

## DRAFT

### Human Toxicity Studies

#### A. Acute Oral Dosing

**MRID 44811002. A Rising Dose Toxicology Study to Determine the NO-Observable-Effect-Levels (NOEL) for Erythrocyte Acetylcholinesterase (AChE) Inhibition and Cholinergic Signs and Symptoms of Chlorpyrifos at Three Dose Levels. Kisicki, J. C.; Seip, C. W.; and Combs, M. L. (1999)**

**MRID 45144101. A Rising Dose Toxicology Study to Determine the NO-Observable-Effect-Levels (NOEL) for Erythrocyte Acetylcholinesterase (AChE) Inhibition and Cholinergic Signs and Symptoms of Chlorpyrifos at Three Dose Levels. Part B. (Pharmacokinetic Paraoxonase Data). Brzak, K. A. (2000).**

In a single-dose human oral toxicity study (MRID 44811002/45144101), 6 human subjects/sex/group (males: age range 19-54 years old; weight range: 66-101 kg; females age range 20-52 years old; weight 45-88 kg) were dosed orally with chlorpyrifos (99.8%; Lot # MM930503-17) in a gelatin capsule at dose levels of 0 (lactose-filled gelatin capsule, 2 control groups), 0.5, 1.0, or 2.0 mg/kg. Baseline measurements of red blood cell (RBC) cholinesterase activity were obtained for each subject (minus 10 hours and 0 hour) and used for comparison. RBC cholinesterase (AChE) activity was monitored at 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours post dose. Plasma cholinesterase was not assessed. The subjects were evaluated by physical examinations (blood pressure and any reactions to treatment), and hematology, clinical chemistry, and urinalysis assessments were performed one week post dose. Blood and urine were collected at selected intervals and analyzed for chlorpyrifos, chlorpyrifos oxon and the principle metabolite 3,5,6-trichloro-2-pyridinol (TCP) to define the pharmacokinetics of chlorpyrifos in humans. The paraoxonase (PON1) status was determined for each subject. Serum paraoxonase activity was measured against chlorpyrifos oxon, paraoxon, and diazoxon, and a PON phenotype was assigned to each subject. Cholinesterase activity was determined using the Ellman method.

Executive Summary

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

There were a total of 60 subjects (30/sex). Each dose group consisted of 6 males and 6 females. Phrase I was conducted first (control, 0.5, and 1.0 mg/kg) and when it was determined that there was no inhibition of RBC AChE or adverse effects, Phrase II was initiated (control and 2.0 mg/kg). The dose levels for each group are shown below.

Study Design.				
Group	Phrase	Dose (mg/kg)	Subjects	Comments
A	I	0.5	6 males 6 females	Blood sampled at -10 and 0 hr pretreatment and at 2, 4, 8, 12, 24, 36, 48, 72, 96, 120 144 and 168 hours post treatment and analyzed for RBC AChE, chlorpyrifos and its metabolites.
B	I	1.0	6 males 6 females	
D(1)	I	0 (placebo)	6 males 6 females	Urine, blood pressure, pulse, ECG and body temperature and clinical laboratory assessments were made at pretest and one week after administration of placebo or chlorpyrifos.  The subjects were released from the study after 7 days.
C	II	2.0	6 males 6 females	
D(2)	II	0 (placebo)	6 males 6 females	

#### Strengths:

- double-blind, randomized, placebo-controlled
- sufficient number of subjects used [6 subjects/sex/dose]
- both sexes tested at all dose levels
- 3 dose levels (0, 0.5, 1.0, 2.0 mg/kg) dose-response information
- RBC ChEI and clinical signs measured (at peak effect time???, 2, 4, 8 hours)
- blood sampling at multiple time points. Cholinesterase (RBC) activity was monitored pre-dose (-10 and 0 hours) and 2, 4, 8, 12, 24, 36, 48, 72, 96, 144, and 168 hours post dose
- assessment of paraoxonase and chlorpyrifos oxonase
- pharmacokinetic data on chlorpyrifos, chlorpyrifos oxon, and TCP
- vital signs (blood pressure, pulse, respiration, temperature) measured prior to dose and one week after dose

#### Weaknesses:

- plasma cholinesterase activity was not assessed
- all data from one subject not available
- hematology, clinical chemistry, urinalysis, and ECG assessments were not performed during the time of peak effect of chlorpyrifos on cholinesterase activity
- alternates used sporadically (confusion) [requesting information]

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### APPENDIX

The following data tables (listed below) were generated for possible inclusion (as an Appendix) in the Data Evaluation Record.

**Table A.** Group Mean RBC Cholinesterase Activity Results

**Table B.** Individual Baseline Paraoxonase/CPOase/RBC Cholinesterase Activity and Phenotype (treatment groups)

**Table C.** Baseline Paraoxonase/CPOase/RBC Cholinesterase Activity and Phenotype (control groups)

**Table D.** Male RBC Cholinesterase Activity, Blood TCP Level, and Chlorpyrifos Level (2.0 mg/kg)

**Table E.** Female RBC Cholinesterase Activity, Blood TCP Level, and Chlorpyrifos Level (2.0 mg/kg)

**Table F.** Male RBC Cholinesterase Activity, Blood TCP Level, and Chlorpyrifos Level (1.0 mg/kg)

**Table G.** Male RBC Cholinesterase Activity, Blood TCP Level, and Chlorpyrifos Level (1.0 mg/kg)

**Table H.** Male and Female RBC Cholinesterase Activity, Blood TCP Level, and Chlorpyrifos Level (0.5 mg/kg)

**Table I.** Male and Female RBC Cholinesterase Activity Level (Phase 1 Control)

**Table J.** Male and Female RBC Cholinesterase Activity Level (Phase 2 Control)

**Table 1A.** Enzyme Status (PON/CPOase/RBC ChE) Grouped by PON Phenotype (sexes combined)

**Table 1B.** Enzyme Status (PON/CPOase/RBC ChE) Grouped by PON Phenotype (males)

**Table 1C.** Enzyme Status (PON/CPOase/RBC ChE) Grouped by PON Phenotype (females)

**Table 1D.** Male and Female Urine TCP Levels (0.5 mg/kg)

**Table 1E.** Male and Female Urine TCP Levels (1.0 mg/kg)

**Table 1F.** Male and Female Urine TCP Levels (2.0 mg/kg)

**Table K.** Serum Paraoxonase/CPOase Activity, Phenotype, Amount of Chlorpyrifos Absorbed