

FINAL PILOT REPORT

Study Title

Oral (Gavage) Repeat Dose Time of Peak Cholinesterase Depression Study of Malathion and Malaoxon in Juvenile Rats

Data Requirement

U.S. Environmental Protection Agency (1998). *Health Effects Test Guidelines*
OPPTS 870.6200: Neurotoxicity screening battery, August, 1998

Japanese Ministry of Agriculture, Forestry and Fisheries (2000). Guidance on Toxicology Study
Data for Application of Agricultural Chemical Registration. 12 Nonsan No. 8147

Organisation for Economic Co-operation and Development (1997). *OECD Guideline for Testing
of Chemicals*. No. 424: Neurotoxicity Study in Rodents, adopted 21 July 1997

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(Unaudited Final Report)

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Charles River Laboratories Preclinical Services Protocol Number: IQC00012

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GOOD LABORATORY PRACTICE STATEMENT

This final report accurately reflects the raw data obtained during the performance of the study. This study was conducted in the spirit of the U.S. Environmental Protection Agency Good Laboratory Practice Standards; Final Rule (40 CFR Part 160), Japanese Ministry of Agriculture, Forestry and Fisheries (1999) Laboratory Practice Standards (11 Nousan No. 6283) and Organisation for Economic Co-operation and Development (1998), The Revised OECD Principles of Good Laboratory Practice [C(97)186/Final], in that the Testing Facility personnel adhered to the Standard Operating Procedures for laboratory operations and data collection. The Testing Facility Quality Assurance Unit (QAU) did not audit the protocol, the raw data or the report and did not perform critical phase inspections for the study. Samples of the test substance formulation were not analyzed.

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FLAGGING STATEMENT

I have applied the criteria of 40 CFR 158.34 for flagging studies for potential adverse effects to the results of the attached study. This study neither meets nor exceeds any of the applicable criteria.

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TITLE: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK
CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND
MALAOXON IN JUVENILE RATS

CHARLES RIVER LABORATORIES PRECLINICAL SERVICES
PROTOCOL NUMBER: TQC00012

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**TITLE: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK
CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND
MALAOXON IN JUVENILE RATS**

**CHARLES RIVER LABORATORIES PRECLINICAL SERVICES
PROTOCOL NUMBER: IQC00012**

ABSTRACT

The objective of this study was to determine the time of peak cholinesterase inhibition after repeated daily dosing of young pre-weaning rats with Malathion or Malaoxon. There were two parts to the study (Parts A and B). Part A evaluated the potential cholinesterase inhibition caused by repeat dose exposure to either malathion or malaoxon at 150 mg/kg/day and 4 mg/kg/day, respectively. Part B evaluated the potential cholinesterase inhibition caused by an acute dose of 0 (Vehicle), 50, 150 and 450 mg/kg of malathion. Below is a table of the study design.

Part	Dosage Group	Dosage (mg/kg/day)	Test Substance	Pups/Sex	Dosage Period	ChE Evaluation (Postdosage)
A	I ^a	0 (Vehicle) ^a	Corn Oil	10 ^a	PNDs 11 through 21	1 hr. ^a and 3 hrs. ^a
A	I ^b	0 (Vehicle) ^b	Corn Oil	10 ^b	PNDs 11 through 21	30 min. ^b and 90 min. ^b
A	II	150	Malathion	20 ^c	PNDs 11 through 21	1, 2, 3 and 4 hrs
A	III	4	Malaoxon	20 ^d	PNDs 11 through 21	30 min., 60 min., 90 min. and 2 hrs.
B	I ^e	0 (Vehicle) ^e	Corn Oil	10 ^e	PNDs 11 through 21	2 hrs. ^e
B	IV	50	Malathion	7	PNDs 11 and 21	2 hrs
B	V	150	Malathion	7	PNDs 11 and 21	2 hrs
B	VI	450	Malathion	6	PNDs 11 and 21	2 hrs

- These pups were assigned as the vehicle control for the malathion dosage group (Group II); 5 pups/sex for each of the two ChE evaluation timepoints.
- These pups were assigned as the vehicle control for the malaoxon dosage group (Group III); 5 pups/sex for each of the two ChE evaluation timepoints.
- Five pups/sex from this dosage group will be assigned to each of the four ChE evaluation timepoints.
- Five pups/sex from this dosage group will be assigned to each of the four ChE evaluation timepoints.
- These pups were assigned as the vehicle control for the malathion dosage group (Group II); 10 pups/sex for the 2 hr. ChE evaluation timepoints.

TIME-OF-PEAK EFFECT STUDY (PART A)

Twelve litters with five male and five female pups per litter were randomly assigned to three dosage groups (Groups I through III) for the time of peak cholinesterase inhibition portion of this study (Part A). The pups from six of these litters were assigned to the vehicle control and the 150 mg/kg/day malathion dosage group (corresponding to Groups I and II). The pups from the other six litters were assigned to the vehicle control and 4 mg/kg/day malaoxon dosage group (corresponding to Groups I and III). Suspensions of the test substances in the vehicle (corn oil) or the vehicle alone were administered via oral gavage once daily to the pups on postnatal days 11 through 21 (PNDs 11^a through 21). The dosage volume was 5 mL/kg for both test substances and the vehicle and was adjusted daily on the basis of individual body weights recorded just prior to dosage administration.

Checks for viability were made twice daily. Clinical observations were recorded daily before dosage administration and 60 ± 10 minutes after administration. Body weights were recorded the day after arrival, on the day of randomization and daily during the dosage period.

At the end of the dosage period (PND 21), whole blood samples were collected from each of the pups following decapitation, and the brains were removed. The samples were collected at 1, 2, 3 and 4 hours postdosage for the pups assigned to the repeat dose malathion dosage groups, and at 30 minutes, 60 minutes, 90 minutes and 2 hours postdosage for the pups assigned to the repeat dose malaoxon dosage groups. These samples were then analyzed for red blood cell (RBC) and brain cholinesterase levels. All pups were then discarded without further evaluation.

-
- a. The day of birth is designated postnatal day 0 (day 0 of lactation) in Addendum 10 to the Pesticide Assessment Guidelines of the U.S. Environmental Protection Agency (EPA). This same day is designated day 1 postpartum (day 1 of lactation) in the Standard Operating Procedures of the Testing Facility. Throughout the protocol and the raw data, the day of birth was designated day 1 postpartum (day 1 of lactation) and all subsequent ages of the F1 generation rats and days of the lactation period were determined and cited accordingly. In the text of this report, as well as the summary and individual tables, the day of birth has been adjusted so that the day of birth and all subsequent postpartum days match the EPA guideline.

MALATHION - RESULTS

No test substance-related mortality occurred.

Clinical signs related to administration of the test substance were observed in both the male and the female pups in the 150 mg/kg/day dosage group during PNDs 13 through 18. These clinical signs included intermittent whole body tremors, decreased motor activity, prostrate, soft or liquid feces, coldness to the touch, impaired righting reflex and dehydration.

No effects on body weights or body weight gains were observed in either the male or female pups during the dosage period.

RBC and brain cholinesterase levels were inhibited at all timepoints evaluated for male and female pups at 150 mg/kg/day compared with the vehicle controls. The greatest RBC cholinesterase inhibition was observed at 2 hours postdosage for the male pups and 2 to 3 hours postdosage for the female pups. The most profound brain cholinesterase inhibition was observed at the 2 hour timepoint.

MALAOXON - RESULTS

No test substance-related mortality occurred.

No test substance-related adverse clinical signs or effects on body weights or body weight gains were observed in either the male or female pups during the dosage period.

RBC cholinesterase inhibition was observed in the 4 mg/kg/day male pups at all timepoints evaluated (beginning at 30 minutes postdosage) compared with the vehicle controls, with the greatest amount of inhibition being observed at 90 minutes postdosage. RBC cholinesterase inhibition was observed in the 4 mg/kg/day female pups at all timepoints evaluated. Brain cholinesterase inhibition was observed in the 4 mg/kg/day male pups at the 30-minute and 2-hour timepoints, with the greater inhibition occurring at the 30-minute timepoint. Brain cholinesterase levels were only slightly inhibited at the 30-minute timepoint in the 4 mg/kg/day female pups compared with the vehicle controls. Brain cholinesterase levels were not affected at the other timepoints for the 4 mg/kg/day female pups.

ACUTE MALATHION EFFECT STUDY (PART B)

Six litters with five male and five female pups per litter were randomly assigned to four dosage groups (Groups I [control], IV, V and VI) for the effect study using malathion (Part B). Doses of 0 (Vehicle) and 150 mg/kg were administered, via gavage, to these pups on PND 11. The pups initially administered 0 (Vehicle) mg/kg received this dosage

daily from PND 11 through 21. However, the pups administered the 150 mg/kg dosage on PND 11 were subsequently divided into three dosage groups and administered an acute dosage of 50, 150 or 450 mg/kg of malathion on PND 21. The dosage volume was 5 mL/kg for both the test substance and the vehicle and was adjusted for body weight recorded just prior to dosage administration.

Checks for viability were made twice daily. Clinical observations were recorded daily before dosage administration and 60 ± 10 minutes after administration. Body weights were recorded the day after arrival, on the day of randomization and daily during the study period.

At the end of the study (PND 21), whole blood samples were collected from each of the pups following decapitation, and the brains were removed. The samples were collected at 2 hours postdosage. These samples were then analyzed for RBC and brain cholinesterase levels. All pups were then discarded without further evaluation.

All pups survived until scheduled sacrifice.

One female pup in the 450 mg/kg dosage group was observed with slight whole body tremors, miosis and urine-stained abdominal fur after dosage administration on PND 21.

No effects on body weights or body weight gains were observed in either the male or female pups at any dose level during the dosage period.

RBC cholinesterase inhibition occurred in a dosage-dependent manner in the male pups at 50, 150 and 450 mg/kg, respectively, compared with vehicle controls. In the female pups, the greatest amount of RBC cholinesterase inhibition compared with vehicle controls was observed at 150 mg/kg; however, the RBC cholinesterase inhibition observed at 450 mg/kg was greater than the inhibition observed at 50 mg/kg.

Slight brain cholinesterase inhibition was observed in the male pups at 450 mg/kg compared with vehicle controls. Brain cholinesterase levels for all other dosage groups were generally comparable with the vehicle control group.

1. OBJECTIVE

The objective of this study was to determine the time of peak cholinesterase inhibition after repeated daily dosing of young pre-weaning rats with Malathion and Malaoxon. There was also an effect study using doses of 0 (Vehicle), 50, 150 and 450 mg/kg of Malathion on day 21 postpartum pups evaluating erythrocyte and brain acetylcholinesterase activity.

2. METHODS^a

2.1. Time of Peak Effect Study (Part A)

The test substances were malathion and malaoxon. Malathion (lot number 9010501) is a pale, yellowish liquid, and malaoxon (lot number 849-B5e-42C) is a clear, colorless liquid. Both test substances were received on 19 October 2005 and stored refrigerated, protected from light. The vehicle, corn oil (lot number O15K0115), a yellow liquid, was received from Sigma-Aldrich Inc., St Louis, MO, on 13 September 2005 and 19 September 2005, respectively, and stored at room temperature. Formulations of each test substance were prepared daily at the Testing Facility. Samples (duplicate, 0.5 mLs each) were taken from each concentration at the PNDs 11, 16 and 21 test substance preparations. These samples will be retained refrigerated (2°C to 8°C) at the Testing Facility.

Twelve litters of ten pups per litter (five male pups and five female pups) were randomly assigned to three dosage groups (Groups I through III) for the time of peak cholinesterase inhibition portion of this study. The pups from six of these litters were assigned to the vehicle control and the 150 mg/kg/day malathion dosage group (corresponding to Groups I and II). The pups from the other six litters were assigned to the vehicle control and 4 mg/kg/day malaoxon dosage group (corresponding to Groups I and III). Suspensions of the test substances in the vehicle (corn oil) or the vehicle alone were administered via oral gavage once daily to the pups on PNDs 11 through 21. The dosage volume was 5 mL/kg for both test substances and the vehicle, and was adjusted daily on the basis of the individual body weights recorded immediately before administration of the test substance.

a Detailed descriptions of all procedures used in the conduct of this study are provided in the appropriate sections of this report and in the attached protocol. Deviations from the Protocol and the Standard Operating Procedures of the Testing Facility are available in the raw data.

Time of Peak Effect Dosage Groups (Part A)

Dosage Group	Number of Pups per Sex	Test Substance	Dosage (mg/kg/day)	Concentration (mg/mL)	Dosage Volume (mL/kg)
I	20	Corn Oil	0 (Vehicle)	0	5
II	20	Malathion	150	30	5
III	20	Malaoxon	4	0.8	5

Checks for viability were made twice daily. Litters were observed for dead pups at least twice daily. The pups in each litter were counted on the day after arrival and on the day of randomization. Clinical observations were recorded daily before dosage administration and 60 ± 10 minutes after administration. Body weights were recorded the day after arrival and daily during the dosage period.

At the end of the dosage period (day 21 postpartum), whole blood samples (approximately 0.30 to 0.50 mLs each) were collected from each of the pups assigned for RBC cholinesterase assay. The whole blood samples were collected from each pup following decapitation without anesthesia. Blood collection was conducted at approximately 1, 2, 3 and 4 hours postdosage for the pups assigned to the repeat dose malathion dosage groups, and at 30 minutes, 60 minutes, 90 minutes and 2 hours postdosage for the pups assigned to the repeat dose malaoxon dosage groups (timing began with the gavage of the animal and ended with decapitation for blood collection).

After blood sample collection, the brain was excised, and the weight was recorded. The brains were stored on wet ice until assayed for cholinesterase levels according to the Testing Facility's Standard Operating Procedure. The pups were then discarded without further evaluation.

Pups not assigned to study were sacrificed by carbon dioxide asphyxiation and discarded without further evaluation. Pups that died before scheduled termination were necropsied for the cause of death or condition on the day the observation was made. The lungs, trachea and esophagus were perfused and saved in neutral buffered 10% formalin for possible future evaluation.

2.2. Malathion - Effect Study (Part B)

The test substance was malathion. The malathion (lot number 9010501) is a pale, yellowish liquid. This test substance was received on 5 December 2005 and stored refrigerated, protected from light. The vehicle, corn oil (lot number O15K0115) a yellow liquid, was received from Sigma-Aldrich Inc., St Louis, MO, on 13 September 2005 and 19 September 2005, respectively, and stored at room temperature. Formulations of the test substance were prepared on PND 21 at the Testing Facility. Samples (duplicate,

0.5 mLs each) were taken from each concentration at the PND 21 preparation. These samples will be retained refrigerated (2°C to 8°C) at the Testing Facility.

Six litters of ten pups per litter (five male pups and five female pups) were utilized for the effect study using malathion. These litters were initially divided into two dosage groups (Groups I and II) and on PND 11 received a single dosage of either the vehicle (corn oil) or a 150 mg/kg dosage of malathion. The vehicle group continued receiving a daily administration of the vehicle from PNDs 11 through 21. However, the pups initially assigned to the 150 mg/kg dosage group were subsequently divided into one of three dosage groups (Groups IV through VI). Acute dosages of 50, 150 and 450 mg/kg of malathion were administered to these pups on PND 21 at a dosage volume of 5 mL/kg, adjusted for body weight recorded just prior to dosage administration.

Effect Study Dosage Groups (Part B)

Dosage Group	Number of Pups per Sex	Test Substance	Dosage (mg/kg) ^a	Concentration (mg/mL)	Dosage Volume (mL/kg)
I	10	Corn Oil	0 (Vehicle)	0	5
IV	7	Malathion	50	10	5
V	7	Malathion	150	30	5
VI	6	Malathion	450	90	5

Checks for viability were made twice daily. Litters were observed for dead pups at least twice daily. The pups in each litter were counted on the day after arrival and on the day of randomization. Clinical observations were recorded daily before dosage administration and 60 ± 10 minutes after administration. Body weights were recorded the day after arrival and daily during the dosage period.

At the end of the study (day 21 postpartum), whole blood samples (approximately 0.30 to 0.50 mLs each) were collected from each of the pups assigned for RBC cholinesterase assay. The whole blood samples were collected from each pup following decapitation without anesthesia. Blood collection was conducted at approximately 2 hours postdosage (timing began with the gavage of the animal and ended with decapitation for blood collection).

After blood sample collection, the brain was excised, and the weight was recorded. The brains were stored on wet ice until assayed for cholinesterase levels according to the Testing Facility's Standard Operating Procedure. The pups were then discarded without further evaluation. Pups not assigned to study were sacrificed by carbon dioxide asphyxiation and discarded without further evaluation.

3. RESULTS - MALATHION - DOSED PNDS 11 THROUGH 21 - TIME-OF-PEAK EFFECT STUDY (PART A)

3.1. Mortality, Clinical and Necropsy Observations (Summaries - Tables B1 and B2; Individual Data - Tables B9 and B10)

3.1.1. Mortality

One male pup in the 0 (Vehicle) mg/kg/day dosage group was found dead on PND 15, and one female pup in the 150 mg/kg/day dosage group was found dead on PND 13. These deaths were not considered to be test substance-related because the male pup was in the vehicle control group and at necropsy it became apparent that the death of the female pup was the result of an intubation error. Clinical and necropsy observations as well as body weights are summarized below. All other male and female pups survived to scheduled sacrifice.

Male pup 8115 in the 0 (Vehicle) mg/kg/day dosage group was found dead on PND 15 (4 hours and 23 minutes after dosage administration), the fourth day after the initiation of dosage administration. There were no adverse clinical signs observed in this pup, and the pup was gaining weight prior to being found dead. All tissues examined at necropsy appeared normal. Although there was no direct evidence at necropsy to attribute this death to an intubation accident, it is presumed that this death was the result of an intubation accident because 1) the death occurred in close proximity to dosage administration; and 2) there were no signs of toxicity observed prior to death.

Female pup 7810 in the 150 mg/kg/day dosage group was found dead on PND 13 (59 minutes after dosage administration), the third day after the initiation of dosage administration. This pup was observed with decreased motor activity, being prostrate, with pale extremities and gasping prior to being found dead on PND 13. This pup was gaining weight prior to being found dead. At necropsy, there was a perforation in the right diaphragmatic lobe of the lungs; all other tissues examined appeared normal. This death was the result of an intubation accident.

3.1.2. Clinical Observations

Clinical signs related to administration of the test substance were observed in both the male and the female pups in the 150 mg/kg/day dosage group during PNDS 13 through 18. These clinical signs included intermittent whole body tremors, decreased motor activity, prostrate, soft or liquid feces, coldness to the touch, impaired righting reflex and dehydration.

All other clinical signs (red perianal substance, urine-stained abdominal fur, enlarged right eye, pale extremities, slight excess salivation, gasping and ungroomed coat) were

considered unrelated to administration of the test substance because these observations occurred as a single incidence in only a few pups in the 150 mg/kg/day dosage group.

**3.2. Body Weights and Body Weight Changes
(Figures 1 and 2; Summaries - Tables B3 and B4; Individual Data -
Tables B11 and B12)**

The body weights and body weight changes were generally comparable among the 150 mg/kg/day dosage group and the 0 (Vehicle) mg/kg/day dosage group for both the male and female pups during the dosage administration period.

**3.3. Red Blood Cell (RBC) Cholinesterase Levels
(Summaries - Tables B5 and B6; Individual Data - Tables B13 and B14)**

As summarized in Text Table 1, RBC cholinesterase levels were inhibited at all timepoints evaluated for male and female pups at 150 mg/kg/day compared with vehicle controls; however, the most profound effect (50.7%) for the male pups was observed at 2 hours postdosage and at 2 to 3 hours (57.0% and 62.2%, respectively) for the female pups.

Text Table 1 PND 21 Pups, RBC Cholinesterase Levels - Time-of-Peak Effect - Malathion

Time Postdosage	Group	Dosage (mg/kg/day)	Mean AChE U/mL \pm S.D. (n) ^a	Percent Decrease Compared with Control
Male Pups				
1 Hour	I	0 (Vehicle)	2.236 \pm 0.249 (5)	--
	II	150	1.380 \pm 0.391 (5)	38.3%
2 Hours ^b	I	0 (Vehicle)	2.236 \pm 0.249 (5)	--
	II	150	1.103 \pm 0.338 (5)	50.7%
3 Hours	I	0 (Vehicle)	1.790 \pm 0.622 (4)	--
	II	150	1.419 \pm 0.250 (5)	20.7%
4 Hours ^c	I	0 (Vehicle)	1.790 \pm 0.622 (4)	--
	II	150	1.256 \pm 0.179 (5)	29.8%
Female Pups				
1 Hour	I	0 (Vehicle)	2.251 \pm 0.129 (5)	--
	II	150	1.383 \pm 0.182 (5)	38.6%
2 Hours ^b	I	0 (Vehicle)	2.251 \pm 0.129 (5)	--
	II	150	0.968 \pm 0.206 (5)	57.0%
3 Hours ^c	I	0 (Vehicle)	2.251 \pm 0.129 (5)	--
	II	150	0.852 \pm 0.329 (2)	62.2%
4 Hours ^d	I	0 (Vehicle)	2.251 \pm 0.129 (5)	--
	II	150	1.095 \pm 0.192 (3)	51.4%

a. n = The number of PND 21 pups evaluated for cholinesterase levels.

b. The cholinesterase data from the 150 mg/kg/day dosage group at the two hour timepoint was compared to the data collected at the one hour timepoint for the 0 (Vehicle) mg/kg/day dosage group.

c. The cholinesterase data from the 150 mg/kg/day dosage group at the three hour timepoint was compared to the data collected at the one hour timepoint for the 0 (Vehicle) mg/kg/day dosage group due to an insufficient volume from the samples to either process or analyze.

d. The cholinesterase data from the 150 mg/kg/day dosage group at the four hour timepoint was compared to the data collected at the one hour timepoint for the 0 (Vehicle) mg/kg/day dosage group due to an insufficient volume from the samples to either process or analyze.

3.4. Brain Cholinesterase Levels (Summaries - Tables B7 and B8; Individual Data - Tables B15 and B16)

As summarized in Text Table 2, the greatest brain cholinesterase inhibition observed was at the 2 hour postdosage timepoint (14.9% for male pups and 21.4% for female pups).

Text Table 2. PND 21 Pups, Brain Time-of-Peak Effect – Malathion

Time Postdosage	Group	Dosage (mg/kg/day)	Mean AChE ChE U/G \pm S.D. (n) ^a	Percent Decrease Compared with Control
Male Pups				
1 Hour	I	0 (Vehicle)	11.410 \pm 0.714 (5)	--
	II	150	10.134 \pm 1.459 (5)	11.2%
2 Hours ^b	I	0 (Vehicle)	11.410 \pm 0.714 (5)	--
	II	150	9.713 \pm 0.830 (5)	14.9%
3 Hours	I	0 (Vehicle)	10.563 \pm 0.439 (4)	--
	II	150	9.347 \pm 0.808 (5)	11.5%
4 Hours ^c	I	0 (Vehicle)	10.563 \pm 0.439 (4)	--
	II	150	9.284 \pm 0.466 (5)	12.1%
Female Pups				
1 Hour	I	0 (Vehicle)	10.793 \pm 0.881 (5)	--
	II	150	8.951 \pm 0.995 (5)	17.1%
2 Hours ^b	I	0 (Vehicle)	10.793 \pm 0.881 (5)	--
	II	150	8.481 \pm 0.693 (5)	21.4%
3 Hours	I	0 (Vehicle)	11.475 \pm 0.207 (5)	--
	II	150	9.307 \pm 0.292 (4)	18.9%
4 Hours ^c	I	0 (Vehicle)	11.475 \pm 0.207 (5)	--
	II	150	10.385 \pm 0.634 (5)	9.5%

a. n = The number of PND 21 pups evaluated for cholinesterase levels.

b. The cholinesterase data from the 150 mg/kg/day dosage group at the two hour timepoint was compared to the data collected at the one hour timepoint for the 0 (Vehicle) mg/kg/day dosage group.

c. The cholinesterase data from the 150 mg/kg/day dosage group at the four hour timepoint was compared to the data collected at the three hour timepoint for the 0 (Vehicle) mg/kg/day dosage group.

4. CONCLUSION - MALATHION - DOSED PNDS 11 THROUGH 21 - TIME-OF-PEAK EFFECT STUDY (PART A)

Based on the results of these data, a 2 hour time-of-peak effect would appear to be adequate to ensure the maximal response to cholinesterase inhibition by malathion in both red blood cell and brain compartments for both male and female pups.

5. RESULTS - MALAOXON - DOSED PNDS 11 THROUGH 21 - TIME-OF-PEAK EFFECT STUDY (PART A)

5.1. Mortality, Clinical and Necropsy Observations (Summaries - Tables C1 and C2; Individual Data - Tables C9 and C10)

5.1.1. Mortality

There were two male pups (one in the vehicle control group and the other in the 4 mg/kg/day dosage group) and one female pup (in the 4 mg/kg/day dosage group) that were found dead prior to scheduled sacrifice. These deaths were not considered to be test substance-related because one of the male pups was in the vehicle control group and at necropsy it became apparent that the deaths in the 4 mg/kg/day dosage group were the result of intubation errors. All other male and female pups survived to scheduled sacrifice.

5.1.1.1. Male Pups

Pup 9601 in the 0 (Vehicle) mg/kg/day dosage group was found dead prior to dosage administration on PND 20, the tenth day after the initiation of dosage administration. There were no adverse clinical signs observed in this pup, and the pup was gaining weight prior to being found dead. This pup was partially cannibalized; however, the tissues that were remaining appeared normal at necropsy. This death was not considered to be test substance-related because it occurred in the vehicle control group.

Pup 9304 in the 4 mg/kg/day dosage group was found dead on PND 17 (5 minutes after dosage administration), the seventh day after the initiation of dosage administration. There were no adverse clinical signs observed in this pup, and the pup was gaining weight prior to being found dead. At necropsy, there was a perforation in the trachea and the trachea and lungs contained a white, foamy material. All other tissues examined appeared normal. This death was the result of an intubation accident.

5.1.1.2. Female Pups

Pup 9208 in the 4 mg/kg/day dosage group was found dead immediately following dosage administration on PND 20, the tenth day after the initiation of dosage administration. There were no adverse clinical signs observed in this pup, and the pup was gaining weight prior to being found dead. At necropsy, the trachea and the lungs contained a white, foamy material and all lobes of the lungs were pale in color. All other tissues examined appeared normal. This death was the result of an intubation accident.

5.1.2. Clinical Observations

All clinical observations were considered unrelated to the administration of the test substance because: 1) the incidences were not dosage dependent; or 2) the observation occurred in only one or two pups in the dosage groups. These clinical observations included urine stained abdominal fur, soft or liquid feces, slight excess salivation and a scab on the head of the pup.

5.2. Body Weights and Body Weight Changes (Figures 3 and 4; Summaries - Tables C3 and C4; Individual Data - Tables C11 and C12)

The body weights and body weight changes were generally comparable among the 4 mg/kg/day dosage group and the 0 (Vehicle) mg/kg/day dosage group for both the male and female pups during the dosage administration period.

5.3. Red Blood Cell (RBC) Cholinesterase Levels (Summaries - Tables C5 and C6; Individual Data - Tables C13 and C14)

As summarized in Text Table 3, RBC cholinesterase inhibition was observed in the 4 mg/kg/day male pups at all timepoints (beginning at 30 minutes postdosage) compared with vehicle controls. The greatest amount of inhibition in the male pups was observed at 90 minutes postdosage (with a similar amount of inhibition observed at 2 hours postdosage). RBC cholinesterase inhibition was observed in the 4 mg/kg/day female pups at all timepoints evaluated, and was similar at each timepoint.

