

DATA EVALUATION RECORD – SUPPLEMENTAL

**CHLORPYRIFOS
NONGUIDELINE
STUDY TYPE: ORAL/DERMAL PHARMACOKINETIC - HUMAN
MRID 00124144**

Prepared for

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Template version 02/06

TXR#: NA

ACC NO. 249203

DATA EVALUATION RECORD - SUPPLEMENTAL

STUDY TYPE: Pharmacokinetic Study, Oral/Dermal; Human
Nonguideline

PC CODE: 059101

DP BARCODE: None

TEST MATERIAL (PURITY): Chlorpyrifos (99.8% a.i.)

SYNONYMS: O,O-diethyl-O-[3,5,6-trichloro-2-pyridyl] phosphorothioate

CITATION: Nolan, R.J., D.L. Rick, N.L. Freshner, and J.H. Saunders (1982). Chlorpyrifos: Pharmacokinetics in human volunteers following single oral and dermal doses. The Dow Chemical Company, Biomedical Medical Research Lab, 607 Building, Toxicology Research Lab, 1803 Building, Midland, MI 48640. Report Number not provided, August 1982. MRID 00124144. Published in Toxicology and Applied Pharmacology 73:8-15, 1984.

SPONSOR: The Dow Chemical Company, Midland, MI

EXECUTIVE SUMMARY:

In a single-dose human oral/dermal toxicity study with chlorpyrifos (1982, MRID 00124144), six male volunteers were given 0.5 mg/kg chlorpyrifos (99.8% a.i., Lot No. AGR 166043) on a lactose tablet. Plasma and RBC cholinesterase activity were monitored at 2, 6, 12, 24 hours, and 2, 3, 4, 8, 14, 22, 27, and 30 days post-dose. Approximately four weeks after the oral treatment, a single dermal dose (5 mg/kg to five subjects; 0.5 mg/kg to one subject) was administered on the volar surface of the forearm. RBC and plasma cholinesterase activity were determined 2, 6, and 12 hours and on days 1, 2, 3, 4, 6, 8, and 9 following dermal treatment. Blood and urine samples were analyzed for chlorpyrifos and 3,5,6-TCP (3,5,6-trichloro-2-pyridinol) concentrations.

No clinical signs of toxicity and essentially no significant inhibition of RBC cholinesterase activity were observed following either the oral or dermal dose. Plasma cholinesterase activity was inhibited 83-89% relative to pre-dose activities following the oral dose (peak inhibition within 6-24 hours post dose) but was essentially unchanged following the dermal dose. Blood chlorpyrifos concentrations were low (<30 ng/mL; limit of detection 5 ng/mL), and chlorpyrifos was not found in the urine following either route of exposure. 3,5,6-TCP blood concentrations peaked by six hours after oral exposure and 24 hours after dermal application. 3,5,6-TCP was cleared from the blood and eliminated in the urine with a half-life of 27 hours following both the oral and dermal doses. Using assumptions of first-order absorption and elimination equations, it was estimated that $72 \pm 11\%$ of the ingested dose and $0.95 \pm 0.559\%$ of the dermal dose were absorbed.

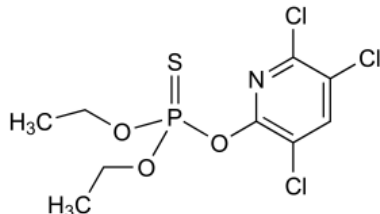
Classification: This studied is classified as *Reserved*.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were not provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. **Test material:** Chlorpyrifos
Description: Not described
Lot/batch #: AGR 166043
Purity: 99.8% a.i. (as stated)
Compound stability: Not reported
CAS # 2921-88-2
Structure:



2. **Vehicle:** Methylene chloride for dissolving chlorpyrifos for placement on a 0.5 gm lactose tablet. DOWANOL DPM (dipropylene glycol methyl ether (DPGME)) was used as vehicle to apply the dermal dose.

3. **Human Subjects:**

- Number:** Six
Race: Caucasian
Sex: Male
Age: 27-50 years
Weight: 71.7-101.1 kg (mean 83.3 ± 10.3 kg)
Source: Volunteers
Instructions: Each volunteer was briefed on the study and asked to provide written consent. None were on oral medication and all were asked to refrain from any drugs including aspirin and alcohol 24 hours before and after each dose.

