

DRAFT

Human Toxicity Studies

C. Single-Dose Oral/Dermal Study:

Griffin, P.; Mason, H.; Heywood, K.; *et al.* (1999). Oral and Dermal Absorption of Chlorpyrifos: A Human Volunteer Study. *Occup. Environ. Med.* 56: 10-13.

In a single-dose human oral/dermal toxicity study with analytical grade chlorpyrifos (no MRID), five subjects (4 males and 1 female; age range 26-45 years; weight range 73-92 kg) were dosed orally with 1 mg chlorpyrifos [analytical grade (Promochem); 2852 nmol] applied to a sugar cube. Four weeks after the oral dose, 28.59 mg (81567 nmol) of chlorpyrifos was administered to the skin of the same subjects by spreading 100 µL of a commercial preparation of chlorpyrifos (Dursban 4, Dow Elanco) diluted in water, onto an area of 78 cm² of the inner forearm, which was then covered with a raised impermeable plastic container for 8 hours. The cover was then removed and swabbed, and the skin was washed with water and soap solution. A sample of blood and urine was taken from each subject prior to oral exposure. Blood samples were collected through an indwelling catheter from a vein in the forearm (contralateral arm for dermal phase). A sample of blood and total void volumes of urine were collected every 2 hours after administration for 8 hours, and a blood sample was taken the next day. From day 2 to day 5, total void volumes of urine were collected for 4-hour periods during the day and for an 8-hour period overnight.

Plasma and erythrocyte (RBC) cholinesterase concentrations were determined for each blood sample [METHOD (ChE): Mason, HJ and Lewis PJ. (1989)]. There were no control (placebo) subjects, but pre-exposure values of plasma and RBC cholinesterase activity were obtained for each subject and used for comparison. The concentrations of two urinary metabolites of chlorpyrifos (diethylphosphate and diethylthiophosphate) were determined for each urine sample.

The objectives of the study were to determine the kinetics of elimination of urinary dialkylphosphate metabolites after oral and dermal doses of chlorpyrifos and whether the doses used affected plasma and erythrocyte cholinesterase activity. The report indicated that cholinesterase activity (plasma and RBC) did not fall below 90% of the pre-dose values, with one exception following the dermal exposure (86% of pre-dose value). It is not clear from the report whether the 14% inhibition was for both compartments (no data provided).

The apparent elimination half-life of urinary dialkylphosphates (corrected for creatinine) was reported as 15.5 hours (oral) and 30 hours (dermal). Most of the oral dose (84%; reported at 93%) was recovered as urinary metabolites (range 55%-115%). Only 1% of the applied dermal dose was recovered as urinary metabolites, with about half of the dose (53%) being recovered from the skin surface. It is noted in the report that 46% of the dermal dose was not accounted for as metabolites in urine or as chlorpyrifos in skin washings.

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

There were a total of 5 subjects (4 men/1 woman (26-45 years of age; wt range 73-92 kg). The five subjects were dosed once orally (1 mg) and once dermally (28.59 mg), four weeks after the oral dose.

Study Design			
Route of exposure	Dose (nmol)	Dose (mg/kg)	Subjects
Oral	2852	1 mg (range 0.01-0.014)	4 males, 1 female
Dermal	81567	28.59 mg (range 0.31-0.39)	4 males, 1 female

Strengths

- Administration using two routes of exposure provides comparative information for single dose.
- 5 subjects/route of exposure; both sexes (4 males/1 female)
- Both plasma and RBC cholinesterase activity were monitored within 24 hours of dose.
- Diethylphosphate and diethylthiophosphate metabolites were monitored in urine.

Weaknesses

- not a double-blind study design
- no concurrent control
- only one dose level – no dose-response information for either route of exposure
- only one female subject

Cholinesterase methodology. Mason, HJ and Lewis PJ. (1989). A study of the intra-individual variation in plasma and red cell cholinesterase activity and its application to the detection of organophosphate pesticides. J. Soc. Occup. Med. 39: 121-124 used for cholinesterase assay.

Summary of Results

ORAL – Each subject consumed 2852 nmol chlorpyrifos. Chlorpyrifos was rapidly absorbed, metabolized, and eliminated as shown by the rise to maximum levels of excretion by 7 hours. This was followed by an exponential excretion profile. The maximum rate of excretion was approximately 190 nmol/hour [slightly lower (160 nmol/hour) when corrected for creatinine concentration] after an oral dose of 2852 nmol. The apparent half-lives of elimination were calculated from values corrected for creatinine (**15.5 hours**) and total dialkylphosphate metabolites (**15.8 hours**). Although both sets of data gave similar half-lives, the values corrected for creatinine fitted the one compartment exponential equation (95% confidence interval of the half-life 12.5 to 20.5 hours, $R^2=0.85$) better than the data derived from total metabolite excretion (95% CI for half-life 10.39 to 32.71 hours, $R^2=0.55$). Therefore, the values corrected for creatinine were used to calculate apparent half-lives of elimination and the time of maximum concentration of metabolites in urine. The total amount of metabolites excreted after the oral dose varied from 55% to 115%, with an average of 84% of the oral dose being excreted as dialkylphosphate metabolites.

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Table 1. Oral Dose		
Subject	Total recovered as urinary metabolites (nmol)	% recovered
1	3264	115
2	2460	86
3	2668	94
4	2045	72
5	1567	55
mean	2401±641	84.4±22.6* (93)

*calculated using reported data; (reported mean)

DERMAL – Each subject was exposed to a dose of 81567 nmol in 100 µL of the concentrate-water formulation, which was spread over 78 cm² of skin. The fraction of the total dose recovered in the urine as dialkylphosphate metabolites over the 5-day sampling period was 1% (809 nmol), and 53% (42926 nmol) was recovered from skin washings. The maximum rate of excretion was approximately 16 nmol/hour after a dermal dose of 81567 nmol compared with 10 times this value for the oral dose of 2852 nmol.

The apparent elimination half-life of the urinary dialkylphosphate metabolites for the dermal dose as measured by results corrected for creatinine was **30 hours** after the start of the study (95% CI 25-39 hours, R'²=0.62), assuming a final urinary dialkylphosphate concentration of zero. This assumption is based on the data for the oral exposure in which the final results fell below the detection limit. The apparent elimination half-life of the urinary dialkylphosphate metabolites for the dermal dose as measured by the rate of excretion expressed as nmol/hour was **41 hours** after the start of the study (95% CI 27-88 hours, R'²0.22) assuming a final urinary dialkylphosphate concentration of zero.

Table 2. Oral Dose			
Subject	Total Recovered		Total Recovered (nmol)
	as urinary metabolites (nmol)	from skin washings (nmol)	
1	986 (1.2)	not available	-
2	581 (0.7)	46734 (57.2)	47315 (58.6)
3	1264 (1.5)	43378 (53.2)	44642 (54.7)
4	765 (0.9)	52156 (63.9)	52921 (64.8)
5	449 (0.6)	29435 (36.0)	29884 (36.6)
mean	809 (1.0)	42925 (52.6)	43734 (53.6)

(%)

CHOLINESTERASE (plasma and RBC) – Blood plasma and erythrocyte cholinesterase activity was never less than 90% of the pre-exposure values for either dosing regime.