Text Table 3. PND 21 Pups, RBC Cholinesterase Levels - Time-of-Peak Effect - Malaoxon

Time Postdosage	Group	Dosage (mg/kg/day)	Mean AChE AChE U/mL \pm S.D. (n) ^a	Percent Decrease Compared with Control
Male Pups				
30 Minutes	I	0 (Vehicle)	2.097 \pm 0.693 (3)	--
	III	4	1.237 \pm 0.142 (6)	41.0%
60 Minutes ^b	I	0 (Vehicle)	2.097 \pm 0.693 (3)	--
	III	4	1.216 \pm 0.296 (4)	42.0%
90 Minutes	I	0 (Vehicle)	2.450 \pm 0.276 (5)	--
	III	4	0.927 \pm 0.207 (6)	62.2%
2 Hours ^c	I	0 (Vehicle)	2.450 \pm 0.276 (5)	--
	III	4	0.994 \pm 0.111 (3)	59.4%
Female Pups				
30 Minutes	I	0 (Vehicle)	1.986 \pm 0.194 (4)	--
	III	4	0.880 \pm 0.209 (4)	55.7%
60 Minutes ^b	I	0 (Vehicle)	1.986 \pm 0.194 (4)	--
	III	4	0.987 \pm 0.251 (6)	50.3%
90 Minutes	I	0 (Vehicle)	2.001 \pm 0.219 (5)	--
	III	4	0.959 \pm 0.195 (4)	52.1%
2 Hours ^c	I	0 (Vehicle)	2.001 \pm 0.219 (5)	--
	III	4	0.813 \pm 0.117 (5)	59.4%

a. n = The number of PND 21 pups evaluated for cholinesterase levels

b. The cholinesterase data from the 4 mg/kg/day dosage group at the two hour timepoint was compared to the data collected at the 30-minute timepoint for the 0 (Vehicle) mg/kg/day dose group

c. The cholinesterase data from the 4 mg/kg/day dosage group at the four hour timepoint was compared to the data collected at the 90-minute timepoint for the 0 (Vehicle) mg/kg/day dosage group.

5.4. Brain Cholinesterase Levels (Summaries - Tables C7 and C8; Individual Data - Tables C15 and C16)

As summarized in Text Table 4, brain cholinesterase inhibition was observed in the 4 mg/kg/day male pups at the 30-minute and 2-hour timepoints, with the greater inhibition occurring at the 30-minute timepoint. Brain cholinesterase levels were only slightly inhibited at the 30-minute timepoint in the 4 mg/kg/day female pups compared with the vehicle controls. Brain cholinesterase levels were not affected at the other timepoints.

Text Table 4. PND 21 Pups, Brain Time-of-Peak Effect - Malaoxon

Time Postdosage	Group	Dosage (mg/kg/day)	Mean AChE ChE U/G \pm S.D. (n) ^a	Percent Decrease Compared with Control
Male Pups				
30 Minutes	I	0 (Vehicle)	12.633 \pm 0.730 (4)	--
	III	4	10.650 \pm 1.406 (6)	15.7%
60 Minutes ^b	I	0 (Vehicle)	12.633 \pm 0.730 (4)	--
	III	4	12.079 \pm 0.916 (4)	4.4%
90 Minutes	I	0 (Vehicle)	12.662 \pm 0.415 (5)	--
	III	4	12.532 \pm 1.015 (6)	1.0%
2 Hours ^c	I	0 (Vehicle)	12.662 \pm 0.415 (5)	--
	III	4	11.397 \pm 0.474 (3)	10.0%
Female Pups				
30 Minutes	I	0 (Vehicle)	11.093 \pm 2.221 (5)	--
	III	4	10.173 \pm 1.264 (4)	8.3%
60 Minutes ^b	I	0 (Vehicle)	11.093 \pm 2.221 (5)	--
	III	4	10.800 \pm 1.032 (6)	2.6%
90 Minutes	I	0 (Vehicle)	12.125 \pm 2.274 (5)	--
	III	4	13.171 \pm 1.276 (4)	d
2 Hours ^c	I	0 (Vehicle)	12.125 \pm 2.274 (5)	--
	III	4	12.183 \pm 1.195 (5)	e

a. n = The number of PND 21 pups evaluated for cholinesterase levels

b. The cholinesterase data from the 4 mg/kg/day dosage group at the two hour timepoint was compared to the data collected at the 30-minute timepoint for the 0 (Vehicle) mg/kg/day dosage group.

c. The cholinesterase data from the 4 mg/kg/day dosage group at the four hour timepoint was compared to the data collected at the 90-minute timepoint for the 0 (Vehicle) mg/kg/day dosage group.

d. No inhibition occurred; value was 8.6% greater than the vehicle control value.

e. No inhibition occurred; value was 0.5% greater than the vehicle control value.

6. CONCLUSION - MALAOXON - DOSED PNDS 11 THROUGH 21 - TIME-OF-PEAK EFFECT STUDY (PART A)

Based on these data, a 30 minute time-of-peak effect would appear to be adequate to ensure the maximal or close to maximal response to cholinesterase inhibition by malaoxon in both red blood cell and brain compartments for both male and female pups.

7. RESULTS - MALATHION - DOSED PNDS 11 AND 21 - EFFECT STUDY (PART B)

**7.1. Mortality and Clinical Observations
(Summaries - Tables D1 and D2; Individual Data - Tables D9 and D10)**

All male and female pups survived until scheduled sacrifice.

On PND 21, one female pup (9110) in the 450 mg/kg dosage group was observed with slight whole body tremors, miosis and urine-stained abdominal fur.

All other clinical signs (urine-stained abdominal fur, ungroomed coat, coldness to the touch and slight excess salivation) were considered unrelated to the administration of the test substance because: 1) the incidences were not dosage dependent; or 2) the observation occurred in only one pup in the dosage groups.

**7.2. Body Weights and Body Weight Changes
(Figures 5 and 6; Summaries - Tables D3 and D4; Individual Data - Tables D11 and D12)**

The body weights and body weight changes were generally comparable among all dosage groups for both the male and female pups during the dosage administration period.

7.3. Red Blood Cell (RBC) Cholinesterase Levels
(Summaries - Tables D5 and D6; Individual Data - Tables D13 and D14)

As summarized in Text Table 5, RBC cholinesterase inhibition occurred in a dosage-dependent manner in the male pups at 50, 150 and 450 mg/kg, respectively, compared with vehicle controls. In the female pups, the greatest amount of RBC cholinesterase inhibition was observed at 150 mg/kg compared with vehicle controls. However, the RBC cholinesterase inhibition observed at 450 mg/kg was greater than the inhibition observed at 50 mg/kg.

Text Table 5: PND 21 Pups, Malathion RBC Cholinesterase Levels			
Group	Dosage on PND 21 (mg/kg)	Mean ChE ChE U/mL \pm S.D. (n) ^a	Percent Decrease Compared with Controls
Male Pups			
I	0 (Vehicle)	2.663 \pm 0.621 (10)	--
IV	50	2.140 \pm 0.684 (7)	19.6%
V	150	1.940 \pm 0.924 (7)	27.1%
VI	450	1.797 \pm 0.168 (6)	32.5%
Female Pups			
I	0 (Vehicle)	2.483 \pm 0.630 (10)	--
IV	50	2.150 \pm 0.455 (7)	13.4%
V	150	1.601 \pm 0.491 (7)	35.5%
VI	450	1.918 \pm 0.480 (6)	22.8%

^a n = The number of PND 21 pups evaluated for cholinesterase levels.

7.4. Brain Cholinesterase Levels
(Summaries - Tables D7 and D8; Individual Data - Tables D15 and D16)

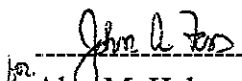
As summarized in Text Table 6, slight brain cholinesterase inhibition was observed in the PND 21 male pups at 450 mg/kg compared with the vehicle controls. The cholinesterase levels for all other dosage groups were generally comparable with the vehicle controls.

Text Table 6: PND 21 Pups, Malathion Brain Cholinesterase Levels			
Group	Dosage (mg/kg)	Mean ChE ChE U/G \pm S.D. (n) ^a	Percent Decrease Compared with Controls
Male Pups			
I	0 (Vehicle)	12.145 \pm 0.471 (10)	--
IV	50	13.315 \pm 1.467 (7)	b
V	150	12.456 \pm 1.394 (7)	c
VI	450	10.341 \pm 3.001 (6)	14.9%
Female Pups			
I	0 (Vehicle)	11.456 \pm 1.283 (10)	--
IV	50	13.354 \pm 3.431 (7)	d
V	150	12.037 \pm 0.706 (7)	e
VI	450	10.799 \pm 2.771 (6)	5.7%

- a. n = The number of PND 21 pups evaluated for cholinesterase levels.
b. No inhibition occurred; value was 9.6% greater than the control value.
c. No inhibition occurred; value was 2.6% greater than the control value.
d. No inhibition occurred; value was 16.6% greater than the control value.
e. No inhibition occurred; value was 5.1% greater than the control value.

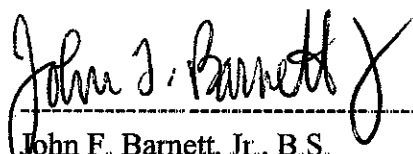
**8. CONCLUSION - MALATHION - DOSED PNDS 11 AND 21 -
EFFECT STUDY (PART B)**

Acute oral (gavage) administration of malathion to male and female pups on PND 21 resulted in no treatment-related effects other than a substantial decrease in RBC cholinesterase levels in all doses evaluated and slight brain cholinesterase inhibition at 450 mg/kg.



Alan M. Hoberman, Ph.D., DABT
Director of Research
2 May 2006

Date



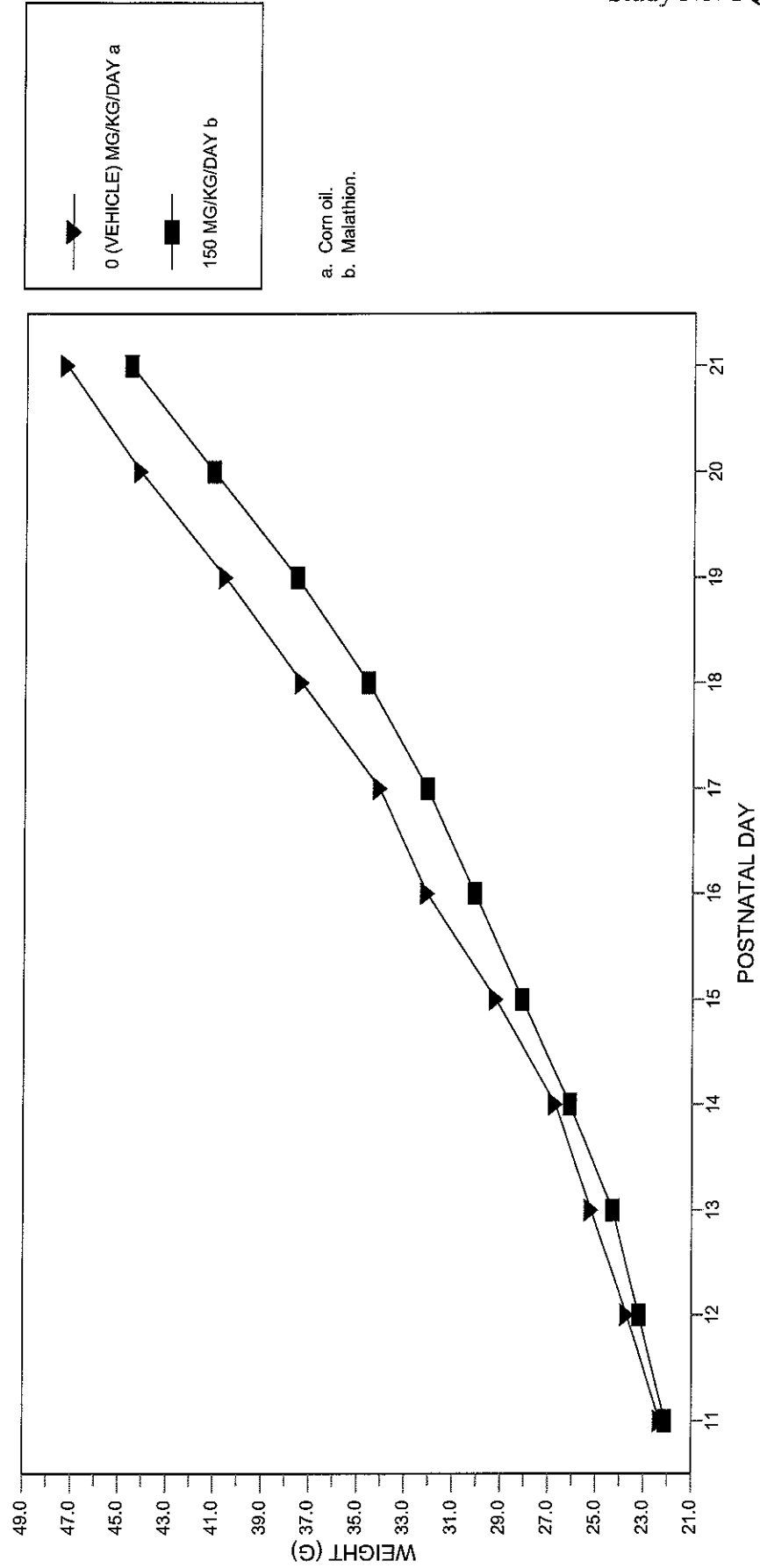
John F. Barnett, Jr., B.S.
Senior Scientist
Study Director
2 May 2006