B. STUDY DESIGN:

1. **Study dates:** Not reported
2. **Study subjects:** Six male volunteers, ages 27-50 years, were included in the study. Subject A served as a "pilot" and was given a single oral dose (0.5 chlorpyrifos mg/kg dissolved in food grade methylene chloride placed on a lactose tablet) of the test material approximately one month before the other participants. Four weeks later, Subject A also received a single (0.5 chlorpyrifos mg/kg) dermal dose (dissolved in methylene chloride). Two weeks after the first dermal dose, Subject A was given a second dermal dose (0.5 chlorpyrifos mg/kg dissolved in DPGME).

The main study consisted of two phases. Five subjects (B – F) were dosed once orally (0.5 chlorpyrifos mg/kg dissolved in food grade methylene chloride and placed on a lactose tablet) and once dermally (5 mg/kg chlorpyrifos in DPGME), thirty days after the oral dose.

Exposure route	Subject A (n=1)	Subjects B-F (n=5)
Oral	0.5 mg/kg	0.5 mg/kg
Dermal	0.5 mg/kg	-
Dermal	0.5 mg/kg	-
Dermal	-	5.0 mg/kg

3. **Dose selection rationale:** Information on the selection of doses was limited to referencing an earlier publication for an oral human tolerance study with chlorpyrifos (Coulston, F., Golberg, L., Abraham, R., et al., 1972, Final report on safety evaluation and metabolic studies on Dowco 179(IN151), Inst. Exp. Pathol Toxicol, Albany Medical College (as cited by WHO, 1972). No rationale was presented for the selection of doses for the dermal study.
4. **Dose preparation and administration:** The oral doses for all subjects were prepared by mixing an appropriate amount of chlorpyrifos in food grade methylene chloride. A sufficient volume of the chlorpyrifos/ methylene chloride mixture was applied to a 0.5 g lactose tablet, and the methylene chloride allowed to evaporate. Following a breakfast meal, the tablet was swallowed whole with ~100 mL water.

The dermal 5.0 mg/kg doses for Subjects B – F were administered by spreading ~10 µL/kg chlorpyrifos dissolved in DPGME over ~100 cm² surface of the volar forearm. The application site was not covered or occluded and no effort was made to influence evaporation. Following dermal application, the subjects were allowed to follow their normal bathing habits 12 to 20 hours later. The dermal doses administered to Subject A were applied similarly, with the exception that the first dermal dose used methylene chloride as the solvent followed by application two weeks later where DPGME was the solvent for the 0.5 mg/kg dose.

Results:

Homogeneity analysis: Not reported

Stability analysis: Not reported

Concentration analysis: Net increases in tablet weight and chemical analysis of duplicate tablets were used to verify the oral doses. Data were not supplied. Thus, verification of dermal doses was not reported.

5. **Statistics:** Plasma and RBC cholinesterase activities were expressed as a percent of the mean of two to three pre-dose determinations. Other statistical methods were limited to the determination of the mean and standard deviation. Concentration-time and urinary excretion data for 3,5,6-trichloro-2-pyridine (TCP) for each volunteer were fit simultaneously to the equation:

$$C_b = \frac{k_a \times \text{Dose} \times F}{V_d \times (k_a - k_e)} \times \exp(k_e \times \text{time} - k_a \times \text{time})$$

$$\text{Urinary excretion rate} = C_b \times k_e \times V_d \times \text{body weight}$$

The equations describe a one-compartment model with first-order absorption and elimination where C_b = the blood 3,5,6-TCP; F = the fraction of dose absorbed; V_d = the volume of distribution; and k_a and k_e are the first order-absorption and elimination constants for 3,5,6-TCP. Optimal estimates for the model parameters were obtained using DACSL (DOW Advanced Continuous Stimulation Language, Agin and Blau, 1981).

