

EPA Reviewer: John Doherty, Ph.D.
Reregistration Branch II, Health Effects Division (7509P)
EPA Secondary Reviewer: Linda Taylor, Ph.D.
Reregistration Branch II, Health Effects Division (7509P)

TXR # 0050308

Data Evaluation Record

Study Type: Special *Non-Guideline* Assessment for RBC Cholinesterase in Humans.

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Test Material: Dursban^R, 99.8% Chlorpyrifos (Lot No.: MM930503-17)

Citations: Kisicki, J.C., Seip, C.W. and Combs, M.L., 1999, "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", MDC Harris Laboratory, Lincoln Nebraska, Study No.: 21438 (for the Harris Project) and DR K-0044793-284 (for DOW AgroSciences), April 19, 1999, MRID No.: 44811002.

Brzak, K.A. "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)". Toxicology and Environmental Research and Consulting, DOW, Study No.: 981176, June 5, 2000. MRID No.: 45144101.

Juberg, D.R. and J.L. Mattsson "Updated DOW AgroSciences Response to EPA Query Regarding Two Toxicology Reports". DOW AgroSciences LLC, Indianapolis, IN, May 28, 2008, MRID No.: 47436401. Unpublished.

Sponsor: DOW AgroSciences.

Executive Summary: In a special acute oral study (1999, MRID 44811002) performed to assess effects on human red blood cell (RBC) acetylcholinesterase (AChE), chlorpyrifos (99.8%; Lot # MM930503-17) in a gelatin capsule was administered to 6 human subjects/sex/dose group at dose levels of 0 (lactose-filled capsule), 0.5 or 1.0 mg/kg (Phase 1). When it was determined that there was no inhibition and no adverse reactions in these subjects, a second phase of 6 human subjects/sex/group were dosed similarly as control and 2.0 mg/kg chlorpyrifos. The subjects vital signs (blood pressure, pulse, respiration and temperature were evaluated the

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morning prior to dosing and at 1, 2, 4, 8, 12, 24, 48 and 168 hours post dosing. In addition hematology, clinical chemistry and urinalysis assessments were performed one week post dose.

Blood was assessed at -10 hours, zero (pre-dose), and at 2, 4, 8, 12, 24, 36, 48, 72, 96, 144 and 168 hours post dose for RBC AChE activity. *Plasma cholinesterase (ChE) was not assessed.* Blood and urine were collected at selected intervals and analyzed for chlorpyrifos, chlorpyrifos oxon, and the principal 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 called chlorpyrifos oxonase (CPOase), paraoxonase, or diazoxonase, respectively (MRID# 45144101). Additionally, the PON phenotype (i.e. QQ, OR and RR) was determined for each subject.

Systemic Effects. There were no apparent clinical reactions or changes in clinical chemistry parameters related to treatment.

Pharmacokinetic Data. Chlorpyrifos was detected in the serum of 4 of the 12 subjects (2-8 hours post dose) in the 1.0 mg/kg dose (range of 1.1-5.6 ng/g) and in 4 of the 12 subjects (2-12 hours post dose) in the 2.0 mg/kg dose (range 1.3-18 ng/g). TCP was detected in the blood of all subjects through 120 hours (0.5 and 1.0 mg/kg) and through 168 hours (2.0 mg/kg). The highest concentration of TCP reached ranged from 110-380 ng/g (0.5 mg/kg), 140-610 ng/g (1.0 mg/kg), and 370-1600 ng/g (2.0 mg/kg). Chlorpyrifos and chlorpyrifos oxon were not found in the urine at any dose level, and chlorpyrifos oxon was not found in the blood of any subject. Subject #56 (QQ phenotype) the only subject demonstrating RBC AChE inhibition had a peak concentration of 18 ng/gm chlorpyrifos at 8 hours following a 2 mg/kg dose, but withdrew from the study after 48 hours for a personal problem. This same subject had the highest levels of serum (6671 ng/gm) and urinary (22.8 mg) TCP accumulated up to 48 hours. The serum chlorpyrifos and serum and urinary TCP data all suggested that this subject absorbed more dose than the other subjects on the study. CPOase for this subject was similar to the other subjects with the phenotype QQ.

RBC AChE. Zero time (predosing) baseline RBC AChE ranged from 8143±982 (±12%) to 9572±539 (±6%) U/L for males and 8576±556 (±6%) and 9165±709 (±8%) U/L for females indicating good precision for the baseline data. These RBC AChE values were within the expected range for humans. Only one individual had a decrease in RBC AChE that suggested inhibition by chlorpyrifos as indicated by being *consistently decreased* at the critical hours post dosing. For this subject (#56, a female dosed with 2 mg/kg), inhibition of RBC AChE was observed at 8 (23% ↓), 12 (maximum 28% ↓), 24 (26%↓), 36 (19%↓) and 48 (21%↓) hours post dose. There were no associated cholinergic symptoms reported, although a transient numbness in the upper arms in this subject was reported at about 2 hours post dosing or well before AChE inhibition and significant levels of TCP in the serum were detected. **The proposed LOAEL is 2 mg/kg/day for RBC AChE based on 28% inhibition in one female subject. The proposed NOAEL is 1 mg/kg.**

Classification: This study is classified as *RESERVED*. This study has a key deficiency, namely that no assessments of plasma cholinesterase were made. The study is considered a useful assessment for potential RBC AChE inhibition and contains important pharmacokinetic data as well as information on the PON status of the volunteers.

Compliance:

No-Data Confidentiality Claims (No claim of confidentiality within the United States), GLP and Quality Assurance Statements were provided. The study was said to be conducted in accordance with all applicable U.S. guidelines as specified in Title 21 of the Code of Federal Regulations parts 50, 556, and 321 and the International Guidelines for Human Testing as promulgated in the Declaration of Helsinki (1964 and as amended 1996).

Part A. Clinical aspects including AChE Assessments (MRID No.: 44811002).**Experimental Constants****A. Test Materials:**

Test Chemical:

Chemical: DursbanR - technical name for chlorpyrifos
Source: DOW AgroSciences LLC
Lot: MM930503-17
Purity: 99.8% (scheduled for decertification in June 2003)
Appearance: White crystalline powder
CAS # 2921-88-2
Chemical
Name: 0,0-diethyl 0-(3,5,6-trichloro-2-pyridinyl) phosphorothioate

Negative Control (placebo):

Chemical: Lactose
Source: Mallinckrodt N.F.
Lot: 6279 KXHA
Purity: Not specifically stated but stated to "meets N.F. requirements"
CAS # 63-42-3

B. Human Subjects:

The subjects were recruited from the Lincoln, Nebraska area in response to an advertisement. The criteria for selection for inclusion and continuation in the study were described on pages 102 to 106 of the study report.

Some of the characteristics of the participants who were actually dosed with either the control (lactose) or chlorpyrifos are as follows:

Number: 30 males and 30 females.
Occupations: Not stated for each individual.
Age: Males: 19 to 54 years; Females: 20 to 52 years.
Weight: Males: 146 to 224 pounds; Females: 98 to 200.
Race: Males: 28 Caucasian, 1 black and 1 Asian; Females: all Caucasian.

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Medical History: Table 4.4 (page 243) presented comments on the medical history of each subject. In the opinion of this reviewer, the medical history appeared to be typical of a group of 60 humans within this age bracket. There did not appear to be any medical conditions that would affect the outcome of the study. The only entries for subject #56 were that she was a non-smoker and was hospitalized twice for childbirth (12/93 and 10/97).

Note: Additional tables presented the results of urinary analysis for drugs (cocaine, ethanol and cannabinoids) taken from samples at screening and "interim". All entries were indicated as being negative. Data were also presented for the results of the pregnancy test and all entries were negative.

C. Experimental Protocol. The experimental protocol is described in Table 1 below.

Table 1. Experimental Design.

Group	Phrase	Dose (mg/kg)	Subjects	Comments
A	I	0.5	6 ♂/6 ♀	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. 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.
B	I	1.0	6 ♂/6 ♀	
D(1)	I	0 (placebo)	6 ♂/6 ♀	
C	II	2.0	6 ♂/6 ♀	
D(2)	II	0 (placebo)	6 ♂/6 ♀	
Total Subjects = 30 ♂ and 30 ♀.				

Phrase I was conducted first and when it was determined that there was no inhibition of RBC AChE and there were no adverse effects, Phrase II was initiated. Phase I groups were dosed on 10/3/98 and Phase II groups were dosed on 10/17/98.

C. Basis for Dose Level Selection:

The low dose of 0.5 mg/kg was based on a previous study (Nolan, 1984; MRID 00124144) in which this dose level produced decreases in plasma ChE by 80% but had no effects on RBC AChE and did not result in clinical signs. This dose was included to provide a NOEL for RBC AChE. The next higher dose of 1 mg/kg was thought to be a dose where noticeable RBC AChE might be expected without showing clinical signs in the subjects. The higher dose of 2 mg/kg was initiated when it was established that there was no inhibition of RBC AChE at 1 mg/kg in order to reach a level where noticeable inhibition of RBC AChE might be attained. It should be noted here that administration of the chlorpyrifos in this study was in a capsule, whereas chlorpyrifos was applied to a lactose tablet in the Nolan study.

D. Dosing Data

Each subject was dosed based on his/her body weight and chlorpyrifos was weighed out to the 0.1 mg and placed in white opaque number zero capsules the day prior to dosing. The capsule was "filled with lactose" and then closed prior to dosing. Data on the actual mg of chlorpyrifos administered to each subject that received the chlorpyrifos were presented in Table 4.27, page 545. This table presents the weight of the capsule, the weight of the capsule plus the chlorpyrifos as well as the weight plus lactose and the subject's weight to assure that each subject was administered the proper dose in mg/kg. For example, subject #56 had a body weight of 87.7 kg and was dosed with 173 mg of chlorpyrifos (268 mg weight of capsule plus chlorpyrifos - 95 mg weight of capsule). The dose this person in the 2 mg/kg dose group received was $173 \text{ mg}/87.7 \text{ kg} = 1.97 \text{ mg/kg}$.

The subjects arrived at the clinic the day before scheduled dosing and at 8 PM were given a "snack" but fasted for the next 10 hours. The subjects were given a bracelet with a unique bar code to identify specimens collected. Starting at approximately 7 AM, each subject was given his/her dose of either lactose only or chlorpyrifos containing capsule. Each subject was watched to assure the capsule was swallowed. Following swallowing, each subject was given 240 mL of water and it was assured by the study team that the capsule was swallowed. The subjects were given their lunch at approximately 11:30 AM and dinner at 4:30 PM and then a snack at 8:30 PM. The subjects were kept at the clinic for 48 hours and were required to return to the clinic at 72, 96, 120, 144 and 168 hours after initial dosing. Although the subjects were asked about strenuous activity prior to coming to the clinic, there were no comments on the level of physical activity the subjects were allowed following dose administration. There were restrictions on the consumption of alcohol and tobacco as well as non-prescription and prescription drugs.

In response to several inquiries that HED made regarding why alternates were needed and the fate of some of the subjects, the DOW company responded in a supplemental report (2008, MRID 47436401). This report indicated that alternates were used because some of the originally assigned subjects either were late reporting or reported with various symptoms that the staff determined might affect the study. Of the alternates used there remains one subject (#47) where there is some confusion as to whether or not his dose was correct based on conflicting body weight and dose administered data. It cannot be determined with certainty if this person was dosed at a rate of 1.63 mg/kg or his group dose of 2 mg/kg.

C. Statistics

(Reproduced from the study report page 23-25).

Demographic variables: Descriptive statistics (mean, standard deviation, minimum, maximum, and sample size) were calculated for continuous demographic variables (age, height, and weight) and frequency counts were tabulated for categorical demographic variables (gender, race, and frame size) by gender, by treatment group, and by phase.

Vital signs: For each phase, descriptive statistics were reported for all vital signs measurements (sitting systolic and diastolic blood pressure, pulse, respiration rate, and temperature) at each time point of collection. If a vital signs measurement was re-tested prior to dosing, the re-test value was used, instead of the original value, to calculate the descriptive statistics. However, if a re-test was required for a post-dose assessment, the original value was used to calculate the descriptive statistics. All collected data were included in the summarization of vital signs assessments. Where individual data points were missing, data were summarized based on reduced denominators.

Signs and symptoms: Signs and symptoms were coded using the 5th Edition of the COSTART Adverse Event dictionary. These data were tabulated by the number of subjects reporting at least one symptom and as percent of number of subjects dosed in each treatment group.

