

M e m o r a n d u m

[HSM no. assigned after original issuance of memo]

**to:** Malcom Black, Registration Specialist  
Pesticide Registration Branch

**Date:** August 2, 1991

**Place:** Sacramento

**via:** Robert I. Krieger, Chief/Supervising Toxicologist  
Worker Health and Safety Branch

5 - 8474

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

**Subject:** Determination of Dermal Absorption of Chlorpyrifos in Humans

BACKGROUND INFORMATION

The Dow Chemical Company submitted data for dermal absorption of chlorpyrifos in human volunteers (Nolan et al., 1982). Percent dermal absorption may not be reliably determined from these data because of the high dermal doses used (0.39 and 4.2 mg/cm<sup>2</sup>). In order to compensate for this discrepancy, dermal absorption of chlorpyrifos was extrapolated from the submitted data and unpublished studies (Krieger, et al., 1991).

Dermal doses and the corresponding percent administered dose (AD) excreted in urine (Table 1) were used to plot the excretion curve (Figure 1).

Table 1. Percent of administered dose excreted in urine following dermal application.

Dermal dose (mg/cm <sup>2</sup> )	Total dermal dose (mmoles)	Dose excreted (%)	Reference
4.20 (n=5)	1.19	1.02	Nolan, et al., 1982.
3.14 (n=1)	0.54	0.20*	Krieger, et al., 1991.
2.99 (n=1)	0.85	0.50*	Krieger, et al., 1991.
0.39 (n=1)	0.11	2.60	Nolan, et al., 1982.

$$* \%Dose\ excreted = \frac{\text{Moles of 3,5,6-TCP or DAPs}}{\text{Moles of chlorpyrifos}} \times 100$$

RESULTS

Percent of administered doses excreted for lower dermal doses (e.g. 3, 10, 32, 100, and 316 ug/cm<sup>2</sup>) was determined from the graph (Figure 1) and shown in Table 2. Percent dermal absorption for each dose level was subsequently determined by the equation listed below (Feldmann and Maibach, 1974). This equation was used under the assumption that percent of dose excreted (70%) after an oral dose (po) was similar to that of intravenous dose (IV). Percent dermal absorption for various dose levels are presented in Table 2.

*[Handwritten signature]*

$$\% \text{ Dermal absorption} = \frac{\% \text{ AD excreted in urine (Dermal)}}{\% \text{ AD excreted in urine (po)}} \times 100$$

**Table 2. Extrapolated percent dose excreted and the corresponding percent dermal absorption**

Dermal dose (ug/cm <sup>2</sup> )	% AD excreted	% Dermal absorption
316	3.0	4.3
100	4.3	6.1
32	5.5	7.9
10	6.7	9.6
3	8.0	11.4

#### CONCLUSION

It was determined that dermal doses used in the submitted dermal absorption study (e.g. 390 and 4200 ug/cm<sup>2</sup>) are very high and are unacceptable, especially under EPA dermal absorption study guidelines (Zendzian, 1989). Percent administered dose excreted was higher at the lower doses (2.60% vs. 1.02%). Dermal absorption of lower occupational exposure may be higher than 2.6%.

#### RECOMMENDATIONS

1. Dermal absorption of 9.6% for a dermal dose of 10 ug/cm<sup>2</sup> (Table 2) will be used in the worker exposure estimates. A dermal dose of 10 ug/cm<sup>2</sup> is considered in normal range for dermal absorption study and occupational exposure. Incidentally, dermal absorption of 9.6% is similar to dermal absorption of 9.3% over 20 hours previously determined (Knaak, 1982) (Attachment I).
2. The registrant may elect to do additional low dose dermal absorption studies as suggested in proposed EPA guidelines. The study protocol should be reviewed by the California Department of Pesticide Regulation prior to the study. The results of the new study should be submitted to this Department by January 1992.
3. The registrant may elect not to do a new study according to the suggestion mentioned in (2.) above, but concur with this Department on the extrapolation method described in (1.).
4. We request that a copy of this memo be forwarded to Dow Chemical Company.

#### REFERENCES

- Feldmann, R. J., and Maibach, H. I. 1974. Percutaneous penetration of some pesticides and herbicides in man. *Toxicol. Appl. Pharmacol.* 28:126-132.
- Knaak, J. B. 1982. Review of the paper entitled "Chlorpyrifos: Pharmacokinetics in human volunteers following single oral and dermal doses". Memorandum, California Department of Food and Agriculture. (December 9, 1982).
- Krieger, R. I., Thongsinthusak, T., and Ross, J. H. 1991. Urinary excretion of 3, 5, 6-trichloro-2-pyridinol and dialkylphosphate in humans following dermal doses. Unpublished.
- Nolan, R. J., Rick, D. L., Freshour, N. L., and Saunders, J. H. 1982. Chlorpyrifos: Pharmacokinetics in human volunteers following single oral and dermal doses. The Dow Chemical Company. Midland, Michigan. California Department of Food and Agriculture. *Pesticide Registration Document Number 342-122, record number 948115.*
- Zendzian, R. P. 1989. Skin penetration method suggested for Environmental Protection Agency requirements. *J. Am. Coll. Toxicol.* 8(5):829-835.

cc: John Ross, Ph.D.

Memorandum

Attachment 1

To: Van Cheney, Program Supervisor

Date : December 9. 1982

Place : Sacramento

2-5031

From : Department of Food and Agriculture - J. B. Knaak, Staff Toxicologist

Subject: Review of the paper entitled "Chlorpyrifos: Pharmacokinetics in Human Volunteers Following Single Oral and Dermal Doses".

