(12-7-98)

DATA EVALUATION REPORT
CHLORPYRIFOS
STUDY TYPE: BLOOD TIME COURSE (PART A), NONGUIDELINE

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 99-1

Primary Reviewer:
H. Tim Borges, Ph.D., MT (ASCP), D.A.B.T. Signature: _____
Date: _____

Secondary Reviewers:
Robert A. Young, Ph.D., D.A.B.T. Signature: _____
Date: _____

Robert H. Ross, M.S., Group Leader Signature: _____
Date: _____

Quality Assurance:
Susan Chang, M.S. Signature: _____
Date: _____

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EPA Reviewer:
J. Doherty., PhD, ReRegistration Branch III, _____, Date _____
EPA: Work Assignment Manager
S. Diwan, Ph.D., Toxicology Branch II _____, Date _____

DATA EVALUATION RECORD

STUDY TYPE: Nonguideline Concentration - time course in blood

DP BARCODE: D249600
P.C. CODE: 05901

SUBMISSION CODE: S548834
TOX. CHEM. NO.: 219AA

TEST MATERIAL (PURITY): Chlorpyrifos (purity = 99.8% nonradiolabeled, 89.4% radiolabeled)

SYNONYMS: *O,O*-diethyl(O-3,5,6-trichloro-2-pyridyl)phosphorothioate; DURSBAN, LORSBAN

CITATION: Mendrala, A.L., Brzak, K.A. (1998) Chlorpyrifos: Part A - concentration-time course of chlorpyrifos and chlorpyrifos-oxon in blood. Health & Environmental Research Laboratories, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID: 971187A. August 31, 1998. MRID 44648101.

SPONSOR: Dow AgroSciences, 9330 Zionsville Rd., Indianapolis, IN 46268

EXECUTIVE SUMMARY: This study (MRID No.: 44648101) was done to help construct and validate a physiologically-based pharmacokinetic model for chlorpyrifos (Unlabeled - 99.8% a.i., Lot # MM930503-17; Labeled - 89.4% a.i., Lot # B930-51 [INV1134]) a weak inhibitor of acetylcholinesterase activity, and its metabolites, chlorpyrifos-oxon (OXON), a strong cholinesterase inhibitor and 3,5,6-trichloropyridinol. Groups of 24 male rats were given a single gavage dose of 0.5, 1, 5, 10, 50, or 100 mg/kg chlorpyrifos in corn oil. Four rats from each group were killed 10 and 20 minutes and 1, 3, 6, and 12 hours after treatment. Cholinesterase activity was measured in the brain and plasma at each time point, as well as the plasma concentration of the test material and its OXON metabolite. In a separate portion of the study, four male rats were given a single gavage dose of labeled chlorpyrifos at a concentration of 5 or 100.0 mg/kg and were sacrificed three hours later. Blood was collected from the animals at sacrifice and the concentration of the test material and its metabolites 3,5,6-trichloropyridinol (TCP) and OXON determined.

Plasma cholinesterase activity decreased in a time- and dose-dependent manner. The plasma cholinesterase activities of rats treated with 0.5, 1, 5 or 10 mg/kg were maximally decreased 3-6 hours after treatment, with both the decrease and recovery of activity being dose-dependent. The decrease in activity of rats treated with 50 or 100 mg/kg began within 10 minutes of treatment. By 12 hours after treatment, both groups was approximately 11% of the control group and had not shown signs of recovery.

Brain cholinesterase activity was not affected as dramatically by test material treatment as plasma activity with only the 10, 50, and 100 mg/kg dose groups showing significant effects. The brain cholinesterase activity of rats treated with 10 mg/kg test material began to decline within three hours of treatment and was significantly decreased by six hours after treatment. The brain cholinesterase activity in the 50 or 100 mg/kg dose groups decreased significantly within one hour of treatment; and by 12 hours, were approximately 30% and 20%, respectively, of control. In none of the affected groups did brain cholinesterase show signs of recovery.