RBC AChE: RBC AChE concentrations were presented by subject and blood collection timepoint and were summarized by treatment group and gender using means and standard deviations. RBC AChE percent of baseline concentration values were presented and summarized in the same way. Percent of baseline at time t was calculated as follows:

$$\text{Percent of Baseline}_t = (\text{AChE}_t * 100) / \text{baseline}$$

where AChE represents the RBC AChE concentrations at time t and that individual's baseline is the average of the concentrations collected at time -10 and time 0 predose. All collected RBC AChE concentrations were included in the summarization by gender and treatment group. Where individual data points were missing, data were summarized based on reduced denominators. These percent of baseline data were inspected and a depression of 20% or more in any subject's RBC AChE activity, relative to the baseline and in the absence of a concomitant shift in the RBC AChE activity for the control group, was considered a significant depression. The RBC AChE activity was also normalized for both baseline and for RBC AChE activity for the concurrent control (placebo) group for gender at the time interval. Percent of baseline normalized to concurrent control at time t was calculated as follows:

$$\text{Normalized Percent of Baseline}_t = (100 * \text{AChE}_t / \text{baseline}) - \text{control}_t + 100$$

where AChE and baseline are defined as above and control is the mean percent of baseline response for the control (placebo) group at time t by gender. These data were presented by subject and timepoint and were summarized by treatment group and gender for each timepoint using means and standard deviations.

For the statistical analysis, the normalized data were truncated after 96 hours for Phase 1 and after 48 hours for Phase 2 so that there would be a value for each subject at each time point. Then the truncated normalized data sets from Phase I and Phase 2 were analyzed, separately, using univariate repeated measures analysis of variance (ANOVA) methods and mixed effects modeling to investigate if there were statistical differences attributed to treatment.

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A univariate repeated measures ANOVA was performed as a split-plot analysis with the gender by treatment combinations, denoted as group, as the whole plot factor and time as the subplot factor. In this setting, the time and group by time interactions are valid only if the data satisfied the sphericity property, which says measurements at all time points are equally correlated. Since this was not expected to be true, statistical tests were adjusted for the violation of the sphericity assumption using Greenhouse-Geisser and Huynh-Feldt adjustments.

Mixed effects models were also used where gender and treatment were considered to be fixed factors and time was considered to be a random continuous covariate.

This approach allowed the modeling of the effect of gender and treatment over time in a structured way, providing the opportunity to identify significant higher-order trends associated with AChE inhibition. Covariance structures and terms in the mixed effects models were tested using likelihood ratio tests comparing nested models. Covariance structures failing to provide adequate fit and terms not statistically significant at the 0.10 level of significance were excluded from the model. Differences among the treatment by gender combination pairs were tested using contrast statements within the final mixed effects model and were considered statistically significant at the 0.05 level of significance.

All summarization and analyses were conducted using SAS. Output from all SAS programs is included in Appendix 3, Supporting Statistical Documents.

Specific Methods and Results

1. Comments on the Subjects and Their Participation During the Course of the Study.

There were sixty individuals (30 males and 30 females) enrolled in the study that were actually dosed with chlorpyrifos (36 subjects, 18 males and 18 females) or placebo (24 subjects, 12 males and 12 females). Of the 60 original subjects selected, about 14 were replaced by alternates prior to administration of the dose for various reasons. This is not considered to affect the outcome.

Two subjects, one female placebo (#32) and one female dosed with 2 mg/kg (#56) did not complete the study. The former did not return for the day 6, 7 or 8 post dosing assessments and was discontinued as per the SOP. Since this subject was in the placebo group, the dismissal of this subject is less consequential. The female (#56) dosed with 2 mg/kg chlorpyrifos was described as having a personal conflict and did not return on days 4, 5, 6, 7 or 8 for post dosing events. This subject will be discussed in the later sections of this review in more detail.

A third subject (#11), a male dosed with 1 mg/kg did not provide a blood sample at 168 hours since he was out of the area at the time. He returned to the clinic for subsequent follow up investigations (physicals) and was not dismissed from the study. This is not considered consequential because 168 hours is well past the expected time of effect of chlorpyrifos.

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One subject (#6), a male in the placebo group, consumed alcohol on post treatment day 6 (equivalent to one Margarita). This is not considered consequential to the interpretation of the study.

Five subjects (#s 35, 43, 49, 50 and 60; mid-dose female, high-dose male, high-dose female, control female, control female, respectively) either failed to provide urine samples for a given interval or did not collect their samples properly such as failure to collect or did not collect in the proper container. This is not considered consequential to the assessment of AChE but may be relevant to the pharmacokinetic studies.

2. **Clinical Signs and Electrocardiogram**

The subjects were instructed to inform the physicians and/or nurses of any signs or symptoms that they experienced. They were also asked if they felt that they received the test material and if they did why. Vital signs included blood pressure, pulse, respiration and body temperature and were assessed on the morning prior to dosing and at 1, 2, 4, 8, 12, 24, 48 and 168 hours post dosing. The observers that examined the subjects classified symptoms as possibly and/or probably related to treatment if a symptom was noted within 48 hours of treatment. Since the observers did not know if a subject actually received chlorpyrifos, some of the subjects receiving the placebo were said to have symptoms possibly or probably related to the test material.

Appendix Table 1 shows the signs that were indicated by the subjects in either the placebo or groups dosed with 0.5, 1 or 2 mg/kg of chlorpyrifos.

Electrocardiograms (ECG) were done on screening and one week after administration of the placebo or chlorpyrifos. Table 4.10 (pages 345 to 351) presented the data for these analyses. All result entries were reported as "normal". There were some subjects with "sinus bradycardia" noted at week one post dosing that was not present in the screen but these occurred in the placebos as often as in the treated subjects. There were no indications of abnormal recordings to indicate that chlorpyrifos affected the heart. The one week interval between the time of test material administration and ECG assessment is considered by this reviewer too long to be meaningful to detect for an acute response to an OP.

The study author asserted that "There were no differences noted during this study attributed to treatment with regard to signs or symptoms, vital signs or clinical laboratory results". HED reviewers concur with this conclusion. There is no indication that a symptom in the treated groups was any greater than similar symptoms in the placebo groups. Other signs occurred at times that did not coincide with any indication of inhibition of RBC AChE.

3. **Clinical Chemistry, Hematology and Urinalysis.**

Clinical chemistry, hematology and urinalysis assessments were made at pretest screening and one week after dose administration. The one week interval following dosing and

clinical chemistry, hematology and urinalysis is not considered by this reviewer to be the most appropriate time.

Serum chemistry included: ALT, AST, albumin, alkaline phosphatase, calcium, chloride, cholesterol, creatinine, GGT, glucose, inorganic phosphorous, LDH, potassium, sodium, total bilirubin, total protein, urea nitrogen and uric acid.

Hematology included: basophils, eosinophils, HCT, Hgb, lymphocytes, monocytes, neutrophils, platelet count, RBC and WBC

Urinalysis included: bacteria, bilirubin, blood, casts, glucose, ketones, leukocyte esterase, nitrite, protein, RBC, specific gravity, urobilinogen, WBC and pH.

Inspection of the data tables (pages 413 to 454) did not indicate that these parameters were affected by chlorpyrifos treatment. It should be noted; however, that subject #56, the only subject showing inhibition of AChE, withdrew from study after 48 hours and did not provide blood or urine samples for clinical chemistry, hematology or urinalysis.

4. AChE Assessments.

Analytical Methods for AChE assessment.

Blood was withdrawn *via* venipuncture on an arm vein and there were a total of 14 blood specimens collected per subject (if they completed the study). Once drawn, the blood samples were centrifuged for 12 minutes at 3000 rpm and the plasma discarded (except for the prescreening sampling). The erythrocytes were then washed with saline and centrifuged for an additional 12 minutes at 3000 rpm. The saline was discarded and the erythrocytes were washed twice by the same procedure. The resulting erythrocytes were stored frozen and shipped on dry ice from the clinical facility located in Lincoln, Nebraska to the MDS Clinical Laboratory located in Toronto, Ontario Canada. AChE was assessed by the Ellman method using acetylthiocholine as the substrate. The analysis was made using a Hitachi 917 automated analyzer. Appendix 5 (pages 547 to 573) described in detail the methods for the preparation and assay and mean data for assessment of the RBC AChE by the Laboratory. It was noted that the standard protocol for this assay called for initially centrifuging the whole blood for 30 minutes (see page 552) and not the 12 minutes as indicated for the subject's samples in this study. This difference is noted but it is not considered to impact the interpretation of the data.

An overview of the results of the RBC AChE assessments is presented in Table 2. Comments on Table 2 are as follows. *Additional mean and individual RBC AChE data are in Appendix – 11 in tables A-J.*

The mean results for all groups for RBC AChE data are presented in Appendix 1. The mean data for RBC AChE in U/L for the untreated male subjects when assessed at 0 hour ranged

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from 8143 ± 982 ($\pm 12\%$) to 9572 ± 539 ($\pm 6\%$) for the five different groups. For females the range was 8576 ± 556 ($\pm 6\%$) to 9165 ± 709 ($\pm 8\%$). The highest mean for both males and females was found in Group B scheduled for dosing with 1.0 mg/kg with chlorpyrifos.

The mean values for males and females are within the expected range for human RBC AChE. In general, the analytical aspects of the measurement of RBC AChE are considered appropriate.

Males. No treatment-related effect was observed in RBC AChE activity at any dose level. Column three of Table 2 shows that the mean RBC AChE value for one of the two male *placebo groups* was 10.2% less than the predosing mean and this difference was noted at 144 hours post dosing. *The treated males* based on mean data had maximum decreases of -10.7%, -13.7% for the 0.5, 1.0 and 2.0 mg/kg dose groups respectively when compared to the predosing values. These maximum depressions of the means were at 96 hours post dose. Since chlorpyrifos is an organophosphate, it would be expected that inhibition would start to occur and remain from about 2 hours to over 24 hours. Thus, 96 hours is well past the critical hours for expected initiation of inhibition.

Females. No treatment-related effect was observed in RBC AChE activity at the 0.5 and 1.0 mg/kg dose levels. At 2.0 mg/kg, one (Subject #56) of the six females displayed RBC AChE apparent inhibition (19%-28%) during the 8-48 hour time interval post dose. All other females at this dose level showed no definite inhibition. Among females, the two control groups demonstrated that there was as much as a 9.6% decrease in RBC AChE and maximum difference was again at 96 hours. The treated female groups demonstrated group means of 6.8%, 8.7% and 10% lower activity readings for all subjects (but only 6.2% lower when one subject that did not complete the study is not included) for the 0.5, 1 and 2 mg/kg dose groups, respectively. Thus, the decreases in the means for all treated groups are near the maximum decrease that was noted in the placebo group but one subject in the high dose appears to show inhibition.

The data from several individual subjects are discussed below.

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Table 2. Overview of the results of the RBC AChE assessments.

Group	Mean Predosing (Hour 0) U/L	Lowest Posttreatment Mean (U/L)	Highest Posttreatment Mean (U/L)	Lowest % for an individual
D: Control 1				
Males	8143±982 (12%) ¹	7316±598 -10.2% @ 144 hr ²	8043±705 +2% @ 12 hr	88.36% @ 144 hr #10 ³
Females	8619±861 (10%)	7795±759 -9.6% @ 96hr	8817±884 +2.3% @ 8 hr	83.26% @ 6 hr #34
A: 0.5 m/kg				
Males	8998±730 (8%)	8036±738 -10.7% @ 96 hr	9189±924 +2.1% @ 8 hr	82.68% @ 96 hr #9
Females	8612±1160 (13%)	8028±917 -6.8% @ 144	8938±917 +3.8% @ 144 h	88.62% @ 36 hr #19
B: 1.0 mg/kg				
Males	9572±539 (6%)	8263±399 -13.7% @ 96 hr	9862±865 +2.9% @ 4 hr	75.47% @ 96 hr #11
Females	9165±709 (8%)	8366±499 -8.7% @ 168 hr	9396±517 +2.5% @ 4 hr	88.99% @ 144 hr #33
D: Control 2				
Males	9171±1112 (12%)	8999±1020 -2% @ 36 hr	9425±1041 +2.8% @ 72 hr	89.71% @ 144 hr #44
Females	8576±556 (6%)	8380±422 -2.2% @ 4 hr	8941±442 +4.3% @ 72 hr	88.40% @ 144 hr #50
C: 2.0 mg/kg				
Males	8608±896 (10%)	8584±806 (no difference)	9004±840 +4.6% @ 72 hr	89.97% @ 36 hr #48
Females	8623±855 (10%)	7761±1239 -10% @ 12 hr. 8089±1088 -6.2% @ 12 hr ⁴	8604±1064 (no difference)	71.77% @ 12 hr #56 92.82% @ 12 hr #58 ⁴

Data are from 5.1.1 and 5.1.2 for Groups A, B, and Control 1 and 9.1.1 and 9.1.2 for Group C and Control 2.

