US EPA ARCHIVE DOCUMENT

US EPA ARCHIVE DOCUMENT

Human Toxicity Studies

D. Single-Dose Dermal Study:

Meuling, J. A.; Ravensberg, L. C.; Roza, L.; *et al.* (2005). Dermal Absorption of Chlorpyrifos in Human Volunteers. Int. Arch Occup. Environ. Health. 78: 44-50.

In a single-dose human dermal toxicity study, chlorpyrifos (CPF) was administered via the skin of six male subjects (age range 20-42 years; weight range 67-81 kg) by spreading approximately 0.5 mL of a dilution of chlorpyrifos (99.2%) in ethanol onto an area of approximately 100 cm^2 of the volar aspect of one forearm of each subject, resulting in approximately 5 mg or 15 mg of chlorpyrifos per subject. The site was not covered. The exposure duration was 4 hours, after which the non-absorbed fraction was washed off (cotton wipes wetted with water) to remove any chlorpyrifos still present on the skin. A sample of urine was taken from each subject prior to exposure, and urine was collected at various intervals after exposure (0-120 hours).

The concentration of the chlorpyrifos metabolite 3,5,6-trichloro-2-pyridinol (TCP) in the urine was determined/monitored throughout the study (0-120 hours). **Cholinesterase measurements were not performed.**

The objective of the study was to assess the dermal absorption of chlorpyrifos in humans *via* urinary excretion of the metabolite 3, 5, 6-trichloro-2-pyridinol (TCP). A relatively large fraction of the applied dose (42%-67%) was washed off following the 4-hour exposure period. Total urinary excretion of TCP 120 hours after exposure was 131.8 µg (5 mg dose) and 115.6 µg (15 mg dose), which shows that a three-fold increase in applied dermal dose to a fixed area (~100 cm^2) of skin did not result in increased absorption. Based on the finding that the clearance of chlorpyrifos was not completed within 120 hours suggests that chlorpyrifos or TCP was retained by the skin and/or accumulated in the body. A mean elimination half-life of 41 hours was established.

Summary of Dosing Regimen for Single-Dose Human Dermal Toxicity Study for Chlorpyrifos

There were a total of 6 male subjects (20-42 years of age; wt range 67-81 kg).

Study Design			
Dose (mg/kg)	**Dose (mg/100 cm^2)**	**Dose (mg/mL)**	**Subjects**
0.067	5	10.8±0.07	3 males
0.199	15	32.39±0.39	3 males

Strengths

- 3 subjects/dose
- 2 dose levels
- 4-hour dermal exposure period
- chlorpyrifos metabolite TCP was monitored in urine for 120 hours post dose

Weaknesses

- not a double-blind study design
- no concurrent control
- only one sex (males)
- cholinesterase activity was not monitored
- blood and urine were not analyzed for chlorpyrifos or chlorpyrifos oxon

Summary of Results

All subjects completed the study, and none displayed any treatment-related signs or symptoms of dermal or systemic toxicity. The mean amount of chlorpyrifos applied was 5.39±0.01 mg and 16.15±0.01 mg, or 0.067 mg/kg and 0.199 mg/kg, respectively.

The percentage of the applied dose washed off following the 4-hour exposure period was 42±12% and 66±16%, respectively (Table 1). The amount of chlorpyrifos recovered in the skin wash was subtracted from the amount applied to the skin, and the result was defined as the "potentially absorbed dose" (PAD) by the body (Table 1). The application of 5 mg or 15 mg to 100 cm^2 skin for 4 hours resulted in a PAD of 3.1 mg or 5.3 mg of chlorpyrifos, respectively. This shows a 3-fold increase in applied dose but only a 1.7-fold increase in PAD. The dose absorbed, calculated from the levels of urinary TCP, was similar for the two dose groups (232 µg and 204 µg, respectively), indicating no increase in absorption at the higher dose level. The authors conclude that the percutaneous penetration rate is constant and not affected by the increase in dermal dose.

The total amount of TCP excreted in the urine was determined through analysis of the urinary concentration of TCP multiplied by the total weighed amount of urine. The cumulative total amount of urinary TCP was calculated to be 131.8±42.7 µg (range: 94.3-178.3 µg) and 115.6±52.8 µg (range: 62.9-168.6 µg) for the low and high doses, respectively. On average, the level of urinary TCP peaked in the 48-72 hour sampling period; thereafter, the excreted amount per 24 hours gradually decreased but was still above background level for the 96-120 hour time interval. The percentage of the applied dose recovered in urine was 4.32±1.4% and 1.23±0.52%, respectively. The elimination half-life of 41 hours (range 39-42 hours) was calculated. The authors conclude that it will take more than 8 days before a complete clearance will be achieved. They also conclude that the calculation of the systemically absorbed dose of chlorpyrifos after dermal application, using the amount of urinary TCP, is bound to lead to underestimation, since the clearance was not completed and no corrections were made for incomplete excretion or metabolism.

US EPA ARCHIVE DOCUMENT

Table1. Results						
Applied dose (mg)	**Amount washed off**		**Cumulative excreted TCP (µg)**	**Calculated equivalent CPF (µg)**	**Absorbed CPF relative to applied dose (%)**	**Potentially absorbed dose (mg) PAD**
	mg	**% applied Dose**				
5 mg/kg						
5.38	1.54	28.6	94.3	166.6	3.10	3.8
5.39	2.56	47.4	123.0	217.3	4.03	2.8
5.39	2.68	49.8	178.3	315.0	5.84	2.7
5.39±0.01	**2.26±0.63**	**42.0±11.6**	**131.8±42.7**	**232.9±75.5**	**4.32±1.39**	**3.1±0.6**
15 mg/kg						
16.15	10.04	62.2	168.6	297.9	1.73	6.1
16.14	12.81	84.6	63.0	111.3	0.69	2.3
16.16	8.66	53.6	115.2	203.5	1.26	7.5
16.15±0.01	**10.5±2.12**	**66.8±16.0**	**115.6±52.8**	**204.2±93.3**	**1.23±0.52**	**5.3±2.7**

Data from Tables 1 and 2, pages 47 and 48 of the report; CPF chlorpyrifos; TCP 3, 5, 6-trichloro-pyridinol

US EPA ARCHIVE DOCUMENT