). Since the raw data were not corrected for laboratory recoveries, the field recoveries used to correct the raw data were also not corrected for laboratory recoveries. Results are presented in Table 2a-c. In Arkansas, the geometric mean net urinary 4-NP values rose from a baseline of 0.067 µg/kg to 1.07 µg/kg after one day of exposure and then declined to 0.12 µg/kg two days after treatment. Thereafter, net urinary excretion of 4-NP declined to below baseline levels (0.05 µg/kg) by 72 hours after exposure. Total adjusted net normalized 4-NP excreted (expressed as µg/70 kg body weight) from Day 0 through 96 hours after exposure ranged from 29.58 to 557.46 µg/kg. In Louisiana, the geometric mean net urinary 4-NP value decreased from a baseline of 0.19 to 0 µg/kg after the first day of exposure. For both sites, creatinine measured in each applicator's daily urine sample was fairly consistent across the 6.5 day monitoring period.

**Table 2a. 4-NP Residues in Post Exposure Urine Samples in AR (5 Replicates)**

Parameters	Sampling Interval=0 to 24 hrs		
	Arith. Mean	Std. Dev.	Geo. Mean
Gross 4-NP (µg/L)	62.67	28.98	56.05
Net 4-NP (µg/L)	59.35	28.51	52.49
Gross 4-NP (total µg)	108.92	50.48	97.74
Net 4-NP (total µg)	103.05	51.39	90.49
Adjusted Net 4-NP (total ug)	707.19	329.49	615.36
Gross 4-NP (µg/kg weight)	1.24	0.47	1.16
Net 4-NP (µg/kg weight)	1.17	0.48	1.07
Adjusted Net 4-NP (ug/kg weight)	7.96	3.00	7.29
Net 4-NP (µg/70 kg weight)	81.85	33.94	75.00
Adjusted Net 4-NP (ug/70 kg weight)	557.46	209.92	510.03
Creatinine (g/24 hr)	2.31	0.67	2.23
Sampling Interval=24-48 hrs			
Gross 4-NP (µg/L)	9.28	6.73	7.51
Net 4-NP (µg/L)	5.96	6.88	--
Gross 4-NP (total µg)	18.65	7.73	17.29
Net 4-NP (total µg)	12.78	9.09	9.71
Adjusted Net 4-NP (total ug)	91.20	63.40	66.05
Gross 4-NP (µg/kg weight)	0.21	0.07	0.20
Net 4-NP (µg/kg weight)	0.14	0.09	0.12
Adjusted Net 4-NP (ug/kg weight)	1.01	0.65	0.78
Net 4-NP (µg/70 kg weight)	9.92	6.43	8.05
Adjusted Net 4-NP (ug/ 70 kg weight)	70.43	45.29	54.75
Creatinine (g/24 hr)	2.07	0.47	2.02
Sampling Interval=48-72 hrs			
Gross 4-NP (µg/L)	6.07	4.19	5.24
Net 4-NP (µg/L)	2.76	4.20	--
Gross 4-NP (total µg)	11.45	3.96	11.00
Net 4-NP (total µg)	5.58	4.32	4.52
Adjusted Net 4-NP (total ug)	38.54	28.03	30.77
Gross 4-NP (µg/kg weight)	0.13	0.03	0.13
Net 4-NP (µg/kg weight)	0.06	0.04	0.05
Adjusted Net 4-NP (ug/kg weight)	0.42	0.25	0.36
Net 4-NP (µg/70 kg weight)	4.30	2.71	3.75
Adjusted Net 4-NP (ug/ 70 kg weight)	29.58	17.68	25.50
Creatinine (g/24 hr)	1.87	0.65	1.78
Sampling Interval=72-96 hrs			
Gross 4-NP (µg/L)	11.90	5.60	10.86
Net 4-NP (µg/L)	6.21	6.80	--
Gross 4-NP (total µg)	12.78	8.40	--
Net 4-NP (total µg)	6.91	9.16	--
Adjusted Net 4-NP (total ug)	43.58	52.30	--
Gross 4-NP (µg/kg weight)	0.14	0.10	--
Net 4-NP (µg/kg weight)	0.07	0.11	--
Adjusted Net 4-NP (ug/kg weight)	0.46	0.63	--
Net 4-NP (µg/70 kg weight)	5.12	7.80	--
Adjusted Net 4-NP (ug/ 70 kg weight)	32.31	44.33	--
Creatinine (g/24 hr)	2.56	0.63	2.50