¹ The number in () is the standard deviation as percent of the mean for the predosing data. ² The percent

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is the difference between the highest or lowest mean vs. the control at the interval given.³ The individual subject number for the person showing the lowest relative reading for AChE and the interval that this reading was made.⁴ Since subject 56 did not complete the study, the reading for the second lowest subject is also presented for this group or the mean for the remaining 5 subjects is presented.

Indications of RBC AChE Inhibition Based on Individual Responses. *Note: Additional data on the phenotypic association with RBC AChE are presented in Appendix 11 Tables. A-C.*

Comment. There is an apparent decrease in the activity noted in Phase I for the males and/or females in the placebo, 0.5 and 1 mg/kg dose groups since at hour 96 many of these (placebos included) suddenly have readings lower than their previous readings for RBC AChE. There was no explanation for this provided. See Table 5.1.2 on page 60 of the study report. Since hour 96 is well past the time when chlorpyrifos would be expected to start to cause inhibition, the impact of this sudden decrease in activity is not such as to seriously impact the interpretation of the data. This sudden decrease in activity was not noted for Phase II of the study when both placebo and 2 mg/kg chlorpyrifos were tested (see Table 9.1.2 page 79 of the study report).

Males. Refer to Table H in Appendix. Column five of Table 2 shows that for the control group males, one individual demonstrated 11.6% (subject # 10) and another demonstrated 10.3% (subject # 44) less than his predosing value. Among the treated groups, there was a maximum of 17.4% (subject #9), 24.5% (subject #11) and 10% (subject # 48) apparent decrease in RBC AChE for the 0.5, 1.0 and 2.0 mg/kg dose groups, respectively. Since there are subjects in both the 0.5 and 1.0 mg/kg dose groups that have apparent decreases in AChE it can be implied that these individuals may be unusually sensitive to inhibition of AChE by chlorpyrifos. Thus, the following will discuss in more detail the overall response of these individuals throughout the study. Selected other subjects will also be discussed for the reasons given below.

Subject # 9. Group A. (0.5 mg/kg chlorpyrifos treatment). Subject # 9 was a 19 year old Caucasian male 75 inches tall and weighing 210 pounds and was a non-smoker. No clinical signs or abnormalities were noted in this person's clinical chemistry or ECG assessments. This subject was reported as having intestinal cramps starting at 2 days, 22 hours and 44 minutes post dosing that lasted 15 hours. This subject replied "no" when asked if he had received the test material and not the placebo.

This subject had RBC AChE readings (in U/L) of 8294, 8602, 8437, 8646, 8844, 8723, 8580, 8261, 8107, 8250, **6985 (-19%), 7535 (-12%), 7376 (-14%) and 7700 (-11%)** for the - 10, zero, 2, 4, 8, 12, 24, 36, 48, 72, **96, 120, 144 and 168** hour assessment times respectively. The apparent decrease in RBC AChE did not begin until 96 hours after dosing. It is noted that the cramps did not coincide with the lower AChE levels. It was noted above that there is a problem with the assays after hour 96 (see comment above).

At the onset of this subject's intestinal cramps (~72 hours), his RBC AChE was at most

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3% less than the zero time reading. However, at 96 hours, his RBC AChE was lowest but his cramps had already disappeared by 85-86 hours (see Appendix I).

In conclusion, there is no justification to support that this individual was unusually sensitive to inhibition of RBC AChE. Inhibition would be expected to appear within a few hours (~ 4-8 hours) post dosing and not 96 hours later. There were also no symptomatic expressions indicative of AChE inhibition (i.e. intestinal cramps are not a specific response to a AChE inhibitor and could be due to many things).

Subject #11. Refer to Table F in Appendix. Group B (1.0 mg/kg chlorpyrifos treatment). Subject # 11 was a 45 year old black male 71 inches tall and weighing 191 pounds and smoked one and a half packages of cigarettes a day. This subject did not report for his day 7 examinations or blood sampling. He did not submit urine for the 144 to 156 hour or 156 to 168 hour collection intervals. He returned to the clinic “the following week” for a post physical exam, ECG and laboratory work up. There was no record of how he responded to whether or not he thought he had received the test material rather than the placebo. This subject's clinical laboratory work up for post treatment indicated he was “moderately lipemic”.

On two occasions (refer to page 468 and Appendix 4.21/1) this subject was reported to have a headache. The first occasion began 3 hours and 40 minutes post dosing and lasted for 19 hours. This means the headache started at 11 am on October 3 and lasted until 6 am on October 4. The second occasion began 22 hours and 40 minutes (approximately 6 am on October 4 post dosing and lasted 1 day and 9 hours. [There seems to be a reporting glitch here because the first headache is reported to be resolved at 6:00 and the second headache starts at 6:00 both on October 4, 1998. There may actually be just one headache.]

This subject had RBC AChE readings (in U/L) of 10307, 10098, 9097 (-10%), 10318, 9768 (-3%), 9779 (-3%), 9977, 9768, 9141 (-10%), 10153, 7700 (-24%), 9185 (-9%), 9218 (-9%) for the -10, zero, 2, 4, 8, 12, 24, 36, 48, 72, 96, 120 and 144 hour assessment times, respectively (not assessed at 168 hours). Thus, there was considerable variation in this individual's readings for RBC AChE but they do not fit an expected pattern of inhibition by an organophosphate. Since maximum apparent decrease occurred at 96 hours post dosing (again there is a problem with the hour 96 readings) and the reading at 72 hours was 10153 or essentially the same as the predosing zero hour, this subject is not considered to have chlorpyrifos related inhibition of ChE.

It is noted that there was no consistent depression of RBC AChE during this interval when the subject experienced his headache. For example, the readings were -10%, similar, -3%, -3%, -3%, and -3% at 2, 4, 8, 12, 24 and 36 hours respectively.

In conclusion, there is no justification to support that this individual was unusually sensitive to RBC AChE inhibition by chlorpyrifos. The headache that this individual was reported as having did not coincide with decreased levels of RBC AChE and it was not present when AChE was lowest.

(non-guideline)

Subject #47. Group C (2 mg/kg chlorpyrifos treatment, but this subject may have actually received a dose of 1.66 mg/kg). Subject #47 was a 24 year old Caucasian male 69 inches tall and 184 pounds. He responded "no" to the question about whether or not he thought he received the test material and did not have any obvious symptoms of AChE intoxication. This subject had highest "estimated dose received" (1.130 mg/kg compared with the group mean of 0.59 mg/kg, see Table 16, page 47 of the Pharmacokinetics report) based primarily on plasma and urinary content of TCP. This subject did not have indications of AChE inhibition since there was at best a 5% decrease in activity at 24 hours but the preceding and succeeding assessments were both higher than the baseline.

Subject #48. Refer to Table D in Appendix. Group C (2.0 mg/kg chlorpyrifos treatment). Subject # 48 was a 23 year old Caucasian male 71 inches tall and weighing 162 pounds and smoked 10-14 cigarettes a day. He responded no to the question about whether or not he thought he received the test material. According to the data table on page 471, this subject did not experience any symptoms during the post dosing phrase.

This subject had RBC AChE readings of 8569, 8206, 8019, 8008, 7887, 7689, 8206, **7546** (-8%), 7832, 8074, 7766, 7766, 7942 and 8184 for the -10, zero, 2, 4, 8, 12, 24, 36, 48, 72, 96, 144 and 168 assessment times respectively. Thus, this subject's maximum decrease at 36 hours was immediately proceeded by a value actually the same as the zero time assessment and thus does not show a pattern consistent with inhibition by an organophosphate.

Females. Refer to Tables I and J in Appendix. Column five of Table 2 shows that for the control group females, one individual demonstrated 16.7% (subject # 34) and another 11.6% (subject # 50) less than her predosing value. Among the treated groups there was a maximum of 11.4% (subject #19), 11% (subject #33) and 28.2% (subject # 56) apparent decrease in RBC AChE for the 0.5, 1.0 and 2.0 mg/kg dose groups, respectively. Since the subjects in both the 0.5 and 1.0 mg/kg dose groups did not exceed the placebo group for apparent decreases in AChE, it is not implied that there are individuals in these dose groups that may be unusually sensitive to inhibition of AChE by chlorpyrifos. Subjects # 51 and 56 are discussed as follows.

Subject #51. Phase II Group C female, 2 mg/kg chlorpyrifos. Refer to Table 4 below for AChE data on this subject. This subject *sustained* a decrease of 5 to 6% RBC AChE over the critical hours of 12, 24, and 36. However, her pretest variation was also near 5%. This subject also had one of the highest levels of TCP in her blood. But the peak level of TCP did not correspond with the lower readings for AChE.

The placebo female group for Phase II was demonstrated to be very stable over the course of the seven days on the study (see last column in Table 4) as indicated by the data from one individual who demonstrated the most variation of the six females in the placebo group. Overall, the 5-6% lower reading in subject #51 is noted but not considered to be definite inhibition caused by chlorpyrifos.

Subject # 56. Group C, 2 mg/kg chlorpyrifos. As indicated previously, subject # 56

(non-guideline)

dropped out of the study after 48 hours. It was originally reported that “repeated attempts were made to contact this individual were unsuccessful and no post study medical evaluation was performed” (refer to page 28 of the study report). However, the supplementary report (2008, MRID 47436401) in response to HED’s questions about the fate of this individual asserts “In, 1999, Richard Nolan PhD was a DAS toxicologist that was the toxicology contact for the Kisicki study. Dr. Joel Mattsson was in 1999 a DAS toxicologist working with Dr. Nolan and was assured that the testing laboratory had contacted subject #56 personally and she reported no problems with the study but had personal reasons for not returning for further evaluations. DAS is not aware of any additional information on subject #56”. There is still ambiguity with regard to statements about this subject regarding the comments in the study report (page 28) where no contact was made and in the supplementary report (page 17) where contact was said to have been made. Overall, failure of this person to have data after 48 hours does not preclude that data on AChE assessment and pharmacokinetics obtained prior to 48 hours are not useful and informative although the lack of data following 48 hours limits the assessment of the total PK picture. The possibility that this subject developed clinical signs in response to treatment cannot be resolved on the basis of available information.

Page 472 of the study report indicates that this subject reported experiencing "numbness of the upper arms" starting 2 hours and 24 minutes after administration of the chlorpyrifos and lasting a total of 42 minutes. On page 510, the table listing the subject's response to the question if they thought they received the test material does not include subject #56.

This subject was the only subject on the study that demonstrated apparent RBC AChE inhibition. Table 3 below provides details about this subject and shows the extent of inhibition at the critical time interval. It is apparent that this individual's RBC AChE is decreased starting at 8 hours and remaining so until 48 hours when she was last tested.