This study was submitted by Dow Chemical to be used for the purpose of setting reentry times for Chlorpyrifos on Citrus. The dislodgeable residue data was submitted to us at an earlier date. The dislodgeable residue studies were conducted by Dr. Tak Iwata at Riverside.

The company spent considerable time and effort on this study. Chlorpyrifos was topically applied to 100 cm (5.0 mg/kg dose) of skin on the forearm. The dose was washed off after 12-20 hrs. Blood cholinesterase measurements were made after and before the dose was applied.

According to our studies with the rat a dermal dose of a pesticide is absorbed at the rate of approximately 1.0 ug/cm/hr. Using this rate, 1.2 to 2.0 mg of chlorpyrifos would be absorbed in 12 to 24 hrs. This is equivalent to .4 to .6% of the dose. According to Dow, the men absorbed less than 3% of the dose. This is in agreement with our work.

In our rat studies we treat 3 to 7% of the body surface (10 to 30 cm<sup>2</sup>). In the Dow study only 0.5% of the body surface was treated. In order for the human studies to be equivalent to our studies they would have to treat 600 to 1,400 cm<sup>2</sup>. If the same dose, or 300 mg. was spread over a 1,400 cm<sup>2</sup> area (214 ug/cm<sup>2</sup>) and 1.0 ug/cm<sup>3</sup>/hrs was used as the rate, 28 mg or 9.3% of the dose would be absorbed over a 20 hr. period. The 28 mg dose is equivalent to the 30 mg oral dose which produced no ChE depressions. Workers harvesting treated citrus would collect 1 to 2 ug of chlorpyrifos - per cm<sup>2</sup> of skin during the work day or 20 to 40 mg. This dose is equivalent to the oral dose administered to the human volunteers (30 mg). The dermal study along with the dislodgeable residue data indicates that a 48-hour reentry interval (safe level less than 0.5 ug/cm<sup>2</sup>) would be adequate to protect the health of workers.

SURNAME 50-106	<i>JPK</i>					
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Percent of administered dose excreted in urine after dermal doses of chlorpyrifos

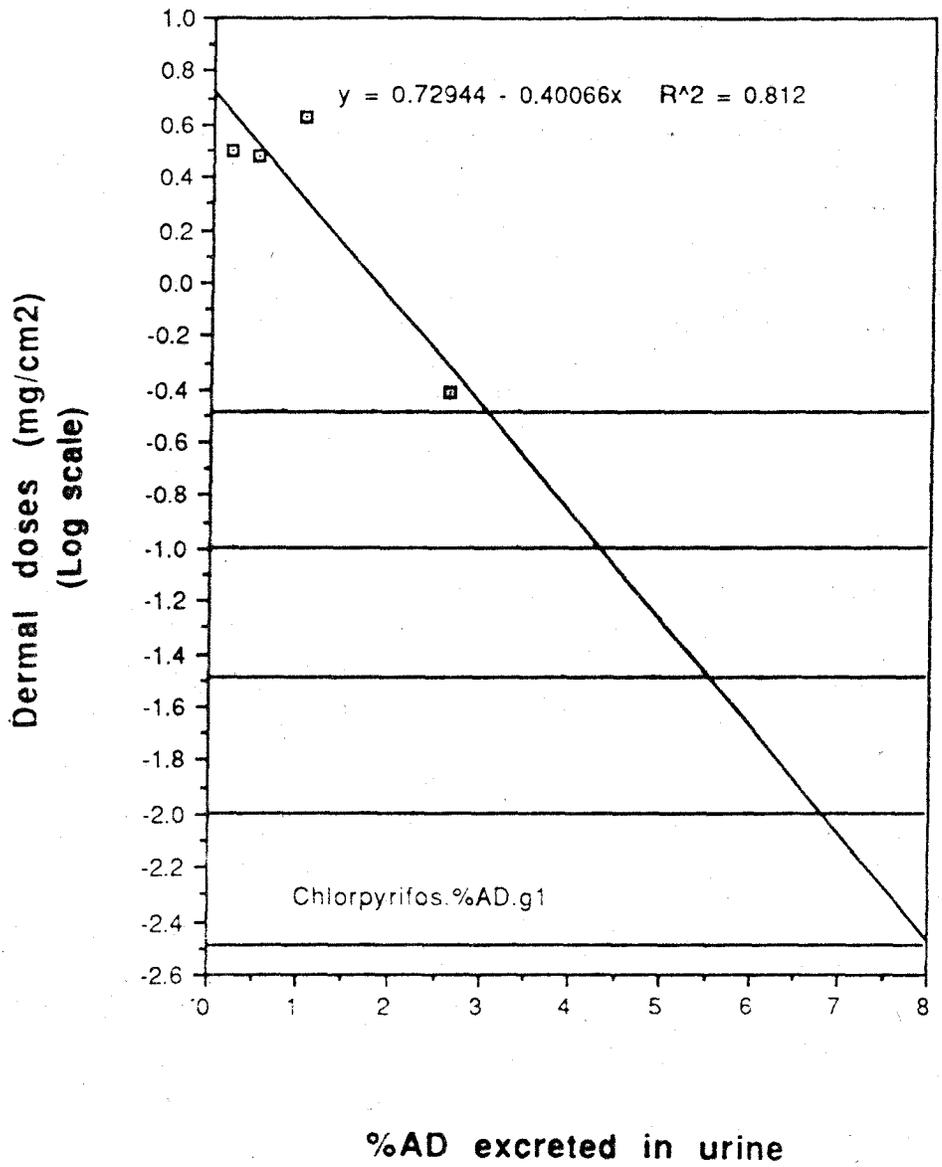


FIGURE I  
EXCRETION CURVE