Date

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

BODY WEIGHTS MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

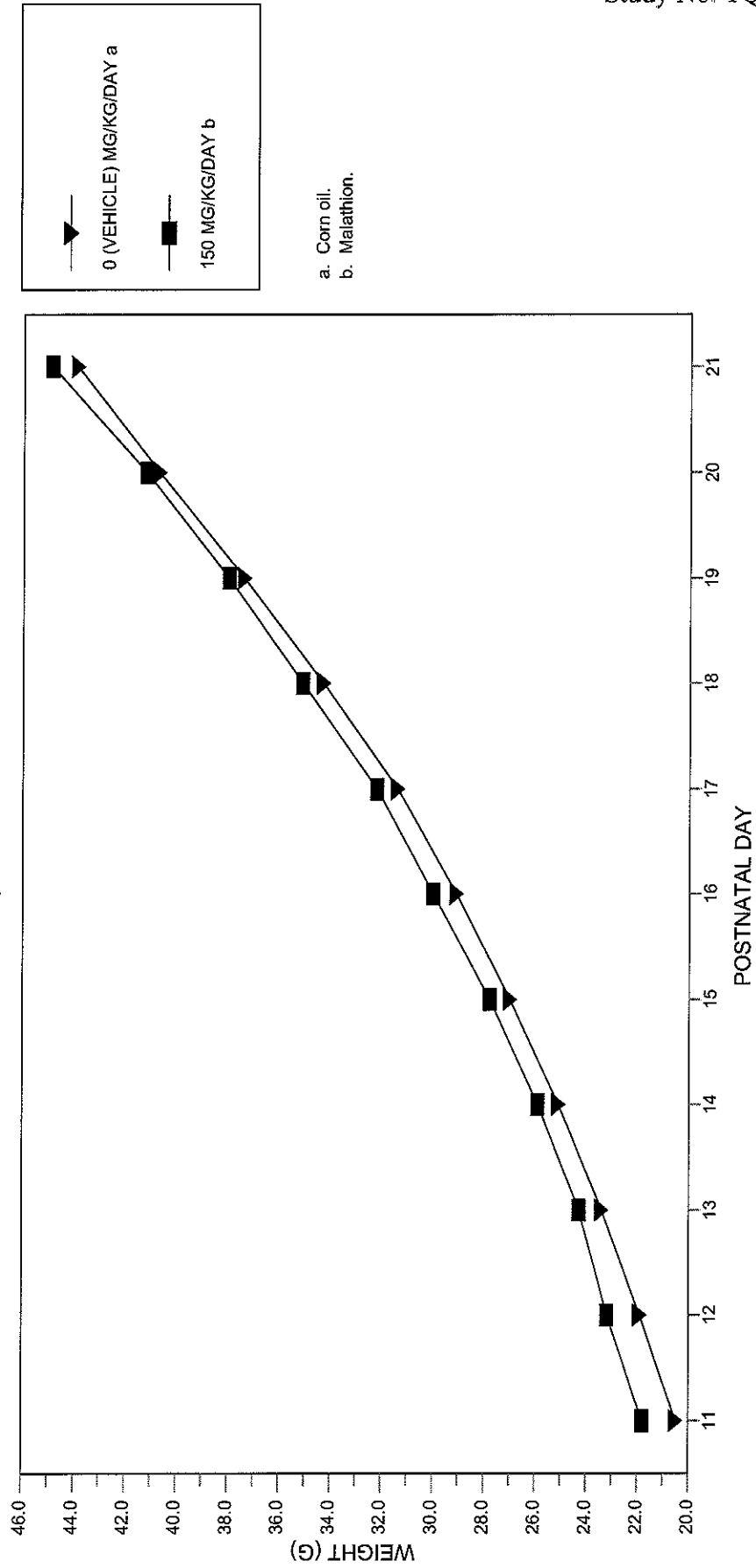
Figure 1



PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

BODY WEIGHTS FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

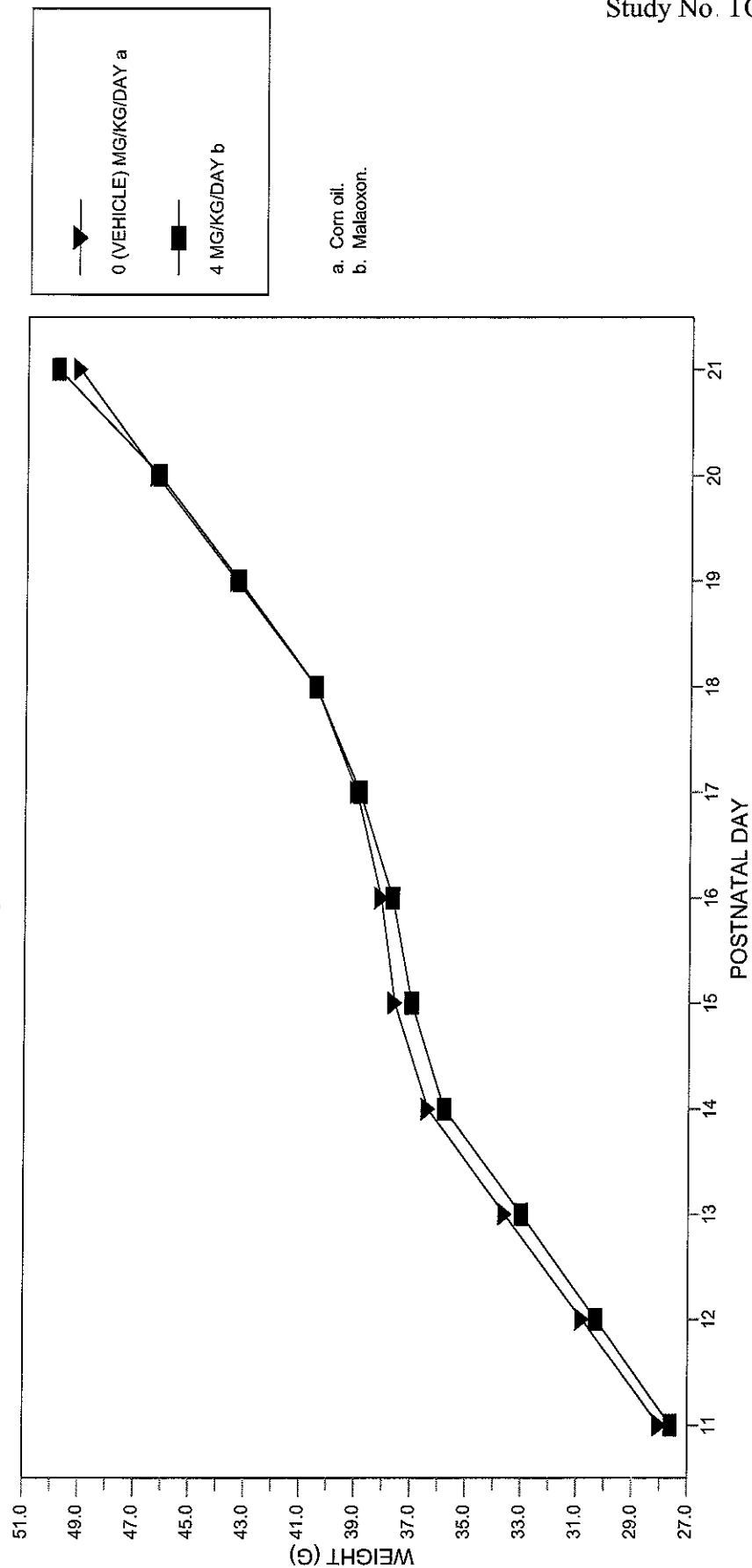
Figure 2



PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

BODY WEIGHTS
MALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

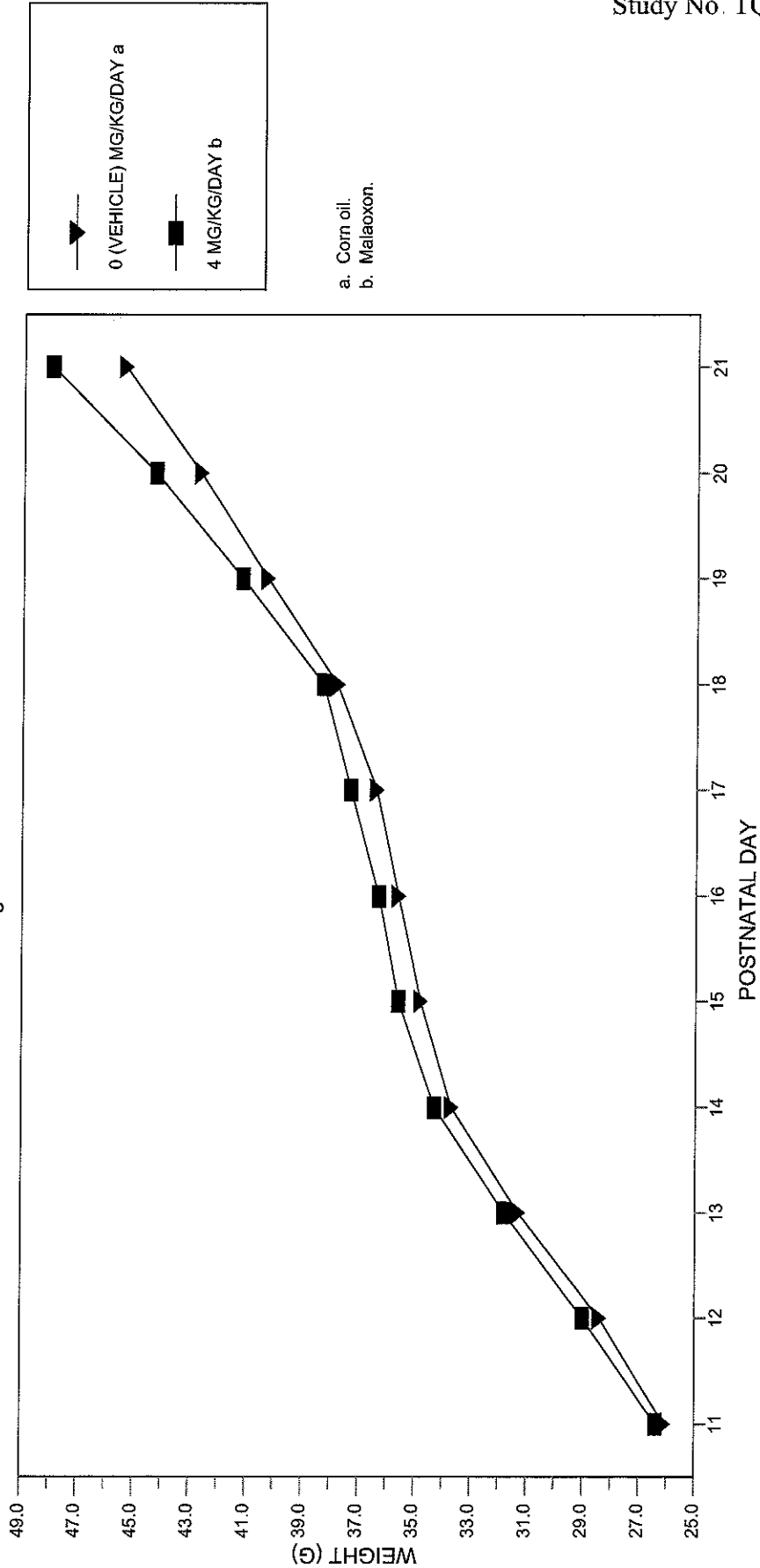
Figure 3



PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

BODY WEIGHTS FEMALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

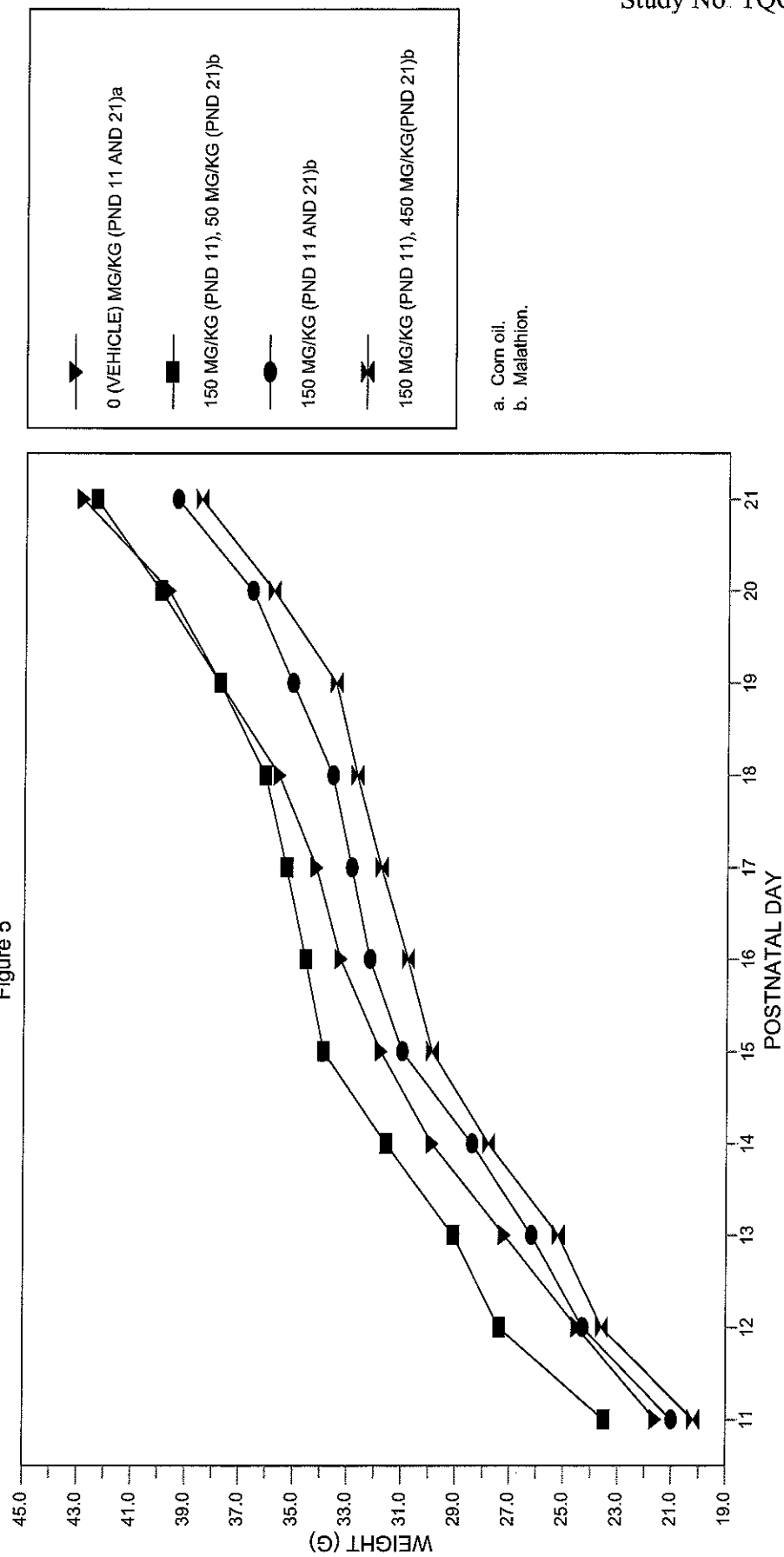
Figure 4



PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

BODY WEIGHTS MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

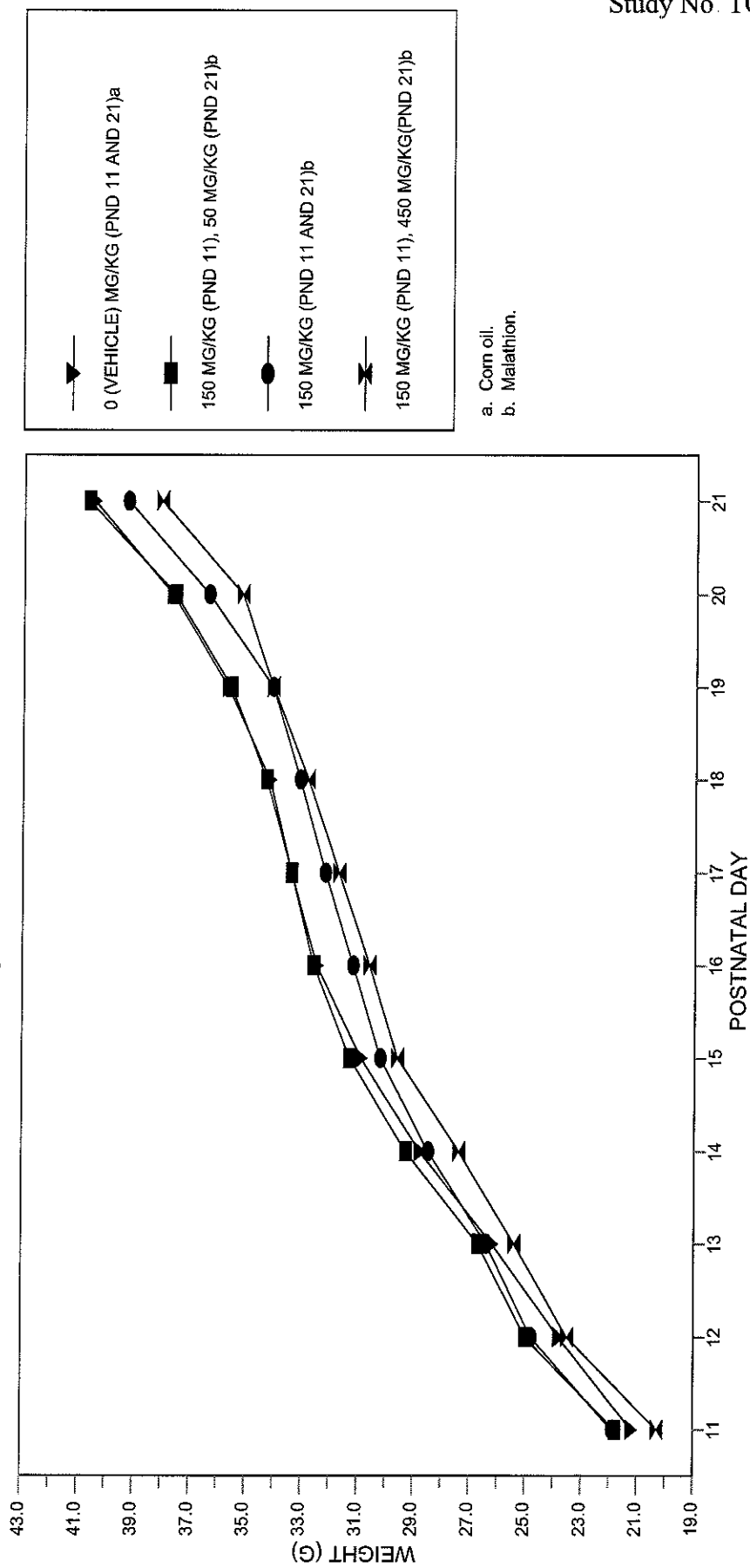
Figure 5



PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

BODY WEIGHTS **FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21**

Figure 6



PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON IN JUVENILE RATS

TABLE B1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP TEST SUBSTANCE DOSAGE (MG/KG/DAY)	I		II	
	CORN OIL 0 (VEHICLE)		MALATHION 150	
MAXIMUM POSSIBLE INCIDENCE	104/ 10		220/ 20	
FOUND DEAD	1a		0	
WHOLE BODY: TREMORS, INTERMITTENT	0/ 0		21/ 8	
DECREASED MOTOR ACTIVITY	0/ 0		5/ 5	
PROSTRATE	0/ 0		3/ 2	
SOFT OR LIQUID FECES	0/ 0		2/ 2	
COLD TO TOUCH	0/ 0		2/ 2	
RED PERIANAL SUBSTANCE	0/ 0		2/ 1	
IMPAIRED RIGHTING REFLEX	0/ 0		1/ 1	
DEHYDRATION	0/ 0		1/ 1	
URINE-STAINED ABDOMINAL FUR	0/ 0		1/ 1	

MAXIMUM POSSIBLE INCIDENCE = (DAYS x PUPS)/NUMBER OF PUPS EXAMINED PER GROUP ON POSTNATAL DAYS 11 THROUGH 21.

N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF PUPS WITH OBSERVATION.

a. Pup 8115 was found dead on postnatal day 15.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON IN JUVENILE RATS

TABLE B2 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP TEST SUBSTANCE DOSAGE (MG/KG)	I		II	
	CORN OIL 0 (VEHICLE)		MALATHION 150	
MAXIMUM POSSIBLE INCIDENCE	110/ 10		212/ 20	
FOUND DEAD	0		1a	
WHOLE BODY: TREMORS, INTERMITTENT	0/ 0		28/ 10	
DECREASED MOTOR ACTIVITY	0/ 0		5/ 5a	
SOFT OR LIQUID FECES	0/ 0		4/ 4	
PROSTRATE	0/ 0		4/ 4a	
IMPAIRED RIGHTING REFLEX	0/ 0		2/ 2	
COLD TO TOUCH	0/ 0		2/ 2	
DEHYDRATION	4/ 1		2/ 2	
RIGHT EYE: ENLARGED	0/ 0		7/ 1	
PALE EXTREMITIES	0/ 0		1/ 1a	
EXCESS SALIVATION - SLIGHT	0/ 0		1/ 1	
GASPING	0/ 0		1/ 1a	
URINE-STAINED ABDOMINAL FUR	0/ 0		1/ 1	
UNGROOMED COAT	0/ 0		1/ 1	

MAXIMUM POSSIBLE INCIDENCE = (DAYS x PUPS)/NUMBER OF PUPS EXAMINED PER GROUP ON POSTNATAL DAYS 11 THROUGH 21.

N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF PUPS WITH OBSERVATION.

a. Pup 7810 was found dead on postnatal day 13.

PROTOCOL IQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON IN JUVENILE RATS

TABLE B3 (PAGE 1): BODY WEIGHTS AND BODY WEIGHT CHANGES - SUMMARY - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP TEST SUBSTANCE DOSAGE (MG/KG)	I		II	
	CORN OIL 0 (VEHICLE)		MALATHION 150	
PUPS TESTED	N	10	20	
BODY WEIGHT (G)				
DAY 11	MEAN±S.D.	22.3 ± 2.7	22.1 ± 2.3	
DAY 12	MEAN±S.D.	23.7 ± 2.7	23.2 ± 2.9	
DAY 13	MEAN±S.D.	25.2 ± 3.0	24.3 ± 3.6	
DAY 14	MEAN±S.D.	26.7 ± 3.7	26.1 ± 3.7	
DAY 15	MEAN±S.D.	29.2 ± 3.4	28.1 ± 3.5	
DAY 16	MEAN±S.D.	32.1 ± 2.0 91a	30.1 ± 3.5	
DAY 17	MEAN±S.D.	34.1 ± 2.5 91a	32.1 ± 3.6	
DAY 18	MEAN±S.D.	37.4 ± 2.4 91a	34.6 ± 3.7	
DAY 19	MEAN±S.D.	40.6 ± 2.7 91a	37.6 ± 3.8	
DAY 20	MEAN±S.D.	44.2 ± 3.7 91a	41.1 ± 4.0	
DAY 21	MEAN±S.D.	47.3 ± 4.3 91a	44.6 ± 4.5	
BODY WEIGHT CHANGE (G)				
DAYS 11 - 14	MEAN±S.D.	+4.4 ± 2.5	+4.0 ± 2.1	
DAYS 14 - 17	MEAN±S.D.	+6.7 ± 2.1 91a	+6.0 ± 1.3	
DAYS 17 - 21	MEAN±S.D.	+13.2 ± 2.3 91a	+12.5 ± 1.8	
DAYS 11 - 21	MEAN±S.D.	+24.7 ± 4.6 91a	+22.5 ± 3.1	

DAY(S) = POSTNATAL DAY(S)

| | = NUMBER OF VALUES AVERAGED

a. Excludes values for pup 8115, which was found dead on postnatal day 15.

PROTOCOL IQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON IN JUVENILE RATS

TABLE B4 (PAGE 1): BODY WEIGHTS AND BODY WEIGHT CHANGES - SUMMARY - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP TEST SUBSTANCE DOSAGE (MG/KG)	I		II	
	CORN OIL 0 (VEHICLE)		MALATHION 150	
PUPS TESTED	N	10	20	
BODY WEIGHT (G)				
DAY 11	MEAN±S.D.	20.5 ± 1.5	21.8 ± 1.8	
DAY 12	MEAN±S.D.	21.9 ± 1.7	23.2 ± 2.1	
DAY 13	MEAN±S.D.	23.4 ± 2.3	24.3 ± 2.9	
DAY 14	MEAN±S.D.	25.1 ± 2.7	25.9 ± 3.4	
DAY 15	MEAN±S.D.	27.0 ± 2.8	27.8 ± 3.1	
DAY 16	MEAN±S.D.	29.1 ± 2.8	30.0 ± 2.9	
DAY 17	MEAN±S.D.	31.4 ± 3.1	32.2 ± 3.1	
DAY 18	MEAN±S.D.	34.3 ± 3.4	35.1 ± 3.3	
DAY 19	MEAN±S.D.	37.4 ± 3.6	38.0 ± 3.5	
DAY 20	MEAN±S.D.	40.7 ± 3.9	41.2 ± 3.4	
DAY 21	MEAN±S.D.	43.9 ± 4.6	44.9 ± 3.6	
BODY WEIGHT CHANGE (G)				
DAYS 11 - 14	MEAN±S.D.	+4.6 ± 2.0	+4.1 ± 2.3	
DAYS 14 - 17	MEAN±S.D.	+6.4 ± 1.2	+6.3 ± 1.3	
DAYS 17 - 21	MEAN±S.D.	+12.5 ± 2.4	+12.6 ± 2.0	
DAYS 11 - 21	MEAN±S.D.	+23.4 ± 3.8	+23.1 ± 3.0	
DAY(S) = POSTNATAL DAY(S)				
I I = NUMBER OF VALUES AVERAGED				
a. Excludes values for pup 7810, which was found dead on postnatal day 13.				

PROTOCOL IQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B5 (PAGE 1): RBC CHOLINESTERASE LEVELS - SUMMARY - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP		I		II	
TEST SUBSTANCE		CORN OIL		MALATHION	
DOSAGE (MG/KG/DAY)		0 (VEHICLE)		150	
<u>1 HOUR POSTDOSAGE:</u>					
PUPS TESTED	N	5		5	
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.	2.236 ± 0.249		1.380 ± 0.391	
% INHIBITION	%			38.3	
<u>2 HOURS POSTDOSAGE:</u>					
PUPS TESTED	N	-		5	
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.			1.103 ± 0.338	
% INHIBITION b	%			50.7	
<u>3 HOURS POSTDOSAGE:</u>					
PUPS TESTED	N	4a		5	
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.	1.790 ± 0.622		1.419 ± 0.250	
% INHIBITION	%			20.7	
<u>4 HOURS POSTDOSAGE:</u>					
PUPS TESTED	N	-		5	
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.			1.256 ± 0.179	
% INHIBITION c	%			29.8	

a. Excludes values for pup 8115, which was found dead on postnatal day 15.
b. Value derived from comparison to the Vehicle Group, 1 hour postdosage value.
c. Value derived from comparison to the Vehicle Group, 3 hours postdosage value.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B6 (PAGE 1): RBC CHOLINESTERASE LEVELS - SUMMARY - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP		I		II	
TEST SUBSTANCE		CORN OIL		MALATHION	
DOSAGE (MG/KG/DAY)		0 (VEHICLE)		150	
<u>1 HOUR POSTDOSAGE:</u>					
PUPS TESTED	N	5		5	
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.	2.251 ± 0.129		1.383 ± 0.182	
% INHIBITION	%			38.6	
<u>2 HOURS POSTDOSAGE:</u>					
PUPS TESTED	N	-		5	
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.			0.968 ± 0.206	
% INHIBITION b	%			57.0	
<u>3 HOURS POSTDOSAGE:</u>					
PUPS TESTED	N	0a		2a,c	
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.			0.852 ± 0.329	
% INHIBITION b	%			62.2	
<u>4 HOURS POSTDOSAGE:</u>					
PUPS TESTED	N	-		3a	
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.			1.095 ± 0.192	
% INHIBITION b	%			51.4	
a. Excludes pups that had insufficient volume to process or analyze sample.					

a. Excludes pups that had insufficient volume to process or analyze sample.

b. Value derived from comparison to the Vehicle Group, 1 hour postdosage value.

c. Excludes values for pup 7810, which was found dead on postnatal day 13.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B7 (PAGE 1): BRAIN CHOLINESTERASE LEVELS - SUMMARY - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP		I		II	
TEST SUBSTANCE		CORN OIL		MALATHION	
DOSAGE (MG/KG/DAY)		0 (VEHICLE)		150	
<u>1 HOUR POSTDOSAGE:</u>					
PUPS TESTED		N	5		5
BRAIN WEIGHT (G)		MEAN±S.D.	1.364 ± 0.145		1.426 ± 0.047
CHOLINESTERASE LEVELS (UNITS/G)		MEAN±S.D.	11.410 ± 0.714		10.134 ± 1.459
% INHIBITION		%			11.2
<u>2 HOURS POSTDOSAGE:</u>					
PUPS TESTED		N	-		5
BRAIN WEIGHT (G)		MEAN±S.D.			1.380 ± 0.074
CHOLINESTERASE LEVELS (UNITS/G)		MEAN±S.D.			9.713 ± 0.830
% INHIBITION a		%			14.9
<u>3 HOURS POSTDOSAGE:</u>					
PUPS TESTED		N	4b		5
BRAIN WEIGHT (G)		MEAN±S.D.	1.378 ± 0.066		1.370 ± 0.116
CHOLINESTERASE LEVELS (UNITS/G)		MEAN±S.D.	10.563 ± 0.439		9.347 ± 0.808
% INHIBITION		%			11.5
a. Value derived from comparison to the Vehicle Group, 1 hour postdosage value.					
b. Excludes values for pup 8115, which was found dead on postnatal day 15.					

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B7 (PAGE 2): BRAIN CHOLINESTERASE LEVELS - SUMMARY - MALE PUPS - MALATHION ~ DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP	I		II	
	CORN OIL	MALATHION		
TEST SUBSTANCE				
DOSAGE (MG/KG/DAY)	0 (VEHICLE)	150		
4 HOURS POSTDOSAGE:				
PUPS TESTED	N	-	5	
BRAIN WEIGHT (G)	MEAN±S.D.		1.455 ± 0.095	
CHOLINESTERASE LEVELS (UNITS/G)	MEAN±S.D.		9.284 ± 0.466	
% INHIBITION a				12.1
a. Value derived from comparison to the Vehicle Group, 3 hours postdosage value.				

PROTOCOL IQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B8 (PAGE 1): BRAIN CHOLINESTERASE LEVELS - SUMMARY - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP		I		II	
TEST SUBSTANCE		CORN OIL		MALATHION	
DOSAGE (MG/KG/DAY)		0 (VEHICLE)		150	
<u>1 HOUR POSTDOSAGE:</u>					
PUPS TESTED	N	5		5	
BRAIN WEIGHT (G)	MEAN±S.D.	1.366 ± 0.572		1.361 ± 0.047	
CHOLINESTERASE LEVELS (UNITS/G)	MEAN±S.D.	10.793 ± 0.881		8.951 ± 0.995	
% INHIBITION	%			17.1	
<u>2 HOURS POSTDOSAGE:</u>					
PUPS TESTED	N	-		5	
BRAIN WEIGHT (G)	MEAN±S.D.			1.325 ± 0.057	
CHOLINESTERASE LEVELS (UNITS/G)	MEAN±S.D.			8.481 ± 0.693	
% INHIBITION a	%			21.4	
<u>3 HOURS POSTDOSAGE:</u>					
PUPS TESTED	N	5		4b	
BRAIN WEIGHT (G)	MEAN±S.D.	1.328 ± 0.098		1.369 ± 0.051	
CHOLINESTERASE LEVELS (UNITS/G)	MEAN±S.D.	11.475 ± 0.207		9.307 ± 0.292	
% INHIBITION	%			18.9	
a. Value derived from comparison to the Vehicle Group, 1 hour postdosage value.					
b. Excludes values for pup 7810, which was found dead on postnatal day 13.					

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B8 (PAGE 2): BRAIN CHOLINESTERASE LEVELS - SUMMARY - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP	I		II	
	CORN OIL	MALATHION		
TEST SUBSTANCE				
DOSAGE (MG/KG/DAY)	0 (VEHICLE)	150		
4 HOURS POSTDOSAGE:				
PUPS TESTED	N	-	5	
BRAIN WEIGHT (G)	MEAN±S.D.		1.362 ± 0.053	
CHOLINESTERASE LEVELS (UNITS/G)	MEAN±S.D.		10.385 ± 0.634	
% INHIBITION a				9.5
a. Value derived from comparison to the Vehicle Group, 3 hours postdosage value.				

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B9 (PAGE 1): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP I	CORN OIL	0 (VEHICLE) MG/KG
PUP #	DESCRIPTION	
7601	NO ADVERSE FINDINGS	
7602	NO ADVERSE FINDINGS	
7701	NO ADVERSE FINDINGS	
7702	NO ADVERSE FINDINGS	
7801	NO ADVERSE FINDINGS	
7802	NO ADVERSE FINDINGS	
7901	NO ADVERSE FINDINGS	
7902	NO ADVERSE FINDINGS	
8001	NO ADVERSE FINDINGS	
8115	PND(15) FOUND DEAD (DEATH OCCURRED 4 HOURS AND 23 MINUTES AFTER DOSAGE ADMINISTRATION) ^a	
PND = POSTNATAL DAY		
a. At necropsy, all tissues appeared normal.		

PROTOCOL IQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B9 (PAGE 2): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP II	MALATHION	150 MG/KG
PUP #	DESCRIPTION	
7603	PND(14- 15)	RED PERIANAL SUBSTANCE
7604		NO ADVERSE FINDINGS
7605		NO ADVERSE FINDINGS
7703		NO ADVERSE FINDINGS
7704	PND(13)	DECREASED MOTOR ACTIVITY
7705		NO ADVERSE FINDINGS
7803	PND(14)	DECREASED MOTOR ACTIVITY
	PND(14)	DEHYDRATION
	PND(14- 15)	PROSTRATE
7804	PND(14- 17)	WHOLE BODY: TREMORS, INTERMITTENT
7805	PND(15- 17)	WHOLE BODY: TREMORS, INTERMITTENT
7903		NO ADVERSE FINDINGS
7904	PND(15- 16)	WHOLE BODY: TREMORS, INTERMITTENT
7905	PND(15- 16)	WHOLE BODY: TREMORS, INTERMITTENT
8002	PND(13)	DECREASED MOTOR ACTIVITY
	PND(13)	IMPAIRED RIGHTING REFLEX
	PND(13)	WHOLE BODY: TREMORS, INTERMITTENT
	PND(16- 17)	WHOLE BODY: TREMORS, INTERMITTENT
8003	PND(13)	DECREASED MOTOR ACTIVITY
	PND(13)	WHOLE BODY: TREMORS, INTERMITTENT
	PND(13)	COLD TO TOUCH
8004	PND(13)	SOFT OR LIQUID FECES
8005		NO ADVERSE FINDINGS
	PND(13)	DECREASED MOTOR ACTIVITY
	PND(13)	PROSTRATE
	PND(13)	COLD TO TOUCH
	PND(13- 17)	WHOLE BODY: TREMORS, INTERMITTENT
	PND(14)	SOFT OR LIQUID FECES
8102	PND(17)	WHOLE BODY: TREMORS, INTERMITTENT
8103		NO ADVERSE FINDINGS
8104		NO ADVERSE FINDINGS
8105	PND(21)	URINE-STAINED ABDOMINAL FUR

PND = POSTNATAL DAY

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B10 (PAGE 1): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP I	CORN OIL	0 (VEHICLE) MG/KG
PUP #	DESCRIPTION	
7606	NO ADVERSE FINDINGS	
7607	NO ADVERSE FINDINGS	
7706	NO ADVERSE FINDINGS	
7707	NO ADVERSE FINDINGS	
7806	NO ADVERSE FINDINGS	
7807	NO ADVERSE FINDINGS	
7906	NO ADVERSE FINDINGS	
7907	NO ADVERSE FINDINGS	
8006	PND(14- 17) DEHYDRATION	
8106	NO ADVERSE FINDINGS	
PND = POSTNATAL DAY		

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B10 (PAGE 2): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP II		MALATHION	150 MG/KG
PUP #		DESCRIPTION	
7608		NO ADVERSE FINDINGS	
7609		NO ADVERSE FINDINGS	
7610		NO ADVERSE FINDINGS	
7708		NO ADVERSE FINDINGS	
7709	PND(13)	DECREASED MOTOR ACTIVITY	
	PND(13)	IMPAIRED RIGHTING REFLEX	
	PND(13)	PROSTRATE	
	PND(14)	DEHYDRATION	
	PND(14)	SOFT OR LIQUID FECES	
	PND(15-18)	WHOLE BODY: TREMORS, INTERMITTENT	
7710	PND(16-22)	RIGHT EYE: ENLARGED	
7808	PND(15-17)	WHOLE BODY: TREMORS, INTERMITTENT	
7809	PND(14-17)	WHOLE BODY: TREMORS, INTERMITTENT	
7810	PND(13)	DECREASED MOTOR ACTIVITY	
	PND(13)	PROSTRATE	
	PND(13)	PALE EXTREMITIES	
	PND(13)	GASPING	
	PND(13)	FOUND DEAD (DEATH OCCURRED 59 MINUTES AFTER DOSAGE ADMINISTRATION) a	
7908	PND(15-16)	WHOLE BODY: TREMORS, INTERMITTENT	
7909	PND(15-17)	WHOLE BODY: TREMORS, INTERMITTENT	
7910	PND(14)	WHOLE BODY: TREMORS, INTERMITTENT	
8007	PND(13)	DECREASED MOTOR ACTIVITY	
	PND(13)	IMPAIRED RIGHTING REFLEX	
	PND(13)	COLD TO TOUCH	
	PND(13)	SOFT OR LIQUID FECES	
	PND(13)	WHOLE BODY: TREMORS, INTERMITTENT	
	PND(13-16)	URINE-STAINED ABDOMINAL FUR	
8008	PND(14)	NO ADVERSE FINDINGS	
8009	PND(13)	DECREASED MOTOR ACTIVITY	
	PND(13)	PROSTRATE	
	PND(13)	COLD TO TOUCH	
	PND(13)	SOFT OR LIQUID FECES	
	PND(14)	WHOLE BODY: TREMORS, INTERMITTENT	
8010	PND(13)	DECREASED MOTOR ACTIVITY	
	PND(13)	PROSTRATE	
	PND(13)	EXCESS SALIVATION - SLIGHT	
	PND(13-17)	WHOLE BODY: TREMORS, INTERMITTENT	
	PND(14)	DEHYDRATION	

PND = POSTNATAL DAY

a. At necropsy, the right diaphragmatic lobe had one perforation (0.3 cm x 0.2 cm). All other tissues appeared normal.