Table 3. Summary of Subject #56

Parameter	Results	Comments
Description (a)	A 34 year old Caucasian female 72 inches tall and weighing 193 pounds and was a non-smoker. This individual did not report for the day 4, 5, 6, 7 or 8 blood collection (see page 28) or assessment of vital signs and did not provide urine samples after 48 hours.	There is nothing obviously different about this subject to suggest an unusual susceptibility to chlorpyrifos. The subject was genotype QQ but about half the persons on the study had this genotype.
Symptoms (b)	Subject had a transient "numbness in upper arms" that started to occur 42 minutes after dosing and lasted for 2 hours and 24 min (self resolved without medication).	The numbness alone does not seem to be a response to an AChE inhibitor and since this occurred and was resolved by three hours, or before there was

(non-guideline)

Parameter	Results	Comments
		appreciable apparent inhibition of AChE at 8 hours post dosing, the finding is not considered treatment-related.
RBC AChE IU/L (c)	8426 at -10 hours 8910 at 0 hour 8668 predosing mean 8602 (no difference) at 2 hours, 8525 (-2%) at 4 hours, 6688 (-23%) at 8 hours, 6221 (-28%) at 12 hours 6424 (-26%) at 24 hours 7051 (-19%) at 36hours 6882 (-21%) at 48 hours No additional assessments.	Subject shows decrease in RBC AChE that can be considered the critical times expected for an OP following an oral administration. No other subject shows a similar pattern of decrease in activity.
Serum chlorpyrifos (d)	18 ng/gm at 8 hours 2.5 ng/gm at 12 hours All other times - not detected (< 1 ng/gm) The highest level in all other subjects was only 5.6 in a female (#21) dosed with 1 mg/kg.	The serum chlorpyrifos data and the serum and urine TCP data all indicate that subject # 56 absorbed chlorpyrifos to a greater extent than the other subjects in this study.
Serum TCP (0 to 48 hours) (e)	Subject has total of 6671 ng/gm TCP in serum with values of 71, 120, 1600, 1500, 1300, 1100 and 980 ng/gm for the 2, 4, 8, 12, 24, 36 and 48 hour intervals, respectively. Note there was little TCP in blood at 2 to 4 hours or at the time the numbness was noted. This is the highest (total ng/gm) for the group dosed with 2 mg/kg since the range for all others (both sexes) was 1404 (#42) to 5860 (#47) ng/gm for up to 48 hours. Among females, the other five had values of 2910, 5010, 2730, 2560 and 3310 ng/gm.	Since no assessments were made after 48 hours, the total TCP picture cannot be determined to compare with the other subjects who seemed to have TCP present in the blood at the later times.
Urine TCP (corrected for creatinine) (0 to 48 hours)	According to Table 14b for the 0-48 hour interval, Subject 56 had a total of 22.8 mg or was highest for the group dosed with 2 mg/kg. The range for the others in this group was 4.8 (#40) to 16.2 (#47) with a mean of 8.4 ± 3 for all individuals excluding #56.	
Estimated internal dose of	0.640 mg/kg. - from Table 16 The group mean of 0.59 ± 0.21 mg/kg (range	The calculation of the total internal dose for subject #56 is limited since no assessments for

(non-guideline)

Parameter	Results	Comments
chlorpyrifos (g)	0.323 (#40) to 1.130 (#47) mg/kg for the group dosed with 2 mg/kg. males 0.61±0.28; females: 0.568±0.12 mg/kg based on collection for 7 days.	TCP or parent chlorpyrifos were made after 48 hours.
CPOase (h)	Subject has reading of 9278 Units/liter comparing favorably with the group mean of 9523±1517 Units/liter. Paraoxonase 367 U/L compared to group mean 737±430 U/L	There is nothing unusual about the serum activity of CPOase, or diazoxonase. Although her paraoxonase level was much lower than the group mean this should not affect dosing with chlorpyrifos. Subject was described as phenotype "QQ low" which was a typical classification for many (about half) of the subjects in the study.

(a) Data are from Appendix 4.3, page 242.. (b) Data are from Appendix 4.21.1, page 472. (c) Data are from Table 4.13.2, page 407. (d) Data are from Table 5, page 34 of the Pharmacokinetics report. (e) Data are from Table 7, page 36 of the Pharmacokinetics report. (f) Data are from Table 14b (corrected for creatinine), page 45 of the Pharmacokinetics report. (g) Data are from Table 16, page 47 of the study report. (h) Data are from Table 17, page 50 of the Pharmacokinetics report.

It is noted that in the screening study this individual had a RBC AChE of 7678 U/L. This was listed as a clinical laboratory comment as “not significant in the context of this study”. When compared to the mean for the -10 and zero hour samplings (mean = 8668 U/L), this would be 11% less. This value of 11% less is not as much as the approximately 28% decrease that was noted for this person following treatment with 2 mg/kg chlorpyrifos. Thus, the decrease in AChE after 8 hours is greater than the spontaneous variation for this subject.

This subject has inhibition rather than random decrease in activity since the decrease in activity starts at 8 hours and rises to a peak at 12 hours and then appears to start to decline at 24, 36 and 48 hours. This would be expected for an organophosphate AChE inhibitor. The pattern of decreased activity also correlates with the amount of TCP in the serum as shown in Table 4.

Table 4. Correlation between RBC AChE activity and blood level of TCP in humans dosed with 2 mg/kg chlorpyrifos.

Hour	Sub. #56(QQ♀)_ RBC AChE	TCP Blood	Sub. #47(QQ♂)_ RBC AChE	TCP Blood	Sub. #51(OR♀)_ RBC AChE	TCP Blood	Sub. #48(OR♂) RBC AChE	TCP Blood	Placebo #44 (OR♂) RBC AChE	Placebo #60 (QQ♀) RBC AChE
2	=	71	+2%	580	-2%	420	-4%	180	-1%	-3%
4	-2%	120	+2%	640	-1%	580	-5%	250	=	-5%
8	-23%	1600	=	790	-2%	1300	-6%	240	-3%	+1%
12	-28%	1500	=	910	-6%	690	-8%	260	-6%	+2%
24	-26%	1300	-5%	980	-5%	540	-2%	380	-6%	-1%
36	-19%	1100	=	960	-5%	750	-10%	460	-4%	=
48	-21%	980	-1%	1000	-3%	730	-7%	470	-5%	=
72	Subject did not return for additional sampling.		+4%	690	+1%	600	-4%	300	+1%	-3%
96			+2%	460	+4%	420	-7%	210	-4%	-3%
120			+7%	320	+6%	150	-7%	140	-4%	=
144			+2%	220	-2%	170	-6%	77	-10%	-3%
168			+7%	150	=	110	-2%	48	=	+1%
Net TCP	0 to 48 hrs 6671 0 to 168 hrs - no data		0 to 48 hrs 5860 0 to 168 hrs 7700		0 to 48 hrs 5010 0 to 168 hrs 6410		0 to 48 hrs 2240 0 to 168 hrs 3015		N/A	N/A
	Definitely shows inhibition correlating with blood level of TCP.		Highest levels of TCP do not correlate with ↓RBC AChE.		Sustains a slight decrease at critical times and is thus <i>possibly</i> showing inhibition.		Subject has lowest level of blood TCP but seems to sustain a decrease in RBC AChE		Shows that activity varies to - 10%.	Shows that female RBC AChE is stable.

TCP data are from Table 7 page 36 in MRID No.: 45144101 and are ng/gm. Note: TCP data were not reported for the blood from the placebo group in Table 7 of the study report. RBC AChE data are from Table 9.1.2 page 78 from MRID No.: 44811002 and are the percent decrease (-) or increase (+) in RBC AChE relative to the baseline. The = sign indicates

that the assessment was within $\pm 1\%$ of the baseline.

Table 4 also presents data on the variation of RBC AChE activity in one other female and two males dosed with 2 mg/kg of chlorpyrifos and the amount of TCP in their blood. In addition, a male and a female from Phase II placebo group are included to show the spontaneous variation of RBC AChE. It is noted that the female (#60) is stable but the male (#44) showed decreases. One other placebo male (Subject #41, data not shown here because of space limitations) also showed what appeared to be sustained decreased activity (4%-7% from 8 hours to 36 hours post dose).

Table 4 indicates that female subject #51 sustains a slight decrease in RBC AChE and also has a high blood level of TCP but not at the critical times of lower AChE readings. Therefore this subject is not considered to show definite evidence of RBC AChE inhibition in response to 2 mg/kg of chlorpyrifos since the level of decrease is too low and not coincident with serum TCP.

Part B. Pharmacokinetic and Paraoxonase Data (Refer to MRID No.: 45144101).

Part B 1. Pharmacokinetic data.

Note: Additional data including individual subject data on the pharmacokinetics are in Appendix II Tables A-K..

The sixty subjects on this study gave blood samples (5 mL) for the purpose of determination of chlorpyrifos, chlorpyrifos oxon and 3,5,6-trichloro-2-pyridinyl (TCP) at -10 hours prior to dosing, at zero hour prior to dosing and at 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post dosing. Urine samples from all urine voided (as per the protocol) for the intervals -48 to -36 hours, -36 to -24 hours, -24 to -12 hours, -12 to 0 hours pretreatment and 0 to 6 hours, 6 to 12 hours, 12 to 24 hours, 24 to 36 hours, 36 to 48 hours, 48 to 60 hours, 60 to 72 hours, 72 to 84 hours, 84 to 96 hours, 96 to 108 hours, 108 to 120 hours, 120 to 132 hours, 132 to 144 hours, 144 to 156 hours and 156 to 168 hours post treatment. The blood and urine were analyzed by GC/MS for chlorpyrifos, its oxon analog and TCP and the method of preparation using internal standards was described. TCP was derivitized prior to analysis.

Data were presented that demonstrated the recovery of spiked samples for chlorpyrifos (98.0 to 99.8%), chlorpyrifos oxon (95.4 to 98.0%) and TCP (91.1 to 97.1%), and the lower limit of detection was about 1 ng/gm of blood for chlorpyrifos and its oxon analog but was about 12.1. ng/gm for TCP. Similarly, recoveries of 96 to 104% for these chemicals from urine were demonstrated. Additional data demonstrated the stability of these chemicals in blood and urine stored -20 or -80 °C for 6 or 10 days.

Blood and urine analysis for chlorpyrifos and chlorpyrifos oxon.

Chlorpyrifos and chlorpyrifos oxon were *not* found in any of the urine samples from any of the subjects (refer to Table 10 of the study report page 39). Chlorpyrifos oxon was not found in the blood of any subject (refer to Table 6 of the study report page 35).

Chlorpyrifos was found only occasionally in the blood (refer to Table 5 page 34 of the study report). No subjects dosed with 0.5 mg/kg chlorpyrifos were found to have chlorpyrifos in their blood. Subjects #11 (1.0 ng/gm at 2 hours), #14 (2.7 and 1.5 ng/gm at 4 and 8 hours), #21 (5.6 and 2.9 ng/gm at 2 and 4 hours) and #30 (1.1 ng/gm at 8 hours) dosed with 1 mg/kg were noted to have chlorpyrifos in their blood at the assessment times indicated. Subjects #47 (3.1, 1.3, 3.4 and 1.8 ng/gm at 2, 4, 8 and 12 hours), #49 (3.1 and 1.7 ng/gm at 2 and 8 hours), #56 (18.0 and 2.5 ng/gm at 8 and 12 hours) and #59 (2.2, 4.1, 4.1 and 1.5 ng/gm at 2, 4, 8 and 12 hours) dosed with 2 mg/kg were also shown to have chlorpyrifos in their blood. These are very small amounts of chlorpyrifos. The highest level (18 ng/gm) was found in subject #56 at 8 hours. These data suggest a short half-life for parent chlorpyrifos in blood but there does not appear to be sufficient data to establish a firm number for the half-life of chlorpyrifos in the blood.

Blood and urine analysis for the principal metabolite TCP.

TCP was detected in the blood of *all* subjects dosed with chlorpyrifos. Refer to Appendix Tables. D, E, F, G, and H.

“The percent recovery corrected for dose as urinary TCP” was reported to be for both sexes combined 34.7±19.6%. 30.8±9.9% and 29.5±10.4% for the 0.5, 1 and 2 mg/kg dose groups, respectively. (Refer to Table 16 “Estimation of dose Received by Volunteers”, page 47.)

The extent of absorption is less than the 70% earlier report from Nolan (1984)¹ and this may be attributed to the fact that the chlorpyrifos in this study was administered in a capsule and this would lead to slower absorption. In contrast, in the Nolan study, chlorpyrifos was dissolved in methylene chloride and placed on a 0.5-gram lactose tablet, which was swallowed with 100 mL of water.

The half-life of TCP as indicated by the blood and urine data are shown in Table 5.

Table 5. Half-lives (in hours) based on TCP in the blood and urine.

Dose (mg/kg)	Blood ^a			Urine ^b		
	Males	Females	Combined	Males	Females	Combined
0.5	29.7±7.4	44.5±32.4	37.1±23.7	29.5±8.9	38.6±24.3	34.3±16.1
1.0	27.7±5.6	30.5±7.4	29.1±6.4	20.5±5.9	33.6±7.4	31.0±7.3

¹ Nolan, R.J. et al, (1984) Chlorpyrifos: Pharmacokinetics in human volunteers. *Toxicol. Appl. Pharmacol.* **73**:8-15.

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2.0	36.2±5.9	35.2±4.8	35.8±5.6	38.1±6.5	32.8±6.5	35.7±6.7
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a. Table 9, page 38. b. Table 15, page 46.

(Note in MRID 45144101) the printing is small and in some places difficult to distinguish 5, 6 and 8. The best read of the number is in Table 5. Since there were only a few and mostly in the standard deviation, these questionable numbers should not impact the interpretation.)

Additional serum TCP data on selected subjects are presented in Table 4.

Part B. 2. Serum Paraoxonase and chlorpyrifos oxonase (CPOase) Assessment.

A 5 mL blood sample was taken prior to dosing and sent to the laboratory of Dr. Clement Furlong, Department of Medicine and Genetics, University of Washington, Seattle, Washington and assessed for paraoxonase activity using a spectrophotometric assay. Paraoxonase was tested with chlorpyrifos oxon, paraoxon, or diazoxonase. When the test substance was chlorpyrifos oxon, the activity was called CPOase.