**Table 2b. 4-NP Residues in Post Exposure Urine Samples in LA (5 Replicates)**

Parameters	Sampling Interval=0 to 24 hrs		
	Arith. Mean	Std. Dev.	Geo. Mean
Gross 4-NP (µg/L)	21.80	10.34	20.24
Net 4-NP (µg/L)	11.93	12.06	7.04
Gross 4-NP (total µg)	29.09	11.14	27.35
Net 4-NP (total µg)	11.73	15.46	--
Adjusted Net 4-NP (total ug)	59.70	77.41	--
Gross 4-NP (µg/kg weight)	0.33	0.07	0.32
Net 4-NP (µg/kg weight)	0.12	0.15	--
Adjusted Net 4-NP (ug/kg weight)	0.62	0.76	--
Net 4-NP (µg/70 kg weight)	8.53	10.68	--
Adjusted Net 4-NP (ug/70 kg weight)	43.34	53.26	--
Creatinine (g/24 hr)	1.52	0.54	1.46
	Sampling Interval=24-48 hrs		
	Arith. Mean	Std. Dev.	Geo. Mean
Gross 4-NP (µg/L)	6.42	2.10	6.06
Net 4-NP (µg/L)	0.000	3.70	--
Gross 4-NP (total µg)	14.93	7.07	13.59
Net 4-NP (total µg)	0.000	4.24	--
Adjusted Net 4-NP (total ug)	0.000	23.43	--
Gross 4-NP (µg/kg weight)	0.18	0.08	0.16
Net 4-NP (µg/kg weight)	0.000	0.05	--
Adjusted Net 4-NP (ug/kg weight)	0.000	0.28	--
Net 4-NP (µg/70 kg weight)	0.000	3.71	--
Adjusted Net 4-NP (ug/ 70 kg weight)	0.000	19.66	--
Creatinine (g/24 hr)	1.65	0.60	1.53
	Sampling Interval=48-72 hrs		
	Arith. Mean	Std. Dev.	Geo. Mean
Gross 4-NP (µg/L)	5.81	4.46	3.78
Net 4-NP (µg/L)	0.000	4.95	--
Gross 4-NP (total µg)	9.88	7.11	7.25
Net 4-NP (total µg)	0.000	4.31	--
Adjusted Net 4-NP (total ug)	0.000	22.14	--
Gross 4-NP (µg/kg weight)	0.11	0.08	0.09
Net 4-NP (µg/kg weight)	0.000	0.07	--
Adjusted Net 4-NP (ug/kg weight)	0.000	0.33	--
Net 4-NP (µg/70 kg weight)	0.000	4.92	--
Adjusted Net 4-NP (ug/ 70 kg weight)	0.000	23.30	--
Creatinine (g/24 hr)	1.58	0.75	1.45
	Sampling Interval=72-96 hrs		
	Arith. Mean	Std. Dev.	Geo. Mean
Gross 4-NP (µg/L)	4.66	3.47	3.89
Net 4-NP (µg/L)	0.000	6.46	--
Gross 4-NP (total µg)	7.75	3.11	7.19
Net 4-NP (total µg)	0.000	8.65	--
Adjusted Net 4-NP (total ug)	0.000	48.80	--
Gross 4-NP (µg/kg weight)	0.09	0.04	0.09
Net 4-NP (µg/kg weight)	0.000	0.09	--
Adjusted Net 4-NP (ug/kg weight)	0.000	0.50	--
Net 4-NP (µg/70 kg weight)	0.000	6.50	--
Adjusted Net 4-NP (ug/ 70 kg weight)	0.000	34.88	--
Creatinine (g/24 hr)	1.58	0.36	1.54