PROTOCOL IQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B10 (PAGE 3): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP II		MALATHION	150 MG/KG
PUP #		DESCRIPTION	
8107	PND(17)	NO ADVERSE FINDINGS	
8108	PND(17)	WHOLE BODY: TREMORS, INTERMITTENT	
8114	PND(14)	NO ADVERSE FINDINGS	
8110	PND(14)	UNGROOMED COAT	
	PND(14)	SOFT OR LIQUID FECES	

PND = POSTNATAL DAY

TABLE B11 (PAGE 1): BODY WEIGHTS - INDIVIDUAL DATA - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DAY = POSTNATAL DAY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON IN JUVENILE RATS

TABLE B12 (PAGE 1): BODY WEIGHTS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

DAY 11																					
PUP #	DOSAGE GROUP I											0 (VEHICLE) MG/KG									
	12	13	14	15	16	17	18	19	20	21											
CORN OIL																					
7606	21.2	21.8	22.6	24.8	26.9	28.9	30.9	34.4	38.5	42.9	48.1										
7607	19.4	22.0	23.1	24.2	26.9	29.3	32.8	35.1	38.2	42.0	46.4										
7706	20.6	22.0	24.6	27.3	29.4	31.5	34.4	37.5	40.1	42.3	46.5										
7707	18.6	20.5	23.4	26.2	28.2	30.6	33.6	36.7	39.5	42.6	45.1										
7806	20.6	22.3	23.8	25.2	27.5	28.3	30.4	33.6	36.6	39.0	41.9										
7807	20.9	22.1	23.8	25.8	28.7	30.5	32.8	36.0	38.8	41.1	43.5										
7906	19.8	21.0	22.5	24.1	24.5	26.9	28.8	30.6	33.1	36.0	38.4										
7907	22.7	24.2	26.3	27.1	28.2	30.4	32.4	34.9	39.1	44.2	46.7										
8006	18.4	18.7	18.1	18.4	20.4	22.3	24.2	26.4	29.2	32.3	34.3										
8106	22.8	24.6	26.0	27.7	29.6	32.2	34.0	37.4	41.0	44.6	48.5										
PUP #	DOSAGE GROUP II											150 MG/KG									
	MALATHION																				
7608	19.2	19.8	20.7	22.8	25.3	27.4	29.9	33.1	35.7	39.1	43.9										
7609	22.1	25.5	28.9	31.9	33.6	36.2	39.4	42.5	45.8	48.5	52.3										
7610	21.6	21.3	22.0	24.2	27.2	29.8	32.0	36.0	38.8	40.8	43.6										
7708	22.3	24.6	25.8	28.5	30.7	33.7	36.7	39.9	42.2	45.3	49.1										
7709	19.1	20.2	19.3	21.5	23.6	25.2	28.1	31.7	33.8	36.4	39.4										
7710	19.9	21.5	22.8	26.3	28.5	30.7	32.3	35.0	38.0	43.0	48.0										
7808	23.4	24.8	26.3	27.5	29.6	30.9	34.0	36.3	38.4	40.3	43.4										
7809	21.9	23.4	24.6	26.1	28.1	29.8	31.6	34.9	36.2	38.8	41.0										
7810	20.2	21.8	23.1	24.6	26.1	28.1	29.8	31.6	34.9	36.2	38.8										
7908	23.7	25.3	27.4	29.6	31.0	32.4	34.4	36.5	39.1	42.2	45.2										
7909	21.0	22.1	23.3	24.6	26.5	29.5	32.2	33.0	35.2	38.2	41.6										
7910	24.2	26.0	28.0	29.8	32.2	32.8	34.9	38.6	42.2	45.9	49.0										
8007	19.8	19.8	19.8	19.5	21.7	24.3	26.8	29.4	32.1	36.0	40.5										
8008	21.8	22.9	22.6	24.1	26.6	28.7	30.8	33.3	37.4	41.6	46.1										
8009	19.3	21.7	21.4	20.4	23.3	26.0	27.4	28.8	31.8	35.3	38.8										
8010	22.2	23.8	23.6	23.2	26.2	28.8	31.3	33.0	37.4	41.3	46.0										
8107	22.6	24.2	25.9	27.4	28.0	30.7	32.5	35.8	40.2	41.4	44.8										
8108	23.1	25.1	26.5	28.7	29.1	31.3	33.1	36.5	38.0	44.0	47.7										
8114	22.4	23.9	25.9	26.9	27.7	29.9	31.6	34.9	38.8	42.1	46.0										
8110	25.3	27.1	28.7	29.6	30.0	31.8	33.9	37.0	40.4	42.7	47.0										

DAY = POSTNATAL DAY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B13 (PAGE 1): RBC CHOLINESTERASE LEVELS - INDIVIDUAL DATA - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	FINAL CHOLINESTERASE (UNITS/ML)		FOOTNOTE	
	DOSAGE GROUP I		CORN OIL	0 (VEHICLE) MG/KG/DAY
	1 HOUR POSTDOSAGE			
7601	2.371			
7602	2.512			
7701	2.050			
7702	1.908			
7801	2.339			
	3 HOURS POSTDOSAGE			
7802	2.588			
7901	1.411			
7902	1.962			
8001	1.198			
8115	FOUND DEAD ON POSTNATAL DAY 15			

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B13 (PAGE 2): RBC CHOLINESTERASE LEVELS - INDIVIDUAL DATA - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	FINAL CHOLINESTERASE (UNITS/ML)		FOOTNOTE
	DOSAGE GROUP II	MALATHION	
	1 HOUR POSTDOSE	150 MG/KG/DAY	
7603	1.589		
7604	1.778		
7605	1.589		
7703	1.100		
7704	0.845		
	2 HOURS POSTDOSE		
7904	1.151		
7905	0.952		
8002	1.647		
8003	0.743		
8004	1.022		
	3 HOURS POSTDOSE		
7705	1.597		
7803	1.636		
7804	1.049		
7805	1.278		
7903	1.537		
	4 HOURS POSTDOSE		
8005	1.117		
8102	1.077		
8103	1.297		
8104	1.531		
8105	1.260		

PROTOCOL TOC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B14 (PAGE 1): RBC CHOLINESTERASE LEVELS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	FINAL CHOLINESTERASE (UNITS/ML)	FOOTNOTE
DOSAGE GROUP 1		CORN OIL
1 HOUR POSTDOSE		0 (VEHICLE) MG/KG/DAY
7606	2.224	
7607	2.369	
7706	2.375	
7707	2.227	
7806	2.061	
3 HOURS POSTDOSE		
7807	a	
7906	a	
7907	a	
8006	a	
8106	a	
a. Insufficient volume to process or analyze sample.		

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B14 (PAGE 2): RBC CHOLINESTERASE LEVELS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	FINAL CHOLINESTERASE (UNITS/ML)	FOOTNOTE
	DOSAGE GROUP III	MALATHION
	1 HOUR POSTDOSAGE	150 MG/KG/DAY
7608	1.348	
7609	1.558	
7610	1.587	
7708	1.190	
7709	1.234	
	2 HOURS POSTDOSAGE	
7909	1.043	
7910	0.957	
8007	1.013	
8008	1.194	
8009	X	DNR
	0.635	
	3 HOURS POSTDOSAGE	
7710	a	
7808	a	
7809	X	DNR
	0.619	
7810	FOUND DEAD ON POSTNATAL DAY 13	
7908	1.084	
	4 HOURS POSTDOSAGE	
8010	0.930	
8107	a	
8108	1.049	
8114	a	
8110	1.305	

X = SAMPLE RESULTS DO NOT MEET ACCEPTABILITY CRITERIA; VALUES WERE NOT REPORTED OR INCLUDED IN SUMMARIZATION AND STATISTICAL ANALYSES.

DNR = DUPLICATE ANALYSIS OF THE SAME SAMPLE DOES NOT MEET REPRODUCIBILITY CRITERIA.

a. Insufficient volume to process or analyze sample.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B15 (PAGE 1): BRAIN CHOLINESTERASE LEVELS - INDIVIDUAL DATA - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	BRAIN (G)	FINAL CHOLINESTERASE (UNITS/G)		FOOTNOTE
		DOSAGE GROUP I	0 (VEHICLE) MG/KG/DAY	
		CORN OIL		
1 HOUR POSTDOSAGE				
7601	1.374		12.033	
7602	1.153		12.331	
7701	1.468		10.876	
7702	1.522		10.846	
7801	1.304		10.965	
3 HOURS POSTDOSAGE				
7802	1.388		10.015	
7901	1.436		10.507	
7902	1.403		10.653	
8001	1.284		11.079	
8115	FOUND DEAD ON POSTNATAL DAY 15			

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B15 (PAGE 2): BRAIN CHOLINESTERASE LEVELS - INDIVIDUAL DATA - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	BRAIN (G)		FINAL CHOLINESTERASE (UNITS/G)		FOOTNOTE
	DOSAGE GROUP III		150 MG/KG/DAY		
	MALATHION				
1 HOUR POSTDOSAGE					
7603	1.403		10.024		
7604	1.364		11.785		
7605	1.421		10.975		
7703	1.477		9.999		
7704	1.467		7.886		
2 HOURS POSTDOSAGE					
7904	1.489		10.794		
7905	1.382		9.299		
8002	1.359		9.572		
8003	1.281		8.656		
8004	1.388		10.242		
3 HOURS POSTDOSAGE					
7705	1.444		10.435		
7803	1.183		8.739		
7804	1.385		8.668		
7805	1.352		9.983		
7903	1.485		8.911		
4 HOURS POSTDOSAGE					
8005	1.302		9.971		
8102	1.472		8.739		
8103	1.564		9.248		
8104	1.471		9.016		
8105	1.464		9.444		

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B16 (PAGE 1): BRAIN CHOLINESTERASE LEVELS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	BRAIN (G)		FINAL CHOLINESTERASE (UNITS/G)		FOOTNOTE
	DOSAGE GROUP I	CORN OIL		0 (VEHICLE) MG/KG/DAY	
	1 HOUR POSTDOSAGE				
7606	1.356		11.681		
7607	1.327		10.472		
7706	1.306		11.759		
7707	1.451		9.793		
7806	1.391		10.262		
	3 HOURS POSTDOSAGE				
7807	1.298		11.566		
7906	1.278		11.625		
7907	1.328		11.123		
8006	1.241		11.605		
8106	1.494		11.453		

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE B16 (PAGE 2): BRAIN CHOLINESTERASE LEVELS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	BRAIN (G)		FINAL CHOLINESTERASE (UNITS/G)		FOOTNOTE
	DOSAGE GROUP III	MALATHION			
	1 HOUR POSTDOSAGE		150 MG/KG/DAY		
7608	1.397		10.018		
7609	1.403		8.056		
7610	1.359		10.010		
7708	1.363		8.072		
7709	1.284		8.597		
2 HOURS POSTDOSAGE					
7909	1.391		8.466		
7910	1.366		8.186		
8007	1.297		8.702		
8008	1.322		9.469		
8009	1.247		7.581		
3 HOURS POSTDOSAGE					
7710	1.436		9.444		
7808	1.312		9.582		
7809	1.361		8.906		
7810	FOUND DEAD ON POSTNATAL DAY 13				
7908	1.367		X		DNR
	1.367		9.295		
4 HOURS POSTDOSAGE					
8010	1.342		9.754		
8107	1.300		10.781		
8108	1.429		9.659		
8114	1.403		11.042		
8110	1.334		10.690		

X = SAMPLE RESULTS DO NOT MEET ACCEPTABILITY CRITERIA; VALUES WERE NOT REPORTED OR INCLUDED IN SUMMARIZATION AND STATISTICAL ANALYSES.

DNR = DUPLICATE ANALYSIS OF THE SAME SAMPLE DOES NOT MEET REPRODUCIBILITY CRITERIA.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY - MALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP	I	III
TEST SUBSTANCE	CORN OIL	MALAOXON
DOSAGE (MG/KG/DAY)	0 (VEHICLE)	4
MAXIMUM POSSIBLE INCIDENCE	109/ 10	216/ 20
FOUND DEAD	1a	1b
URINE-STAINED ABDOMINAL FUR	0/ 0	3/ 1
SOFT OR LIQUID FECES	1/ 1	0/ 0
MAXIMUM POSSIBLE INCIDENCE = (DAYS x PUPS)/NUMBER OF PUPS EXAMINED PER GROUP ON POSTNATAL DAYS 11 THROUGH 21.		
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF PUPS WITH OBSERVATION.		
a. Pup 9601 was found dead on postnatal day 20.		
b. Pup 9304 was found dead on postnatal day 17.		

PROTOCOL TOC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C2 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY - FEMALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP	I	III
TEST SUBSTANCE	CORN OIL	MALAOXON
DOSAGE (MG/KG/DAY)	0 (VEHICLE)	4
MAXIMUM POSSIBLE INCIDENCE	110/ 10	219/ 20
FOUND DEAD	0	1a
EXCESS SALIVATION - SLIGHT	0/ 0	2/ 2
URINE-STAINED ABDOMINAL FUR	1/ 1	2/ 1
HEAD: SCAB	4/ 1	0/ 0

MAXIMUM POSSIBLE INCIDENCE = (DAYS x PUPS)/NUMBER OF PUPS EXAMINED PER GROUP ON POSTNATAL DAYS 11 THROUGH 21.

N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF PUPS WITH OBSERVATION.

a. Pup 9208 was found dead on postnatal day 20.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C3 (PAGE 1): BODY WEIGHTS AND BODY WEIGHT CHANGES - SUMMARY - MALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP TEST SUBSTANCE DOSAGE (MG/KG/DAY)	I		III	
	CORN OIL 0 (VEHICLE)		MALAOXON 4	
PUPS TESTED	N	10	20	
BODY WEIGHT (G)				
DAY 11	MEAN±S.D.	28.0 ± 2.6	27.6 ± 1.8	
DAY 12	MEAN±S.D.	30.8 ± 2.8	30.5 ± 2.0	
DAY 13	MEAN±S.D.	33.6 ± 3.1	33.0 ± 2.4	
DAY 14	MEAN±S.D.	36.4 ± 3.1	35.8 ± 2.4	
DAY 15	MEAN±S.D.	37.6 ± 3.0	37.0 ± 2.6	
DAY 16	MEAN±S.D.	38.1 ± 3.4	37.7 ± 2.8	
DAY 17	MEAN±S.D.	39.0 ± 3.4	38.9 ± 2.8	
DAY 18	MEAN±S.D.	40.5 ± 3.7	40.5 ± 3.0	
DAY 19	MEAN±S.D.	43.4 ± 3.6	43.3 ± 3.2	
DAY 20	MEAN±S.D.	46.3 ± 4.6	46.2 ± 3.8	
DAY 21	MEAN±S.D.	49.1 ± 5.0	49.9 ± 4.7	
BODY WEIGHT CHANGE (G)				
DAYS 11 - 14	MEAN±S.D.	+8.4 ± 1.0	+8.2 ± 0.8	
DAYS 14 - 17	MEAN±S.D.	+2.7 ± 0.7	+3.1 ± 1.1	
DAYS 17 - 21	MEAN±S.D.	+10.5 ± 2.4	+10.9 ± 2.6	
DAYS 11 - 21	MEAN±S.D.	+21.4 ± 3.0	+22.3 ± 3.2	

DAY(S) = POSTNATAL DAY(S)

I = NUMBER OF VALUES AVERAGED

a. Excludes pups that were found dead.

PROTOCOL TC000012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C4 (PAGE 1): BODY WEIGHTS AND BODY WEIGHT CHANGES - SUMMARY - FEMALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP TEST SUBSTANCE DOSAGE (MG/KG/DAY)	I		III	
	CORN OIL 0 (VEHICLE)		MALAOXON 4	
PUPS TESTED	N	10	20	
BODY WEIGHT (G)				
DAY 11	MEAN±S.D.	26.1 ± 2.5	26.4 ± 2.0	
DAY 12	MEAN±S.D.	28.4 ± 2.7	29.0 ± 2.2	
DAY 13	MEAN±S.D.	31.3 ± 2.8	31.8 ± 2.4	
DAY 14	MEAN±S.D.	33.7 ± 2.6	34.3 ± 2.4	
DAY 15	MEAN±S.D.	34.8 ± 2.8	35.6 ± 2.6	
DAY 16	MEAN±S.D.	35.6 ± 2.9	36.3 ± 2.6	
DAY 17	MEAN±S.D.	36.4 ± 3.0	37.3 ± 2.9	
DAY 18	MEAN±S.D.	37.8 ± 2.6	38.3 ± 2.5	
DAY 19	MEAN±S.D.	40.3 ± 3.4	41.2 ± 3.1	
DAY 20	MEAN±S.D.	42.7 ± 4.3	44.3 ± 3.9	
DAY 21	MEAN±S.D.	45.4 ± 4.6	48.0 ± 4.5	191a
BODY WEIGHT CHANGE (G)				
DAYS 11 - 14	MEAN±S.D.	+7.6 ± 0.8	+7.9 ± 1.0	
DAYS 14 - 17	MEAN±S.D.	+2.7 ± 0.6	+3.0 ± 0.8	
DAYS 17 - 21	MEAN±S.D.	+9.0 ± 1.8	+10.6 ± 2.7	191a
DAYS 11 - 21	MEAN±S.D.	+19.3 ± 2.3	+21.5 ± 3.3	191a

DAY(S) = POSTNATAL DAY(S)

I = NUMBER OF VALUES AVERAGED

a. Excludes values for pup 9208, which was found dead on postnatal day 20.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C5 (PAGE 1): RBC CHOLINESTERASE LEVELS - SUMMARY - MALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP		I		III	
TEST SUBSTANCE		CORN OIL		MALAOXON	
DOSAGE (MG/KG/DAY)		0 (VEHICLE)		4	
<u>30 MINUTES POSTDOSAGE:</u>					
PUPS TESTED	N	3a	6		
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.	2.097 ± 0.693	1.237 ± 0.142		
% INHIBITION	%		41.0		
<u>60 MINUTES POSTDOSAGE:</u>					
PUPS TESTED	N	-	4		
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.		1.216 ± 0.296		
% INHIBITION b	%		42.0		
<u>90 MINUTES POSTDOSAGE:</u>					
PUPS TESTED	N	5	6		
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.	2.450 ± 0.276	0.927 ± 0.207		
% INHIBITION	%		62.2		
<u>2 HOURS POSTDOSAGE:</u>					
PUPS TESTED	N	-	3a		
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.		0.994 ± 0.111		
% INHIBITION c	%		59.4		

a. Excludes values for pups that were found dead or had samples clotted during processing.

b. Value derived from comparison to the Vehicle Group, 30 minutes postdosage value.

c. Value derived from comparison to the Vehicle Group, 90 minutes postdosage value.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C6 (PAGE 1): RBC CHOLINESTERASE LEVELS - SUMMARY - FEMALE PUPS - MALAOXON - Dosed POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP		I		III	
TEST SUBSTANCE		CORN OIL		MALAOXON	
DOSAGE (MG/KG/DAY)		0 (VEHICLE)	4		
30 MINUTES POSTDOSAGE:					
PUPS TESTED	N	4a	4		
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.	1.986 ± 0.194	0.880 ± 0.209		
% INHIBITION	%		55.7		
60 MINUTES POSTDOSAGE:					
PUPS TESTED	N	-	6		
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.		0.987 ± 0.251		
% INHIBITION b	%		50.3		
90 MINUTES POSTDOSAGE:					
PUPS TESTED	N	5	4		
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.	2.001 ± 0.219	0.959 ± 0.195		
% INHIBITION	%		52.1		
2 HOURS POSTDOSAGE:					
PUPS TESTED	N	-	5a		
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.		0.813 ± 0.117		
% INHIBITION c	%		59.4		

a. Excludes values for pups that were found dead or had samples clotted during processing.

b. Value derived from comparison to the Vehicle Group, 30 minutes postdosage value.

c. Value derived from comparison to the Vehicle Group, 90 minutes postdosage value.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C7 (PAGE 1): BRAIN CHOLINESTERASE LEVELS - SUMMARY - MALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP		I		III	
TEST SUBSTANCE	CORN OIL	MALAOXON			
DOSAGE (MG/KG/DAY)	0 (VEHICLE)	4			
<u>30 MINUTES POSTDOSAGE:</u>					
PUPS TESTED	N	4a	6		
BRAIN WEIGHT (G)	MEAN±S.D.	1.368 ± 0.119	1.412 ± 0.051		
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.	12.633 ± 0.730	10.650 ± 1.406		
% INHIBITION	%		15.7		
<u>60 MINUTES POSTDOSAGE:</u>					
PUPS TESTED	N	-	4		
BRAIN WEIGHT (G)	MEAN±S.D.		1.466 ± 0.066		
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.		12.079 ± 0.916		
% INHIBITION b	%		4.4		
<u>90 MINUTES POSTDOSAGE:</u>					
PUPS TESTED	N	5	6		
BRAIN WEIGHT (G)	MEAN±S.D.	1.478 ± 0.087	1.443 ± 0.035		
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.	12.662 ± 0.415	12.532 ± 1.015		
% INHIBITION	%		1.0		
a. Excludes values for pup 9601, which was found dead on postnatal day 20.					
b. Value derived from comparison to the Vehicle Group, 30 minutes postdosage value.					

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C7 (PAGE 2): BRAIN CHOLINESTERASE LEVELS - SUMMARY - MALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP	I	III
TEST SUBSTANCE	CORN OIL	MALAOXON
DOSAGE (MG/KG/DAY)	0 (VEHICLE)	4

2 HOURS POSTDOSAGE:

PUPS TESTED	N	3a
BRAIN WEIGHT (G)	MEAN±S.D.	1.491 ± 0.546
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.	11.397 ± 0.474

% INHIBITION b

% 10.0

a. Excludes values for pup 9304, which was found dead on postnatal day 17.

b. Value derived from comparison to the Vehicle Group, 90 minutes postdosage value.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C8 (PAGE 1): BRAIN CHOLINESTERASE LEVELS - SUMMARY - FEMALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP		I		III	
TEST SUBSTANCE	CORN OIL	MALAOXON			
DOSAGE (MG/KG/DAY)	0 (VEHICLE)		4		
<u>30 MINUTES POSTDOSAGE:</u>					
PUPS TESTED	N	5	4		
BRAIN WEIGHT (G)	MEAN±S.D.	1.357 ± 0.071	1.397 ± 0.022		
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.	11.093 ± 2.221	10.173 ± 1.264		
% INHIBITION	%		8.3		
<u>60 MINUTES POSTDOSAGE:</u>					
PUPS TESTED	N	-	6		
BRAIN WEIGHT (G)	MEAN±S.D.		1.415 ± 0.044		
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.		10.800 ± 1.032		
% INHIBITION a	%		2.6		
<u>90 MINUTES POSTDOSAGE:</u>					
PUPS TESTED	N	5	4		
BRAIN WEIGHT (G)	MEAN±S.D.	1.411 ± 0.081	1.393 ± 0.049		
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.	12.125 ± 2.274	13.171 ± 1.276		
% INHIBITION	%		-8.6		
a. Value derived from comparison to the Vehicle Group, 30 minutes postdosage value.					

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C8 (PAGE 2): BRAIN CHOLINESTERASE LEVELS - SUMMARY - FEMALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

DOSAGE GROUP	I	III
TEST SUBSTANCE	CORN OIL	MALAOXON
DOSAGE (MG/KG/DAY)	0 (VEHICLE)	4

2 HOURS POSTDOSAGE:

PUPS TESTED	N	-	5a
BRAIN WEIGHT (G)	MEAN±S.D.		1.386 ± 0.032
CHOLINESTERASE LEVELS (UNITS/ML)	MEAN±S.D.		12.183 ± 1.195

% INHIBITION b

a. Excludes values for pup 9208, which was found dead on postnatal day 20.

b. Value derived from comparison to the Vehicle Group, 90 minutes postdosage value.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C9 (PAGE 1): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - MALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	DESCRIPTION	
DOSAGE GROUP I	CORN OIL	0 (VEHICLE) MG/KG/DAY
9201	NO ADVERSE FINDINGS	
9202	SOFT OR LIQUID FECES	
9301	NO ADVERSE FINDINGS	
9302	NO ADVERSE FINDINGS	
9401	NO ADVERSE FINDINGS	
9402	NO ADVERSE FINDINGS	
9501	NO ADVERSE FINDINGS	
9601	FOUND DEAD (DEATH OCCURRED OVERNIGHT) ^a	
9602	NO ADVERSE FINDINGS	
9701	NO ADVERSE FINDINGS	
DOSAGE GROUP III	MALAOXON	4 MG/KG/DAY
9203	NO ADVERSE FINDINGS	
9204	NO ADVERSE FINDINGS	
9205	NO ADVERSE FINDINGS	
9303	URINE-STAINED ABDOMINAL FUR	
9304	FOUND DEAD (DEATH OCCURRED 5 MINUTES AFTER DOSAGE ADMINISTRATION) ^b	
9305	NO ADVERSE FINDINGS	
9403	NO ADVERSE FINDINGS	
9404	NO ADVERSE FINDINGS	
9405	NO ADVERSE FINDINGS	
9502	NO ADVERSE FINDINGS	
9503	NO ADVERSE FINDINGS	
9504	NO ADVERSE FINDINGS	
9505	NO ADVERSE FINDINGS	
9603	NO ADVERSE FINDINGS	
9604	NO ADVERSE FINDINGS	
9605	NO ADVERSE FINDINGS	
9702	NO ADVERSE FINDINGS	
9703	NO ADVERSE FINDINGS	
9704	NO ADVERSE FINDINGS	
9705	NO ADVERSE FINDINGS	
PND = POSTNATAL DAY		
a.	At necropsy, pup was partially cannibalized. All other tissues appeared normal.	
b.	At necropsy, the trachea had a perforation just cranial to bifurcation (0.2 cm x 0.1 cm) and lungs and trachea contained foamy, white material. All other tissues appeared normal.	

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON IN JUVENILE RATS

TABLE C10 (PAGE 1): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - FEMALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	DESCRIPTION	
DOSAGE GROUP I	CORN OIL	0 (VEHICLE) MG/KG/DAY
9206	NO ADVERSE FINDINGS	
9207	PND(15- 18)	NO ADVERSE FINDINGS
9306	HEAD: SCAB (0.3 CM X 0.2 CM)	
9307	NO ADVERSE FINDINGS	
9406	URINE-STAINED ABDOMINAL FUR	
9506	NO ADVERSE FINDINGS	
9507	NO ADVERSE FINDINGS	
9606	NO ADVERSE FINDINGS	
9706	NO ADVERSE FINDINGS	
9707	NO ADVERSE FINDINGS	
DOSAGE GROUP III	MALAOXON	4 MG/KG/DAY
9208	PND(20)	FOUND DEAD (DEATH OCCURRED IMMEDIATELY FOLLOWING DOSAGE ADMINISTRATION) ^a
9209	PND(19)	EXCESS SALIVATION - SLIGHT
9210		NO ADVERSE FINDINGS
9308		NO ADVERSE FINDINGS
9309		NO ADVERSE FINDINGS
9310		NO ADVERSE FINDINGS
9407		NO ADVERSE FINDINGS
9408	PND(21)	EXCESS SALIVATION - SLIGHT
9409		NO ADVERSE FINDINGS
9410	PND(19- 20)	URINE-STAINED ABDOMINAL FUR
9508		NO ADVERSE FINDINGS
9509		NO ADVERSE FINDINGS
9510		NO ADVERSE FINDINGS
9607		NO ADVERSE FINDINGS
9608		NO ADVERSE FINDINGS
9609		NO ADVERSE FINDINGS
9610		NO ADVERSE FINDINGS
9708		NO ADVERSE FINDINGS
9709		NO ADVERSE FINDINGS
9710		NO ADVERSE FINDINGS
PND = POSTNATAL DAY		
a. At necropsy, lungs and trachea contained foamy, white material and all lobes of lungs were pale. All other tissues appeared normal.		