Table 17 of the study report presented data for each subject and group means for the subjects dosed in both phase I (October 3, 1998) and II (October 17, 1998). Table 6 summarizes the CPOase data in this study. Paraoxonase (range - ~250 to ~2502 units/L, when paraoxon was the substrate) and diazoxonase (range ~6548 to 22452 units, when diazinon oxon was the substrate) data were also presented but not shown in this review since the subject of the review is chlorpyrifos.

Table 5. CPOase Data

Group	CPOase	Range	Comment
Phase 1 Control	8418±1639	5430 to 10410	56 subjects were QQ, 5 were QR, and 1 was RR. were "QQAow". Both the high and low readings were from OR individuals.
Phase 1 0.5 mg/kg	7965±1536	5412 to 13341	5 were QQ and 7 were QR. The low was from a QQ and the high was from a QR.
Phase 1 1 mg/kg	8463±1386	6599 to 11615	6 were QQ, 5 were QR and 1 was RR. The high value was from a QQ and the low value was also from a QQ.
Phase 2 Control	11357±3097	6904 to 17333	6 were QQ and 5 were QR and one was RR. The high value was from the RR person and the low value was from a QQ person.

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Group	CPOase	Range	Comment
Phase 2 2 mg/kg	9523±1517	7048 to 13018	6 were QQ, 5 were QR and 1 was RR. The high value was from a QR person and the low value was also from a QR person. Subject # 56 has a value of 9278 Units/liter and is very close to the group mean and thus does not have an unusual ability to metabolize chlorpyrifos oxon.

Conclusions, Discussion, Study Deficiencies and Classification.

1. Study author's conclusions.

The study author (page 10 of the study report) concluded "The NOEL for signs and symptoms in fasted humans following a single oral dose was 2.0 mg chlorpyrifos/kg of body weight. The NOEL for RBC AChE inhibition in humans given a single oral dose of chlorpyrifos was 1.0 mg/kg of body weight. The 2.0 mg chlorpyrifos/kg of body weight dose level represented a threshold in that it produced greater than 17.3% depression in 1 of 12 volunteers."

2. Reviewer's conclusion and discussion.

Signs and Symptoms. There was no indication that any of the signs and symptoms that were noted in the subjects dosed with chlorpyrifos were different in either their nature or degree of severity from the signs and symptoms that were noted in the placebo groups. Some reported symptoms in the subjects that were dosed with chlorpyrifos occurred either well before or after the time when chlorpyrifos absorption was maximal or when the blood or urine level of TCP the principal metabolite of chlorpyrifos was at its maximal level. Also, the only subject showing definite inhibition of RBC AChE did not display any symptoms when maximum inhibition of AChE was attained and this subject's only reported sign ("upper arm numbness") occurred and resolved well before her RBC AChE was shown to be inhibited and before her serum level of TCP reached higher levels. If the "upper arm numbness" was related to some other cause due to chlorpyrifos than inhibition of RBC AChE it would still be expected for the numbness to persist while the absorption of chlorpyrifos increased. Thus, the proposed NOAEL for symptoms is > 2 mg/kg chlorpyrifos.

Pharmacokinetic Data. Based on the pattern of occurrence of TCP, the principal metabolite of chlorpyrifos in the blood and urine, chlorpyrifos is absorbed rather slowly from the gut and requires about 8 to 12 hours for the TCP blood level to reach a maximum. Based on the blood level of TCP, subject # 56 absorbed more chlorpyrifos in the first 48 hours than any other

subject and this subject also had clear evidence of RBC AChE inhibition.

The rate and extent of absorption of chlorpyrifos in this study was slower and lower than reported in an earlier study (Nolan, 1984), and this was attributed by the study author to be due to the differences in administration. In this study, chlorpyrifos was administered in a capsule but in the earlier study it was administered on top of a lactose pill. The need for the capsule itself to dissolve in the g-I tract may be a factor.

RBC AChE Inhibition. Review of this study identified one subject (#56, a female dosed with 2 mg/kg, with genotype QQ) as demonstrating inhibition of RBC AChE. The decreases in RBC AChE were shown to correlate with high levels of TCP in her serum. As much as 28% inhibition was noted at 12 hours post dosing.

A second subject (#51, with genotype OR) was considered as possibly also showing inhibition and also had one of the highest levels of serum TCP for the group dosed with 2 mg/kg. Although this subject had decreases to only 5 to 6% of her predosing mean, this level of decrease was sustained over the critical hours of expected time for an OP to inhibit blood AChE (i.e. 8 to 24 hours). Inspection of the other four females in Phase II indicated that their RBC AChE activity was very stable over the 168-hour post dosing period. Overall, subject #51 is considered to have only very minimum and indefinite inhibition.

None of the males were determined to be showing definite decreases in RBC AChE. It was noted that one subject (# 48, 2 mg/kg group, OR) had decrease of 8% at 12 hours and 10% at 36 hours but two placebo males indicated that variation in RBC AChE activity can also vary to a decrease of 10%. Also subject # 48 had one of the lowest net totals of TCP in his blood for the group receiving 2 mg/kg.

Thus, the proposed NOAEL for RBC AChE inhibition is 1 mg/kg and the LOAEL is 2 mg/kg. Only one female was concluded to have definite inhibition.

CPOase

This study has important data on each person's PON and CPOase. The single person showing inhibition had CPOase similar to other individuals in the group dosed with 2 mg/kg, but this person also had the highest absorption of chlorpyrifos. Thus, the person's ability to absorb chlorpyrifos from the gastro-intestinal tract may be more important than the CPOase status of the individual.

Study Classification.

This study is being classified as RESERVED.

4. Study deficiencies and compromising issues.

-Plasma ChE was not assessed for. This is considered important since other recent studies with humans and OPs include plasma ChE assessment. Also it was reported in the earlier (Nolan, 1984) study with humans that plasma ChE is inhibited at lower doses than RBC AChE by chlorpyrifos. This deficiency is considered a potentially serious omission.

-The only subject that showed definite inhibition of RBC AChE did not complete the study after the 48th hour assessments. This subject did not provide blood samples for hematology or clinical chemistry at the scheduled one-week post treatment time. The supplementary report (2008, MRID 47436401) indicated that this person was contacted via telephone and did not report adverse effects and that she had to leave the study for personal reasons.

-The hematology, clinical chemistry, urinalysis and ECG assessments were made one week following the administration of chlorpyrifos. This is considered a poor design. These assessments should have been done during the time of peak effect of chlorpyrifos on AChE. The assessments after one week are of little value since the chlorpyrifos has been cleared from the body and it would be expected that inhibition of AChE would have been partially reversed by this time or that the body adapted to the decreased AChE activity.

(non-guideline)

Appendix I - Individual Subject Analysis for subjects showing symptoms or variation in AChE

Subject #	Symptoms or Events (a)	RBC AChE Comments	HED's Conclusion
Placebo-Males			
2 (no)	Increased appetite, headache (moderate)- vomited. Starting 47 hrs postdosing, lasting for 4 days, 6 hrs. <i>Possibly related to treatment.</i> "One can coca-cola next day".	Maximum decrease 12% @ 48 hrs. Other values are 89% to 105%. of predose	Since these subjects are in the placebo group, there symptoms or events cannot be due to chlorpyrifos treatment.
8 (yes)	Headache (mild)- Starting 10 hrs postdosing, lasting ~13 hrs. <i>Possibly related to treatment.</i>	Maximum decrease 9% @ 48 hrs. Other values are 94% to 103%.	
10 (yes)	No symptoms or events.	Maximum decrease 14% @ 96 hrs. Other values are 88% to 103%.	
13 (yes)	No symptoms or events.	Maximum decrease 12% @ -10 hrs. Other values are 97% to 112%.	
37 (yes)	Dizzy, feels weak, nausea, vomited, body aches - Starting 2 days, 18 hrs lasting (some symptoms) for up to 2 days 11 hrs. <i>Possibly related to treatment.</i>	Maximum decrease 3% @ 96 hrs. Other values 97% to 107% of predose.	
41 (no)	Itching of insect bite. Starting 2 days 5 hrs, lasting 11 hrs. <i>Unrelated to treatment.</i>	Maximum decrease 7% @ 24 hrs. Other values 95% to 107% of predose.	
45 (no)	Nausea, vomited. Starting 2 days. Lasting ~20 min. <i>Possibly related to treatment.</i>	No decreases. Values are 100 to 110% of the predose.	
46 (no)	Headache (mild). Starting ~ 3 hrs. Lasting ~ 3hrs. <i>Possibly related to treatment.</i>	Maximum decrease 6% @ 2 hrs. Other values 98% to 108% of predose.	
<p>3/12 subjects have headaches. 4/12 thought they received the chlorpyrifos when it was not given. As much as a 14% decrease in RBC AChE can occur within the untreated group over the 7 day period.</p>			
Placebo-Females			
20 (yes)	No symptoms or events.	Maximum decrease 7% at -10 hrs. Other values 94% to 107%.	Since these subjects are in the placebo group,

(non-guideline)

Subject #	Symptoms or Events (a)	RBC AChE Comments	HED's Conclusion
23 (yes)	No symptoms or events.	Maximum decrease 7% at 144 hrs. Other values 96 to 110%.	there reactions cannot be due to chlorpyrifos treatment.
29 (no)	"hiccough", heartburn. Starting 11 hrs, lasting 11 hrs. Unrelated to treatment.	Maximum decrease 13% at 96 hrs. Other values 95 to 107%.	
32 (no)	No symptoms.	Maximum decrease 17% and sustains from 96 to 144 hrs. Other values 85 to 105%. Subject included to show variation in AChE.	
50 (no)	Headache (mild)- Starting 1 day 21 hrs. lasting 3 hrs. <i>Unlikely related to treatment.</i>	Maximum decrease 12% at 144 hrs. Other values 97 to 108% of predose.	
52 (yes)	Headache (mild), loose stool, nausea, intestinal cramps, vomited. Starting on days 3 and 4, lasting 6-10 hrs (some symptoms). <i>Possibly related to treatment.</i>	Maximum decrease 7% at 24 hrs. Other values 97 to 103% of predose.	
54 (no)	Headache (moderate and mild), nausea. Starting 4-5 hrs, and again at 11 hrs. Lasting 6-7 hrs and 17 hours. <i>Possibly related to treatment.</i>	Maximum decrease 4% at 36 hrs. Other values 97 to 107% of predose.	
60 (yes)	lack of appetite, headache (mild), nausea. Starting at 3-5 hrs or 13 hours. Lasting 5 to 17 hrs. <i>Possibly related to treatment.</i>	Maximum decrease 5% at 4 hrs. Other values 97 to 102% of predose.	
<p>4/12 (33%) females had headaches. 4/12 thought they received the chlorpyrifos when it was not given. As much as 17% reduction in RBC AChE can be attained in the untreated female group.</p>			
0.5 mg/kg Chlorpyrifos-Males			
3 (no)	Increased appetite. Starting 1 day and 23 hrs. Lasting 4 days. <i>Unlikely related to treatment.</i>	Maximum decrease 15% at 48 hrs. Other values 94 to 102% of predose.	<i>Increased appetite is not an expected response to an OP. Not related to treatment Maximum decrease not supported by earlier or later decreases.</i>

(non-guideline)

Subject #	Symptoms or Events (a)	RBC AChE Comments	HED's Conclusion
5 (yes)	Subject implied excessive salivation was why he thought he received the test material but there were no indications of excessive salivation listed in the events Table.	Maximum decrease 8% at 96 hours. Other values 90 to 108%.	No support from either the symptoms or AChE data to for subjects "yes" response.
9 (no)	Intestinal cramps. Starting 2 days 22 hours. Lasting 15 hrs. <i>Unlikely related to treatment.</i>	Maximum decrease 17% at 96 hrs followed by 11%, 13% and 9% at 120, 144 and 168 hours. Other values Other values were 87% to 105% of predose.	Not related to treatment since onset did not coincide with AChE ↓.
None have headaches. 1/6 thought they received the chlorpyrifos. Note hour 96 had largest decrease in RBC AChE for all but one subject in this group suggesting some assay problem. Since it is hour 96, this should not confound the interpretation of the data.			
0.5 mg/kg Chlorpyrifos-Females			
26 (no)	Nausea. Starting at 1 hr. Lasting 90 min. <i>Probably related to treatment.</i>	Maximum decrease 8% at 96, 144 and 168 hrs. Other values are 93% to 104%.	An initial localized nausea may result from an OP administration in a capsule without concomitant ↓ in AChE. Maximum ↓ in AChE does not coincide with symptoms. Not considered a definite response to chlorpyrifos.
31 (no)	Headache (moderate). Starting 1 day and 3 hrs. Lasting ~2 hrs. <i>Unlikely related to treatment.</i>	Maximum decrease 14% at 96 hrs. Other values were 90% to 104% of predose.	Onset of headache does not coincide with maximum ↓ in AChE occurring much later. Not related to treatment.
36 (yes)	Headache (mild), lightheaded, headache (mild). Starting 1 hr or 6 hrs. Lasting ~2 hrs or ~11 hrs. <i>Possibly related to treatment.</i>	Maximum decrease 9% at 4 and 96 hrs. Other values were 92% to 106%.	Onset of headaches did not coincide with maximum ↓ in AChE.
2/6 (33%) females had headaches. 1/6 thought they received the chlorpyrifos. Maximum decrease in RBC AChE does not exceed the placebo group.			