**Table 2c. 4-NP Residues in Post Exposure Urine Samples From Both Sites (10 Replicates)**

Parameters	Sampling Interval=0 to 24 hrs		
	Arith. Mean	Std. Dev.	Geo. Mean
Gross 4-NP (µg/L)	42.23	29.74	33.68
Net 4-NP (µg/L)	35.64	32.41	19.22
Gross 4-NP (total µg)	69.01	54.39	51.70
Net 4-NP (total µg)	57.39	59.97	--
Adjusted Net 4-NP (total ug)	383.45	409.11	--
Gross 4-NP (µg/kg weight)	0.79	0.57	0.61
Net 4-NP (µg/kg weight)	0.65	0.65	--
Adjusted Net 4-NP (ug/kg weight)	4.29	4.39	--
Net 4-NP (µg/70 kg weight)	45.19	45.34	--
Adjusted Net 4-NP (ug/70 kg weight)	300.40	307.03	--
Creatinine (g/24 hr)	1.92	0.71	1.81
	Sampling Interval=24-48 hrs		
	Arith. Mean	Std. Dev.	Geo. Mean
Gross 4-NP (µg/L)	7.85	4.93	6.75
Net 4-NP (µg/L)	1.25	7.20	--
Gross 4-NP (total µg)	16.79	7.26	15.33
Net 4-NP (total µg)	5.18	10.44	--
Adjusted Net 4-NP (total ug)	39.52	70.70	--
Gross 4-NP (µg/kg weight)	0.20	0.07	0.18
Net 4-NP (µg/kg weight)	0.06	0.11	--
Adjusted Net 4-NP (ug/kg weight)	0.43	0.77	--
Net 4-NP (µg/70 kg weight)	3.90	8.05	--
Adjusted Net 4-NP (ug/ 70 kg weight)	30.05	53.81	--
Creatinine (g/24 hr)	1.86	0.55	1.76
	Sampling Interval=48-72 hrs		
	Arith. Mean	Std. Dev.	Geo. Mean
Gross 4-NP (µg/L)	5.94	4.08	4.45
Net 4-NP (µg/L)	0.000	5.63	--
Gross 4-NP (total µg)	10.67	5.49	8.93
Net 4-NP (total µg)	0.000	7.99	--
Adjusted Net 4-NP (total ug)	0.000	47.31	--
Gross 4-NP (µg/kg weight)	0.12	0.06	0.11
Net 4-NP (µg/kg weight)	0.000	0.10	--
Adjusted Net 4-NP (ug/kg weight)	0.000	0.55	--
Net 4-NP (µg/70 kg weight)	0.000	6.84	--
Adjusted Net 4-NP (ug/ 70 kg weight)	0.000	38.65	--
Creatinine (g/24 hr)	1.73	0.68	1.61
	Sampling Interval=72-96 hrs		
	Arith. Mean	Std. Dev.	Geo. Mean
Gross 4-NP (µg/L)	7.88	5.68	6.14
Net 4-NP (µg/L)	0.50	8.68	--
Gross 4-NP (total µg)	10.27	6.53	--
Net 4-NP (total µg)	0.000	12.09	--
Adjusted Net 4-NP (total ug)	0.000	69.44	--
Gross 4-NP (µg/kg weight)	0.12	0.08	--
Net 4-NP (µg/kg weight)	0.000	0.14	--
Adjusted Net 4-NP (ug/kg weight)	0.000	0.78	--
Net 4-NP (µg/70 kg weight)	0.000	9.72	--
Adjusted Net 4-NP (ug/ 70 kg weight)	0.000	54.84	--
Creatinine (g/24 hr)	2.07	0.71	1.96

**Notes for Tables 2a-c:**

Sample results were corrected for 75% field fortification recovery in Arkansas and 73.2% field fortification recovery for Louisiana.

Arith. Mean = Arithmetic Mean (average)    Geo. Mean = Geometric Mean

Std. Dev. = Standard Deviation

Gross 4-NP = Total 4-NP found in sample

Net 4-NP = Gross 4-NP - (Average 4-NP found in samples collected at two days and one day prior to exposure)

Adjusted Net 4-NP = (Net 4-NP ÷ total time exposed) x 8 hours

Note: If the calculation of a net 4-NP value resulted in a negative number, then the result is expressed as 0.000.

The geometric mean is shown as (--) if a zero was a data point in the calculation. Calculations by EXCEL 97 spreadsheet software.

**Guideline Compliance Review**

Compliance with US-EPA-OPPTS's Series 875 - Occupational and Residential Exposure Test Guidelines is critical. The following listing summarizes the major relevant requirements found in OPPTS Series 875 Part A: 875.1500, Biological Monitoring - Handler.

**Guideline 875.1500**

- *Investigators should submit protocols for review purposes prior to the inception of the study. Adequate pharmacokinetic data must exist to effectively interpret the data. This criterion was met.*
- *Expected deviations from GLPs should be presented concurrently with any protocol deviations and their potential study impacts. This criterion was met.*
- *The test substance should be a typical end use product of the active ingredient. This criterion was met.*
- *The application rate used in this study should be provided and should be the maximum rate specified on the label. However, monitoring following application at a typical application rate may be more appropriate in certain cases. This criterion was met.*
- *Selected sites and seasonal timing of monitoring should be appropriate to the activity. This criterion was met.*
- *A sufficient number of replicates should be generated to address the exposure issues associated with the population of interest. Specifically, each study should include a minimum of 15 individuals (replicates) per activity. This criterion was met as this study is a follow-up study to a previously submitted study (MRID # 453271-01). In this study there were 10 individuals (replicates)*
- *Test subjects should be regular workers, volunteers trained in the work activities required, or typical homeowners. This criterion was met. The volunteers who participated in this study either had previous experience or were given training on site.*