Peak chlorpyrifos blood concentrations occurred within three hours of treatment in all but the lowest dose group. The area under the curve (AUC) was calculated as 0.4, 1.1, 5.0, and 12.5 μmole hr L^{-1} for the 5.0, 10.0, 50.0, and 100 mg/kg groups, respectively and yielded calculated blood half-lives of chlorpyrifos of 2.7,1.5, 2.1, and 7.3 hours for the 5.0, 10.0, 50.0, and 100.0 mg/kg dose groups, respectively. Regardless of dose, the highest concentration of OXON detected was 2.5 ng/g found in the blood of rats treated with 50 mg/kg test material one hour post-treatment. Following treatment with 5 or 100 mg/kg labeled test material, ≥98% of the activity detected in the blood was identified as TCP metabolite with the remaining attributed to the parent compound. Since OXON is an intermediate in the formation of TCP and none of the metabolite was detected, these studies support that the half-life of the OXON metabolite is short (reportedly 10 seconds) and that *in vivo* metabolism of chlorpyrifos is rapid.

This study is considered acceptable (nonguideline). It may partially fulfill guideline requirements in other areas.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided in the study report.

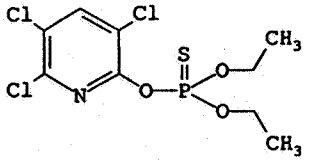
I. MATERIALS AND METHODS

A. MATERIALS

1. Test compound: Clorpyrifos
   Purity: Unlabeled - 99.8% a.i.
   Labeled - 89.4% a.i. (impurities - 6.1% 3,5,6-trichloropyridinol (TCP), 3.5% chlorpyrifos-oxon (OXON), 1% unidentified)

Lot No.: Unlabeled - MM930503-17(TSN100227); Labeled - B930-51 (INV1134)
Description: amber solid
CAS No.: 2921-88-2
Radiolabel Location: ^{14}C at ring positions 2 and 6
Specific Activity: 25.3 mCi/mmol

Structure:



2. Vehicle: USP/NF corn oil

3. Test animals

Species: rat
Strain: Fischer 344
Age and weight at study initiation: 10-11 weeks, males 179-232 g
Source: Charles River Laboratories Inc., Raleigh, NC
Acclimation period: not reported
Housing: individually in stainless steel or plastic cages after dosing
Diet: Purina Certified Rodent Lab Diet #5002, *ad libitum*
Water: tap water, *ad libitum*
Environmental conditions:
Temperature: 22-24°C
Humidity: 44-52%
Air changes: not reported
Photoperiod: 12 hour light/dark

4. Preparation of dosing solutions

Stock unlabeled dose solution was prepared by dissolving the test material in a measured volume of corn oil. The corn oil volume was then adjusted to the desired test material concentration and warmed to 50°C. While mixing with a magnetic stirrer, aliquots of the stock solution were serially diluted with corn oil to obtain the

desired working dose solutions of 0.5, 1.0, 5.0, 50.0, and 100 mg/kg. The working dose solutions were mixed approximately 24 hours before treatment. According to the study author, the dose solutions were stable in corn oil for approximately 42 days.

The radiolabeled dose solutions were prepared by dissolving ^{14}C-chlorpyrifos (~0.7 mCi/mL) in acetone and adding an aliquot of this solution to corn oil. For the 5 mg/kg labeled dose solution, unlabeled test material was also dissolved in acetone and a measured aliquot added to the labeled corn oil solution. For the 100 mg/kg-labeled dose, a measured amount of unlabeled test material was mixed directly in the labeled test material corn oil solution. All dose solutions were mixed with a magnetic stirrer before and during use.

B. STUDY DESIGN AND METHODS

1. Dosing and sample collection

Unlabeled Dose Study - The study was done to determine the time course in blood of the test material and its metabolite, chlorpyrifos-oxon (OXON), and their effects on plasma and brain cholinesterase activity. Rats fasted for 16 hours were given a single gavage dose of 0.0, 0.5, 1.0, 5.0, 10.0, 50.0, or 100 mg/kg test material. All treatment groups contained 24 animals except the 50 and 100 mg/kg treatment groups which contained 48 animals. Four rats from each group were sacrificed and blood and/or brain were collected 10 and 20 minutes and 1, 3, 6, and 12 hours post-treatment for chemical analysis and cholinesterase activity.

Labeled Dose Study - The study was done to determine the plasma concentration of the test material and its metabolites OXON and 3,5,6-trichloropyridinol (TCP) three hours post-treatment. Four rats fasted for 16 hours per group were given a single gavage dose of 5 or 100 mg/kg labeled test material. Three hours after treatment, the rats were sacrificed and blood collected for chemical and radioactivity analysis.