(non-guideline)

Subject #	Symptoms or Events (a)	RBC AChE Comments	HED's Conclusion
1.0 mg/kg chlorpyrifos-Males			
1 (yes)	Increased appetite. Starting 1 day and 23 hrs. Lasting 4 days six hrs. <i>Unlikely related to treatment.</i>	Maximum decrease 7% @ 48 hrs. Other values are 95% to 113% of predose.	Symptom not expected of an OP exposure and does not coincide with maximum ↓ AChE.
4 (yes)	Loose stool. Starting 2 days and 15-20 hrs and again on day 4 and 12 hrs. Lasting 1 min. <i>Unlikely related to treatment.</i>	Maximum decrease 15% @ 96 hrs followed by decreases of 8%, 12% and 8% at 120, 144 and 168 hrs. Other values 90% to 107%.	Symptoms do not coincide with maximum ↓ in AChE.
7 (yes)	No symptoms or events.	Maximum decrease 16% at 96 hours. Other values are 91% to 116%.	No support for subjects "yes" response.
11 not listed	Headache (moderate and mild). Starting ~3 hrs and again at ~23 hrs. Lasting ~19 hrs and 1 day 9 hrs. <i>Possibly related to treatment.</i>	Maximum decrease 25% @ 96 hrs. Other values were 89% (at 2 hrs) to 101% (at 4 hrs) of predose.	First headache may be associated with ~11% ↓ in AChE. Second headache not associated with ↓ AChE or maximum decrease.
14 (yes)	Queasy stomach. Starting 24 min. Lasting 10 min. <i>Possibly related to treatment.</i>	Maximum decrease 15% @ 144 hrs. Other values 88% to 99% of predose.	An initial unsettled (queasy) stomach may result from the capsule. Symptom does not coincide with ↓AChE.
1/6 has a headache. This is less than the placebo group and there is no indication that this subjects headache was more severe. 4/6 thought they received the chlorpyrifos. The maximum decrease in this group was in an individual at 96 hrs postdosing.			
1.0 mg/kg Chlorpyrifos-Females			
24 (no)	Lost voice. Starting ~18 hrs. Lasting 8 hrs.	Maximum decrease 11% @ 168 hrs. Other values 95% to 105% of predose.	Lost voice not an expected response to an OP. Symptom does not coincide with ↓ AChE. Not related to treatment.
25 (yes)	Tired. Starting ~4 hrs. Lasting 1 hrs. <i>Possibly related to treatment.</i>	Maximum decrease 9% @ 96 and 120 hrs. Other values 92% to 102%.	Symptom does not coincide with maximum ↓ ACHE.

(non-guideline)

Subject #	Symptoms or Events (a)	RBC AChE Comments	HED's Conclusion
			Not related to treatment.
30 (no)	Headache (mild), tired and repeated headaches (mild). Starting 22 min, ~ 2hrs, ~ 10 hrs and ~ 23 hrs. lasting. Up to 8 days and 7 hrs. <i>Possibly related to treatment.</i>	Maximum decrease 8% @ 96 hrs. Other values 95% to 109% of predose/	Onset and duration of symptoms so not coincide with ↓AChE.
33 (no)	Headache (mild). Starting ~ 2hrs. Lasting 4 hrs. <i>Possibly related to treatment.</i>	Maximum decrease 11% @ 144 hrs. Values from 96 hrs to 168 hrs were 89% to 95%. Other values were 97% to 111%.	Onset of symptom does not coincide with maximum of any ↓ in AChE.
35 (no)	Back stiffness. Starting 22 min. Lasting ~4 hrs. <i>Unlikely related to treatment.</i>	Maximum decrease 6% @ 168 hrs. Other values 94% to 115%.	Symptom not an expected response to OP treatment and does not coincide with maximum ↓ AChE. Not related to treatment.
2/6 (33%) females had headaches. 1/6 thought they received the chlorpyrifos. Maximum decrease does not exceed placebo group for RBC AChE.			
2.0 mg/kg Chlorpyrifos-Males			
40 (yes)	No symptoms or events.	Maximum decrease 2% at 48 hrs. Other values 99% to 103%.	No support for subjects "yes" response.
47 (no)	Cut on chin. Starting 2 days. Lasting 6 days. <i>Unrelated to treatment.</i>	Maximum decrease 5% at 24 hrs. Other values 98% to 107% of predose.	Not related to treatment.
None have headache. 1/6 thought they received the chlorpyrifos. Maximum decrease in group was to 10% for one subject (#48 at 36 hours) and dose not exceed the placebo.			
2.0 mg/kg Chlorpyrifos-Females			
51 (yes)	Headache (mild - moderate). Starting at 47 min and again at 3 hrs 7 min and lasting 2-7 hrs. <i>Possibly/probably related to treatment. One can coca-cola.</i>	Maximum decrease 6% at 12 hrs. Other values were 95 to 105% of the predose.	Onset of headache does not coincide with AChE↓. Not related to treatment.
55 (no)	Headache (mild). Starting 3 hrs, lasting 19 hrs. <i>Possibly related to</i>	Maximum decrease 5% at 120 hrs. Other values were 97 to	Onset of headache does not coincide with

(non-guideline)

Subject #	Symptoms or Events (a)	RBC AChE Comments	HED's Conclusion
	<i>treatment.</i>	107% of predose.	AChE↓.
56 not listed	Numbness in upper arms. Starting 42 min. Lasting 2 hrs and 24 min. <i>Possibly related to treatment.</i>	Maximum decrease 28% at 12 hrs. ↓ starts at 8 hours (23%↓),	See special discussion. Numbness does not coincide with AChE ↓.
58 (yes)	No symptoms or events.	Maximum decrease 7% at 12 hrs. Other values are 96% to 101%	No support for subjects "yes" response.
59 (yes)	Tired, headache (mild), chest tightness, shortness of breath, headache . Starting ~ 2hrs, and 10 hrs. Lasting 3-13 hrs. <i>Possibly related to treatment.</i>	Maximum decrease 7% at 12 hrs. Other values were 95% to 104% of predose.	First headache does not coincide with ↓ AChE, the onset of the second headache is two hours before maximum↓ in AChE but ↓ is only 7%. HED does <i>not</i> conclude that the headache is treatment related.
<p>3/6 (50%) females had headaches. Severity of headache not greater than placebo subjects and onset does not coincide with AChE decrease. 3/6 thought they received the chlorpyrifos. One subject has definite inhibition of RBC AChE based on sustained decrease at critical times.</p>			

(a) Only those subjects having reports of symptoms, "events" or responded "yes" (column 1) to the question if they thought they received the test material are listed.

Symptom data are from Appendix 4. Under symptoms, the entry in *italics* refers to the study author's conclusion regarding whether or not the symptom was related to treatment was made before the subjects were identified as to their dose group.

AChE data are from Table 5.1.2 for phase I and Table 9.1.2 for Phase II.

Appendix II - List of Tables*

Table A. Mean RBC Cholinesterase Activity (for all groups and all times).

Table B. Serum Paraoxonase/CPOase and 0-hour RBC AChE Activity and Phenotype for dosed groups.

Table C. Serum Paraoxonase/CPOase and 0-hour RBC AChE Activity and Phenotype for control groups.

Table D. Male RBC AChE Activity, Blood TCP Level and CP Level for the Group Dosed with 2 mg/kg.

Table E. Female RBC AChE Activity, Blood TCP Level and CP Level for the Group Dosed with 2 mg/kg.

Table F. Male RBC AChE Activity, Blood TCP Level and CP Level for the Group Dosed with 1 mg/kg.

Table G. Female RBC AChE Activity, Blood TCP Level and CP Level for the Group Dosed with 1 mg/kg.

Table H. Male and Female RBC AChE Activity and Blood TCP Level for the Group Dosed with 0.5 mg/kg.

Table I. Individual Male and Female RBC AChE Activity (Phase I Control).

Table J. Individual Male and Female RBC AChE Activity (Phase 2 control)

Table K. Individual Male and Female Urinary TCP levels.

* Tables were prepared by Dr. L. Taylor, HED.

Table A. Mean RBC Cholinesterase Activity (U/L; mean \pm s.d.)					
Time/Dose (mg/kg)	0^A	0^B	0.5^A	1.0^A	2.0^B
Males					
-10	7520 \pm 733	9292 \pm 1130	8758 \pm 706	9317 \pm 790	8802 \pm 753
0	8143 \pm 982	9171 \pm 1112	8998 \pm 730	9572 \pm 539	8608 \pm 896
2	8023 \pm 795	9282 \pm 1026	9145 \pm 714	9568 \pm 427	8675 \pm 844
4	7948 \pm 756	9145 \pm 1066	9046 \pm 623	9862 \pm 865	8642 \pm 924
8	8008 \pm 645	9189 \pm 1101	9189 \pm 924	9524 \pm 352	8613 \pm 872
12	8043 \pm 705	9198 \pm 1003	8848 \pm 663	9543 \pm 678	8584 \pm 806
24	8036 \pm 815	9051 \pm 852	9046 \pm 817	9599 \pm 637	8637 \pm 878
36	7674 \pm 556	8999 \pm 1020	8716 \pm 821	9295 \pm 626	8663 \pm 937
48	7505 \pm 845	9042 \pm 904	8246 \pm 896	8694 \pm 669	8567 \pm 881
72	7920 \pm 838	9425 \pm 1041	8974 \pm 810	9623 \pm 652	9004 \pm 840
96	7421 \pm 745	9209 \pm 849	8036 \pm 738	8263 \pm 399	8815 \pm 868
120	7536 \pm 694	9337 \pm 765	8571 \pm 691	8939 \pm 255	8807 \pm 904
144	7316 \pm 598	9302 \pm 800	8764 \pm 837	8714 \pm 418	8857 \pm 907
168	7770 \pm 734	9304 \pm 994	8527 \pm 764	8600 \pm 470	8793 \pm 562
Females					
-10	8488 \pm 829	8485 \pm 373	8804 \pm 1068	8833 \pm 597	8503 \pm 939
0	8619 \pm 861	8576 \pm 556	8612 \pm 1160	9165 \pm 709	8523 \pm 855
2	8611 \pm 915	8444 \pm 494	8666 \pm 1194	9095 \pm 366	8395 \pm 855
4	8762 \pm 902	8380 \pm 422	8412 \pm 1368	9396 \pm 517	8557 \pm 1181
8	8817 \pm 884	8716 \pm 535	8547 \pm 1010	9060 \pm 528	8230 \pm 1274
12	8404 \pm 696	8589 \pm 499	8334 \pm 917	8886 \pm 400	7761 \pm 1239
24	8503 \pm 900	8510 \pm 667	8434 \pm 857	9053 \pm 241	8092 \pm 1191
36	8089 \pm 829	8399 \pm 476	8244 \pm 1015	8617 \pm 379	8166 \pm 1100
48	8349 \pm 735	8545 \pm 496	8459 \pm 1068	8895 \pm 641	8057 \pm 1202
72	8551 \pm 583	8941 \pm 442	8938 \pm 1083	9181 \pm 477	8604 \pm 1064
96	7795 \pm 759	8620 \pm 537	8147 \pm 1213	8508 \pm 791	8551 \pm 812
120	8092 \pm 721	8712 \pm 507	8301 \pm 857	8466 \pm 612	8591 \pm 682
144	8144 \pm 872	8428 \pm 727	8028 \pm 917	8462 \pm 714	8526 \pm 1111
168	8036 \pm 876	8549 \pm 571	8198 \pm 910	8366 \pm 499	8419 \pm 814

Data from Tables 5.1.1 (pages 55-57) and 9.1.1 (pages 76-77) of MRID 44811002; ^A Phase 1; ^B Phase 2

(non-guideline)