- *The monitored activity should be representative of a typical working day for the specific task in order to capture all related exposure activities. This criterion was met.*
- *The exposure monitoring period must be of sufficient length to ensure reasonable detectability of residues in biological media (e.g., blood and urine) consistent with pharmacokinetic data such as excretion profile, duration time, etc. It is uncertain whether this criterion was met. The duration of the mixing loading period ranged from 39 minutes to 100 minutes.*
- *Biomonitoring should be conducted using methodologies based on the pharmacokinetic properties of the pesticide (parent compound and its metabolites) of concern (e.g., need validated pharmacokinetic models from humans or appropriate animal surrogate and appropriate route of exposure). This criterion was met. The Registrant reported that justification for their approach was submitted in a separate white paper (MRID 44974401, submitted 11/18/1999) which demonstrates the effectiveness of biomonitoring for 4-NP to determine directly whole-body exposure to methyl parathion.*
- *The quantity of active ingredient handled and the duration of the monitoring period should be reported for each replicate. This criterion was met.*
- *Any protective clothing worn by the study participants should be identified and should be consistent with the product label. This criterion was met.*
- *If urine monitoring is being conducted, urine samples should be collected one or two days before participating in the applicator exposure monitoring activities and should continue on the day of exposure and for an appropriate time period after these activities have been completed, depending on the excretion kinetics of the compound. The 24-hour sample collection cycle should begin with the first void after beginning work activities and end with the first void on the following morning, continuing this 24-hour cycle on subsequent days. These criteria were met. Baseline 24-hour urine samples were collected each day beginning 48 hours before the exposure event, and for 96 hours after the exposure began. Kinetics observed in the field data indicated a rapid drop-off of 4-nitrophenol concentrations within this time period.*
- *Materials used for sample collection should not interfere with (e.g., absorb) the analytes of interest. This criterion was met. Samples were collected in three-liter Urisafe containers.*
- *Creatinine levels should be determined as a way of qualitatively monitoring completeness of urine collection samples. Specific gravity, as another measure of 24-hour sample completeness, should be performed as soon after collection as possible (and before sample storage). This criterion was partially met. Creatinine levels were determined; however, the specific gravity of the samples were not reported.*

- Prior exposures to the test pesticide or structurally related compounds may interfere with study results. A brief history should be taken from each participant in relation to known prior exposures to pesticides for at least 2 weeks, including reentry into potentially treated fields. For urine monitoring, there should also be a sufficient time period between such exposures and participation in the study to ensure adequate urinary clearance of the compound and its metabolites, based on pharmacokinetic data. This criterion was not met. No formal discussion of activities performed by subjects within the last two weeks prior to biomonitoring was provided in the report or in the protocol. The test subjects were prescreened one to two weeks prior to exposure monitoring. However, baseline 4-NP levels at the Louisiana site were higher than the first day of exposure.*
- Validated analytical methods for the biological analyte (parent compound and its metabolites) of sufficient sensitivity are needed. Information on method efficiency and limit of quantitation (LOQ) should be provided. This criterion was met.*
- Samples should be stored in a manner that will minimize deterioration and loss of analytes between collection and analysis. Biological monitoring samples (e.g., serum, plasma, and urine) should be refrigerated or stored frozen prior to analysis. Whole blood should not be frozen. Information on storage stability should be provided. This criterion was met.*
- Data should be corrected if any appropriate field fortified, laboratory fortified or storage stability recovery is less than 90%. This criterion was not met. Although the field fortification recoveries for both sites were less than 90%, data were not corrected. Rather the Registrant corrected field fortified recovery values with concurrent laboratory control data to reach an average recovery of 100%.*
- Unless stability of the analyte has been established prior to initiation of the study, three samples of control (nonparticipant) should be fortified with two levels of the biological analyte (parent or metabolite (s), whichever is appropriate) for each experimental site. This criterion was probably not met. The storage stability results presented in this Study Report (31 days from Study No. KP-2000-02, MRID 45204701) support the period of frozen storage pertinent to this study with the exception of 13 exposure samples from Louisiana which were stored frozen for 48 days prior to analysis. The Registrant concluded that since analysis of field fortified samples (stored frozen for 73 days prior to analysis) produced acceptable results (73%), that 4-NP residues are stable in frozen urine for up to 48 days. However, this result is below the acceptable recovery of 90% and does not indicate that 4-NP residues are stable in frozen urine for the period of frozen storage pertinent to this study.*

- *Each subject's absorbed dose should be expressed in terms of body weight using his/her own measured value, and as a cumulative total for each exposure period. The arithmetic mean, range, standard deviation, and coefficient of variation should be calculated from the results of all individuals. Geometric mean, range and standard deviation may be calculated if the results are shown to be log-normally distributed. Other distributional data should be reported, to the extent possible (e.g., percentiles). This criterion was met.*

Other identified issues:

- Tank mix samples were not collected or analyzed.
- The specific gravity of the samples were not reported.
- The only meteorological information presented was the temperature and percent relative humidity for the day of mixing/loading. The source of these weather data was not reported.
- A brief history from each participant in relation to known prior exposures to pesticides for at least 2 weeks was not provided. It is only reported that test subjects were prescreened one to two weeks prior to exposure monitoring.