PROTOCOL IQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C11 (PAGE 1): BODY WEIGHTS - INDIVIDUAL DATA - MALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

		DAY 11	12	13	14	15	16	17	18	19	20	21
		0 (VEHICLE) MG/KG/DAY										
PUP #	DOSAGE GROUP I	0 (VEHICLE) MG/KG/DAY										
9201	26.6	29.6	32.0	34.6	35.7	36.5	37.9	39.3	42.3	44.8	47.3	
9202	23.8	26.5	28.7	31.8	33.6	32.9	34.2	35.8	38.2	40.1	44.4	
9301	28.4	30.4	32.7	35.2	36.1	36.6	37.2	39.3	41.9	43.7	46.3	
9302	26.2	28.4	31.5	34.0	34.8	35.0	35.3	37.1	39.9	41.2	43.4	
9401	28.1	31.0	33.6	36.2	37.6	37.9	39.7	40.3	44.6	49.6	53.3	
9402	27.6	30.7	33.4	35.3	36.4	36.6	37.9	38.1	42.0	47.4	50.1	
9501	32.3	35.3	39.3	41.8	41.9	42.6	44.4	48.0	50.7	54.6	58.7	
9601	30.1	33.0	36.1	39.9	41.4	42.3	42.6	43.9	45.9	a	53.0	
9602	31.0	34.7	37.0	39.9	41.7	42.5	43.2	44.2	46.6	50.3	53.0	
9701	25.6	28.5	31.6	35.0	37.1	38.0	38.1	39.2	42.1	44.7	45.8	
PUP #	DOSAGE GROUP III	4 MG/KG/DAY										
9203	25.9	28.6	31.2	34.0	35.9	36.0	37.8	38.8	40.9	42.9	45.4	
9204	26.1	28.8	31.5	33.6	35.8	35.9	38.2	38.4	41.6	42.5	44.6	
9205	25.3	27.9	30.2	33.6	34.1	34.7	36.0	37.5	40.0	41.1	45.0	
9303	28.5	31.4	33.4	37.2	37.4	37.4	37.5	39.9	42.0	44.3	48.3	
9304	28.1	29.9	32.0	34.7	35.1	35.7	36.3	b				
9305	25.7	27.5	29.0	31.6	32.5	33.3	33.8	36.2	38.2	39.2	42.0	
9403	26.9	29.8	32.3	35.2	35.8	36.9	38.2	38.0	42.4	45.7	50.3	
9404	27.3	30.5	33.0	35.3	36.4	37.5	39.5	39.2	43.6	48.6	53.0	
9405	25.6	28.0	30.3	33.3	34.0	34.9	36.4	36.6	40.2	44.1	47.0	
9502	28.7	31.5	34.7	37.5	37.8	38.8	40.2	44.1	45.9	50.1	54.0	
9503	24.3	26.3	29.5	31.8	32.6	32.8	34.5	37.8	39.4	41.7	43.2	
9504	29.2	31.8	35.0	37.9	38.6	39.4	41.0	43.2	46.7	50.8	56.1	
9505	30.2	33.1	36.5	39.6	39.7	40.8	43.0	45.3	49.6	53.1	58.2	
9603	29.2	32.4	36.4	38.2	40.5	41.1	41.7	43.2	44.6	48.7	51.0	
9604	29.9	32.9	35.2	38.5	40.0	40.6	41.4	42.7	45.1	47.7	52.1	
9605	29.4	32.6	35.7	37.7	40.4	42.0	43.6	43.9	46.6	48.6	51.9	
9702	25.7	28.3	30.8	33.8	35.3	36.2	36.3	36.8	39.6	42.7	46.3	
9703	28.4	30.8	33.9	36.7	38.5	38.9	40.0	41.2	43.5	47.3	51.4	
9704	29.9	32.6	35.7	38.8	40.9	41.5	42.4	43.9	47.0	50.5	56.0	
9705	28.6	31.4	33.8	37.1	39.3	40.0	40.4	43.5	45.9	48.2	52.9	

DAY = POSTNATAL DAY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Pup 9601 was found dead on postnatal day 20.

b. Pup 9304 was found dead on postnatal day 17.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C12 (PAGE 1): BODY WEIGHTS - INDIVIDUAL DATA - FEMALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

		DAY 11	12	13	14	15	16	17	18	19	20	21
		0 (VEHICLE) MG/KG/DAY										
PUP #	DOSAGE GROUP I	0 (VEHICLE) MG/KG/DAY										
9206	24.1	26.0	28.4	30.5	31.7	32.9	33.4	34.7	37.3	38.2	40.2	
9207	24.3	26.4	29.5	31.1	32.5	33.1	33.9	35.6	37.2	39.1	42.2	
9306	24.4	26.6	29.2	32.0	32.9	33.5	34.0	36.1	37.2	38.5	42.4	
9307	22.5	24.7	27.3	30.7	31.2	31.4	32.9	34.3	36.2	37.9	39.8	
9406	31.5	34.0	36.6	38.5	40.1	40.8	42.4	42.1	47.1	50.9	54.7	
9506	26.1	28.4	31.9	34.7	35.0	35.6	36.7	39.3	41.9	45.0	47.3	
9507	26.2	29.0	32.7	35.1	35.3	36.8	37.4	39.8	43.1	46.5	48.4	
9606	26.9	29.1	32.5	34.9	37.3	38.0	38.3	39.1	41.4	43.7	47.3	
9706	28.2	30.9	33.7	35.9	37.2	38.4	39.0	39.5	41.9	45.1	47.6	
9707	26.6	28.5	31.3	33.7	34.6	35.4	36.2	37.3	39.3	42.0	44.1	

		4 MG/KG/DAY										
PUP #	DOSAGE GROUP III	4 MG/KG/DAY										
9208	25.7	28.5	31.8	33.8	35.7	36.1	37.4	38.0	41.0	42.1	a	
9209	27.3	29.9	32.3	34.9	37.0	36.1	37.3	38.3	40.9	42.9	45.3	
9210	25.6	27.8	30.5	31.9	33.6	34.3	34.7	36.3	37.5	39.0	41.8	
9308	24.2	26.6	28.0	30.7	31.5	32.3	32.6	34.6	36.8	38.8	41.1	
9309	22.2	24.5	27.1	29.9	30.9	31.3	32.0	34.1	35.8	37.4	40.0	
9310	24.8	27.1	29.9	32.0	33.8	33.6	34.2	35.9	37.4	38.8	42.7	
9407	26.8	29.3	32.1	34.3	35.5	36.5	37.8	37.2	41.4	45.7	49.9	
9408	27.7	30.4	33.2	35.9	37.4	37.4	39.4	38.2	42.5	47.0	50.8	
9409	28.0	30.7	34.0	37.0	38.0	38.7	39.5	37.6	42.3	45.2	48.0	
9410	30.6	33.1	35.3	37.3	38.4	39.2	40.5	39.9	44.7	48.4	52.8	
9508	26.1	28.6	32.2	34.5	35.0	36.6	37.0	41.2	46.0	48.6	54.2	
9509	25.1	27.2	30.3	33.2	33.7	34.6	35.9	39.0	42.0	45.8	50.3	
9510	25.8	28.7	31.8	34.1	34.2	35.8	35.9	38.1	41.4	44.4	47.6	
9607	26.9	29.6	32.6	35.4	37.0	37.2	39.3	39.7	41.5	47.0	51.4	
9608	24.0	26.7	29.1	32.5	34.8	35.8	35.7	36.9	39.1	42.4	45.0	
9609	26.2	30.1	32.7	36.1	38.3	38.5	41.0	41.8	43.4	48.4	52.2	
9610	27.2	30.0	33.3	35.9	37.8	38.4	40.5	41.1	43.7	48.2	49.9	
9708	31.0	34.0	37.7	40.3	41.8	42.8	43.3	44.1	47.8	51.3	54.5	
9709	26.3	28.8	31.1	33.6	35.0	35.5	37.3	36.7	38.6	40.9	44.6	
9710	26.1	27.8	30.7	32.8	33.7	34.5	35.5	37.5	40.8	44.5	49.1	

DAY = POSTNATAL DAY

ALL WEIGHTS WERE RECORDED IN GRAMS (G).

a. Pup 9208 was found dead on postnatal day 20.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C13 (PAGE 1): RBC CHOLINESTERASE LEVELS - INDIVIDUAL DATA - MALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	FINAL CHOLINESTERASE (UNITS/ML)	FOOTNOTE	0 (VEHICLE) MG/KG/DAY
	DOSAGE GROUP I	CORN OIL	
	30 MINUTES POSTDOSAGE		
9201	a		
9301	2.489		
9401	1.296		
9501	2.505		
9601	FOUND DEAD ON POSTNATAL DAY 20		
	90 MINUTES POSTDOSAGE		
9202	2.485		
9302	2.427		
9402	2.002		
9602	2.727		
9701	2.611		
a. Sample clotted during processing.			

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C13 (PAGE 2): RBC CHOLINESTERASE LEVELS - INDIVIDUAL DATA - MALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	FINAL CHOLINESTERASE (UNITS/ML)	FOOTNOTE
	DOSAGE GROUP III	MALAOXON
	30 MINUTES POSTDOSAGE	4 MG/KG/DAY
9203	1.464	
9305	1.211	
9403	1.285	
9503	1.126	
9605	1.276	
9705	1.057	
	60 MINUTES POSTDOSAGE	
9204	1.591	
9404	0.917	
9504	1.301	
9702	1.054	
	90 MINUTES POSTDOSAGE	
9205	0.914	
9303	1.138	
9405	0.729	
9505	1.219	
9603	0.820	
9703	0.743	
	2 HOURS POSTDOSAGE	
9304	FOUND DEAD ON POSTNATAL DAY 17	
9502	0.943	
9604	1.121	
9704	0.918	

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C14 (PAGE 1): RBC CHOLINESTERASE LEVELS - INDIVIDUAL DATA - FEMALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	FINAL CHOLINESTERASE (UNITS/ML)	FOOTNOTE
	DOSAGE GROUP I	CORN OIL
	30 MINUTES POSTDOSAGE	0 (VEHICLE) MG/KG/DAY
9206	a	
9306	1.834	
9406	1.888	
9506	2.268	
9606	1.955	
	90 MINUTES POSTDOSAGE	
9207	2.248	
9307	2.066	
9507	1.658	
9706	2.083	
9707	1.951	

a. Sample clotted during processing.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C14 (PAGE 2): RBC CHOLINESTERASE LEVELS - INDIVIDUAL DATA - FEMALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	FINAL CHOLINESTERASE (UNITS/ML)	FOOTNOTE
DOSAGE GROUP III	MALAOXON	
30 MINUTES POSTDOSAGE	4 MG/KG/DAY	
9209	1.099	
9408	X	DNR
	0.596	
9509	0.908	
9610	0.916	
60 MINUTES POSTDOSAGE		
9210	1.043	
9308	0.742	
9409	1.328	
9510	0.815	
9607	0.766	
9708	1.227	
90 MINUTES POSTDOSAGE		
9309	1.178	
9410	1.034	
9608	0.719	
9709	0.906	
2 HOURS POSTDOSAGE		
9208	FOUND DEAD ON POSTNATAL DAY 20	
9310	0.689	
9407	0.884	
9508	0.691	
9609	0.851	
9710	0.948	

X = SAMPLE RESULTS DO NOT MEET ACCEPTABILITY CRITERIA; VALUES WERE NOT REPORTED OR INCLUDED IN SUMMARIZATION AND STATISTICAL ANALYSES.

DNR = DUPLICATE ANALYSIS OF THE SAME SAMPLE DOES NOT MEET REPRODUCIBILITY CRITERIA.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C15 (PAGE 1): BRAIN CHOLINESTERASE LEVELS - INDIVIDUAL DATA - MALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	BRAIN (g)	FINAL CHOLINESTERASE (UNITS/G)		FOOTNOTE
		DOSAGE GROUP 1	CORN OIL	
		30 MINUTES POSTDOSAGE		0 (VEHICLE) MG/KG/DAY
9201	1.230		11.810	
9301	1.357		12.423	
9401	1.363		12.735	
9501	1.520		13.564	
9601	FOUND DEAD ON POSTNATAL DAY 20			
		90 MINUTES POSTDOSAGE		
9202	1.353		13.178	
9302	1.502		12.963	
9402	1.435		12.652	
9602	1.577		12.313	
9701	1.524		12.204	

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C15 (PAGE 2): BRAIN CHOLINESTERASE LEVELS - INDIVIDUAL DATA - MALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	BRAIN (G)		FINAL CHOLINESTERASE (UNITS/G)		FOOTNOTE
	DOSAGE GROUP III	MALAOXON	4 MG/KG/DAY		
30 MINUTES POSTDOSAGE					
9203	1.383			11.056	
9305	1.364			11.168	
9403	1.486			9.355	
9503	1.402			9.542	
9605	1.466			9.740	
9705	1.372			13.041	
60 MINUTES POSTDOSAGE					
9204	1.412			12.445	
9404	1.443			10.726	
9504	1.562			12.387	
9702	1.448			12.756	
90 MINUTES POSTDOSAGE					
9205	1.413			11.927	
9303	1.446			10.865	
9405	1.411			13.632	
9505	1.423			13.054	
9603	1.503			12.462	
9703	1.462			13.249	
2 HOURS POSTDOSAGE					
FOUND DEAD ON POSTNATAL DAY 17					
9304					
9502	1.431			11.496	
9604	1.538			10.881	
9704	1.503			11.814	

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C16 (PAGE 1): BRAIN CHOLINESTERASE LEVELS - INDIVIDUAL DATA - FEMALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	BRAIN (G)	FINAL CHOLINESTERASE (UNITS/G)		FOOTNOTE
		DOSAGE GROUP 1	CORN OIL	
		30 MINUTES POSTDOSAGE		0 (VEHICLE) MG/KG/DAY
9206	1.373		12.291	
9306	1.245		13.202	
9406	1.338		12.600	
9506	1.415		8.660	
9606	1.415		8.713	
		90 MINUTES POSTDOSAGE		
9207	1.373		8.124	
9307	1.376		13.676	
9507	1.552		12.888	
9706	1.403		13.327	
9707	1.349		12.609	

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE C16 (PAGE 2): BRAIN CHOLINESTERASE LEVELS - INDIVIDUAL DATA - FEMALE PUPS - MALAOXON - DOSED POSTNATAL DAYS 11 THROUGH 21

PUP #	BRAIN (G)		FINAL CHOLINESTERASE (UNITS/G)		FOOTNOTE
	DOSAGE GROUP III	MALAOXON	4 MG/KG/DAY		
30 MINUTES POSTDOSAGE					
9209	1.417		10.184		
9408	1.397		8.824		
9509	1.408		9.823		
9610	1.366		11.860		
60 MINUTES POSTDOSAGE					
9210	1.364		9.592		
9308	1.468		11.511		
9409	1.466		11.672		
9510	1.412		11.596		
9607	1.403		9.414		
9708	1.375		11.013		
90 MINUTES POSTDOSAGE					
9309	1.327		12.054		
9410	1.444		14.953		
9608	1.412		12.491		
9709	1.389		13.186		
2 HOURS POSTDOSAGE					
FOUND DEAD ON POSTNATAL DAY 20					
9208					
9310	1.390		13.074		
9407	1.432		12.394		
9508	1.382		13.542		
9609	1.387		10.917		
9710	1.341		10.989		

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

DOSAGE GROUP	I	IV	V	VI
TEST SUBSTANCE	CORN OIL	MALATHION	MALATHION	MALATHION
POSTNATAL DAY 11 DOSAGE (MG/KG)	0 (VEHICLE)	150	150	150
POSTNATAL DAY 21 DOSAGE (MG/KG)	0 (VEHICLE)	50	150	450
MAXIMUM POSSIBLE INCIDENCE	110/ 10	77/ 7	77/ 7	66/ 6
MORTALITY	0	0	0	0
URINE-STAINED ABDOMINAL FUR	1/ 1	0/ 0	0/ 0	1/ 1
UNGROOMED COAT	0/ 0	0/ 0	0/ 0	1/ 1
COLD TO TOUCH	0/ 0	0/ 0	1/ 1	0/ 0
EXCESS SALIVATION - SLIGHT	1/ 1	1/ 1	0/ 0	0/ 0
MAXIMUM POSSIBLE INCIDENCE = (DAYS x PUPS)/NUMBER OF PUPS EXAMINED PER GROUP ON POSTNATAL DAYS 11 THROUGH 21.				
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF PUPS WITH OBSERVATION.				

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON IN JUVENILE RATS

TABLE D2 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

DOSAGE GROUP	I	IV	V	VI
TEST SUBSTANCE	CORN OIL	MALATHION	MALATHION	MALATHION
POSTNATAL DAY 11 DOSAGE (MG/KG)	0 (VEHICLE)	150	150	150
POSTNATAL DAY 21 DOSAGE (MG/KG)	0 (VEHICLE)	50	150	450
MAXIMUM POSSIBLE INCIDENCE	110/ 10	77/ 7	77/ 7	66/ 6
MORTALITY	0	0	0	0
URINE-STAINED ABDOMINAL FUR	3/ 2	1/ 1	2/ 2	2/ 2
WHOLE BODY: TREMORS, SLIGHT	0/ 0	0/ 0	0/ 0	1/ 1
MIOSIS	0/ 0	0/ 0	0/ 0	1/ 1
EXCESS SALIVATION - SLIGHT	0/ 0	1/ 1	0/ 0	0/ 0
UNGROOMED COAT	1/ 1	0/ 0	0/ 0	0/ 0
MAXIMUM POSSIBLE INCIDENCE = (DAYS x PUPS)/NUMBER OF PUPS EXAMINED PER GROUP ON POSTNATAL DAYS 11 THROUGH 21.				
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF PUPS WITH OBSERVATION.				

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D3 (PAGE 1): BODY WEIGHTS AND BODY WEIGHT CHANGES - SUMMARY - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

DOSAGE GROUP		I		IV		V		VI	
TEST SUBSTANCE		CORN OIL		MALATHION		MALATHION		MALATHION	
POSTNATAL DAY 11 DOSAGE (MG/KG)		0 (VEHICLE)		150		150		150	
POSTNATAL DAY 21 DOSAGE (MG/KG)		0 (VEHICLE)		50		150		450	
PUPS TESTED	N	10		7		7		6	
BODY WEIGHT (G)									
DAY 11	MEAN±S.D.	21.6 ± 1.6		23.5 ± 1.3		21.0 ± 2.2		20.2 ± 1.6	
DAY 12	MEAN±S.D.	24.5 ± 1.8		27.4 ± 2.0		24.3 ± 2.6		23.6 ± 1.4	
DAY 13	MEAN±S.D.	27.2 ± 2.2		29.1 ± 1.9		26.2 ± 2.5		25.2 ± 1.4	
DAY 14	MEAN±S.D.	29.9 ± 2.2		31.6 ± 2.0		28.4 ± 2.4		27.8 ± 1.7	
DAY 15	MEAN±S.D.	31.8 ± 2.0		33.9 ± 2.6		31.0 ± 2.7		29.9 ± 1.9	
DAY 16	MEAN±S.D.	33.5 ± 2.5		34.6 ± 3.3		32.2 ± 3.1		30.8 ± 2.0	
DAY 17	MEAN±S.D.	34.2 ± 2.5		35.3 ± 3.0		32.9 ± 3.3		31.8 ± 1.8	
DAY 18	MEAN±S.D.	35.6 ± 2.4		36.1 ± 2.8		33.6 ± 3.1		32.7 ± 2.3	
DAY 19	MEAN±S.D.	37.8 ± 2.9		37.8 ± 2.4		35.1 ± 3.3		33.5 ± 2.0	
DAY 20	MEAN±S.D.	39.7 ± 3.2		40.0 ± 2.3		36.6 ± 3.2		35.8 ± 2.8	
DAY 21	MEAN±S.D.	42.9 ± 4.0		42.4 ± 2.3		39.4 ± 3.2		38.5 ± 2.9	
BODY WEIGHT CHANGE (G)									
DAYS 11 - 14	MEAN±S.D.	8.3 ± 0.8		8.1 ± 1.2		7.4 ± 1.1		7.6 ± 0.5	
DAYS 14 - 17	MEAN±S.D.	4.3 ± 1.5		3.7 ± 1.5		4.6 ± 1.6		4.0 ± 0.6	
DAYS 17 - 21	MEAN±S.D.	8.7 ± 3.5		7.1 ± 2.1		6.4 ± 1.7		6.7 ± 1.9	
DAYS 11 - 21	MEAN±S.D.	21.4 ± 3.1		18.9 ± 1.5		18.3 ± 1.7		18.3 ± 1.6	
DAY (S) = POSTNATAL DAY (S)									

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D4 (PAGE 1): BODY WEIGHTS AND BODY WEIGHT CHANGES - SUMMARY - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

DOSAGE GROUP		I		IV		V		VI	
TEST SUBSTANCE	DOSAGE (MG/KG)	CORN OIL 0 (VEHICLE)	MALATHION 150 50	MALATHION 150 50	MALATHION 150 150	MALATHION 150 150	MALATHION 150 450		
POSTNATAL DAY 11	POSTNATAL DAY 21	N		10		7		6	
PUPS TESTED									
BODY WEIGHT (G)									
DAY 11	MEAN±S.D.	21.2 ± 2.5		21.8 ± 2.0		21.9 ± 2.6		20.3 ± 2.4	
DAY 12	MEAN±S.D.	23.8 ± 3.3		25.0 ± 2.3		24.8 ± 3.2		23.5 ± 2.9	
DAY 13	MEAN±S.D.	26.2 ± 3.3		26.7 ± 2.6		26.4 ± 3.1		25.4 ± 2.7	
DAY 14	MEAN±S.D.	28.8 ± 3.3		29.3 ± 2.6		28.5 ± 3.2		27.4 ± 3.0	
DAY 15	MEAN±S.D.	30.9 ± 3.5		31.3 ± 2.6		30.2 ± 3.5		29.6 ± 3.2	
DAY 16	MEAN±S.D.	32.5 ± 4.0		32.6 ± 3.1		31.2 ± 4.0		30.6 ± 4.0	
DAY 17	MEAN±S.D.	33.4 ± 3.9		33.4 ± 3.1		32.2 ± 4.2		31.7 ± 4.4	
DAY 18	MEAN±S.D.	34.2 ± 3.7		34.3 ± 2.7		33.1 ± 3.8		32.8 ± 4.2	
DAY 19	MEAN±S.D.	35.7 ± 3.8		35.6 ± 2.9		34.1 ± 4.4		34.1 ± 4.4	
DAY 20	MEAN±S.D.	37.7 ± 3.7		37.6 ± 2.7		36.4 ± 4.0		35.2 ± 4.5	
DAY 21	MEAN±S.D.	40.5 ± 3.5		40.7 ± 2.4		39.3 ± 3.7		38.1 ± 3.6	
BODY WEIGHT CHANGE (G)									
DAYS 11 - 14	MEAN±S.D.	7.6 ± 1.3		7.5 ± 0.9		6.6 ± 1.2		7.2 ± 0.9	
DAYS 14 - 17	MEAN±S.D.	4.6 ± 1.3		4.1 ± 1.4		3.7 ± 1.5		4.3 ± 1.7	
DAYS 17 - 21	MEAN±S.D.	7.1 ± 2.0		7.3 ± 2.7		7.1 ± 1.6		6.4 ± 2.2	
DAYS 11 - 21	MEAN±S.D.	19.3 ± 1.8		18.9 ± 1.4		17.4 ± 2.1		17.8 ± 1.9	
DAY (S) = POSTNATAL DAY (S)									

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D5 (PAGE 1): RBC CHOLINESTERASE LEVELS - SUMMARY - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

DOSAGE GROUP	I	IV	V	VI
TEST SUBSTANCE	CORN OIL	MALATHION	MALATHION	MALATHION
POSTNATAL DAY 11 DOSAGE (MG/KG)	0 (VEHICLE)	150	150	150
POSTNATAL DAY 21 DOSAGE (MG/KG)	0 (VEHICLE)	50	150	400
PUPS TESTED	N 10	7	7	6
CHOLINESTERASE LEVELS (UNITS/ML) MEAN±S.D.	2.663 ± 0.621	2.140 ± 0.684	1.940 ± 0.924	1.797 ± 0.168
% INHIBITION		19.6	27.1	32.5

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D6 (PAGE 1): RBC CHOLINESTERASE LEVELS - SUMMARY - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

DOSAGE GROUP	I	IV	V	VI
TEST SUBSTANCE	CORN OIL	MALATHION	MALATHION	MALATHION
POSTNATAL DAY 11 DOSAGE (MG/KG)	0 (VEHICLE)	150	150	150
POSTNATAL DAY 21 DOSAGE (MG/KG)	0 (VEHICLE)	50	150	400
PUPS TESTED	N 10	7	7	6
CHOLINESTERASE LEVELS (UNITS/ML) MEAN±S.D.	2.483 ± 0.630	2.150 ± 0.455	1.601 ± 0.491	1.918 ± 0.480
% INHIBITION		13.4	35.5	22.8

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D7 (PAGE 1): BRAIN CHOLINESTERASE LEVELS - SUMMARY - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

DOSAGE GROUP	I	IV	V	VI
TEST SUBSTANCE	CORN OIL	MALATHION	MALATHION	MALATHION
POSTNATAL DAY 11 DOSAGE (MG/KG)	0 (VEHICLE)	150	150	150
POSTNATAL DAY 21 DOSAGE (MG/KG)	0 (VEHICLE)	50	150	450
PUPS TESTED	N 10	7	7	6
BRAIN WEIGHT (G)	MEAN±S.D. 1.357 ± 0.064	1.397 ± 0.062	1.362 ± 0.063	1.343 ± 0.074
CHOLINESTERASE LEVELS (UNITS/G)	MEAN±S.D. 12.145 ± 0.471	13.315 ± 1.467	12.456 ± 1.394	10.341 ± 3.001
% INHIBITION		-9.6	-2.6	14.9

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D8 (PAGE 1): BRAIN CHOLINESTERASE LEVELS - SUMMARY - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

DOSAGE GROUP	I	IV	V	VI
TEST SUBSTANCE	CORN OIL	MALATHION	MALATHION	MALATHION
POSTNATAL DAY 11 DOSAGE (MG/KG)	0 (VEHICLE)	150	150	150
POSTNATAL DAY 21 DOSAGE (MG/KG)	0 (VEHICLE)	50	150	450
PUPS TESTED	N 10	7	7	6
BRAIN WEIGHT (G)	MEAN±S.D. 1.338 ± 0.027	1.342 ± 0.059	1.350 ± 0.062	1.308 ± 0.077
CHOLINESTERASE LEVELS (UNITS/G)	MEAN±S.D. 11.456 ± 1.283	13.354 ± 3.431	12.037 ± 0.706	10.799 ± 2.771
% INHIBITION		-16.6	-5.1	5.7

PROTOCOL IQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D9 (PAGE 1): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

PUP #	DESCRIPTION	
DOSAGE GROUP I	CORN OIL	0 (VEHICLE) MG/KG (PND 11 AND 21)
8601	PND(21)	NO ADVERSE FINDINGS
8602		URINE-STAINED ABDOMINAL FUR
8701		NO ADVERSE FINDINGS
8702		NO ADVERSE FINDINGS
8801		NO ADVERSE FINDINGS
8802		NO ADVERSE FINDINGS
8901		NO ADVERSE FINDINGS
9001		NO ADVERSE FINDINGS
9002	PND(20)	EXCESS SALIVATION - SLIGHT
9101		NO ADVERSE FINDINGS
DOSAGE GROUP IV	MALATHION	150 MG/KG (PND 11), 50 MG/KG (PND 21)
8603	PND(20)	EXCESS SALIVATION - SLIGHT
8703		NO ADVERSE FINDINGS
8803		NO ADVERSE FINDINGS
8902		NO ADVERSE FINDINGS
9003		NO ADVERSE FINDINGS
9102		NO ADVERSE FINDINGS
9105		NO ADVERSE FINDINGS
DOSAGE GROUP V	MALATHION	150 MG/KG (PND 11 AND 21)
8604		NO ADVERSE FINDINGS
8704		NO ADVERSE FINDINGS
8804		NO ADVERSE FINDINGS
8903		NO ADVERSE FINDINGS
8905		NO ADVERSE FINDINGS
9004	PND(11)	COLD TO TOUCH
9103		NO ADVERSE FINDINGS
DOSAGE GROUP VI	MALATHION	150 MG/KG (PND 11), 450 MG/KG (PND 21)
8605		NO ADVERSE FINDINGS
8705		NO ADVERSE FINDINGS
8805	PND(21)	UNGROOMED COAT
8904		NO ADVERSE FINDINGS
9005	PND(21)	URINE-STAINED ABDOMINAL FUR
9104		NO ADVERSE FINDINGS