Table B. Serum Paraoxonase/CPOase and 0-hour RBC AChE Activity and Phenotype			
#/phenotype	CPOase (U/L)	Paraoxonase (U/L)	RBC AChE (U/L)
0.5 mg/kg [range]			
3M (OR)	6850	706	8613
5M (QQ)	8666	317	7942
9M (QQ)	10446	417	8602
12M (QQ)	5412	250	9471
15M (OR)	6871	745	9889
18M (OR)	5412	562	9471
	7276±1963 (male)	500±204 (male)	8998±730 (male)
19F (OR)	8073	595	7282
22F (OR)	6994	717	9218
26F (QQ)	8954	373	8602
28F (OR)	8091	895	9900
31F (QQ)	6671	261	9515
36F (OR)	13341	1346	7156
	8687±2424 (female)	698±391 (female)	8612±1160 (female)
mean±s.d.	7965±1536 (both)	599±315 (both)	
1.0 mg/kg [range]			
1M (QQ)	6599	317	9108
4M (RR)	8505	1479	9669
7M (OR)	9008	984	9713
11M (QQ)	7785	361	10098
14M (QQ)	8774	367	10087
16M (OR)	8325	834	8756
	8166±874 (male)	724±464 (male)	9572±539 (male)
21F (QQ)	11615	467	9900
24F (QQ)	7534	295	9757
25F (QQ)	7426	339	9548
30F (OR)	10141	923	9130
33F (OR)	8019	1040	8140
35F (OR)	7821	756	8514
	8754±1719 (female)	637±314 (female)	9165±709 (female)
mean±s.d.	8463±1386 (both)	680±380 (both)	
2.0 mg/kg [range]			
38M (OR)	13018	1234	8283
40M (QQ)	8918	345	10021
42M (OR)	7048	890	9372
43M (OR)	9134	801	8118
47M (QQ)	10213	456	7645
48M (OR)	8199	823	8206
	9422±2051 (male)	758±320 (male)	8608±896 (male)
49F (QQ)	9997	367	7766
51F (OR)	10716	1234	7942
55F (RR)	9422	1590	10076
56F (QQ)	9278	367	8910
58F (QQ)	10141	389	8195
59F (QQ)	8199	345	8250
	9626±871 (female)	715±551 (female)	8523±855 (female)
mean±s.d.	9523±1517 (both)	737±430 (both)	

pages 48-50, 55-57, and 76-77 (MRID 45144101); QQ (low); OR (mid); RR (high)

Table C. Serum Paraoxonase/CPOase and 0-hour RBC AChE Activity (control) and Phenotype			
Subject #	CPOase (units/L)	Paraoxonase (units/L)	RBC AChE (U/L)
Control [range]			
2M (RR)	9565	1668	9196
6M (OR)	5430	645	8921
8M (OR)	6329	728	6809
10M (OR)	9350	882	7821
13M (QQ)	7678	317	8833
17M (QQ)	8001	311	7277
mean±s.d.	7726±1632 (male)	558±500 (male)	8143±982 (male)
20F (QQ)	10015	411A	8239
23F (QQ)	6329	284	8723
27F (QQ)	8217	350	10208
29F (OR)	9871	834	7865
32F (QQ)	9817	434	8723
34F (OR)	10410	1207	7953
mean±s.d.	9110±1556 (female)	586±360 (female)	8619±861 (female)
mean±s.d.	8418±1639 (both)	673±425 (both)	
Control [range]			
37M (OR)	9997	1001	9361
39M (QQ)	15894	567	8569
41M (QQ)	9206	378	9592
44M (OR)	9709	1045	10835
45M (OR)	11723	1112	7486
46M (OR)	11363	1134	9185
mean±s.d.	11315±2445 (male)	872±319 (male)	9171±1112 (male)
50F (QQ)	10141	423	8492
52F (QQ)	10069	456	7744
53F (OR)	14096	1134	8261
54F (QQ)	6904	289	8602
57F (RR)	17333	2502	9086
60F (QQ)	9853	367	9273
mean±s.d.	11400±3700 (female)	862±860 (female)	8576±556 (female)
mean±s.d.	11357±3097 (both)	867±618 (both)	

Pages 57 and 77 (MRID 44811002); QQ (low); OR (mid); RR (high)

(non-guideline)

Table D. Male RBC AChE Activity, Blood TCP Level, and CP Level (2.0 mg/kg)						
Subject #	38	40	42	43	47	48
Hour	AChE (U/L)					
-10	9141	9680	9493	8041	7887	8569
0	8283	10021	9372	8118	7645	8206
2	8437	9922	9537	8206	7931	8019
4	8360	10109	9471	7964	7942	8008
8	9097	9856	9152	7942	7744	7887
12	8800	9768	9130	8327	7788	7689
24	8877	9790	9350	8228	7370	8206
36	8998	9889	9405	8437	7700	7546
48	8481	9636	9658	8129	7667	7832
72	9372	9966	9834	8668	8107	8074
96	8976	9966	9648	8690	7942	7766
120	9108	10021	9592	8052	8305	7766
144	8844	9955	9911	8569	7920	7942
168	8734	9691	9174	8668	8305	8184
Chlorpyrifos concentrations (ng/g) in blood samples						
0	ND	ND	ND	ND	ND	ND
2	ND	ND	ND	ND	3.1	ND
4	ND	ND	ND	ND	1.3	ND
8	ND	ND	ND	ND	3.4	ND
12	ND	ND	ND	ND	1.8	ND
24	ND	ND	ND	ND	ND	ND
36	ND	ND	ND	ND	ND	ND
48	ND	ND	ND	ND	ND	ND
72	ND	ND	ND	ND	ND	ND
96	ND	ND	ND	ND	ND	ND
120	ND	ND	ND	ND	ND	ND
144	ND	ND	ND	ND	ND	ND
168	ND	ND	ND	ND	ND	ND
TCP concentrations (ng/g) in blood samples						
0	ND	ND	ND	ND	ND	ND
2	420	61	44	230	580	180
4	560	220	130	340	640	250
8	510	320	230	330	790	240
12	440	340	270	410	910	260
24	430	340	ns	520	980	380
36	500	360	360	610	960	460
48	530	410	370	610	1000	470
72	1100	270	320	320	690	300
96	290	170	220	190	460	210
120	160	120	160	90	320	140
144	85	75	96	66	220	77
168	41	98	220	40	150	48

Data from Tables 5 and 7 (pages 34 and 36) of MRID 45144101; ns no sample; ~~value not used~~

Table E. Female RBC AChE Activity, Blood TCP Level and CP Level (2 mg/kg)						
Subject #	49	51	55	56	58	59
hours	AChE (U/L)					
-10	7832	8283	10373	8426	8041	8063
0	7766	7942	10076	8910	8195	8250
2	7700	7931	10032	8602	8041	8063
4	7662	7997	10901	8525	8096	8162
8	8008	7986	10582	6688 (25)	7931	8184
12	7513	7640	10032	6221 (30)	7535 (8)	7623 (8)
24	8008	7722	10131	6424 (28)	8107	8162
36	8710	7700	10274	7051 (21)	8107	8052
48	7568	7876	10395	6892 (23)	7821	7788
72	7920	8195	10461	X	8503	7942
96	7986	8415	9933	X	7931	8492
120	8019	8569	9757	X	8228	8382
144	7931	7975	10472	X	7832	8415
168	8327	8074	9845	X	7876	7975
Chlorpyrifos concentrations (ng/g) in blood samples						
0	ND	ND	ND	ND	ND	ND
2	3.1	ND	ND	ND	ND	2.2
4	xx	ND	ND	ND	ND	4.1
8	1.7	ND	ND	18.0	ND	4.1
12	ND	ND	ND	2.5	ND	1.5
24	ND	ND	ND	ND	ND	ND
36	ND	ND	ND	ND	ND	ND
48	ND	ND	ND	ND	ND	ND
72	ND	ND	ND	X	ND	ND
96	ND	ND	ND	X	ND	ND
120	ND	ND	ND	X	ND	ND
144	ND	ND	ND	X	ND	ND
0168	ND	ND	ND	X	ND	ND
TCP concentrations (ng/g) in blood samples						
0	ND	ND	ND	ND	ND	ND
2	290	420	290	71	240	250
4	450	580	220	120	310	470
8	490	1300	520	1600	480	610
12	440	690	500	1500	340	610
24	470	540	600	1300	400	500
36	430	750	600	1100	430	480
48	360	730	530	980	360	390
72	200	600	340	X	190	220
96	130	420	210	X	110	110
120	84	150	120	X	65	58
144	52	170	73	X	37	32
168	35	110	45	X	24	23

Data from Tables 5 and 7 (pages 34 and 36) of MRID 45144101; (% inhibition from 0 hour); xx sample not analyzed; X subject left study

(non-guideline)

Table F. Male RBC AChE Activity, Blood TCP Level and CP Level (1.0 mg/kg)						
Subject #	1	4	7	11	14	16
AChE (U/L)						
-10	8272	9416	9603	10307	9823	8481
0	9108	9669	9713	10098	10087	8756
2	9625	9438	10230	9097	9845	9174
4	9823	9405	11198	10318	9801	8624
8	9284	9361	9834	9768	9878	9020
12	9042	10219	10109	9779	9658	8448
24	9306	10219	9966	9977	9658	8470
36	9119	9702	9746	9768	9295	8140
48	8074	8624	9196	9141	9174	7953
72	9295	10164	9801	10153	9867	8459
96	8283	8151	8096	7700 (↓24)	8899	8448
120	9218	8723	8800	9185	9086	8624
144	8833	8426	9141	9218	8492	8173
168	8228	8734	9174	-	8844	8019
Chlorpyrifos concentrations (ng/g) in blood samples						
0	ND	ND	ND	Ns	ND	ND
2	ND	ND	ND	1.0	ND	ND
4	ND	ND	ND	ND	2.7	ND
8	ND	ND	ND	ND	1.5	ND
12	ND	ND	ND	ND	ND	ND
24	ND	ND	ND	ND	ND	ND
36	ND	ND	ND	ND	ND	ND
48	ND	ND	ND	ND	ND	ND
72	ND	ND	ND	ND	ND	ND
96	ND	ND	ND	ND	ND	ND
120	ND	ND	ND	ND	ND	ND
144	ND	ND	ND	ND	ND	ND
168	ND	ND	ND	Ns	ND	ND
TCP concentrations (ng/g) in blood samples						
0	ND	ND	ND	ND	ND	ND
2	140	49	370	260	170	150
4	280	130	430	450	570	200
8	340	290	440	400	610	170
12	340	300	350	340	540	170
24	440	250	270	270	520	200
36	430	240	160	200	440	280
48	310	230	140	160	420	300
72	160	160	54	75	280	210
96	84	98	23	36	220	130
120	41	54	10	20	150	84
144	18	34	ND	ND	84	48
168	11	20	ND	Ns	50	29

Data from page 56 of 578 and Tables 5 and 7 (pages 34 and 36) of MRID 45144101; ns no sample;

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Table G. Female RBC AChE Activity, Blood TCP Level and CP Level (1.0 mg/kg)						
Subject #	21	24	25	30	33	35
AChE (U/L)						
-10	9416	9295	9031	9064	7942	8250
0	9900	9757	9548	9130	8140	8514
2	9460	9460	9240	8932	8965	8514
4	10087	9999	9152	9229	8866	9042
8	9394	9570	9427	9119	8624	8228
12	9361	9350	8855	8822	8470	8459
24	9317	9097	9339	8943	8877	8745
36	8789	9218	8624	8536	8074	8459
48	9361	9604	9174	8998	7766	8569
72	9064	9240	9460	9900	8503	8921
96	8637	8844	8437	8349	7178	9603
120	8954	9086	8426	8855	7601	7876
144	8932	9207	8580	8613	7156	8283
168	8624	8525	8855	8712	7678	7799
Chlorpyrifos concentrations (ng/g) in blood samples						
0	ND	ND	ND	ND	ND	ND
2	5.6	ND	ND	ND	ND	ND
4	2.9	ND	ND	ND	2ND	ND
8	ND	ND	ND	1.1	1ND	ND
12	ND	ND	ND	ND	ND	ND
24	ND	ND	ND	ND	ND	ND
36	ND	ND	ND	ND	ND	ND
48	ND	ND	ND	ND	ND	ND
72	ND	ND	ND	ND	ND	ND
96	ND	ND	ND	ND	ND	ND
120	ND	ND	ND	ND	ND	ND
144	ND	ND	ND	ND	ND	ND
168	ND	ND	ND	ND	ND	ND
TCP concentrations (ng/g) in blood samples						
0	ND	ND	ND	ND	ND	ND
2	220	96	160	10	32	72
4	350	430	180	160	93	250
8	310	340	190	310	100	490
12	300	310	190	290	110	430
24	300	320	220	290	140	370
36	290	320	200	280	140	310
48	280	300	160	280	110	350
72	140	250	85	240	70	190
96	75	180	30	160	45	140
120	43	120	16	85	29	99
144	22	73	ND	45	17	75
168	13	47	ND	23	13	30