2. Sample preparation/analysis

Unlabeled Dose Study - Whole blood samples were collected by cardiac puncture 10 and 20 minutes and 1, 3, 6, and 12 hours post-treatment. During the initial 100 mg/kg dose group study, the blood samples were drawn into heparinized syringes and then dispensed into vials containing a 2.5N acetic acid/saturated sodium chloride solution to halt the hydrolysis of OXON in the blood samples. Because of the approximate 10 second half-life of OXON in blood and the concern that hydrolysis during collection would affect the study results, blood samples (~1.0 mL) at subsequent dose levels

collected by cardiac puncture were drawn into heparinized syringes containing ~0.5 mL of the acidic salt solution. After collection, the blood was mixed and dispensed into two vials to provide duplicate samples. With the exception of the 50 mg/kg group where both vials were analyzed, one vial was immediately frozen at -80°C. The other vial was weighed and ~20-35 ng of the internal standards $^{13}C_2$-^{15}N-chlorpyrifos and $^{13}C_2$-^{15}N-oxon were added. The samples were then extracted for five minutes with methanol/hexane, the layers separated by centrifugation, and the extract evaporated to dryness under nitrogen. The sample was reconstituted to 50 μL with toluene prior to analysis. Because of the change in blood collection procedure, an additional 24 rats were treated with 100 mg/kg test material and blood samples obtained using the modified collection procedure described.

Additional blood samples were collected at each time point, centrifuged, and the plasma retained to determine cholinesterase activity. The brain of each animal was also removed and frozen in liquid nitrogen. All plasma and brain samples were stored at -80°C until time of analysis. During the initial 50 mg/kg study, the brain and blood for determination of cholinesterase activity were not collected. The 50 mg/kg test material portion of the study was repeated with an additional 24 rats to obtain these samples.

Labeled Dose Study - Blood samples were collected by cardiac puncture and processed as described for the parent and OXON metabolite analysis. In addition, duplicate 100 μL blood samples for TCP analyses were collected and dispensed into vials containing 150 μL of the saturated salt solution and 10 μL concentrated HCl. Approximately 50 ng of the internal standard, $^{13}C_2$-trichloropyridinol, was then added to the vial. The vials were extracted with 2.5 mL ethyl acetate, the layers separated by centrifugation, and the extract evaporated to dryness under nitrogen. The sample was reconstituted with 75 μL of toluene and 15 μL of the derivatizing agent N-methyl-N-(t-butyldimethylsilyl)-trifluoroacetamide. The solution was mixed and heated to 60°C for one hour before analysis.

3. Analytical techniques

Radioactivity was measured in a Beckman LS 3801 scintillation counter with correction for background and quench. The scintillation cocktail used was not reported.

The frozen brains were weighed, placed in nine times their weight of cold pH 8.0 0.1M sodium phosphate buffer/1% Triton X-100, and homogenized. Brain and plasma cholinesterase activity were measured at 37°C on a Hitachi 914 clinical chemistry analyzer using reagents supplied by Boehringer Manheim. The reaction

measured the hydrolysis of acethylthiocholine to thiocholine with the chromogenic rate determined through thiocholine's reaction with dithiobisnitrobenzoic acid.

The concentration of chlorpyrifos and its oxon metabolite was measured using negative-ion chemical ionization gas chromatograph-mass spectrometry (GC/MS). The analyses were done using either a DB-17 30 meter/0.25 mm or a ZB-50 30 meter/0.25 mm columns. Following injection of a 1 μL sample, the column was held at 80°C for one minute, ramped at 20°C/min. to 250°C and held for two minutes. When the alternate column was used, the initial column injection temperature of 280°C was increased to 320°C at a rate of 8°C/min. The chemical ionization gas was methane and those ions with a m/z of 297 and 302 (m/z 299 for confirmation of OXON) and 313 and 318 (chlorpyrifos) were investigated by mass spectrometry. Because of a closely eluting interference at m/z 297, samples with detectable amounts of OXON were reanalyzed with the alternate column setup for confirmation only. Using this system, the limit of detection for chlorpyrifos and OXON were 0.7 ng/g.

TCP was measured by GC/MS using a DB5ms 30 meter/0.25 mm column. Following injection of a 2 μL sample, the column was held at 150°C for one minute and then increased to 300°C at a rate of 15°C/min. Methane was used as the ion source and those peaks with a m/z of 161, 165, and 166 investigated by MS. The limit of detection of TCP was not reported.

