



# Department of Pesticide Regulation



Paul Helliker  
Director

## MEMORANDUM

Arnold Schwarzenegger  
Governor

TO: Joseph P. Frank, D.Sc.  
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HSM-03025

FROM: Thomas Thongsinthusak, Ph.D.  
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*[original signed by T. Thongsinthusak]*

DATE: December 19, 2003

SUBJECT: DETERMINATION OF DERMAL ABSORPTION OF METHYL PARATHION

You asked me to review dermal absorption studies of methyl parathion and provide a recommended dermal absorption value. In the past, Tareq Formoli used a dermal absorption value of 14% to determine absorbed doses in his exposure assessment document (Formoli, 2000). This dermal absorption was based on an *in vitro* dermal absorption study and an *in vivo* study with the surrogate ethyl parathion. The United States Environmental Protection Agency used a default dermal absorption value of 100% (U.S. EPA, 1999). Cheminova Agro A/S disagreed with the U.S. EPA of using the dermal absorption of 100% and suggested that the dermal absorption should be in the range of 10% to 25% (Cheminova Agro A/S, 1998). However, Cheminova did not provide data to support the suggested dermal absorption.

In order to establish a recommended dermal absorption value for methyl parathion, I reviewed the following four dermal absorption/pharmacokinetic studies of methyl parathion in laboratory rats conducted by Abu-Qare and Abou-Donia (2000), Abu-Qare, *et al.* (2000), Sved (2001), and Kramer, *et al.* (2002). The suggested dermal absorption ranges from some of these studies were significantly greater than what Tareq Formoli used in his exposure assessment document.

The followings are brief descriptions of the four studies, including the test system (animals, dose levels, preparation of dosing formulations, exposure and sacrifice times), caveats of each study, results, conclusion, and recommendation.

1. Abu-Qare, A. W., and Abou-Donia, M. B. 2000. Urinary excretion of metabolites following a single dermal dose of [<sup>14</sup>C]-methyl parathion in pregnant rats. *Toxicology* 150:119-127.
2. Abu-Qare, A. W., Abdel-Rahman, A. A., Kishk, A. M., and Abou-Donia, M. B. 2000. Placental transfer and pharmacokinetics of a single dermal dose of [<sup>14</sup>C]-methyl parathion in rats. *Tox. Sci.* 53:5-12.

These two published articles reported results from the same group of animals in one study. Pregnant Sprague-Dawley rats (body weight 240-350 grams), at 14-18 days of gestation, were used in the study. Uniformly phenyl-labeled [<sup>14</sup>C]-methyl parathion was prepared in acetone for dosing. A single dose of 10 mg/kg in 0.1 mL acetone was applied with a micropipette to an unprotected 1-cm<sup>2</sup> area of pre-clipped skin on the back of animal's neck. The dose was



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equivalent approximately to  $3 \text{ mg/cm}^2$ . Eight groups of three rats each were killed at time intervals of 1, 2, 4, 12, 24, 48, 72, and 96 hours.

This study was not specifically designed for a dermal absorption study according to requirements in the U.S. EPA's guideline (Zendzian, 1994) or that recommended by the Worker Health and Safety Branch (Thongsinthusak, *et al.*, 1993). The main objectives of this study were to determine urinary excretion of metabolites, placental transfer, and pharmacokinetics of methyl parathion. There was no clear indication of dermal absorption based on 8 to 10 hours of exposure as we typically used. Of the total  $^{14}\text{C}$  urinary excretion, 14, 30, 50, and 90% of the administered dose were recovered in urine at 1, 4, 24, and 96 hours post-administration of the dose. Only about 3% of the administered dose was detected in the feces.

Since the treated skin was not washed at 8 or 10 hours post-administration of the dose, it is not possible to determine the total excretion for the 8 or 10-hour exposure time. Typically, after the treated skin was washed off the animals must be kept until excretion of the dose is minimal. Results of tissue residues in this study do not facilitate calculation of absorbed dose.

Conclusion: This study could not be used to estimate dermal absorption due to the following reasons: 1) The dermal dose of  $3 \text{ mg/cm}^2$  was very high compared to the recommended dermal doses (Zendzian, 1994, Thongsinthusak, *et al.*, 1993). Normalized exposure levels should be in the range of 1 to  $100 \text{ }\mu\text{g/cm}^2$ ; 2) The dosing solution should be prepared in a commercial formulation of methyl parathion and diluted in water. Acetone may facilitate absorption of methyl parathion into the rat skin because acetone is oil or lipid soluble (The Merck Index, 1996). These two studies are not acceptable for use in determining dermal absorption.

3. Sved, D. W. 2001. A study to determine the urinary elimination of para-nitrophenol and its conjugates following dermal exposure of rats to methyl parathion. Data Package Number 121-149, Record Number 185856. Department of Pesticide Regulation, Sacramento.