Data from page 56 of 578 and Tables 5 and 7 (pages 34 and 36) of MRID 45144101; ns no sample;

(non-guideline)

Table H. Male and Female RBC AChE Activity and Blood TCP Level (0.5 mg/kg)						
Subject #	3	5	9	12	15	18
MALES AChE (U/L)						
-10	8393	7865	8294	8877	9713	9405
0	8613	7942	8602	9471	9889	9471
2	8668	8547	8437	9218	10021	9977
4	8514	8481	8646	9031	9944	9658
8	8228	8217	8844	9482	9845	10516
12	8118	8030	8723	9229	9471	9515
24	8393	8074	8580	9394	9680	10153
36	7997	7810	8261	8910	9670	9746
48	7244	7128	8107	9053	9119	8822
72	8426	8074	8260	9504	9889	9702
96	8558	7282	6985 (↓19)	8096	8525	8767
120	8679	7920	7535 (↓12)	8921	9207	9163
144	8283	8712	7376 (↓14)	9537	9548	9130
168	8107	7931	7700 (↓11)	8547	9295	9581
MALES TCP concentrations (ng/g) in blood samples						
0	ND	ND	ND	ND	ND	ND
2	23	49	24	29	160	51
4	95	53	140	83	250	100
8	97	51	130	96	240	130
12	96	130	240	97	210	130
24	130	98	130	100	190	120
36	140	100	130	110	190	110
48	140	100	120	110	190	110
72	87	59	70	96	130	73
96	58	24	41	67	88	48
120	38	8	25	38	56	29
144	22	ND	14	19+	33	15
168	14	ND	10	ND	23	9
Subject #	19	22	26	28	31	36
FEMALES AChE (U/L)						
-10	9724	9086	8063	10010	8800	7139
0	7282	9218	8602	9900	9515	7156
2	7986	8932	8448	10252	9526	6853
4	7810	9141	8239	10593	8239	6501
8	8041	9097	8305	9966	8866	7007
12	7843	8349	8437	9779	8602	6996
24	7832	8866	8041	9746	8756	7365
36	7535	8987	7810	9834	8228	7068
48	7623	8921	8129	10109	8855	7117
72	7953	9394	8701	10516	9482	7579
96	7997	8646	7689	10153	7920	6474
120	7931	8437	7975	9581	8811	7073
144	7689	8195	7744	9218	8734	6589
168	7744	8657	7733	9130	9086	6837
FEMALES TCP concentrations (ng/g) in blood samples						
0	ND	ND	ND	ND	ND	ND
2	110	190	12	61	77	62
4	190	380	89	91	120	220
8	210	350	110	140	220	260
12	ND	310	110	130	230	230
24	189	220	130	140	210	220
36	179	150	190	110	200	230
48	180	140	180	91	190	230
72	110	59	160	46	130	150

(non-guideline)

96	88	31	140	25	64	83
120	58	17	120	14	41	49
144	35	ND	107	ND	22	27
168	23	ND	88	ND	14	19

Data from Tables 5 and 7 (pages 34 and 36) of MRID 45144101

(non-guideline)

Table I. Male and Female RBC AChE Activity (Phase 1 control)						
Subject #	2	6	8	10	13	17
MALES AChE (U/L)						
-10	8294	7810	6562	8327	6985	7139
0	9196	8921	6809	7821	8833	7277
2	8910	8558	6782	8019	8448	7420
4	8382	8580	6622	8118	8481	7502
8	8239	8701	6886	7986	8481	7755
12	8360	8635	6886	7876	8789	7711
24	8734	8723	6655	8426	8173	7502
36	8448	7700	6864	8052	7689	7288
48	7711	7964	6083	7678	8536	7057
72	8569	8921	6672	7920	8195	7244
96	8151	7536	6336	6771	8206	7524
120	8404	7799	6457	7321	8041	7194
144	7810	7733	6281	7134	7799	7139
168	8206	8778	6677	7623	8019	7315
Subject #	20	23	27	29	32	34
FEMALES AChE (U/L)						
-10	7178	8481	9724	8382	8294	8866
0	8239	8723	10208	7865	8723	7953
2	7568	9053	10010	8382	8932	7722
4	7953	9504	10076	8426	8855	7755
8	8239	9174	10373	8701	8569	7843
12	7898	8657	9713	8118	8085	7953
24	7645	8844	10098	8195	8481	7755
36	7249	8712	9284	7843	8261	7183
48	7931	8800	9603	8184	8008	7568
72	7843	8789	9416	8437	8822	7997
96	7415	8272	8800	7073	8305	7002
120	7513	8360	9053	8283	-	7249
144	7722	7975	9570	8206	-	7249
168	7689	8437	9317	7722	-	7013

Data from Table 5.1.1 (pages 57) of MRID 44811002

(non-guideline)

Table J. Male and Female RBC AChE Activity (Phase 2 control)						
Subject #	37	39	41	44	45	46
MALES AChE (U/L)						
-10	9878	8910	9240	10769	7387	9570
0	9361	8569	9592	10835	7486	9185
2	9394	8723	10197	10681	7898	8800
4	9757	8470	9240	10703	7590	9108
8	10318	8382	8998	10494	7645	9295
12	9999	8723	8998	10164	7613	9790
24	9680	8547	8789	10197	7810	9284
36	9669	8294	8910	10318	7453	9350
48	9713	8481	9119	10208	7645	9086
72	9482	8657	9394	10923	7975	10120
96	9306	8778	9460	10329	7810	9570
120	9427	8976	9504	10406	8096	9614
144	9416	8811	9174	9691	8184	10538
168	9823	8437	9548	10802	8041	9174
Subject #	50	52	53	54	57	60
FEMALES AChE (U/L)						
-10	8107	7975	8712	8470	8734	8910
0	8492	7744	8261	8602	9086	9273
2	8327	7623	8547	8294	9020	8855
4	8239	7645	8349	8558	8866	8624
8	8415	7865	9031	8558	9218	9207
12	8404	7854	8723	8327	8987	9240
24	8415	7293	8756	8437	9174	8987
36	8063	7810	8470	8228	8668	9152
48	8184	7854	8844	8327	8954	9108
72	9108	8096	9273	9108	9229	8833
96	8426	7623	8811	9108	8899	8855
120	8965	7810	8569	8646	9229	9053
144	7337	7854	9339	8415	8778	8844
168	8382	7634	8591	8382	9086	9218

Data from Table 9.1.1 (pages 77) of MRID 44811002

(non-guideline)

Table K1. Male and Female Urine TCP Level (0.5 mg/kg)						
Subject #	3 (QR)	5 (QQ)	9 (QQ)	12 (QQ)	15 (QR)	18 (QR)
Time interval (hr)	MALES TCP concentrations (ng/mL) in urine samples					
-12-0	BLOQ	3.4	4.4	BLOQ	3.4	7.1
0-6	98	520	1396	152	417	200
6-12	593	724	1217	427	1256	482
12-24	964	907	940	678	1256	1388
24-36	636	1440	1512	712	687	836
36-48	981	739	1472	1239	ns	1688
48-60	1103	298	1108	1398	ns	1605
60-72	636	453	94.5	959	1389	690
72-84	496	360	600	680	465	500
84-96	278	70	316	422	ns	366
96-108	178	140	146	345	112	298
108-120	120	63	223	464	315	184
120-132	148	44	96	211	ns	196
132-144	161	9	56	115	190	136
144-156	98	9.3	11.4	122	ns	137
156-168	70	5.8	11	110	91	78
Subject #	19	22	26	28	31	36
	FEMALES TCP concentrations (ng/mL) in urine samples					
-12-0	19	BLOQ	5.2	4.5	BLOQ	2.4
0-6	618	1369	284	500	347	622
6-12	1292	719	344	238	393	468
12-24	4292	1578	2057	509	730	608
24-36	2065	490	716	360	365	671
36-48	974	755	805	366	590	726
48-60	1972	673	2012	162	169	232
60-72	2973	597	653	200	384	362
72-84	ns	359	691	66	230	514
84-96	919	159	1530	115	234	246
96-108	714	96	1090	50	57	554
108-120	688	112	1107	75	100	276
120-132	ns	38	356	41	42	130
132-144	711	12	1754	29	62	158
144-156	ns	84	1502	22	26	161
156-168	132	24	504	46	42	98

Data from Appendix Table 3 (pages 68 -70) of MRID 45144101; ns no sample;

(non-guideline)

Table K2. Male and Female Urine TCP Level (1.0 mg/kg)						
Subject #	1 (QQ)	4 (RR)	7 (QR)	11 (QQ)	14 (QQ)	16 (QR)
Time interval (hr)	MALES TCP concentrations (ng/mL) in urine samples					
-12-0	3.4	5	3.2	5.3	8.8	3.4
0-6	496	212	1286	2128	4496	1614
6-12	1373	1779	2499	2764	7952	658
12-24	3217	1636	2941	4758	3602	716
24-36	2224	2034	3706	1967	3382	3666
36-48	2896	1334	1126	3109	4526	2370
48-60	928	2520	845	ns	2900	2486
60-72	1414	974	306	1790	3202	759
72-84	889	502	107	ns	2976	1579
84-96	816	1169	142	390	2455	1301
96-108	321	690	51	ns	ns	1418
108-120	142	807	44	174	808	590
120-132	220	308	9	ns	1254	1304
132-144	268	462	20	98	1216	299
144-156	134	362	8	ns	1137	360
156-168	74	70	8	ns	568	231
Subject #	21 (QQ)	24 (QQ)	25 (QQ)	30 (QR)	33 (QR)	35 (QR)
Time interval (hr)	FEMALES TCP concentrations (ng/mL) in urine samples					
-12-0	6.4	2.8	2.8	7.2	12.8	BLOQ
0-6	517	1126	808	722	169	390
6-12	2859	1784	1422	3332	737	466
12-24	2402	1302	1472	1914	1278	935
24-36	1240	1744	2341	2515	852	451
36-48	2593	2054	740	2642	1289	806
48-60	3114	1533	1118	2228	ns	324
60-72	716	1193	792	1562	752	424
72-84	1351	1626	706	1848	574	404
84-96	1885	1308	426	1148	598	191
96-108	402	466	218	1091	402	216
108-120	550	1027	192	1131	352	142
120-132	280	455	140	894	ns	161
132-144	264	300	76	766	336	110
144-156	52	136	56	592	168	98
156-168	184	220	48	556	204	49

Data from Appendix Table 4 (pages 71 -73) of MRID 45144101; ns no sample;

Table K3. Male and Female Urine TCP Level (2.0 mg/kg)						
Subject #	38 (QR)	40 (QQ)	42 (QR)	43 (QR)	47 (QQ)	48 (QR)
Time interval (hr)	MALES TCP concentrations (ng/mL) in urine samples					
-12-0	4.8	BLOQ	BLOQ	8.4	7	3.0
0-6	1308	189	878	850	1506	949
6-12	2030	578	3282	1314	4704	784
12-24	2794	2224	6164	2672	15323	3360
24-36	3263	1196	4532	5188	5549	3262
36-48	2822	1931	2818	5725	8610	2662
48-60	2674	1218	3458	1688	8865	853
60-72	2216	730	1213	2344	8129	1848
72-84	1318	560	ns	1126	5416	752
84-96	1656	371	1556	1618	3905	659
96-108	900	572	ns	886	2444	427
108-120	542	454	2398	870	2342	722
120-132	501	184	1507	747	1298	428
132-144	464	185	622	794	1512	642
144-156	507	170	1707	659	1482	452
156-168	414	264	994	402	-	-
Subject #	49 (QQ)	51 (QR)	55 (RR)	56 (QQ)	58 (QQ)	59 (QQ)
Time interval (hr)	FEMALES TCP concentrations (ng/mL) in urine samples					
-12-0	4.4	10.9	5.1	10.9	4.5	4.2
0-6	882	1413	676	1246	1690	1881
6-12	2183	3688	1850	7966	994	4682
12-24	3310	6064	5275	8148	1868	5036
24-36	1453	1786	1658	6270	2304	6622
36-48	1897	3736	4537	7068	2458	3822
48-60	958	2114	1662	-	1538	2902
60-72	1130	1443	2548	-	1469	2370
72-84	645	1286	533	-	1496	1855
84-96	570	2526	354	-	1530	1198
96-108	218	1078	332	-	604	842
108-120	286	1014	448	-	631	1113
120-132	226	918	206	-	84	805
132-144	288	474	329	-	85	636
144-156	150	696	212	-	182	228
156-168	133	616	98	-	147	156

Data from Appendix Table 5 (pages 74 -76) of MRID 45144101; ns no sample;