C. METHODS:

1. **Observations:** Following treatment, the volunteers were observed for clinical signs of toxicity. Further details were not provided.
2. **Sample Collection: Blood** – Heparinized blood samples were collected prior to treatment and 2, 6, and 12 hours, and 1, 2, 3, 4, 8, 14, 22, 27, and 30 days post dose for analysis of plasma and RBC cholinesterase following oral treatment. RBC and plasma cholinesterase activity were determined 2, 6, and 12 hours and on Days 1, 2, 3, 4, 6, 8, and 9 following dermal treatment. In addition, the blood samples were analyzed for the concentration of chlorpyrifos and 3,5,6-TCP.

Urine – Urine was collected 24-48 hours prior to dosing. Samples were pooled for the following intervals: 0, 6, 12, 24, 36, 48, 60, 72, and 96 hours post-dose. Two additional 12-hour urine collections were made starting at 156 hours and 180 hours after the 5.0 mg/kg dermal application. The urine volume and creatinine were determined for each sample, as well as the concentration of chlorpyrifos and 3,5,6-TCP.

3. **Cholinesterase Activity:** RBC and plasma cholinesterase activity were determined using the micro-Michel method (Michel, O.H., 1961, Cholinesterase in human RBC and plasma. In Standard Methods of Clinical Chemistry, D. Seligson ed., Academic Press, NY, pp 93-98). The method was not further described. (The principle of the method relies on plasma or RBC acetylcholinesterase hydrolyzing the substrate acetylcholine in a standard buffer solution (typically pH 8) to form acetate which causes a decrease in the pH of the buffer solution. The measured change in pH is proportional to acetylcholinesterase activity.
4. **Chlorpyrifos and 3,5,6-TCP Concentration:** Blood chlorpyrifos concentration was determined by extracting the sample with acetone, evaporating the acetone and mixing the residual with hexane, and eluting the hexane through a 20% deactivated silica gel column. The hexane was collected and concentrated by evaporation before injection into an FID gas chromatograph equipped with a 3% OV-17 and 8% QF-1 column. Urine samples were analyzed similarly following direct extraction with hexane.

Blood 3,5,6-TCP was analyzed by mixing a sample with 0.12N HCl and filtered through a C_{18} Sep-Pak column. The column was washed with two additional 10 mL volumes of 0.12N HCl before being eluted with methanol. The eluent-containing methanol was mixed with 10 mL equal volumes of sodium bicarbonate and benzene. Following centrifugation, the benzene was discarded and sodium chloride, HCl and benzene were added. After mixing and centrifugation, the benzene was removed and the extract silylated. Aliquots of the silylated benzene extract were injected into an ECD gas chromatograph equipped with a 3%OV-1 column. Urine 3,5,6-TCP was extracted and quantitated similarly following hydrolysis of the urine with concentrated H_2SO_4 for one hour at 90°C.

II. RESULTS:**A. CLINICAL SIGNS OF TOXICITY:**

No clinical signs of toxicity were observed during the study

B. CHOLINESTERASE ACTIVITY:

1. Plasma: Following oral exposure, greater than 60% decreased activity was observed in two of the five subjects two hours post-dose (first time point monitored), and four of five subjects displayed >70% lower activity at six hours post-dose (Table 2). Three of the six subjects displayed significant decreased plasma cholinesterase two hours post-dose (↓63%, ↓70%, ↓30%), and peak decreases occurred at 6 hours in one subject (↓87%), at 12 hours in two subjects (↓86%, ↓89%), and at 24 hours in three subjects (↓71%, ↓85%, ↓86%). Recovery (target < 20% decrease in activity) was observed by 22-30 days post dose.

As shown in Table 3, following dermal exposure, three of the five subjects dosed with 5 mg/kg displayed apparently biologically significant (>20%) plasma decreased activity on or after 12 hours post-dose (Subject E – 22%), on day 2 (Subject E - 26%) or day 3 (Subject C – 21%) that persisted at subsequent assessment times. Subject F (- 35% at Day 3 only) was not considered to display actual inhibition since the lower reading did not persist. Since only marginal inhibition was seen with 5 mg/kg, data from subject A that was dosed twice with 0.5 mg/kg are not included in Table 3.