4. Statistics

Descriptive statistics were limited to the determination of the mean and standard deviation. The plasma half-life (T½) and area under the concentration-time curves (AUC) of chlorpyrifos were determined using the WinNonlin® pharmacokinetic modeling program (Scientific Consulting, Inc., Apex, NC).

II. RESULTS

A. ANALYTICAL STUDIES

1. Dose

In the unlabeled portion of the study, the actual dose the rats received was within 2% of the target dose for all groups. Rats treated with labeled test material received 61-63% of the target dose and 8.34-8.61 μCi in the 5.0 and 100.0 mg/kg dose.

2. Cholinesterase Activity

Plasma - As shown in Figure 1, the decrease in plasma cholinesterase activity after treatment with the test material was dose dependent. The activity of rats treated with 100 mg/kg test material was statistically decreased ($p<0.05$) within 10 minutes and continued to decline through the remainder of the study. In addition, the decreased activity of rats treated with 50 mg/kg of test material closely mirrored that of the 100 mg/kg group at 20 minutes and all subsequent time points. By 12 hours after treatment, the plasma cholinesterase activity of rats in the 50 and 100 mg/kg groups was approximately 11% of the control group. The plasma cholinesterase activity of rats treated with <50 mg/kg test material was maximally decreased 3-6 hours after treatment. Both the decrease and recovery of cholinesterase activity of rats in these groups were dose-dependent.

Brain - As shown in Figure 2, the brain cholinesterase activity of rats treated with 50 or 100 mg/kg test material was statistically decreased within one hour of treatment. The activity continued to decline so that by 12 hours, the activity was approximately 30% and 20% that of control in the 50 and 100 mg/kg dose groups, respectively. In addition to the decrease in the two high dose groups, the brain cholinesterase activity of rats treated with 10 mg/kg test material began to decline within three hours of treatment and was statistically decreased by six hours after treatment. By the end of the study, the brain cholinesterase activity of rats treated with 10 mg/kg test material was approximately 85% of the control animals.

B. PHARMACOKINETICS STUDIES

As shown in Table 1, peak chlorpyrifos blood concentrations occurred by three hours after dosing in all but the lowest dose group. No chlorpyrifos was detected in the blood of animals treated with 0.5 mg/kg test material. The area under the curve (AUC) was calculated as 0.4, 1.1, 5.0, and 12.5 μmole hr L^{-1} for the 5.0, 10.0, 50.0, and 100 mg/kg groups, respectively. Based on these, the calculated half-lives of chlorpyrifos in the blood were 2.7,1.5, 2.1, and 7.3 hours for the 5.0, 10.0, 50.0, and 100.0 mg/kg dose groups, respectively. Half-lives for the 0.5 and 1.0 mg/kg dose groups could not be calculated because of the limited data.

Regardless of dose, the highest concentration of OXON detected was 2.5 ng/g in the blood of rats treated with 50 mg/kg test material one hour post-treatment. OXON was also detected one and three hours post-treatment in the blood of rats treated with 100 mg/kg test material and three hours after treatment in the blood of rats treated with 10 mg/kg test material. This metabolite was not detected in any other dose groups or time periods.

Table 1. Concentration of Chlorpyrifos and Chlorpyrifos-oxon in blood												
Time (Hrs)	Chlorpyrifos Concentration (ng/g)						Chlorpyrifos-oxon Concentration (ng/g)					
	Dose (mg/kg)						Dose (mg/kg)					
	0.5	1.0	5.0	10.0	50.0	100.0	0.5	1.0	5.0	10.0	50.0	100.0
0.17	NQ[a]	NQ	NQ	NQ	NQ	<0.8	NQ	NQ	NQ	NQ	NQ	NQ
0.33	NQ	NQ	NQ	NQ	<1.7	7.6	NQ	NQ	NQ	NQ	NQ	NQ
1.0	NQ	NQ	1.4	4.9	66.2	262.7	NQ	NQ	NQ	NQ	2.5	<1.7
3.0	NQ	2.8	30.4	112.7	444.5	798.1	NQ	NQ	NQ	1.2	NQ	0.8
6.0	NQ	NQ	14.3	17.9	102.3	248.8	NQ	NQ	NQ	NQ	NQ	NQ
12.0	NQ	NQ	NQ	1.7	21.9	287.9	NQ	NQ	NQ	NQ	NQ	NQ