PND = POSTNATAL DAY

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D10 (PAGE 1): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

PUP #	DESCRIPTION	
DOSAGE GROUP I	CORN OIL	0 (VEHICLE) MG/KG (PND 11 AND 21)
8606	NO ADVERSE FINDINGS	
8607	NO ADVERSE FINDINGS	
8706	NO ADVERSE FINDINGS	
8707	NO ADVERSE FINDINGS	
8806	NO ADVERSE FINDINGS	
8906	NO ADVERSE FINDINGS	
8912	NO ADVERSE FINDINGS	
9006	URINE-STAINED ABDOMINAL FUR	
	PND (20)	
	UNGROOMED COAT	
	PND (20)	
9106	URINE-STAINED ABDOMINAL FUR	
	PND (20)	
	URINE-STAINED ABDOMINAL FUR	
	PND (21)	
9107	NO ADVERSE FINDINGS	
DOSAGE GROUP IV	MALATHION	150 MG/KG (PND 11), 50 MG/KG (PND 21)
8608	NO ADVERSE FINDINGS	
8708	NO ADVERSE FINDINGS	
8807	EXCESS SALIVATION - SLIGHT	
8810	NO ADVERSE FINDINGS	
8908	NO ADVERSE FINDINGS	
9007	URINE-STAINED ABDOMINAL FUR	
9108	NO ADVERSE FINDINGS	
DOSAGE GROUP V	MALATHION	150 MG/KG (PND 11 AND 21)
8609	NO ADVERSE FINDINGS	
8709	NO ADVERSE FINDINGS	
8808	NO ADVERSE FINDINGS	
8909	URINE-STAINED ABDOMINAL FUR	
9008	URINE-STAINED ABDOMINAL FUR	
9010	NO ADVERSE FINDINGS	
9109	NO ADVERSE FINDINGS	

PND = POSTNATAL DAY

PROTOCOL IQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D10 (PAGE 2): CLINICAL OBSERVATIONS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

PUP #	DESCRIPTION
DOSAGE GROUP VI	MALATHION
	150 MG/KG (PND 11), 450 MG/KG (PND 21)
8610	NO ADVERSE FINDINGS
8711	NO ADVERSE FINDINGS
8809	NO ADVERSE FINDINGS
8910	NO ADVERSE FINDINGS
9009 PND (21)	URINE-STAINED ABDOMINAL FUR
9110 PND (21)	WHOLE BODY: TREMORS, SLIGHT
PND (21)	MIOSIS
PND (21)	URINE-STAINED ABDOMINAL FUR
PND = POSTNATAL DAY	

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON IN JUVENILE PUPS

TABLE D11 (PAGE 1): BODY WEIGHTS - INDIVIDUAL DATA - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

		DAY 11	12	13	14	15	16	17	18	19	20	21
		0 (VEHICLE) MG/KG (PND 11 AND 21)										
PUP #	DOSAGE GROUP I	CORN OIL										
8601	21.5	24.5	26.9	30.2	32.4	34.7	35.1	36.2	37.6	40.3	43.3	
8602	23.5	27.0	29.2	32.1	34.7	37.4	38.1	38.6	40.3	41.1	42.8	
8701	21.1	23.9	26.4	28.7	31.4	32.5	34.2	35.5	42.1	39.8	44.0	
8702	21.5	23.8	26.3	28.8	30.9	32.8	34.2	36.0	38.2	42.7	46.5	
8801	22.7	26.0	29.1	30.8	31.2	32.8	33.7	35.1	36.9	38.9	41.9	
8802	24.0	26.7	30.3	33.8	33.6	34.9	36.8	38.1	41.0	45.9	51.1	
8901	22.2	25.2	28.7	30.9	34.1	34.9	35.8	37.2	38.4	39.3	40.1	
9001	19.0	21.5	23.4	26.1	27.5	28.0	29.1	30.3	32.2	33.8	36.8	
9002	21.3	24.1	26.9	30.1	31.2	31.7	31.8	33.9	35.1	38.1	44.2	
9101	19.1	22.5	24.6	27.6	31.1	33.0	33.6	34.8	36.1	37.1	38.7	
PUP #	DOSAGE GROUP IV	MALATHION										
		150 MG/KG (PND 11), 50 MG/KG (PND 21)										
8603	25.0	30.0	32.0	34.4	36.9	39.8	40.5	41.0	42.3	43.4	44.2	
8703	21.9	24.5	26.1	28.6	31.8	31.2	32.6	34.1	36.0	38.3	42.0	
8803	23.5	27.8	29.3	30.9	31.6	32.3	34.2	35.1	37.8	40.4	42.9	
8902	22.7	27.8	28.9	32.7	35.5	35.9	36.2	36.3	37.3	39.5	41.1	
9003	22.9	25.9	28.7	31.0	31.3	31.4	32.0	32.7	35.0	37.2	38.8	
9102	23.0	26.1	27.8	30.1	33.2	34.1	34.1	35.0	36.9	38.7	41.7	
9105	25.7	29.5	30.9	33.5	37.2	37.7	37.6	38.4	39.2	42.9	46.1	
PUP #	DOSAGE GROUP V	MALATHION										
		150 MG/KG (PND 11 AND 21)										
8604	24.2	27.7	29.8	29.8	34.5	36.3	37.8	37.9	39.2	40.4	42.8	
8704	21.2	24.4	25.8	28.6	30.4	32.2	32.9	34.5	36.5	38.7	42.8	
8804	23.3	27.2	28.8	31.5	32.5	33.6	34.9	35.4	37.3	38.7	40.8	
8903	20.2	23.6	25.3	28.5	31.2	31.6	32.3	32.4	33.9	34.9	37.4	
8905	20.7	23.9	25.9	28.7	31.7	32.9	33.1	33.6	34.5	36.5	38.9	
9004	17.7	20.0	22.3	23.6	25.6	26.1	26.8	27.9	28.7	30.7	33.9	
9103	19.9	23.3	25.6	28.0	31.0	32.5	32.8	33.8	35.6	36.1	39.0	
PUP #	DOSAGE GROUP VI	MALATHION										
		150 MG/KG (PND 11), 450 MG/KG (PND 21)										
8605	20.6	24.1	26.1	28.4	30.6	32.4	32.9	33.7	34.6	35.3	36.7	
8705	22.7	25.6	27.2	29.7	31.7	32.7	34.1	35.5	35.6	40.6	43.7	
8805	18.5	22.2	24.1	26.2	27.0	28.1	30.3	30.3	31.5	33.5	37.0	
8904	20.9	24.2	25.2	28.6	31.5	32.9	32.9	34.5	35.3	37.1	39.3	
9005	20.3	23.5	25.5	28.8	30.5	29.9	31.7	32.4	33.0	35.5	39.0	
9104	18.3	21.7	23.4	25.4	28.0	29.3	29.1	29.7	30.9	32.6	35.5	

DAY = POSTNATAL DAY PND = POSTNATAL DAY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON IN JUVENILE RATS

TABLE D12 (PAGE 1): BODY WEIGHTS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

		DAY 11	12	13	14	15	16	17	18	19	20	21
		0 (VEHICLE) MG/KG (PND 11 AND 21)										
PUP #	DOSAGE GROUP I	CORN OIL										
8606	21.8	24.5	27.3	29.9	32.6	34.5	33.4	34.5	35.6	36.7	37.7	37.7
8607	22.1	24.6	27.4	29.8	32.3	34.7	35.7	36.8	38.0	39.7	41.6	41.6
8706	19.7	22.0	23.9	26.9	28.9	30.2	31.7	33.1	35.3	38.0	41.9	41.9
8707	19.9	20.1	22.1	24.4	26.7	28.1	29.6	31.0	32.5	35.3	38.5	38.5
8806	23.9	28.0	30.1	32.7	32.5	34.2	35.7	35.8	38.3	40.8	44.8	44.8
8906	18.2	20.8	23.7	27.0	29.9	31.3	31.7	32.1	33.7	34.9	37.2	37.2
8912	20.2	22.5	25.2	28.3	31.2	31.9	33.7	33.6	34.7	37.5	40.1	40.1
9006	17.8	20.0	22.0	24.1	24.8	25.4	26.0	27.6	28.4	30.7	35.1	35.1
9106	22.4	25.7	28.1	30.6	33.3	34.8	36.0	35.9	37.7	38.7	41.5	41.5
9107	26.0	29.6	31.7	34.3	37.1	39.5	40.0	41.4	42.7	44.3	46.3	46.3
PUP #	DOSAGE GROUP IV	MALATHION										
		150 MG/KG (PND 11), 50 MG/KG (PND 21)										
8608	22.4	25.8	27.6	30.2	32.6	35.5	36.2	37.0	37.5	38.5	38.8	38.8
8708	20.3	22.4	23.6	25.8	27.7	28.8	30.2	31.7	32.9	34.6	39.5	39.5
8807	22.8	26.7	28.7	30.7	30.7	31.8	33.0	33.9	35.4	37.1	41.5	41.5
8810	24.2	27.6	29.8	32.1	33.3	34.4	36.0	36.6	38.6	40.9	44.0	44.0
8908	19.4	22.7	24.3	27.1	31.0	31.3	31.7	32.6	33.5	35.8	37.5	37.5
9007	19.7	22.9	24.1	27.1	28.6	29.5	29.3	30.8	32.0	35.0	40.3	40.3
9108	23.7	27.1	28.6	31.9	35.2	37.1	37.1	37.3	39.2	41.0	43.3	43.3
PUP #	DOSAGE GROUP V	MALATHION										
		150 MG/KG (PND 11 AND 21)										
8609	25.4	29.7	30.4	32.5	35.1	37.2	38.0	38.6	39.8	41.4	43.5	43.5
8709	21.3	23.7	25.0	27.9	29.8	31.2	32.6	32.8	34.5	37.0	41.2	41.2
8808	24.9	28.1	30.2	31.7	32.3	33.3	34.9	36.0	37.7	40.2	42.6	42.6
8909	19.1	21.6	23.4	25.5	28.2	29.1	29.9	30.5	31.3	33.2	35.2	35.2
9008	18.9	22.1	24.0	26.5	27.1	27.4	28.5	29.8	30.1	33.1	37.8	37.8
9010	20.5	22.3	23.6	24.5	25.5	25.8	26.1	28.2	27.9	31.0	33.9	33.9
9109	23.2	26.1	28.3	30.7	33.1	34.3	35.2	35.8	37.2	38.8	40.9	40.9
PUP #	DOSAGE GROUP VI	MALATHION										
		150 MG/KG (PND 11), 450 MG/KG (PND 21)										
8610	24.2	28.9	29.9	32.8	35.4	37.6	39.0	40.0	40.2	41.6	42.8	42.8
8711	21.4	23.8	25.6	27.8	29.9	31.4	33.7	34.3	38.2	38.8	41.3	41.3
8809	20.8	24.0	26.6	28.0	29.0	30.1	31.1	31.8	33.6	35.1	37.8	37.8
8910	19.0	22.2	24.5	26.7	30.3	30.9	31.5	33.4	33.2	35.1	37.9	37.9
9009	17.8	21.0	23.2	24.7	25.9	25.4	26.3	28.4	28.7	29.8	35.8	35.8
9110	18.4	21.1	22.3	24.6	27.4	28.5	28.8	29.1	30.5	31.0	32.9	32.9

DAY = POSTNATAL DAY PND = POSTNATAL DAY
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D13 (PAGE 1): RBC CHOLINESTERASE LEVELS - INDIVIDUAL DATA - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

FINAL CHOLINESTERASE (UNITS/ML)		FOOTNOTE
PUP #	DOSAGE GROUP I	CORN OIL
8601	2.372	0 (VEHICLE) MG/KG (PND 11 AND 21)
8602	2.907	
8701	2.428	
8702	2.204	
8801	2.706	
8802	2.366	
8901	2.584	
9001	2.351	
9002	2.377	
9101	4.331	
DOSAGE GROUP IV		MALATHION
8603	1.947	150 MG/KG (PND 11), 50 MG/KG (PND 21)
8703	2.177	
8803	2.175	
8902	3.601	
9003	1.722	
9102	1.814	
9105	1.547	

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D13 (PAGE 2): RBC CHOLINESTERASE LEVELS - INDIVIDUAL DATA - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

FINAL CHOLINESTERASE (UNITS/ML)		FOOTNOTE
PUP #	DOSAGE GROUP V	MALATHION
8604	2.083	150 MG/KG (PND 11 AND 21)
8704	4.314a	
	3.606	
8804	2.377	
8903	2.005	
8905	1.360	
9004	0.693	
9103	1.455	
PUP #	DOSAGE GROUP VI	MALATHION
8605	2.057	150 MG/KG (PND 11), 450 MG/KG (PND 21)
8705	1.941	
8805	1.658	
8904	1.747	
9005	1.745	
9104	1.631	

a. Sample did not produce a linear response; value excluded from summarization and statistical analyses.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D14 (PAGE 1): RBC CHOLINESTERASE LEVELS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

PUP #	FINAL CHOLINESTERASE (UNITS/ML)		FOOTNOTE
	DOSAGE GROUP I	0 (VEHICLE) MG/KG (PND 11 AND 21)	
8606	3.872		CORN OIL
8607	2.187		
8706	2.335		
8707	1.994		
8806	2.570		
8906	2.186		
8912	2.089		
9006	1.917		
9106	3.324		
9107	2.356		
<hr/>			
PUP #	DOSAGE GROUP IV	MALATHION	
8608	2.279	150 MG/KG (PND 11), 50 MG/KG (PND 21)	
8708	1.854		
8807	2.821		
8810	2.086		
8908	X	DNR	
9007	1.528		
	2.616		
9108	1.866		

X = SAMPLE RESULTS DO NOT MEET ACCEPTABILITY CRITERIA; VALUES WERE NOT REPORTED OR INCLUDED IN SUMMARIZATION AND STATISTICAL ANALYSES.
DNR = DUPLICATE ANALYSIS OF THE SAME SAMPLE DOES NOT MEET REPRODUCIBILITY CRITERIA.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D14 (PAGE 2): RBC CHOLINESTERASE LEVELS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

PUP #	FINAL CHOLINESTERASE (UNITS/ML)		FOOTNOTE
	DOSAGE GROUP V	MALATHION	
8609	1.730	150 MG/KG (PND 11 AND 21)	
8709	X	HIGH	
	1.443		
8808	1.687		
8909	1.717		
9008	1.114		
9010	1.015		
9109	2.498		
PUP #	DOSAGE GROUP VI		MALATHION
	DOSAGE GROUP VI	150 MG/KG (PND 11), 450 MG/KG (PND 21)	
8610	1.910		
8711	1.537		
8809	1.889		
8910	X	DNR	
	1.816		
9009	2.833		
9110	1.520		

X = SAMPLE RESULTS DO NOT MEET ACCEPTABILITY CRITERIA; VALUES WERE NOT REPORTED OR INCLUDED IN SUMMARIZATION AND STATISTICAL ANALYSES.
HIGH = REPORTED VALUE IS ABOVE THE HIGHEST STANDARD.

DNR = DUPLICATE ANALYSIS OF THE SAME SAMPLE DOES NOT MEET REPRODUCIBILITY CRITERIA.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D15 (PAGE 1): BRAIN CHOLINESTERASE LEVELS - INDIVIDUAL DATA - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

PUP #	BRAIN (G)		FINAL CHOLINESTERASE (UNITS/G)		FOOTNOTE	
	DOSAGE GROUP I	CORN OIL			0 (VEHICLE) MG/KG (PND 11 AND 21)	
8601	1.212	13.361				
8602	1.369	12.110				
8701	1.405	11.871				
8702	1.408	11.896				
8801	1.289	X				DNR
	1.289	12.250				
8802	1.416	X				DNR
	1.416	12.038				
8901	1.338	12.131				
9001	1.359	12.042				
9002	1.387	11.559				
9101	1.391	12.190				
<hr/>						
PUP #	DOSAGE GROUP IV		MALATHION		150 MG/KG (PND 11), 50 MG/KG (PND 21)	
8603	1.381	8.507a				
	1.381	15.397				
8703	1.391	X				DNR
	1.391	X				DNR
	1.391	11.425				
8803	1.361	X				DNR
	1.361	15.155				
8902	1.392	X				DNR
	1.392	12.635				
9003	1.302	13.138				
9102	1.468	12.261				
9105	1.483	13.191				

X = SAMPLE RESULTS DO NOT MEET ACCEPTABILITY CRITERIA; VALUES WERE NOT REPORTED OR INCLUDED IN SUMMARIZATION AND STATISTICAL ANALYSES.
DNR = DUPLICATE ANALYSIS OF THE SAME SAMPLE DOES NOT MEET REPRODUCTIBILITY CRITERIA.

a. Sample did not produce a linear response; value excluded from summarization and statistical analyses.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D15 (PAGE 2): BRAIN CHOLINESTERASE LEVELS - INDIVIDUAL DATA - MALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

PUP #	BRAIN (G)	FINAL CHOLINESTERASE (UNITS/G)		FOOTNOTE
		MALATHION	150 MG/KG (PND 11 AND 21)	
8604	1.431	X		HIGH
	1.431	X		DNR
	1.431		12.313	
8704	1.378		14.188	
8804	1.316		14.360	
8903	1.356		11.068	
8905	1.405		10.859	
9004	1.247		12.650	
9103	1.402		11.754	
PUP #	DOSAGE GROUP VI	MALATHION	150 MG/KG (PND 11), 450 MG/KG (PND 21)	
8605	1.218	X		HIGH
	1.218		11.847	
8705	1.412		8.463	
8805	1.413		13.205	
8904	1.353		5.182	
9005	1.357		12.332	
9104	1.305		11.020	

X = SAMPLE RESULTS DO NOT MEET ACCEPTABILITY CRITERIA; VALUES WERE NOT REPORTED OR INCLUDED IN SUMMARIZATION AND STATISTICAL ANALYSES.
HIGH = REPORTED VALUE IS ABOVE THE HIGHEST STANDARD.

DNR = DUPLICATE ANALYSIS OF THE SAME SAMPLE DOES NOT MEET REPRODUCIBILITY CRITERIA.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D16 (PAGE 1): BRAIN CHOLINESTERASE LEVELS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

PUP #	BRAIN (G)		FINAL CHOLINESTERASE (UNITS/G)		FOOTNOTE
	DOSAGE GROUP I	CORN OIL		0 (VEHICLE) MG/KG (PND 11 AND 21)	
8606	1.306	12.046			
8607	1.350	12.646			
8706	1.344	X			DNR
	1.344	11.668			
8707	1.395	X			DNR
	1.395	11.335			
8806	1.329	12.100			
8906	1.333	11.073			
8912	1.318	8.051			
9006	1.308	12.147			
9106	1.366	12.052			
9107	1.326	11.437			
<hr/>					
PUP #	DOSAGE GROUP IV		MALATHION		FOOTNOTE
				150 MG/KG (PND 11), 50 MG/KG (PND 21)	
8608	1.313	X			HIGH
	1.313	X			DNR
	1.313	12.388			
8708	1.402	20.764			
8807	1.344	11.336			
8810	1.341	10.541			
8908	1.248	12.630			
9007	1.321	13.881			
9108	1.425	11.940			

X = SAMPLE RESULTS DO NOT MEET ACCEPTABILITY CRITERIA; VALUES WERE NOT REPORTED OR INCLUDED IN SUMMARIZATION AND STATISTICAL ANALYSES.
HIGH = REPORTED VALUE IS ABOVE THE HIGHEST STANDARD.

DNR = DUPLICATE ANALYSIS OF THE SAME SAMPLE DOES NOT MEET REPRODUCIBILITY CRITERIA.

PROTOCOL TQC00012: ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE DEPRESSION STUDY OF MALATHION AND MALAOXON
IN JUVENILE RATS

TABLE D16 (PAGE 2): BRAIN CHOLINESTERASE LEVELS - INDIVIDUAL DATA - FEMALE PUPS - MALATHION - DOSED POSTNATAL DAYS 11 AND 21

PUP #	BRAIN (G)		FINAL CHOLINESTERASE (UNITS/G)		FOOTNOTE
	DOSAGE GROUP V	MALATHION	DOSAGE GROUP V	MALATHION	
8609	1.384	X			150 MG/KG (PND 11 AND 21) DNR
	1.384	X			DNR
	1.384		11.420		DNR
8709	1.366	X			DNR
	1.366		12.840		
8808	1.358		11.462		
8909	1.276		11.386		
9008	1.400		12.794		
9010	1.251		11.630		
9109	1.412		12.725		
PUP #	DOSAGE GROUP VI	MALATHION			150 MG/KG (PND 11), 450 MG/KG (PND 21)
8610	1.278	X			HIGH
	1.278		10.638		
8711	1.442		12.799		
8809	1.254		10.374		
8910	1.356		12.510		
9009	1.238		12.870		
9110	1.279		5.605		

X = SAMPLE RESULTS DO NOT MEET ACCEPTABILITY CRITERIA; VALUES WERE NOT REPORTED OR INCLUDED IN SUMMARIZATION AND STATISTICAL ANALYSES.
HIGH = REPORTED VALUE IS ABOVE THE HIGHEST STANDARD.

DNR = DUPLICATE ANALYSIS OF THE SAME SAMPLE DOES NOT MEET REPRODUCIBILITY CRITERIA.

ADDENDUM 1
PROTOCOL AND PROTOCOL AMENDMENT



PROTOCOL TQC00012

STUDY TITLE

Oral (Gavage) Repeat Dose Time of Peak Cholinesterase Depression Study of Malathion and Malaoxon in Juvenile Rats

OBJECTIVE

The objective of this study is to determine the time of peak cholinesterase inhibition after repeated daily dosing of young pre-weaning rats with Malathion and Malaoxon on erythrocyte and brain acetyl cholinesterase activity.

TESTING FACILITY

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REGULATORY CITATIONS

U.S. Environmental Protection Agency (1998). *Health Effects Test Guidelines*.
OPPTS 870.6200: Neurotoxicity screening battery, August, 1998.

Japanese Ministry of Agriculture, Forestry and Fisheries (2000). Guidance on
Toxicology Study Data for Application of Agricultural Chemical Registration.
12 Nousan No. 8147.

Organisation for Economic Co-operation and Development (1997). *OECD Guideline for
Testing of Chemicals*. No. 424: Neurotoxicity Study in Rodents, adopted 21 July 1997.

U.S. Environmental Protection Agency. Federal Insecticide, Fungicide and Rodenticide
Act (FIFRA); Good Laboratory Practice Standards; Final Rule. 40 CFR Part 160.

Japanese Ministry of Agriculture, Forestry and Fisheries (1999). Good Laboratory
Practice Standards. 11 Nousan No. 6283.

Organisation for Economic Co-operation and Development (1998). The Revised OECD
Principles of Good Laboratory Practice [C(97)186/Final].

REGULATORY COMPLIANCE

This study will be conducted using good scientific practices and according to the SOPs of
the Testing Facility. The Testing Facility Quality Assurance Unit (QAU) will not audit
the protocol, the raw data or the report with the exception of the cholinesterase data,
which will be audited by QAU, and will not perform critical phase inspections for the
study.

All changes or revisions of this protocol shall be documented, signed by the Study Director, the Study Monitor and the Sponsor, dated and maintained with the protocol.

STUDY SCHEDULE

See ATTACHMENT 1 to the protocol.

TEST SUBSTANCES AND VEHICLES

Identification

Test Substances

Malathion (synonymous with Fyfanon Technical which may appear in study records and on labels for the test substance) (lot identification: 9010501)

Lot Number:	9010501
Purity:	96.0%
CAS Number:	121-75-5

Malaoxon (lot identification: 849-BSe-42C)

Lot Number:	849-BSe-42C
Purity:	97.7%
CAS Number:	1634-78-2

The Sponsor will provide to the Testing Facility documentation or certification of the identity, composition, strength and purity of the test substance (Certificate of Analysis). This documentation will be included in the final report. Certificates of Analysis for both Malathion (lot number 9010501) and the Malaoxon (lot number 849-BSe-42C) are attached to this protocol (ATTACHMENT 2). The Sponsor Representative's signature and approval of the protocol indicates that appropriate documentation of the method of synthesis, fabrication or derivation of the test substance is on file and that it is available to the appropriate regulatory agencies should it be requested.

Vehicles

Corn Oil (lot identification and Supplier will be documented in the raw data).

Neither the Sponsor nor the Study Director is aware of any potential contaminants likely to be present in the vehicle that would interfere with the results of this study. Therefore, no analyses other than those mentioned in this protocol will be conducted.

Safety Precautions

Double nitrile gloves, full faced positive pressure hood, appropriate eye protection and Tyvek® suit are to be worn during formulation preparation and dosage administration. Bulk test substances will be handled in a chemical fume hood. Gloves will be washed with soap and water or sprayed with an appropriate cleaning solution prior to removal and then disposed of in a biohazard container. For all other activities, standard safety precautions will be followed. The Material Safety Data Sheets (MSDS) are attached to the protocol (ATTACHMENT 3).

Storage

Bulk Test Substances:	Malathion - refrigerated (2°C to 8°C), protected from light Malaoxon – frozen (approximately -20°C), protected from light
Bulk Vehicle:	Room temperature
Prepared Formulations:	Room temperature and protected from light.

All test substance shipments should be addressed to the attention of Mark Coker, Manager of Formulations, at the previously cited Testing Facility address and telephone number.

Shipments should include information concerning storage conditions and shipping cartons should be labeled appropriately. The recipient should be notified in advance of shipment.

FORMULATION**Frequency of Preparation**

Formulations (suspensions) will be prepared daily at the Testing Facility.

Detailed preparation procedures are attached to this protocol (ATTACHMENT 4).

Adjustment for Purity

The test substances will be considered 100% pure for the purpose of dosage calculations.

Testing Facility Reserve Samples

No reserve samples will be retained.

Samples and Possible Analyses of Prepared Formulations

Concentration

Concentration samples of the prepared formulations will be collected on postnatal days (PNDs) 12, 17 and 22 for each of the test substances and stored refrigerated at the Testing Facility for possible future analyses. Duplicate samples (0.5 mL each) will be taken from the middle of each concentration on the day of preparation. The disposition of these samples will be documented in the raw data.

Stability

Stability data for prepared formulations in the corn oil vehicle bracketing the concentrations in this study are on file with the Sponsor and will not be determined during the conduct of this study.

DISPOSITION

Prepared formulations will be discarded at the Testing Facility. Disposition of the remaining bulk test substances will be documented in the raw data.

TEST SYSTEM

Species/Strain and Reason for Selection

The CrI:CD(SD) rat was selected as the Test System because this strain of rat has been widely used throughout the industry for nonclinical studies.

Number

Neonatal Rats:

Fo generation population
acclimated:

Fourteen female rats with litters of ten pups (five
male pups and five female pups).

F1 generation population
selected for study:

Twelve litters of ten pups per litter (five males and
five females) will be evaluated. Six of these litters
will be administered malathion (with control) and
six will be administered malaoxon (with control).

Body Weight and Age

Six dams and pups will be ordered to arrive at the Testing Facility on day 8 postpartum and the remaining six will arrive on day 9 postpartum. Actual body weights will be recorded the day after receipt and will be documented in the raw data. The weight range will be included in the final report.

Sex

Dams will be used only as breeders to produce the pups and are not considered part of the Test System.