TABLE 2. Plasma cholinesterase percent decrease following a single 0.5 mg/kg oral dose

Phase/interval	Subject					
	A (pilot)	B	C	D	E	F
Pretest ¹	1.29 ± 0.13^a	1.13 ± 0.12^a	0.87 ± 0.09	1.16 ± 0.12	1.26 ± 0.04	1.42 ± 0.17
2 hours	- ²	-	63#	-	70#	30#
6 hours	57	14#	87#	72#	84#	78#
12 hours	70	65#	85#	86	89	83
Day 1	71	85	86	84	85	86
Day 2	68	80	77	75	78	78
Day 3	37	73	74	71	71	76
Day 4	34	68	64	65	67	68
Day 8	37%(7) ³	58	48	49	56	54
Day 14	37%(12)	28	17	30	36	27
Day 22	26%	12	22	30	37	28
Day 27	12%(26)	9	-	18	41	15
Day 30	13%(29)	23	8	4	21	21
Chlorpyrifos*	X ⁴	6-12	2-12	1-6	1-6	0-6

Percent inhibition calculated by reviewer from data on pages 18 and 19 of MRID 00124144

¹ Pre-test activity is the average of two (Subject A) or three (Subjects B-F) measurements and expressed as Δ pH units/hr

² - value greater than pre-test

³ Subject A was not assessed on the same days as the other volunteers and the number in () is the day the assessment was made.

⁴ X not detected at detection limit of 0.005 μg/mL

Bolded numbers are peak inhibition

hours post oral dose chlorpyrifos was detected in blood

^a Differ from the study report which lists for subject A 1.19 ± 0.13 and the numbers 1.20 and 1.38 and for subject B that has 1.09±0.09. The values are 1.23, 0.99 and 1.16 from a mean of 1.13.

Note: The actual times for subject A differ slightly for

Phase/interval	Subject				
	B	C	D	E	F
Initial value ¹	0.87	0.80	1.1	0.99	1.12
2 hours	13 ²	+ ³	10	12	+
6 hours	+	-	12	14	+
12 hours	+	12	14	22	+
Day 1	+	15	18	19	19
Day 2	6	18	18	26	+
Day 3	8	21	18	18	35
Day 4	9	12	16	12	+
Day 6	+	6	8	9	+
Day 8	+	+	-	8	+
Day 9	+	15	9	14	+
Chlorpyrifos*	0	6	6, 24	0, 2, 10, 24	10

Percent inhibition calculated by reviewer from data on pages 18 and 19 of MRID 00124144

¹ Cholinesterase activity (Δ pH units/hr) on day 30 following acute oral dose

² Bolded numbers are peak inhibition

³ No inhibition

* Sample interval when chlorpyrifos detected in blood

- 2. Blood:** Following oral exposure, one subject (E) displayed RBC lower (\downarrow 37%) cholinesterase two hours post-dose, but normal activity thereafter until day 14. Two other subjects (C and D) displayed RBC cholinesterase lower activity (\downarrow 53% and \downarrow 46%) at 4 days post-dose. One of these subjects also displayed lower RBC cholinesterase on day 30 post-dose (\downarrow 62%). These latter findings are considered spurious in light of the findings at prior and later assessment times which show comparable levels of activity among all subjects. Overall, no sustained decrease (i.e. $> 30\%$) indicative of true enzyme inhibition was found in any of these subjects.

Following dermal exposure (Table 5), none of the five subjects displayed RBC cholinesterase greater than 11% lower than the predosing mean at any time point.

Phase/interval	Subject					
	A (pilot)	B	C	D	E	F
Pretest ¹	0.92 ± 0.08	0.89 ± 0.18	0.94 ± 0.08	0.91 ± 0.15	0.90 ± 0.17	0.95 ± 0.18
2 hours	10	+	2	+	37	5
6 hours	10	+	+	+	+	+
12 hours	18 ²	+	2	+	+	+
Day 1	16	+	5	+	+	+
Day 2	8	+	1	+	+	+
Day 3	1	+	+	+	+	+
Day 4	11	53	46	14	11	13
Day 8	+(7) ³	+	11	8	+	+
Day 14	22(12)	17	21	10	27	11
Day 22	16	X	X	X	X	X
Day 27	18(26)	8	23	9	+	11
Day 30	22(29)	62	19	12	+	-

Percent inhibition calculated by reviewer from data on pages 18 and 20 of MRID 00124144

¹ Cholinesterase activity (Δ pH units/hr)

² Bolded numbers are peak inhibition

³ Subject A was not assessed on the same days the other subjects were. The day closest to the day in column 1 that subject A was assessed is included in ().