Table from page 28 of Chlorpyrifos: Part A - concentration-time course of chlorpyrifos and chlorpyrifos-oxon in blood, Mendrala, A.L., Brzak, K.A., 1998

[a]NQ = Non-quantifiable

C. METABOLITE CHARACTERIZATION STUDIES

The amount of radioactivity in the blood and the concentration of chlorpyrifos, TCP, and OXON were determined three hours after treatment in blood collected from rats treated with 5.0 or 100 mg/kg labeled test material. Following treatment with 100 mg/kg test material (actual dose 63 mg/kg, 8.3 μCi), the average amount of radioactivity in the blood was equivalent to 21.4 ± 4.6 μg eq chlorpyrifos/g. When measured by GC/MS, mean concentrations of 10.9 μg TCP and 0.3 μg chlorpyrifos/g of blood were found, while the average concentration of OXON was below the detection limit. If the recovered TCP concentration is converted to an equivalent chlorpyrifos concentration, a total of 19.3 μg/eq chlorpyrifos/g of blood was found. This equates to approximately 93% of the measured radioactivity. Greater than 98% of the equivalents were recovered as TCP, with the remainder as chlorpyrifos. At the target dose of 5 mg/kg labeled chlorpyrifos (actual dose 3 mg/kg and 8.6 μCi), the average amount of radioactivity recovered was equivalent to 2.8 ± 0.5 μg eq chlorpyrifos. When measured by GC/MS, 3.4 ± 0.7 μg eq chlorpyrifos was found; or approximately 123% of the measured radioactivity. As with the high dose, approximately 98% was identified as TCP with <0.1% identified as chlorpyrifos.

III. DISCUSSION

According to the author, the goal of the above study was to help construct and validate a

physiologically-based pharmacokinetic model for chlorpyrifos, a weak inhibitor of acetylcholinesterase activity, and its metabolite OXON, a strong cholinesterase inhibitor. Chlorpyrifos and OXON are rapidly metabolized *in vivo* to TCP and diethylphosphate, both of which lack an inhibitory effect on cholinesterase. The study was done to determine the dose-dependent time-course of chlorpyrifos and OXON in the blood of rats and to determine the extent of cholinesterase inhibition in the brain and plasma. The goal of a second portion of the study, not reported here, will be to determine the kinetic constants for cholinesterase activity in rat liver and blood.

In this study, groups of 24 male rats were given a single gavage dose of 0.0, 0.5, 1.0, 5.0, 10.0, 50.0, or 100 mg/kg chlorpyrifos. Four rats from each group were killed 10 and 20 minutes and 1.0, 3.0, 6.0, and 12.0 hours after treatment. Cholinesterase activity was measured in the brain and plasma at each time point, as well as the plasma concentration of the test material and its OXON metabolite. In a separate portion of the study, four male rats were given a single gavage dose of labeled test material at a concentration of 5.0 or 100.0 mg/kg and were killed three hours later. Blood was collected from the animals at sacrifice and the concentration of the test material and its TCP and OXON metabolites determined.

Following treatment with the test material, plasma cholinesterase activity decreased in a time- and dose-dependent manner. The decrease in activity of rats treated with 50 or 100 mg/kg began within 10 minutes of treatment and closely mirrored each other; suggesting that the mechanism of inhibition may have been saturated. By 12 hours after treatment, the plasma cholinesterase activity of rats in the 50 and 100 mg/kg groups had continued to decline; was approximately 11% of the control group; and did not show signs of recovery. The plasma cholinesterase activity of rats treated with doses of the test material <50 mg/kg was maximally decreased 3-6 hours after treatment, with both the decrease and recovery of activity being dose-dependent.

Brain cholinesterase activity was not affected as dramatically by test material treatment as plasma activity. The brain cholinesterase activity of rats treated with 50 or 100 mg/kg test material decreased significantly within one hour of treatment and as with the plasma activity mirrored each other. The brain cholinesterase activity continued to decline so that by 12 hours, it was approximately 30% and 20%, respectively, that of control. In addition to the decrease in the two high dose groups, the brain cholinesterase activity of rats treated with 10 mg/kg test material began to decline within three hours of treatment and was statistically decreased by six hours after treatment. By 12 hours after treatment, the brain cholinesterase activity of rats treated with 10 mg/kg test material was approximately 85% of the control animals. No evidence for recovery of brain cholinesterase activity was found during the study in the three affected groups. No decrease in brain cholinesterase activity was found in the remaining treatment groups.