Male and female pups will be given one of the test substances and/or the vehicle. Equal numbers of male and female pups from each litter will be used (when possible).

Source

Charles River Laboratories, Inc.

Fo generation female rats and F1 generation pups will be shipped in filtered cartons by air freight and/or truck from Charles River Laboratories, Inc., to the Testing Facility.

Identification

Adult Rats:

Female rats are assigned temporary animal numbers at receipt. The rats will be permanently identified using Monel[®] self-piercing ear tags (Gey Band and Tag Co., Inc., No. MSPT 20101).

Neonatal Rats:

On days 9 or 10 postpartum, pups selected for study will be individually identified by tattoo according to the Standard Operating Procedures of the Testing Facility. Ink will be injected under the skin of the paws to identify individual pups.

ANIMAL HUSBANDRY

All cage sizes and housing conditions are in compliance with the *Guide for the Care and Use of Laboratory Animals*⁽¹⁾.

Housing

Each dam with a litter of male and female pups will be housed in a common nesting box during the postpartum period.

Nesting Material

Nesting material (bed-o'cobs[®]) will be provided.

Bedding will be changed as often as necessary to keep the animals dry and clean. Bedding changes will be documented in the raw data. Analyses for possible contamination are conducted annually and documented in the raw data.

Room Air, Temperature and Humidity

The animal room is independently supplied with at least ten changes per hour of 100% fresh air that has been passed through 99.97% HEPA filters. Room temperature will be maintained at 64°F to 79°F (18°C to 26°C) and monitored constantly. Room humidity will also be monitored constantly and maintained at 30% to 70%.

Light

An automatically controlled 12-hour light:12-hour dark fluorescent light cycle will be maintained. Each dark period will begin at 1900 hours. The light cycle may be adjusted by the Study Director or designee if deemed necessary to accommodate scheduled laboratory activities. Any such adjustment will be documented in the raw data.

Diet

Rats will be given Certified Rodent Diet® #5002 (PMI® Nutrition International, Inc.) available *ad libitum* from individual feeders.

Water

Water will be available *ad libitum* from individual bottles attached to the cages or from an automatic watering access system. All water will be from a local source and passed through a reverse osmosis membrane before use. Chlorine will be added to the processed water as a bacteriostat; processed water is expected to contain no more than 1.2 ppm chlorine at the time of analysis. Water is analyzed monthly for possible bacterial contamination and twice annually for possible chemical contamination.

Contaminants

Neither the Sponsor nor the Study Director is aware of any potential contaminants likely to be present in the certified diet, the drinking water or the nesting material at levels that would interfere with the results of this study. Therefore, no analyses other than those routinely performed by the feed supplier or those mentioned in this protocol will be conducted.

DAY NUMBERING SYSTEM

The day of birth is designated postnatal day 0 (day 0 of lactation) in Addendum 10 to the Pesticide Assessment Guidelines of the U.S. Environmental Protection Agency (EPA). This same day is designated day 1 postpartum (day 1 of lactation) in the Standard Operating Procedures of the Testing Facility. Throughout this protocol, the day of birth will be designated day 1 postpartum (day 1 of lactation) and all subsequent ages of the F1 generation rats and days of the lactation period will be determined and cited accordingly. Therefore, the day of sacrifice for the day 12 postpartum female pups is actually day 11 postpartum using the EPA designation. Also, throughout the study observation day (OD) will be equivalent to day of postpartum.

RANDOMIZATION**Dams:**

The female rats will be naturally bred at the Supplier's facility by breeder male rats of the same source and strain. The day of delivery will be designated day 1 of lactation (postpartum). The female rats will be allowed to deliver their litters at the Supplier and shipped to arrive at the Testing Facility on days 8 or 9 postpartum.

Pups:

On days 9 or 10 postpartum, twelve litters of approximately ten pups per litter (five males and five females) will be randomized to study. The pups from six of these litters will be assigned to the malathion dosage groups (with control and 150 mg/kg/day), and the other six litters will be assigned to the malaoxon dosage groups (with control and 4 mg/kg/day). The pups will be of good general health (no adverse clinical signs) following physical examination of the pups and adequate body weights.

ADMINISTRATION**Route and Reason for Choice**

The oral (gavage) route was selected for use because: 1) the exact dosage can be accurately administered via gavage; and 2) the oral route is a potential route of exposure.

Method and Frequency**Dams:**

Dams will not be administered the test substance or the vehicle.

Pups:

The pups will be administered the test substance and/or the vehicle once daily from day 12 through day 22 postpartum.

Rationale for Dosage Selection

Dosages were selected by the Sponsor on the basis of previously conducted acute toxicity studies using higher dosage levels of malaoxon and malathion in postnatal day 11 male and female pups in which cholinesterase inhibition was demonstrated. Concentrations may be adjusted by amendment if observed toxicity indicative of cholinesterase inhibition occurs (e.g., tremors, ataxia, lacrimation, salivation, etc.).

Dosage Levels, Concentrations and Volumes

Dosage Group	Number of Pups per Sex	Test Substance	Dosage (mg/kg/day) ^a	Concentration (mg/mL)	Dosage Volume (mL/kg)	Batch Number
I	20	Corn Oil	0 (Vehicle)	0	5	B-TQC00012-A(Day.Month.Year)
II	20	Malathion	150	30	5	B-TQC00012-B(Day.Month.Year)
III	20	Malaoxon	4	0.8	5	B-TQC00012-C(Day.Month.Year)

a The test substance will be considered 100% pure for the purpose of dosage calculations.

TESTS, ANALYSES AND MEASUREMENTS - DAMS

Viability observations will be recorded at least twice daily. Maternal behavior, clinical observations and body weights will be recorded the day after arrival. Clinical observations may be recorded more frequently than cited above. Feed consumption will be monitored as feed is replenished on an as-needed basis. This information will be recorded to monitor the general health and well-being of the dams; these data will not be tabulated or summarized in the final report.

METHOD OF SACRIFICE - DAMS

The dams will be sacrificed by carbon dioxide asphyxiation.

NECROPSY - DAMS**Scheduled Sacrifice of Dams with Litters Assigned to Study**

On day 22 postpartum, dams will be sacrificed and discarded without further evaluation.

Scheduled Sacrifice of Dams with Litters Not Assigned to Study

Dams with litters not assigned to the study will be sacrificed after dosage administration of pups assigned to the study. Carcasses will be discarded without further evaluation.

Dams with No Surviving Pups

Dams with no surviving pups will be sacrificed after the last pup is found dead or missing (presumed cannibalized). Carcasses will be discarded without further evaluation.

Dams Found Dead or Moribund

Dams that die or are sacrificed because of moribund condition will be discarded without further evaluation. Litters from these dams will be excluded from the study.

TESTS, ANALYSES AND MEASUREMENTS - PUPS**Viability**

All Periods: Litters will be observed for dead pups at least twice daily. The pups in each litter will be counted on the day after arrival and on the day of randomization.

Clinical Observations and/or General Appearance

Predosage Period: Once daily after the day of arrival (by litter).

Dosage Period: Prior to and 60 ± 10 minutes after dosage administration, except on the day of sacrifice when clinical observations will be performed just prior to sacrifice.

Clinical observations may be recorded more frequently than cited above.

Body Weights

Predosage Period: Day after arrival (days 9 or 10 postpartum).

Dosage Period: Daily.

CHOLINESTERASE ASSAY**Blood and Brain Sample Collection**

At the end of the dosage period (day 22 postpartum), whole blood samples (approximately 0.30 to 0.50 mLs each) will be collected from each of the pups assigned for cholinesterase assay⁽²⁻³⁾. The whole blood samples will be collected within 10 seconds from each pup following decapitation. The whole blood samples will be collected from five pups per sex at approximately 1 hour, 2 hours, 3 hours and 4 hours postdosage for the pups assigned to the 150 mg/kg Malathion dosage group and 30 minutes, 60 minutes, 90 minutes and 2 hours postdosage for the pups assigned to the 4 mg/kg/day Malaoxon dosage group. There will be five pups per sex from the 0 (Vehicle) dosage group which will also have blood samples collected at 1 hour and 3 hours postdosage along with the Malathion dosage group and 30 minutes and 90 minutes postdosage along with the Malaoxon dosage group (timing begins with the gavage of the animal and ends with decapitation for blood collection). The time of each blood collection will be recorded in the raw data. (If necessary, blood may be collected from an alternate site; if so, the alternate site will be documented in the raw data). All samples will be labeled with study number, date of collection, animal number, group, sex and timepoint.

RBC

Approximately 0.30 to 0.50 mLs of whole blood will be collected into EDTA-coated (lavender-top) tubes. Blood samples will be stored on ice until being processed for RBC cholinesterase levels according to the Testing Facility's Standard Operating Procedure.

Brains

After blood sample collection, the brain will be excised, and the weight will be recorded to three decimal places. The brains will be stored on ice until being assayed for cholinesterase levels according to the Testing Facility's Standard Operating Procedure.

METHOD OF SACRIFICE - PUPS

Pups assigned to study that survive to scheduled termination will be sacrificed by decapitation. All other pups will be sacrificed by an intraperitoneal injection of sodium pentobarbital (pups \leq 14 days of age) or by carbon dioxide asphyxiation (pups \geq 15 days of age).

NECROPSY - PUPS

Scheduled Sacrifice

Pups assigned to the study will be sacrificed by decapitation on day 22 postpartum. Sacrifice will be immediately followed by blood collection and brain dissection, and the pups will then be discarded without further evaluation.

Pups Found Dead Before Dosage Administration on Day 12 Postpartum or Unscheduled Sacrifice

Pups that die before dosage administration or are sacrificed because of moribund condition will be discarded without further evaluation.

Pups Not Selected for Study

All pups not selected for study will be sacrificed and discarded without further evaluation.

Pups Found Dead or Unscheduled Sacrifice After Initiation of Dosage Administration

Pups that die or are sacrificed before scheduled termination will be necropsied for the cause of death or condition on the day the observation is made. The lungs, trachea and esophagus will be perfused and saved in neutral buffered 10% formalin for possible future evaluation. Additional tissues may be retained at the discretion of the Study Director.

STATISTICAL EVALUATION

Averages and percentages will be calculated. Additional procedures and/or analyses may be performed if deemed appropriate.

DATA ACQUISITION, VERIFICATION AND STORAGE

Data generated during the course of this study will be recorded either by hand or using the *Argus Automated Data Collection and Management System* and the *Vivarium Temperature and Relative Humidity Monitoring System*. All data will be tabulated, summarized and/or statistically analyzed using the *Argus Automated Data Collection and Management System*, the *Vivarium Temperature and Relative Humidity Monitoring System*, *Microsoft® Excel* (part of *Microsoft® Office 97/2000/XP*), *Quattro Pro 8* and/or *The SAS System* (version 6.12) and/or *Softmax® Pro* (version 4.0).

Records will be reviewed by the Study Director and/or appropriate management personnel within 21 days after generation. All original records will be stored in the archives at the Testing Facility. All raw data will be bound and indexed. The archived raw data will be scanned and retained as an Adobe® Acrobat PDF file. A copy of all raw data will be supplied to the Sponsor upon request. Preserved tissues will be stored at the Testing Facility at no additional charge for two years after mailing of the draft final report, after which time the Sponsor will be contacted to determine the disposition of these materials.

RECORDS TO BE MAINTAINED

Protocol, Amendments and Deviations.
Study Schedules
Test Substance, Vehicle and/or Reagent Receipt, Preparation and Use.
Animal Acquisition.
Randomization Schedules.
Treatment (if prescribed by Staff Veterinarian).
General Comments.
Clinical Observations and/or General Appearance.
Body Weights.
Litter Observations.
Blood Sample Collection and Processing.
Cholinesterase Data.
Photographs (if required).
Study Maintenance (room and environmental records).
Feed, Water and Bedding Analyses.
Packing and/or Shipment Lists.

KEY PERSONNEL

Director of Research: Alan M. Hoberman, Ph.D., DABT
Senior Scientist and Study Director: John F. Barnett Jr., B.S.
Director of Operations: John F. Barnett, B.S.
Senior Manager of Study Management: Jo Anne Vico, B.S.
Senior Manager, Regulatory Compliance: Nancy A. Catricks, M.S.
Attending Veterinarian: Dena C. Lebo, V.M.D., Division Veterinarian
Chair, Institutional Animal Care and Use Committee: Douglas B. Learn, Ph.D.
Consultant, Veterinary Pathology: W. Ray Brown, D.V.M., Ph.D., Diplomate, ACVP

FINAL REPORT

The day of birth is designated postnatal day 0 (day 0 of lactation) in Addendum 10 to the Pesticide Assessment Guidelines of the U.S. Environmental Protection Agency (EPA). This same day is designated day 1 postpartum (day 1 of lactation) in the Standard Operating Procedures of the Testing Facility. In the report text, as well as summary and individual tables, the day of birth will be adjusted so that the day of birth and all subsequent lactation/postpartum days match the EPA guideline.

The Study Director may provide periodic updates of study progress to the Sponsor's Representative. Draft summary tables of unaudited computer-recorded data may accompany these updates. Statistical analyses will not be performed on these interim data. The cholinesterase data only will be audited by the Testing Facility QAU. The report will be formatted to comply with EPA's PR Notice 86-5 report formatting requirements.

An unaudited report will be prepared including: all applicable items listed in 40 CFR Part 160, abstract, summaries of the methods, results and conclusion; table of contents; copy of the protocol; amendments; summary and individual tables; and reports of supporting data.

The Sponsor's Representative will receive one copy of the draft report. A copy of the final report will be provided on CD-ROM in Adobe Acrobat PDF format. The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Testing Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation. A hard copy printed from the electronic file will accompany the final report on CD-ROM. The hard copy of the report with original signatures retained at the Testing Facility will be considered the original.

Study reports should be finalized within six months of submission of the unaudited draft final report. Two Sponsor-requested revisions to the draft report will be addressed by the Testing Facility at no charge. Additional revisions to the draft report or amendments to the final report may incur additional costs. If the Sponsor has not provided comments to the report within six months of draft submission, the report will be finalized by the Testing Facility.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE STATEMENT

The procedures described in this protocol have been reviewed by the Testing Facility's Institutional Animal Care and Use Committee. All procedures described in this protocol that involve study animals will be conducted in a manner to avoid or minimize discomfort, distress or pain to the animals.

The signature of the Sponsor's Representative below is assurance that the study is not an unnecessary duplication of previous work. Documentation for the necessity of this study may be obtained from the Sponsor. No alternative procedures were available to meet the stated purposes of the study.

REFERENCES

1. Institute of Laboratory Animal Resources (1996). *Guide for the Care and Use of Laboratory Animals*. National Academy Press, Washington, D.C.
2. U.S. Environmental Protection Agency (1997). A set of scientific issues being considered by the agency concerning the office of pesticide programs (OPP) cholinesterase inhibition policy. Scientific Advisory Panel (SAP) June, 1997, Meeting.
3. Lassiter, T.L., Barone, S. Jr., and Padilla, S. Ontogenetic differences in the regional and cellular acetylcholinesterase and butyrylcholinesterase activity in the rat brain. *Dev Brain Res* 1998; 105 :109-123.

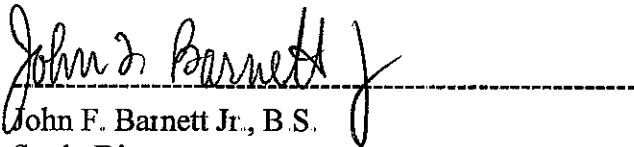
PROTOCOL APPROVAL

FOR THE TESTING FACILITY



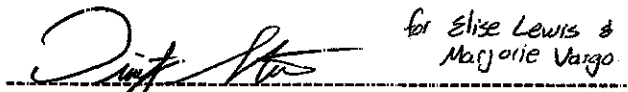
Alan M. Hoberman, Ph.D., DABT
Director of Research

23-Nov-05
Date



John F. Barnett Jr., B.S.
Study Director

23 Nov 2005
Date



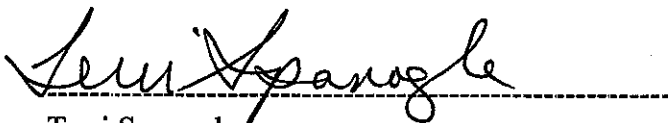
Marjorie B. Vargo, B.A.
Member, Institutional Animal Care and
Use Committee

11-23-05
Date

FOR THE SPONSOR

Sponsor approval received via e-mail on:

23 November 2005
Date



Terri Spanogle
Sponsor's Representative
Senior Scientist
Cheminova, Inc.

28 November 2005
Date

ATTACHMENT 1
STUDY SCHEDULE

STUDY SCHEDULE^a

22 NOV 05	Dams and Pups Arrive - Acclimation Begins.
25 NOV 05 – 06 DEC 05	Dosage Administration - Pups - Days 12 through 22 postpartum.
05 DEC 05 - 06 DEC 05	Dams and Pups Sacrificed on Day 22 Postpartum.
27 DEC 05	Unaudited Letter Report
25 JAN 06	Unaudited Summary Report.

a. The study initiation date is the day the Study Director signs the protocol.

ATTACHMENT 2
CERTIFICATES OF ANALYSIS



CHEMINOVA A/S
R.O. Box 9
DK-7120 Lemvig
Denmark

Phone (+45) 96 96 96 90
Fax (+45) 96 96 96 91
www.cheminova.com
CVR No. DK12783043

BATCH ANALYTICAL CERTIFICATE

ARTICLE IDENTIFICATION

Article Name: Malacoxon
Manufacturer: Cheminova A/S
Origin of Production: Commercial ☐; Pilot plant ☐; Laboratory ☒
Reg. Dept. Code: -
Batch No.: 349-BSe-42C

PHYSICAL PROPERTIES

Technical Product ☐; Preparation of Technical Product ☐; Analytical Standard ☒; Liquid ☒; Solid ☐; Colour: Colourless

Recommended Storage Conditions

Ambient temperature in the dark _____
In refrigerator
In deep freezer ☒
Additional Comments: _____
Expiry Date:
The article is stable at least 4 years from date of analysis/last date of reanalysis when stored at recommended conditions.

ACTIVE INGREDIENT IDENTIFICATION

Common Name/ISO-Name: Malacoxon
CAS No.: 1634-76-2
Empirical Formula: $C_{10}H_{16}O_6PS$
Molecular Weight: 314.3
Identified by means of: _____
CAS-Name: Butanedioic acid, [(dimethoxyphosphoryl)thio]-, diethyl ester
Structural Formula:

NMR ☒; IR ☒; UV ☒; MS ☒; Other Methods: _____

ANALYTICAL DATA

Certified Purity/Content of a.i.: 97.7% w/w
Analytical Method: ^{31}P -NMR
Analytical Report (incl. amendments): REF 029-07

Date of analysis/ reanalysis (yy/mm/dd)	05/02/04					
-For article stored at -	Cheminova A/S					

GLP-COMPLIANCE

The identification and determination of purity/content of active ingredient were performed at Cheminova A/S and conducted in accordance with FIFRA Good Laboratory Practice Standards, 40 CFR Part 160 and the OECD Principles of Good Laboratory Practices. All raw data, documentation, records, study plans, test articles, reference samples, and report are retained in the GLP archives of Cheminova A/S, Denmark.

Date: April 25, 2005

Signature: _____

Tina Rusk



Cheminova A/S
P.O. Box 9
DK-7000 Lemvig
Denmark

Phone (+45) 96909690
Fax (+45) 96 96 96 91
www.cheminova.com
CVR-No. DK 22763043

BATCH ANALYTICAL CERTIFICATE

ARTICLE IDENTIFICATION						
Article Name:		Fyfanon Technical			Reg. Dept. Code:	
Manufacturer:		Cheminova A/S			Batch No.: 9010501	
Origin of Production:		Commercial	<input checked="" type="checkbox"/>	Pilot plant	<input type="checkbox"/>	Laboratory
PHYSICAL PROPERTIES						
Technical Product		<input checked="" type="checkbox"/>	Preparation of technical Product	<input type="checkbox"/>	Analytical Standard	<input type="checkbox"/>
				Liquid	<input checked="" type="checkbox"/>	Solid
						Colour:
						Faint yellowish
Recommended Storage Conditions						
Ambient temperature in the dark		Expiry Date:				
In refrigerator		The article is stable at least 2 years from date of analysis/last date of reanalysis when stored at recommended conditions.				
In deep freezer						
Additional Comments:						
ACTIVE INGREDIENT IDENTIFICATION						
Common Name/ISO-Name:		Malathion		CAS-Name: Butanedioic acid, (dimethoxyphosphinothioyl thio)-, diethyl ester		
CAS No.:		121-75-5				
Empirical Formula:		C ₁₀ H ₁₉ O ₆ P ₂ S ₂		Structural Formula:		
Molecular Weight:		330.4				
Identified by means of:		NMR <input checked="" type="checkbox"/> ; IR <input checked="" type="checkbox"/> ; UV <input checked="" type="checkbox"/> ; MS <input checked="" type="checkbox"/> ; Other Methods:				
ANALYTICAL DATA						
Certified Purity/Content of a.i.: 96.0% w/w						
Analytical Method: VAM 001-02						
Analytical Report (incl. amendments): TEM 010-02						
Date of analysis/ reanalysis (yyymmdd)	990223	000105	001206	011106	021024	041103
-for article stored at -	Cheminova A/S. Regist. storage, DK	Cheminova A/S	Cheminova A/S. Regist. storage, DK	Cheminova A/S. Regist. storage, DK	Cheminova A/S. Regist. storage, DK	Cheminova A/S. Regist. storage, DK
GLP-COMPLIANCE						
The identification and determination of purity/content of active ingredient were performed at Cheminova A/S and conducted in accordance with FIFRA Good Laboratory Practice Standards, 40 CFR Part 160 and the OECD Principles of Good Laboratory Practices. All raw data, documentation, records, study plans, test articles, reference samples, and report are retained in the GLP archives of Cheminova A/S, Denmark.						
Date: 11 November 2004		Signature: Barbara Hinz				

ATTACHMENT 3
MATERIAL SAFETY DATA SHEETS

Name: Malaaxon
Material Type: Analytical Standard
Chemical Code: REF 029

CHB/January 1999
Page 1 of 3

MATERIAL SAFETY DATA SHEET

Malaaxon

1. IDENTIFICATION OF THE SUBSTANCE/ PREPARATION AND OF THE COMPANY/ UNDERTAKING



Name: Malaaxon

CHEMINOVA AGRO A/S

P.O. Box 9

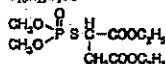
DK-7620 Lemvig

Denmark

Emergency Telephone No.: (+45) 97 83 53 53

2. COMPOSITION/ INFORMATION ON INGREDIENTS

Common Name: Malaaxon
CAS Name: Botulinic acid, [(dimethoxyphosphoryl)thio]-, diethyl ester
Other Name(s): S-1,2-Bis(ethoxycarbonyl)ethyl O,O-dimethyl phosphorothioate
CAS No.: 1634-78-2
EU Classification: T+R24/25
Molecular Weight: 314.29
Empirical Formula: C₁₀H₂₀O₆PS
Structural Formula:



3. HAZARDS IDENTIFICATION

3.1. Health Hazards (Acute and Chronic)

Malaaxon is a poison (cholinesterase inhibitor). It rapidly enters the body on contact with all skin surfaces and eyes. Clothing contaminated with material must be removed immediately and all skin washed thoroughly. Exposed persons must receive prompt medical treatment. Repeated exposures to cholinesterase inhibitors such as malaaxon may, without warning, cause increased susceptibility to doses of any cholinesterase inhibitor.

3.2. Signs and Symptoms of Exposure

Headache, nausea, vomiting, cramps, weakness, blurred vision, pin-point pupils, tightness in chest, laboured breathing, nervousness, sweating, watering of eyes, drooling or frothing of mouth and nose, muscle spasms and coma.

4. FIRST AID MEASURES

4.1. Emergency and First Aid Procedures

Call a doctor (physician), clinic or hospital immediately. Explain that the victim has been exposed to malaaxon, an organophosphorus insecticide, and describe his/her condition. Move the exposed person immediately from the area where the substance is present.

If breathing has stopped, start artificial respiration immediately and maintain until physician takes care of the exposed person.

If swallowed and the exposed person is conscious, make him/her vomit quickly. Have the exposed person drink 1 or 2 glasses of water and induce vomiting by reaching the back of throat with finger. Repeat until vomit is clear. Never give anything by mouth to an unconscious person. Make the exposed person lie down and keep him/her steady. Get medical attention immediately.

In case of contact, immediately flush eyes or skin with plenty of water while removing contaminated clothing and shoes. See physician immediately.

4.2. Note to Physician

Malaaxon is a cholinesterase inhibitor affecting the central and peripheral nervous systems producing cardiac and respiratory depression.

Antidote: Administer atropine sulfate in large doses. TWO to FOUR mg intravenously or intramuscularly as soon as cyanosis is overcome. Repeat at 5 to 10 minute intervals until signs of atropinisation appear.

Cholinesterase Inhibition - Treatment

The information presented herein is believed to be accurate and reliable, but is presented without any warranty, express nor implied, on the part of Cheminova Agro A/S.

Name: Malaoxon
Material Type: Analytical Standard
Chemnova Code: REF 029

GH/January 1999
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		Obidoxime chloride (Tokogonin) is a pharmacological antidote and may be administered as an adjunct to, but not a substitute for, atropine, which is a symptomatic and often lifesaving antidote. DO NOT GIVE MORPHINE OR TRANQUILLIZERS. At first sign of pulmonary oedema the patient should be given supplemental oxygen and treated symptomatically. Continued absorption of malaoxon may occur and relapse may occur after initial improvement. VERY CLOSE SUPERVISION OF THE PATIENT IS INDICATED FOR AT LEAST 48 HOURS.
5.	FIRE-FIGHTING MEASURES	
5.1.	Extinguishing Media and Procedure	Dry chemical, carbon dioxide, water spray or foam.
5.2.	Hazardous Products in a Fire	The essential breakdown products are sulfur dioxide, carbon monoxide, carbon dioxide and phosphorus pentoxide.
6.	ACCIDENTAL RELEASE MEASURES	
6.1.	Personal Protection	Observe all protection and safety precautions when cleaning up spills - see §.
6.2.	Steps to Be Taken in Case of Spill	Spills on the floor or other impervious surface should be swept up with an inert absorbent material such as hydrated lime, sawdust, Fuller's earth or other absorbent clays. Collect the contaminated absorbent, place in an appropriate container and dispose of in accordance with the instructions provided under Disposal (see 13). Rinse area with soda lye. Malaoxon can be hydrolysed in water by heating and adjusting the pH (alkaline). Malaoxon may also be disposed of through proper incineration.
7.	HANDLING AND STORAGE	
7.1.	Precautions to Be Taken in Handling	See Personal Protection - Section 8.
7.2.	Precautions to Be Taken in Storing	Store in deep freezer. The article is stable for at least 3 years from date of analysis when stored under recommended conditions.
7.3.	Fire and Explosion Precautions	-
8.	EXPOSURE CONTROLS/PERSONAL PROTECTION	
8.1.	Respiratory Protection	In case of insufficient ventilation, wear a respirator in conformity with local regulations.
	Protective Gloves	Wear chemical resistant gloves, such as barrier laminate, butyl rubber, nitrile rubber or viton.
	Eye Protection	Wear safety glasses.
	Other Protection	Wear appropriate chemical resistant clothing.
8.2.	Work/Hygienic Practices	If handled indoors, provide mechanical exhaust ventilation. Persons working with this product for a longer period should have frequent blood tests of their cholinesterase levels. If the cholinesterase level falls below a critical point, no further exposure should be allowed until it has been determined by means of blood tests that the cholinesterase level has returned to normal. Before removing gloves wash them with soap and water. Always wash hands, face and arms with soap and water before smoking, eating or drinking.
9.	PHYSICAL AND CHEMICAL PROPERTIES	
9.1.	Physical State	Liquid
9.2.	Colour	Colourless
9.3.	Odour	-
9.4.	Melting Point	<20°C
9.5.	Boiling Point	114°C
9.6.	Specific Gravity	-
9.7.	Vapour Pressure	-
9.8.	Viscosity	-
9.9.	Solubility in Water	0.5-1.0 g/100 ml at 20°C
9.10.	Solubility in Organic Solvents	-
9.11.	Partition Coefficient n-Octanol/Water	-
9.12.	pH	-
9.13.	Flash Point	100°C
9.14.	Autoignition Temperature	-
9.15.	Flammable Limits	-

The information presented herein is believed to be accurate and reliable, but is presented without any warranty, express or implied, on the part of Chemnova Agro A/S

Name: Malaoxon
Material Type: Analytical Standard
Chemnova Code: REF 029

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Page 3 of 3

10. STABILITY AND REACTIVITY

- 10.1. Conditions to Avoid -
10.2. Hazardous Decomposition Products See 5.2.
10.3. Materials to Avoid Strong alkalis and strong oxidizing compounds.