+ value greater than pre-dose

X result not included in assessment – no explanation provided

Phase/interval	Subject				
	B	C	D	E	F
Pretest ¹	0.34 ²	0.76	0.80	0.93	0.96
2 hours	5	-	+	3	2
6 hours	+	3	+	3	2
12 hours	+	11	+	10	+
Day 1	5 ³	+	+	+	6
Day 2	+	+	+	+	4
Day 3	+	+	+	+	1
Day 4	+	+	8	11	9
Day 6	+	+	+	+	4
Day 8	+	+	+	1	3
Day 9	+	+	+	+	+

Percent inhibition calculated by reviewer from data on pages 18 and 20 of MRID 00124144

¹ Cholinesterase activity (Δ pH units/hr) on day 30 following acute oral dose

² Subject B activity was 0.82 on day 27 and 0.34 on day 30. Day 27 activity used for calculation

³ Bolded numbers are peak inhibition

+ No inhibition

- 3. Chlorpyrifos and 3,5,6-TCP Concentration:** Chlorpyrifos was detected sporadically in the blood of all but one (subject A) at various times following oral (Table 6, from not detected to ~0.005 up to 0.03 $\mu\text{g}/\text{mL}$) or dermal (Table 6, from not detected to ~0.005 up to about 0.010 $\mu\text{g}/\text{mL}$) exposures.

3,5,6-TCP was detected in the blood of all subjects at most time intervals following both oral (up to 1.43 $\mu\text{g}/\text{mL}$) and dermal (up to 0.122 $\mu\text{g}/\text{mL}$ in subject C) exposures (Table 7). Following the oral dose, the highest level of 3,5,6-TCP in the blood occurred at 2 (Subject C), 4 (Subjects E, F), 6 (Subjects A and D), and 24 hours (Subject B) post dose. Peak TCP level following the dermal dose was at 24 hours for all five subjects.

3,5,6-TCP concentrations in urine were detected in each subject throughout the monitoring interval (Table 8), with the highest concentrations ranging from 438 to 510 µg/mL (oral dose) and 17.7 to 59.3 µg/mL (dermal dose). In all oral subjects, the highest 3,5,6-TCP concentration in urine was observed in 9 hours or less. Following dermal administration, the highest levels were generally reached in about 24 hours or up to 42 hours (for one subject).

As shown in Table 9 (column 6), the apparent volume of distribution was 181 ± 18 mL/kg (mean for the group), and the average half life for 3,5,6-TCP elimination from the blood was 26.9 hours (column 8) after oral treatment. No similar calculation for the half life following dermal application was presented in the report table but the half life was also estimated to be similar to 27 hours. Based on the model parameters, $72 \pm 11\%$ chlorpyrifos would be absorbed after oral treatment and $0.95 \pm 0.56\%$ after dermal treatment. These results were in agreement with the concentration of 3,5,6-TCP recovered in the urine following oral ($70 \pm 11\%$) or dermal ($1.02 \pm 0.57\%$).

Hours After Dosing	Subject					
	A	B	C	D	E	F
Oral Dose						
0	ND	ND	ND	ND	ND	0.009
1	ND	ND	ND	0.006	0.005	0.009
2	ND	ND	0.019	NA	0.011	0.015
4	ND	ND	0.009	0.021	0.008	0.009
6	ND	0.012	0.012	0.021	0.008	0.018
8	ND	0.007	0.030	ND	ND	ND
10	ND	0.008	0.006	ND	ND	ND
12	ND	0.028	0.015	ND	ND	ND
Dermal Dose¹						
0	ND	0.007	ND	ND	0.010	ND
2	ND	ND	ND	ND	0.008	ND
6	ND	ND	0.005	0.005	ND	ND
10	ND	ND	ND	ND	0.010	0.005
24	ND	ND	ND	0.006	0.007	ND
48	ND	ND	ND	NA	NA	NA

Data from pages 21 and 22 of MRID 00124144

¹ Subject A received a single 0.5 mg/kg dermal dose while Subjects B-F received a single 5.0 mg/kg dermal dose