This study was conducted to determine dermal absorption of methyl parathion in male Sprague-Dawley<sup>®</sup> rats. The report of this study was submitted to the Department of Pesticide Regulation and was reviewed by Thongsinthusak (2003). The animals were about nine weeks old and the body weights ranged from 242 to 269 grams. In brief, methyl[Ring- $^{14}\text{C}$ ]parathion was prepared in acetone for dosing at  $1.03 \text{ }\mu\text{g/cm}^2$  (actual low dose) and  $11.6 \text{ }\mu\text{g/cm}^2$  (actual high dose). The dosing solution was applied to the skin inside the "O"-ring. The treated skin site was covered with an occlusive, circular-cut piece of X-ray film glued to the O-ring. Five animals were used for each dose. At 10 hours after dosing, 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. The animals were sacrificed at the end of 96 hours

post-dosing. The mean dermal absorption values (adjusted to reflect 100% recovery) were 96% for the low dose and 95% for the high dose.

Conclusion: This study used appropriate dose levels of 1.03 and 11.6  $\mu\text{g}/\text{cm}^2$ . However, the dosing formulations were prepared from [ $^{14}\text{C}$ ]-methyl parathion in acetone. The U.S. EPA guidelines recommend preparing the test substance in a commercial formulation and diluted in water (Zendzian, 1994). Water is recommended because it is typically used as a solvent to dilute pesticides before application to crops. Some vehicles can change the integrity of the skin and thus influence absorption (Wester and Maibach, 1983). Acetone is oil and lipid soluble (The Merck Index, 1996). Acetone might influence absorption of methyl parathion into the rat skin. The protective cover must allow air circulation over the application site to allow normal evaporation of surface water from the skin (Zendzian, 1994). A filter paper or gauze should be used instead of an X-ray film, which is an impermeable barrier to evaporation of surface water from the skin. The dermal absorption of 96% from the low dose was recommended as an interim dermal absorption value for exposure assessment (Thongsinthusak, 2003).

4. Kramer, R. E., Wellman, S. E., Rockhold, R. W., and Baker, R. C. 2002. Pharmacokinetics of methyl parathion: A comparison following single intravenous, oral or dermal administration. *J. Biomed. Sci.* 9:311-320.

This study was conducted to obtain results on pharmacokinetic parameters for methyl parathion after intravenous injection and to apply a described model to an examination of its pharmacokinetics after a single oral or dermal administration. However, the dermal absorption could be approximated from the results of the study. In brief, 50-65-day old female rats with body weights ranged from 190 to 250 grams were used in the study. Methyl parathion was prepared in ethanol for the dermal doses of 6.25, 12.5, and 25 mg/kg. The dose was applied to a clipped area of 2-2.5  $\text{cm}^2$  on the nape of the neck. The administered doses are equivalent approximately to 0.625, 1.25, and 2.5  $\text{mg}/\text{cm}^2$ . The treated skin was not washed after dosing. Blood was withdrawn before and then 2, 4, 6, 12, 26, 50, 74, 98, and 122 hours after administration.

The fraction of methyl parathion absorbed following a single dermal dose was determined by a comparison of the area under the curve for the dermal and intravenous concentration-time curve after correction for the amount (in mg) of administered methyl parathion. This method is similar to that used by Feldmann and Maibach (1974) or Wester and Maibach (1985) where dermal absorption in non-human primates or human subjects was determined from the ratio of % dose recovered in excreta after dermal application and intravenous injection. In this study, dermal absorption values of methyl parathion were reported to be 39, 61, and 48% for the dermal doses of 0.625, 1.25, and 2.5  $\text{mg}/\text{cm}^2$ , respectively. Since the dermal absorption values were not in a specific pattern of absorption, an average dermal absorption value of 49% was calculated.

Conclusion: Dermal dose levels are much higher than those experienced by agricultural workers or those recommended by the U.S. EPA guidelines (Zendzian, 1994) or by the Worker Health and Safety Branch (Thongsinthusak, *et al.*, 1993). In this study, the dosing solution of methyl parathion was not prepared in a commercial formulation and diluted in water. This is in contrast to the recommendation provided in the aforementioned guidelines. As such, this study was not acceptable for determining dermal absorption for use in exposure assessment.

5. *In vitro* absorption studies.

Currently, the Worker Health and Safety Branch, Department of Pesticide Regulation does not accept *in vitro* dermal absorption for use in exposure assessment. One of the reasons is that *in vitro* dermal absorption has not been fully validated if it can be used as a replacement of *in vivo* dermal absorption.

Recommendation: Absent of an appropriate dermal absorption study, an interim dermal absorption value of 96% obtained from a study conducted by Sved (2001) be used in exposure assessment. A dermal absorption study in rats or non-human primates should be conducted following the U.S. EPA guidelines (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.

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