



Department of Pesticide Regulation



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Director

MEMORANDUM

Arnold Schwarzenegger
Governor

TO: Denise Webster **HSM-03024**
Senior Pesticide Use Specialist
Pesticide Registration Branch

VIA: Joseph P. Frank, D.Sc.
Senior Toxicologist
Worker Health and Safety

FROM: Thomas Thongsinthusak, Ph.D. *[original signed by T. Thongsinthusak]*
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DATE: December 19, 2003

SUBJECT: BRAND NAME: N/A
ACTIVE INGREDIENT: Methyl parathion
COMPANY NAME: Cheminova A/S
TRACKING I.D. NUMBER: SBRA 193157 E
RECORD NUMBER (RN): 185856
DATA PACKAGE NUMBER (DPN): 121-149
EPA REGISTRATION NUMBER: 4581
TITLE: A STUDY TO DETERMINE THE URINARY ELIMINATION OF
PARA-NITROPHENOL AND ITS CONJUGATES FOLLOWING
DERMAL EXPOSURE OF RATS TO METHYL PARATHION

WIL Research Laboratories, Inc. (Ashland, Ohio) conducted a dermal absorption study of methyl parathion in male rats. This study was initiated on February 13, 2001. Sample analyses were completed on June 21, 2001. The study was performed in compliance with the U.S. EPA FIFRA Good Laboratory Practice Standards (40 CFR Part 160). The submitted study indicated that it was unknown whether the characterization analyses of methyl parathion, p-nitrophenyl sulfate potassium salt, and p-nitrophenyl beta-D-glucuronide reference standard were conducted in compliance with the Good Laboratory Practice Standards by the sponsors (Griffin, L.L.C., Cheminova A/S, and Cerexagri, Inc.). This memorandum contains a summary of the study and determination of dermal absorption of methyl parathion.

A. Preparation of Animals

Male Sprague-Dawley[®] rats (CrI:CD (SD)IGS BR) obtained from Charles River Laboratories were used in this study. The animals were approximately nine weeks old and the weights ranged from 242 to 269 grams. After receiving, animals were quarantined acclimatized for about one week. Five animals were randomly allocated to each of the two dose groups using a computer program. Food and water was available ad libitum during the course of the study. All animals were housed individually in suspended wire-mesh cages in an environmentally controlled room



with at least 10 fresh air changes per hour. The room conditions were: 12-hour light/dark cycle, temperature ranged from 69 °F to 75 °F, and relative humidity ranged from 22% to 48%.

On the day prior to dosing, the anterior dorsal hair from the shoulders to the rump and halfway down each side was removed from each animal using a small electric animal clipper. At least 24 hours prior to dose application, the shaved area was wiped with acetone to remove oily secretions. A small linked jeweler's chain was attached to the rear legs of each animal to prevent the animal from scratching the application area. The application site was surrounded by a piece of Stomahesive[®] (ConvaTec, Princeton, NJ) with a circular opening of 36 mm in diameter that was secured into place with Skin-Bond[®] cement (Smith & Nephew United, Inc., Largo, FL). Two "O"-rings (36 mm ID x 5 mm ht.) were glued together with cyanoacrylate cement and glued on top of the Stomahesive[®] with Skin-Bond[®].

B. Preparation and Administration of the Doses

The test substance, Methyl[Ring-U-¹⁴C]parathion was obtained from ChemSyn Science Laboratories (Lenexa, KS). The dosing formulations were prepared by diluting the [¹⁴C]-methyl parathion in acetone to achieve concentrations of 2.5 mg/20 mL for low dose (actual dose was 1.03 µg/cm²) and 2.5 mg/2 mL for high dose (actual dose was 11.6 µg/cm²). The radiopurity of the dosing formulations were assessed on the day of preparation and after use by employing radio-high performance liquid chromatography. The purity of the dosing formulations averaged 98.5% for the low dose and 98.1% for the high dose. Only minor (≤1%) impurities were evident in any of the chromatograms.

The dosing formulations were applied to the shaved skin (10 cm²) inside the "O"-rings using a 100-µL positive displacement pipet with a glass capillary tip. The dose was spread evenly over the entire application site using the pipet tip. The pipet tip was then washed internally and externally with 15 mL of acetone. A matrix animal was prepared in the same manner as treated animals but not dosed. Housing and collection of urine and feces were the same as treated animals. Following application of the dose, an occlusive, circular-cut piece of X-ray film was glued on top of the "O"-rings to enclose the dose site. The animal was then placed into a plastic metabolism unit. The plastic metabolism unit was designed for separate collection of urine and feces.