ND = Below detection limit of 0.005 µg/mL

NA = Not analyzed

TABLE 7. Blood 3,5,6-TCP concentration (µg/mL)						
Hours After Dosing	Subject					
	A (pilot)	B	C	D	E	F
Oral Dose						
1	ND	ND	0.046	0.009	0.012	0.216
2	0.126	0.067	1.18	0.180	1.09	0.996
4	0.714	0.229	1.12	0.691	1.19	1.43
6	0.715¹	0.509	0.939	1.35	1.07	1.29
8	0.650	0.597	0.907	1.16	0.994	1.16
10	0.606	0.813	0.853	0.973	0.810	1.04
12	0.544	0.763	0.790	0.934	0.818	1.05
24	0.390	0.823	0.598	0.774	0.624	NA
48	0.185	0.560	0.345	0.540	0.268	0.423
72	0.081	0.354	0.199	0.342	0.081	0.215
96	0.040	0.194	0.117	0.201	0.060	0.136
Dermal Dose²						
4	NA	ND	0.019	0.018	ND	ND
6	NA	ND	0.067	0.018	0.019	0.013
8	NA	0.028	0.079	0.020	0.024	0.028
10	NA	0.023	0.107	0.037	0.020	0.014
12	NA	0.043	0.102	0.035	0.022	0.019
24	NA	0.070	0.122	0.057	0.036	0.029
48	NA	0.068	0.106	0.056	0.031	0.028
72	NA	0.049	0.080	0.046	0.022	0.019
96	NA	0.032	0.060	0.031	0.016	0.018
144	NA	0.019	0.015	0.017	0.009	ND

Data from pages 23 and 24 of MRID 00124144

¹ **Bolded** concentrations represent peak

² Subject A received a single 0.5 mg/kg dermal dose while Subjects B-F received a single 5.0 mg/kg dermal dose

ND = Below detection limit of 0.005 µg/mL

NA = Not analyzed

TABLE 8. Urine 3,5,6-TCP concentration (µg/mL) following oral dose						
Hours After Dosing	Subject					
	A (pilot)	B	C	D	E	F
Oral Dose						
3	177	64	231	167	438	451
9	268	457	510	492	409	427
18	199	328	269	212	368	273
30	131	257	229	177	229	184
42	119	181	140	134	208	175
54	73	152	121	116	178	129
66	53	109	96	95	57	91
84	31	87	65	73	67	64
108	16	49	38	34	30	36
Dermal Dose						
3	NA	1.4	2.2	3.3	ND	ND
9	NA	7.8	35.9	8.8	4.5	10.8
18	NA	21.1	49.1	10.0	15.2	13.2
30	NA	25.9	59.3	17.5	21.0	7.9
42	NA	24.8	43.5	13.4	16.1	55.5
54	NA	17.6	41.4	17.7	13.3	24.2
66	NA	20.6	31.4	12.1	10.7	8.7
84	NA	14.3	24.8	6.4	10.3	16.4
108	NA	9.5	15.4	5.1	5.3	9.9
162	NA	4.5	6.1	4.8	2.4	3.8

Data from pages 25 and 26 of MRID 00124144

¹ **Bolded** concentrations represent peak

ND = Below detection limit of 0.0025 µg/mL

NA = Not analyzed

TABLE 9. Model parameters describing blood concentrations and urinary excretion of 3,5,6-TCP by individual volunteers following oral and dermal administration of chlorpyrifos