Peak chlorpyrifos blood concentrations occurred within three hours of treatment in all but the lowest dose group. The AUC was calculated as 0.4, 1.1, 5.0, and 12.5 μmole hr L^{-1} for the 5.0, 10.0, 50.0, and 100 mg/kg groups, respectively and yielded calculated half-lives of chlorpyrifos in the blood of 2.7, 1.5, 2.1, and 7.3 hours for the 5.0, 10.0, 50.0, and 100.0 mg/kg dose groups, respectively. The peak blood levels and AUC were proportional to dose in all groups, but a slight deviation from proportionality was found with AUC in rats treated with 100 mg/kg test material and the T½ was longer. This is likely a result of the small change in blood chlorpyrifos concentration between 6 and 12 hours and also suggests saturation of metabolic processes. Regardless of dose, the highest concentration of OXON detected was 2.5 ng/g found in the blood of rats treated with 50 mg/kg test material one hour post-treatment. OXON was also detected one and three hours post-treatment in the blood of rats treated with 100 mg/kg test material and one hour after treatment in the blood of rats treated with 10 mg/kg test material.

The amount radioactivity in the blood and the concentration of chlorpyrifos, TCP, and OXON were determined three hours after treatment in blood collected from rats treated with 5.0 or 100 mg/kg labeled test material. Following treatment with 5 or 100 mg/kg test material, ≥98% of the activity detected in the blood was identified as TCP metabolite with the remaining attributed to the parent compound. Since OXON is an intermediate in the formation of TCP and none of the metabolite was detected, these studies support that the half-life of the OXON metabolite is short (reportedly 10 seconds) and that *in vivo* metabolism of chlorpyrifos is rapid.

B. STUDY DEFICIENCIES

The study report does not provide information on the clinical signs of toxicity observed during the study. While this type of study can be interpreted without such observations, these would have helped to correlate decreased cholinesterase activities with the clinical signs.

Figure file too large for diskette see hard copy

Figure 1. Adapted from pages 31-32 of Chlorpyrifos: Part A - concentration-time course of chlorpyrifos and chlorpyrifos-oxon in blood, Mendrala, A.L., Brzak, K.A., 1998

Figure 2. Adapted from pages 31-32 of Chlorpyrifos: Part A - concentration-time course of chlorpyrifos and chlorpyrifos-oxon in blood, Mendrala, A.L., Brzak, K.A., 1998

Notes added by J. Doherty (EPA HED Reviewer)

Pages 7 and 8 of the review.

Figures 1 and 2 were generated by the contractor reviewer from the data tables. However, the study report also contains essentially the same figures (refer to Figures 4 and 5 on pages 36 and 37 of the study report) but the study authors figures include the *standard deviations.* Standard deviations are very important in cholinesterase activity assays. The study authors figures are attached to illustrate the same data with the standard deviations.

Page 9 of the review.

Table 1 of the review is considered poorly constructed because the standard deviations are not included. This is important because the standard deviation for the values when there was either parent compound or oxon metabolite present were very large. Examples are for 100 mg/kg at 1, 3, 6, and 12 hours that the means and the standard deviations were 262.7 ± 102.2, 798.1 ± 279.6, 248.8 ± 240.8 and 287.9 ± 287.9 representing about 40%, 25%, 97% and 110% of the means, respectively.

The following was photocopied from the study report and is attached to the paper copy of the DER. This may not be included with the electronic copy of this review.

Figures 4 and 5. Cholinesterase inhibition data for plasma and brain showing the standard deviations and time course for inhibition and recovery (when it is present).

Table 5. Kinetic parameters showing half life, peak blood level and Area Under the Curve. It is noted that the half life for the 5 mg/kg sample is not consistent with the higher dose levels. This may be due to the low levels of detectable parent and metabolites in blood. HED considers the half-lives for the higher doses to be more appropriate.

Table 6. Concentration of trichloropyridinol (TCP), chlorpyrifos-oxon, and chlorpyrifos in blood three hours following the administration of ^{14}C-chlorpyrifos. Data illustrate the high concentration of TCP to indicate rapid metabolism of chlorpyrifos and low concentration of the oxon to indicate its short existence.

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Toxicology Branch:	RRB3