C. Sample Collection and Analysis

At 10 hours after dose administration, the dose site was washed four times: twice with gauze soaked in dilute detergent (Dove Dishwashing Detergent:deionized water, 1:50) and twice with gauze soaked in deionized water. After washing, the animals were returned to their metabolism units where they were held for post-exposure urine and feces collections. Urine and feces were collected separately for each animal. For all animals, a collection of urine and feces was made during the course of exposure (0-10 hours post-dosing) and at the following intervals: 10-24, 24-

48, 48-72, and 72-96 hours post-dosing. Before animals were sacrificed, they were euthanized by asphyxiation with carbon dioxide. Samples collected for analysis were: water wash, soap wash, the treated skin, the skin underneath the Stomahesive[®], carcass, metabolism cage washes, urine, and feces. All samples were analyzed for total ¹⁴C radioactivity using liquid scintillation techniques.

D. Results/Summary

The mean recoveries of radioactivity as percent of the administered doses were 92.1% and 86.1% for the low and high dose groups, respectively (Table 1). The treated-skin residue is considered absorbed unless bioavailability of the residue can be determined using the exponential saturation model (Thongsinthusak, *et al.*, 1999). For this study, the average skin residue is low (3.7% for the low dose and 4.0% for the high dose) compared to the excreted dose (83.6% for the low dose and 79.1% for the high dose). The estimated dermal absorption was calculated as the percentage of dose found in the treated and adjacent skin, urine, feces, carcass, and cage wash. The adjusted average dermal absorption values were 96% for the low dose and 95% for the high dose (Table 1).

E. Recommendation

It is recommended that an interim dermal absorption value of 96% for the low dose be used in exposure assessment of methyl parathion. The registrant is encouraged to conduct a dermal absorption study in rats or non-human primates by following the test system suggested by the U.S. EPA (Zendzian, 1994) or other published articles (Thongsinthusak *et al.*, 1999; Felmann and Maibach, 1974; Wester and Maibach, 1985). It is recommended that a study protocol be submitted to the Department of Pesticide Regulation for peer review prior to conduct of the study.

References:

- Feldmann, R. J., and Maibach, H. I. 1974. Percutaneous penetration of some pesticides and herbicides in man. *Toxicol. Appl. Pharmacol.* 28:126-132.
- Thongsinthusak, T., Ross, J. H., Saiz, S. G., and Krieger, R. I. 1999. Estimation of dermal absorption using the exponential saturation model. *Regul. 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.
- 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: Tareq Formoli (WH&S)
Svetlana E. Koshlukova, Ph.D. (MT)
Roger Cochran, Ph.D. (MT)

Table 1. Distribution of Methyl Parathion Equivalentents (as Percent of Administered Dose) in Male Rats Following a 10-Hour Dermal Exposure to Methyl Parathion

Animal No.	Soap Wash	Water Wash	Treated Skin	Adjacent Skin	Cage Wash	Urine	Feces	Carcass	Total Recovery	Dermal Absorption ^a	Dermal Absorption (Adjusted) ^b
<u>Low dose group (Actual dose 1.03 µg/cm²)</u>											
61114	1.06	1.04	1.00	0.81	0.39	89.97	1.13	0.88	96.3	94.2	98
61118	2.90	1.68	2.52	1.48	0.42	84.72	1.03	1.08	95.8	91.3	95
61119	2.02	1.14	1.64	2.22	0.23	71.78	1.92	0.49	81.4	78.3	96
61120	1.77	1.14	1.01	3.35	0.41	86.88	1.20	0.89	96.6	93.7	97
61127	4.50	2.73	2.16	2.32	0.67	75.59	1.54	0.74	90.3	83.0	92
Mean	2.45	1.54	1.66	2.04	0.43	81.79	1.36	0.82	92.1	88.1	96
SD	1.32	0.71	0.68	0.96	0.16	7.75	0.37	0.22	6.5	7.1	2
<u>High dose group (Actual dose 11.6 µg/cm²)</u>											
61121	3.55	2.02	2.68	1.73	0.68	72.34	0.63	0.31	83.9	78.4	93
61122	3.80	2.08	2.02	0.41	0.25	77.62	0.63	0.35	87.2	81.3	93
61123	2.58	1.65	2.84	0.15	0.39	77.31	0.68	0.25	85.8	81.6	95
61125	2.73	1.23	3.03	2.89	0.36	79.28	0.82	0.40	90.7	86.8	96
61128	2.62	1.15	2.53	1.94	0.45	83.22	0.73	0.19	92.8	89.1	96
Mean	3.06	1.63	2.62	1.42	0.42	77.96	0.70	0.30	88.1	83.4	95
SD	0.57	0.43	0.38	1.14	0.16	3.92	0.08	0.08	3.6	4.4	1

^a Sum of the percentage of the administered dose found in the treated and adjacent skin, cage wash, urine, feces, and carcass.

^b Adjusted for % total recovery (observed % dermal absorption x 100/% total recovery).