Volunteer	Weight (kg)	Absorption lag time (hr)	Absorption rate constant (hr ⁻¹)	Absorption half-life - (hr)	Volume distribution (mL/kg)	Elimination rate constant (hr ⁻¹)	Elimination half-life (hr)	Area under plasma time curve (µg/hr/mL)	Renal clearance (mL/hr/kg) ^a	Model predicted % dose absorbed	% Dose recovered in urine
Oral 0.5 mg/kg											
A	77.1	1.9	1.7	0.4	190	0.0318	21.8	24.4	6.0	52	49
B	80.7	1.6	0.1	6.9	192	0.0219	31.7	56.6	4.2	84	81
C	83.7	1.0	3.0	0.2	204	0.0232	29.9	45.3	4.7	75	67
D	71.7	1.0	0.3	2.1	180	0.0205	33.9	58.0	3.7	75	73
E	101.8	1.1	2.7	0.3	160	0.0326	21.3	37.1	5.2	69	70
F	85.0	0.9	1.3	0.5	160	0.0249	27.8	54.7	4.0	77	79
Mean	83.3	1.3	1.5	0.5	181	0.0258	26.9 ^c	46.0	4.6	72	70
SD	10.2	0.4	1.2		18	0.0052		13.3	0.9	11	11
Dermal 5.0 mg/kg											
A ^b	77.1	—	0.0223	31.1	—	—	—	1.42	—	3.18	2.60
B	80.7	—	0.0270	25.7	—	—	—	7.06	—	1.05	1.00
C	83.7	—	0.0496	14.0	—	—	—	11.17	—	1.87	1.98
D	71.7	—	0.0335	20.7	—	—	—	6.16	—	0.80	0.70
E	95.0	—	0.0241	28.8	—	—	—	3.26	—	0.60	0.50
F	85.0	—	0.0287	24.2	—	—	—	3.18	—	0.45	0.90
Mean	83.2		0.0326	22.7				6.17		0.95 ^d	1.02
SD	8.4		0.0100					3.29		0.56	0.57

Data from page 12 of MRID 00124144

^a Calculated as volume distribution times elimination rate constant

^b Volunteer A was given a 0.5 mg/kg dermal dose and is not included in mean and standard deviation calculations

^c HED secondary reviewer calculates the mean and standard deviation as 27.7±5.2.

^d Based on the values from subjects B-F and not including subject A.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

Following oral or dermal treatment, no clinical signs of toxicity were observed nor was RBC cholinesterase decreased. Plasma cholinesterase was decreased to 15% (i.e. 85% inhibition) of pre-dose activities following oral treatment with 0.5 mg/kg chlorpyrifos but was essentially unchanged following dermal treatment with 5.0 mg/kg. Blood chlorpyrifos concentrations were low (<30 ppb), and no unchanged chlorpyrifos was found in the urine following either route of administration. Average blood 3,5,6-TCP concentrations peaked at six hours after ingestion of the oral dose and at 27 hours after the 5.0 mg/kg dermal dose. 3,5,6-TCP was cleared from the blood and eliminated in the urine with a $T_{1/2}$ of 24 hours following both oral and dermal treatment. An average of 70% of the oral dose, but <2% of the dermal dose was excreted in the urine as 3,5,6-TCP; indicating only a small fraction of the dermal chlorpyrifos dose was absorbed. The data also suggest that chlorpyrifos and its metabolite have a low potential to accumulate in man on repeated exposures.

B. REVIEWER COMMENTS:

The objective of the study was to provide data on the fate of orally and dermally administered chlorpyrifos in the human. The kinetics of chlorpyrifos and its principal metabolite 3, 5, 6-trichloro-2-pyridinal (TCP) were investigated. No clinical signs of toxicity or sustained inhibition of RBC cholinesterase activity were observed following either the oral or dermal dose. In all five subjects, plasma cholinesterase was inhibited 83-89% relative to pre-dose activities following the oral dose (peak inhibition within 6-24 hours post dose) but was essentially unchanged following the dermal dose. Blood chlorpyrifos levels were low (≤ 30 ng/mL; limit of detection 5 ng/mL), and chlorpyrifos was not found in the urine following either route of exposure. 3,5,6-TCP blood concentrations peaked by six hours after oral exposure and 24 hours after dermal application. 3,5,6-TCP was cleared from the blood and eliminated in the urine with a mean half-life of ~27 hours following both the oral and dermal doses. Using assumptions of first-order absorption and elimination, it was estimated that $72 \pm 11\%$ of the ingested dose and $0.95 \pm 0.559\%$ (based on the 5 subjects receiving 5 mg/kg dermal dose) and 3.18% (based on one subject receiving 0.5 mg/kg dermal dose) of the dermal dose were absorbed.

C. STUDY DEFICIENCIES:

- not a double-blind study design.
- same subjects administered oral and dermal doses of chlorpyrifos
- only one sex (males)
- only one dose level – no dose-response information for either route of exposure