11. TOXICOLOGICAL INFORMATION

- 11.1. Acute toxicity
 - Ingestion LD₅₀, oral, rat: 158 mg/kg
 - Skin LD₅₀, dermal, rabbit: 119 mg/kg
 - Inhalation LC₅₀, inhalation, rat: -
11.2. Irritancy of Material Unknown
11.3. Carcinogenicity Not carcinogenic

12. ECOLOGICAL INFORMATION

Malaoxon is biodegradable. It undergoes rapid degradation in the environment and without problems in sewage treatment plants.

Malaoxon is toxic to birds, fish and aquatic invertebrates. The acute toxicity is:

- Fish 48 h-LC₅₀, Perch (*Perca fluviatilis*) 150 µg/l
- Invertebrates 24 weeks-EC₅₀, Midge (*Chironomus riparius*) 5.4 µg/l

13. DISPOSAL CONSIDERATIONS

- Waste Disposal Method Spill and waste disposal procedures in conformity with state and local regulations must be followed.
Do not contaminate water, food or feed by storage or disposal.

14. TRANSPORT INFORMATION

- UN Classification Toxic Liquid, Organic, N.O.S. (Malaoxon), UN No. 2810, Class 6.1, PG II, Primary Hazard: Toxic

15. REGULATORY INFORMATION

In the EU:



Toxic

R24/25: Toxic in contact with skin and if swallowed.

S28-36/37-45: After contact with skin, wash immediately with plenty of water and soap. Wear suitable protective clothing and gloves. In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

16. OTHER INFORMATION

-

The information presented herein is believed to be accurate and reliable, but is presented without any warranty, express nor implied, on the part of Chemnova Agro A/S.

SAFETY DATA SHEET

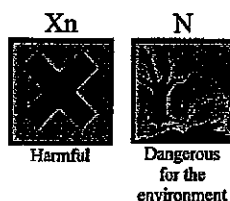
FYFANON[®] TECHNICAL

Table of contents

1. ♣ Identification of the substance/preparation and of the company/undertaking	9. ♣ Physical and chemical properties
2. ♣ Composition/information on ingredients	10. ♣ Stability and reactivity
3. ♣ Hazards identification	11. ♣ Toxicological information
4. ♣ First aid measures	12. ♣ Ecological information
5. ♣ Fire-fighting measures	13. ♣ Disposal considerations
6. ♣ Accidental release measures	14. ♣ Transport information
7. ♣ Handling and storage	15. ♣ Regulatory information
8. ♣ Exposure controls/personal protection	16. ♣ Other information

Revision: Sections containing a revision or new information are marked with a ♣.

1. ♣ IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING



Product name **FYFANON[®] TECHNICAL**

Intended use Active ingredient in insecticides

Manufacturer **CHEMINOVA A/S**
P.O. Box 9
DK-7620 Lemvig
Denmark

Emergency telephone no. (+45) 97 83 53 53

2. ♣ COMPOSITION/INFORMATION ON INGREDIENTS

2.1. FYFANON[®]

CAS name	Butanedioic acid, [(dimethoxyphosphinothioyl)thio]-, diethyl ester
CAS no.	121-75-5
IUPAC name(s)	Diethyl (dimethoxythiophosphorylthio)succinate S-[1,2-Bis(ethoxycarbonyl)ethyl] O,O-dimethyl phosphoro-dithioate
ISO name/EU name	Malathion
EC no. (EINECS no.)	204-497-7
EU index no.	015-041-00-X
Empirical formula	C ₁₀ H ₁₉ O ₆ PS ₂
Molecular weight	330.36
Structural formula	$ \begin{array}{c} \text{CH}_3\text{O} \quad \text{S} \\ \quad \quad \parallel \\ \text{CH}_3\text{O} - \text{P} - \text{S} - \text{CH} - \text{COOC}_2\text{H}_5 \\ \quad \quad \quad \quad \\ \quad \quad \quad \text{CH}_2\text{COOC}_2\text{H}_5 \end{array} $

2.2. Typical content 96-97%

3. ✦ HAZARDS IDENTIFICATION**3.1. CLASSIFICATION**EU classification Xn;R22 N;R50/53; see 15.1.
(according to 67/548/EEC as amended)

WHO classification Class III: Slightly hazardous

3.2. Health hazards (acute and chronic)

Fyfanon® (malathion) is a cholinesterase inhibitor of low mammalian toxicity. However, storage at too high temperatures may induce formation of the much more toxic and synergistic contaminant isomalathion (LD₅₀, acute oral, rat, 89 mg/kg). Both malathion and isomalathion rapidly enter the body on contact with all skin surfaces and eyes.

Repeated exposures to cholinesterase inhibitors such as **Fyfanon®** may, without warning, cause increased susceptibility to doses of any cholinesterase inhibitor.

3.3. Environmental hazards

The substance is very toxic to aquatic organisms, see section 12.

4. ✦ FIRST AID MEASURES**4.1. Signs and symptoms of exposure**

Headache, nausea, vomiting, cramps, weakness, blurred vision, pin-point pupils, tightness in chest, laboured breathing, nervousness, sweating, watering of eyes, drooling or frothing of mouth and nose, muscle spasms and coma.

4.2. Emergency and first aid procedures**General**

Exposed persons must receive prompt medical treatment. When any of the signs of exposure occurs, call a doctor (physician), clinic or hospital immediately. Explain that the victim has been exposed to malathion, an organophosphorus insecticide, and describe his/her condition. Immediately remove the victim from the area where the product is present.

Clothing contaminated with material must be removed immediately and all skin washed thoroughly.

If breathing has stopped, immediately start artificial

respiration and maintain until a physician takes charge of the exposed person.

Inhalation	If experiencing any discomfort, immediately remove from exposure. Get medical attention immediately if symptoms develop.
Ingestion	If the exposed person is conscious, make him/her vomit quickly. Make the exposed person rinse mouth and drink 1 or 2 glasses of water or milk if available. Let him/her induce vomiting by touching the back of the throat with a finger. Repeat until vomit is clear. Never give anything by mouth to an unconscious person. Get medical attention immediately.
Eye contact	Immediately flush with much water or eyewash solution, occasionally opening eyelids, until no evidence of chemical remains. Remove contact lenses after a few minutes and flush again. See physician immediately.
Skin contact	Immediately flush with plenty of water while removing contaminated clothing and shoes. Wash with water and soap. See physician immediately if symptoms develop.

4.3. Note to physician **Fyfanon® (malathion)** is a cholinesterase inhibitor affecting the central and peripheral nervous systems producing respiratory depression.

Cholinesterase inhibition – treatment
Decontamination procedures such as whole body washing, gastric lavage and administration of activated charcoal are often required.

Antidote: If symptoms (see 4.1.) are present, administer atropine sulphate, which often is a lifesaving antidote, in large doses, TWO to FOUR mg intravenously or intramuscularly as soon as possible. Repeat at 5 to 10 minute intervals until signs of atropinisation appear and maintain full atropinisation until all organophosphate is metabolised.

Obidoxime chloride (Toxogonin), alternatively pralidoxime chloride (2-PAM), may be administered as an adjunct to, but not a substitute for atropine sulphate. Treatment with oxime should be maintained as long as atropine sulphate is administered.

At first sign of pulmonary oedema the patient should be given supplementary oxygen and treated symptomatically.

Relapse can occur after initial improvement.
VERY CLOSE SUPERVISION OF THE PATIENT IS INDICATED FOR AT LEAST 48 HOURS, DEPENDING ON THE SEVERITY OF POISONING.

5. ♣ FIRE-FIGHTING MEASURES

- | | |
|---|---|
| 5.1. Extinguishing media and procedure | <p>Dry chemical or carbon dioxide for small fires, water spray or foam for large fires.</p> <p>Use water spray to keep fire-exposed containers cool. Approach fire from upwind to avoid hazardous vapours and toxic decomposition products. Fight fire from protected location or maximum possible distance. Avoid heavy hose streams. Dike area to prevent water runoff. Firemen should wear self-contained breathing apparatus and protective clothing.</p> |
| 5.2. Hazardous decomposition products in a fire | <p>The essential breakdown products are volatile, toxic, malodorous, irritant and inflammable compounds such as dimethyl sulphide, sulphur dioxide, carbon monoxide, carbon dioxide and phosphorus pentoxide.</p> |
| 5.3. Unusual fire and explosion hazards | <p>See 10.1.</p> |

6. ♣ ACCIDENTAL RELEASE MEASURES

- | | |
|---|--|
| 6.1. Personal protection | <p>Observe all protection and safety precautions when cleaning up spills. Depending on the magnitude of the spill, this may mean wearing eye protection or face mask, coveralls, protective gloves and boots when cleaning up spills. See section 8, Personal protection.</p> |
| 6.2. Steps to be taken in case of spill | <p>It is recommended to have a predetermined plan for the handling of spills.</p> <p>Stop the source of the spill if it is safe to do so. Keep unprotected persons away from the spill area. Contain the spill to prevent any further contamination of surface, soil or water.</p> |

Spills on the floor or other impervious surface should be contained or diked and then absorbed onto an absorptive material such as universal binder, hydrated lime, Fuller's earth or other absorbent clays. Collect contaminated absorbent in suitable containers. Rinse area with soda lye and much water. Absorb wash liquid onto suitable absorbent as well and collect in suitable containers. Washings must be prevented from entering surface water drains.

Large spills which soak into the ground should be dug up and transferred to suitable containers.

Spills in water should be contained as much as possible by isolation of the contaminated water. The contaminated water must be collected and removed for treatment or disposal. Uncontrolled discharge into water courses must be alerted to the appropriate regulatory body.

The used containers should be properly closed and labelled. Refer to section 13 for disposal.

7. + HANDLING AND STORAGE

7.1. Precautions to be taken in handling

In an industrial environment it is recommended to avoid all personal contact with the product, if possible by using closed systems and remote system control. Otherwise the material should preferably be handled by mechanical means. Adequate ventilation or local exhaust ventilation is required. The exhaust gases should be filtered or treated otherwise. For personal protection in this situation, see section 8.

For its use as a pesticide, first look for precautions and personal protection measures on the officially approved label on the packaging or for other official guidance or policy in force. If these are lacking, see section 8.

7.2. Precautions to be taken in storing

The product is stable when stored at temperatures not exceeding 20-25°C.

The product should never be heated above 55°C. Local heating above this temperature should be avoided as well. Protect against strong heat from sunshine or other source, e.g. fire.

Do not contaminate water, foodstuffs, feed or seed by storage or disposal.

Store in closed, labelled containers.

- 7.3. Specific use The product is an active ingredient for the production of registered pesticides which may only be used for the applications they are registered for in accordance with a label approved by the regulatory authorities.

- 7.4. Fire and explosion precautions ---

8. * EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1. Exposure limit values

		Year	
Malathion	OSHA (USA) PEL	200	IWA 15 mg/m ³ total dust; skin notation
		2	
	ACGIH (USA)	200	TWA 10 mg/m ³ ; skin notation; BEI
	TLV	5	
	EU, 2000/39/EC	200	Not established
		0	
Germany, MAK		200	TWA 15 mg/m ³ measured as inhalable fraction of
		4	the aerosol
			CEILING 60 mg/m ³
			BAT
HSE (UK) OEL		200	8-hr IWA 10 mg/m ³ ; skin notation
		3	

However, other personal exposure limits defined by local regulations may exist and must be observed.

- 8.2. Personal protection When used in a closed system, personal protection equipment will not be required. The following is meant for other situations, when the use of a closed system is not possible, or when it is necessary to open the system. Consider the need to render equipment or piping systems non-hazardous before opening.

- Respiratory protection The product does not automatically present an airborne exposure concern when handled carefully due to low vapour pressure, but in the event of a discharge of the

material which produces a heavy vapour or mist, workers should put on an officially approved face mask or respiratory protection equipment with a universal filter type including particle filter.

Protective gloves

Wear chemical resistant gloves, such as barrier laminate, butyl rubber, nitrile rubber or viton. The breakthrough times of these materials for malathion are unknown, but it is expected that they will give adequate protection based on the low dermal toxicity of the substance.

Eye protection

Wear safety glasses. It is recommended to have an eye wash fountain immediately available in the workplace.

Other protection

Wear coveralls or long sleeved shirt and long pants. Wear shoes plus socks.

8.3. Work/hygienic practices

Persons working with this product for a longer period should have frequent blood tests of their cholinesterase levels. If the cholinesterase level falls below a critical point, no further exposure should be allowed until it has been determined by means of blood tests that the cholinesterase level has returned to normal.

Keep all unprotected persons and children away from working area.

Avoid contact with eyes, skin or clothing. Avoid breathing vapour or mist. Before removing gloves, wash them with water and soap. Wash thoroughly with water and soap after handling. Remove contaminated clothing immediately and wash before reuse.

After work, take off all work clothes and shoes. Shower, using soap and water. Wear only clean clothes when leaving job. Do not wear contaminated clothing. Wash protective clothing and protective equipment with soap and water after each use. Respirator should be cleaned and filter replaced according to instructions included with respirator.

8.4. Environmental exposure controls

See section 13.

9.4. PHYSICAL AND CHEMICAL PROPERTIES

9.1. Physical state

Liquid

9.2. Colour	Colourless to light yellow or light pink
9.3. Odour	Slightly aromatic odour
9.4. Melting point	2.85°C
9.5. Boiling point	Decomposes; decomposition starts at 174°C. 156-157°C at 0.7 mm Hg
9.6. Specific gravity	1.23 g/ml at 20°C
9.7. Vapour pressure	3.4 x 10 ⁻⁶ mm Hg at 25°C 1.4 x 10 ⁻⁴ mm Hg at 45°C
9.8. Viscosity	16.4 cP at 40°C 30.0 cP at 25°C
9.9. Surface tension	57.8 mN/m at 20°C for a saturated solution in water
9.10. Solubility in water	148.2 mg/l at 25°C
9.11. Solubility in organic solvents	Solubility of malathion in: Acetone > 250 g/l at 20°C Methanol > 250 g/l at 20°C Ethyl acetate > 250 g/l at 20°C 1,2-Dichloroethane > 250 g/l at 20°C Xylene > 250 g/l at 20°C Heptane 57-67 g/l at 20°C K _{ow} = 560
9.12. Partition coefficient n-octanol/water	
9.13. pH	When equal amounts of Fyfanon® and distilled water are dispersed at 20°C, the pH measured in the water phase is 3.7-3.8.
9.14. Flash point	163°C (Pensky-Martens closed tester; see, however, 10.1.)
9.15. Autoignition temperature	278°C
9.16. Explosive properties	Not explosive
9.17. Oxidising properties	Not oxidising

10. STABILITY AND REACTIVITY

- 10.1. Thermal decomposition
- Fyfanon® will decompose rapidly when heated to temperatures above 140°C, significantly increasing the risk of explosion. Direct local heating such as electric heating or by steam must be avoided.
- The decomposition is dependent on time as well as temperature due to self-accelerating exothermic and autocatalytic reactions. The reactions involve rearrangements and polymerisation releasing volatile malodorous and inflammable compounds such as diethyl sulphide.
- 10.2. Hazardous decomposition products
- Storage at too high temperatures may induce formation of the more toxic and synergistic contaminant isomalathion. See also 5.2

- 10.3. Materials to avoid Strong alkalis, amines and strong oxidising compounds.
The product can corrode iron, steel, tin plate and copper.
Fyfanon® is rapidly hydrolysed at pH > 7.0.

11. TOXICOLOGICAL INFORMATION



- 11.1. Acute toxicity The product is not considered to be harmful, neither by inhalation, in contact with skin nor if swallowed. However, it may become harmful after storage at too high temperatures, see 3.1.
- | | | |
|-------------------|--------------|--|
| Route(s) of entry | - Ingestion | LD ₅₀ , acute oral, rat: approx. 5500 mg/kg ^{*)} |
| | - Skin | LD ₅₀ , acute dermal, rat: > 2000 mg/kg |
| | - Inhalation | LC ₅₀ , inhalation, rat: > 5.2 mg/l/4 h |
- ^{*)} Values from 1000 to 2830 mg/kg are mentioned in literature as well as in WHO Data Sheet No. 29, VBC/DS/77 29
- 11.2. Irritancy Slightly irritating to eyes and skin.
- 11.3. Allergic sensitisation In animal tests mixed results were obtained:
Magnusson-Kligman maximisation test: positive
Buehler test: negative
Local Lymph Node Assay: negative.
The meaning of these results for humans cannot be fully evaluated.
- 11.4. Carcinogenicity IARC evaluation: The available data provide no evidence that **malathion** is likely to present a carcinogenic risk to humans.
- 11.5. Effects on reproduction No effects on fertility are found for **malathion** in rats and rabbits at maternal non-toxic doses.
- 11.6. Teratogenicity No indications of teratogenic effects of **malathion** are found.
- 11.7. Mutagenicity **Malathion** is not mutagenic.

12. ECOLOGICAL INFORMATION



- 12.1. Ecotoxicity **Malathion** is very toxic to fish, aquatic invertebrates, aquatic life stages of amphibians and insects. It is less toxic to aquatic plants, birds and soil macro- and microorganisms.

The ecotoxicity is measured to be:

- Fish	Rainbow trout (<i>Oncorhynchus mykiss</i>)	96 h-LC ₅₀ : 0.18 mg/l
		37-day NOEC: 21 µg/l
- Invertebrates	Daphnids (<i>Daphnia magna</i>)	48 h-EC ₅₀ : 0.72 µg/l
		21-day NOEC: 0.06 µg/l

- Algae	Green algae (<i>Selenastrum capricornutum</i>)	72-h IC ₅₀ : 4.06 mg/l
- Birds	Bobwhite quail (<i>Colinus virginianus</i>)	LD ₅₀ : 359 mg/kg
		5-day dietary LC ₅₀ : 3497 mg/kg
	Mallard duck (<i>Anas platyrhynchos</i>)	LD ₅₀ : 1485 mg/kg
- Earthworms	<i>Eisenia foetida foetida</i>	14-day LC ₅₀ : 613 mg/kg soil
- Bees	Honey bees (<i>Apis mellifera</i>)	LD ₅₀ , acute oral: 0.38 µg/bee
	Honey bees (<i>Apis mellifera</i>)	LD ₅₀ , topical: 0.27 µg/bee

- 12.2. Mobility Under normal conditions **malathion** is of medium mobility in soil, but is degraded rapidly.
- 12.3. Persistence and degradability **Malathion** is biodegradable, but does not fulfil the criteria for being readily biodegradable. It undergoes rapid degradation in the environment and in waste water treatment plants. No adverse effects are found at concentrations up to 100 mg/l in waste water treatment plants. Degradation occurs both aerobically and anaerobically, mostly biologically.
- Degradation half-lives vary with circumstances, but are usually one to a few days in aerobic soil and water.
- 12.4. Bioaccumulative potential ... **Malathion** is not expected to bioaccumulate. It is rapidly metabolised and excreted (with half-life of approx. 3 days). The measured bioconcentration factor (BCF) of malathion is 95 (average for several fish species).

13. DISPOSAL CONSIDERATIONS



- 13.1. Waste disposal method Waste material can be removed by controlled discharge to a waste water treatment plant. Other possible methods of disposal are controlled incineration with flue gas scrubbing or removal to a licensed chemical destruction plant.
- Fyfanon®** can be hydrolysed in water by heating and adjusting the pH (alkaline).
- Do not contaminate water, foodstuffs, feed or seed by storage or disposal.
- 13.2. Container disposal Triple rinse (or equivalent) and offer for recycling or reconditioning. Alternatively, the packaging can be punctured to make it unusable for other purposes and then be disposed of in a sanitary landfill.
- Disposal of waste and packagings must always be in accordance with all applicable local regulations.

14. TRANSPORT INFORMATION**ADR/RID****CLASSIFICATION**

Proper shipping name Environmentally hazardous substance, liquid, n.o.s.
(Malathion)

Class 9

UN no. 3082

Packaging group III

IMDG CLASSIFICATION

Proper shipping name Environmentally hazardous substance, liquid, n.o.s.
(Malathion)

Class 9

UN no. 3082

Packaging group III

Marine pollutant (P/PP) Marine pollutant

IATA/ICAO**CLASSIFICATION**

Proper shipping name Environmentally hazardous substance, liquid, n.o.s.
(Malathion)

Class 9

UN no. 3082

Packaging group III

15. REGULATORY INFORMATION**15.1. IN THE EU****Classification and labelling**

(according to 67/548/EEC as amended):

Hazard symbols**Xn**

Harmful

NDangerous
for the
environment**R-phrases**

R22-50/53: Harmful if swallowed. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

S-phrases

S24-60-61: Avoid contact with skin. This material and its container must be disposed of as hazardous waste. Avoid release to the environment. Refer to special instructions/safety data sheets.

Other mentions

To avoid risks to man and the environment, comply with the instructions of use.

15.2. Regulatory status

The product is covered by EU chemical legislation.

16. OTHER INFORMATION

♣

This material should only be used by persons who are made aware of its hazardous properties and have been instructed in the required safety precautions.

The information provided in this safety data sheet is believed to be accurate and reliable, but uses of the product may vary and situations unforeseen by Cheminova A/S may exist. The user of the material has to check the validity of the information under local circumstances.

ATTACHMENT 4
TEST SUBSTANCE PREPARATION PROCEDURES

ATTACHMENT 4

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TEST SUBSTANCE PREPARATION PROCEDURE

Test Substances: Malathion (synonymous with Fyfanon Technical) and Malaoxon

Vehicle: Corn Oil

A. Purpose:

The purpose of this procedure is to provide a method for the preparation of dosage formulations of the test substances for oral (gavage) administration to rats on Protocol TQC00012.

B. General Information:

1. All formulation containers will be labeled and color-coded. Each label will specify the protocol number, test substance identification, batch number, concentration, dosage level, dosage group, preparation date, expiration date and storage conditions.
2. Formulations (suspensions) of each test substance will be prepared daily at the Testing Facility.
3. Formulations will be administered at a final dosage volume of 5 mL/kg.
4. Safety:
 - ☒ Double nitrile gloves, uniform/lab coat, goggles or safety glasses with side shields.
 - ☐ Dust-Mist/HEPA-filtered Mask
 - ☐ Half-Face Respirator
 - ☒ Full-Face Respirator/Positive Pressure Hood
 - ☒ Tyvek[®] Suit
 - ☐ Full Face Shield
 - ☒ Bulk TA/S will be handled in a chemical fume hood
 - ☒ Gloves will be washed with soap and water or sprayed with an appropriate cleaning solution prior to removal and then disposed of in a biohazard container.
5. The test substances will be considered 100% pure for the purpose of dosage calculations.

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TEST SUBSTANCE PREPARATION PROCEDURE

6. Sampling requirements: Cited in protocol.

7. Storage: Cited in protocol.

C. Dosage Formulation Preparation:

NOTE: Prior to dosage formulation preparation accurately measure the required amount of the appropriate vehicle (R.O. deionized water should be used for calibration purposes) in a graduated cylinder and pour the required amount of vehicle into an appropriately sized container. Carefully mark each container at the meniscus. This mark will be used during the preparation to bring the dosage formulations up to volume.

1. Weigh the required amount of test substance into an appropriately sized and labeled, pre-calibrated container (See TA/S PREPARATION CALCULATIONS).
2. QS ad with vehicle to the required volume in the pre-calibrated container (See TA/S PREPARATION CALCULATIONS).
3. Add a magnetic stir bar to the container, place the container on a magnetic stir plate and thoroughly mix the formulation. Continue to mix the formulation prior to and during sampling, aliquotting and/or dosage administration.

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TEST SUBSTANCE PREPARATION PROCEDURE

4. If necessary, aliquot the formulation into an appropriately sized and labeled container for dosage administration. Add a magnetic stir bar to the container, place the container on a magnetic stir plate and mix the formulation thoroughly prior to and during dosage administration.
5. Repeat steps C1 through C4 for each concentration of each test substance.

Written by: Christy K Ruppert

Approved by: John J. Barnard Date: 23 Nov 2005

Clarification: ☒ No ☐ Yes (See attached clarification form.)

Initials/Date: ARO / 12/09/05



PROTOCOL TQC00012

ORAL (GAVAGE) REPEAT DOSE TIME OF PEAK CHOLINESTERASE
DEPRESSION STUDY OF MALATHION AND MALAOXON IN JUVENILE RATS

Amendment 1 - 16 December 2005

1. Objective (page 1 of the protocol):

[Effective Date: 05 December 2005] The objective of this study is to determine the time of peak cholinesterase inhibition after repeated daily dosing of young pre-weaning rats with Malathion and Malaoxon. There will also be an effect study using doses of 0 (Vehicle) 50, 150 and 450 mg/kg of Malathion on PND 22 pups and evaluating erythrocyte and brain acetyl cholinesterase activity.

Reason for Change:

This change is being made to clarify the purpose of the study based on the lack of test substance to initially complete the repeat dose portion of the protocol.

2. Method and Frequency (page 9 of the protocol):

[Effective Date: 29 November 2005] Administration of the test substance Malathion will be postponed until receipt from the Sponsor. The revised schedule will be added by amendment.

Reason for Change:

This change is being made to postpone administration of the test substance Malathion until receipt of the test substance from the Sponsor.

3. Concentration (page 5 of the protocol):

[Effective Date: 02 December 2005] Concentration samples of the prepared formulations will be collected on postnatal days (PNDs) 22 for each of the malathion concentrations and stored refrigerated at the Testing Facility for

Any revisions to this finalized amendment must be made by subsequent amendment.

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possible future analyses. Duplicate samples (0.5 mL each) will be taken from the middle of each concentration. The disposition of these samples will be documented in the raw data.

Method and Frequency (page 9 of the protocol):

[Effective Date: 02 December 2005] Administration of the test substance Malathion will be conducted on postnatal days 12 and 22, rather than postnatal day 12 through 22.

Rationale for Dosage Selection (page 10 of the protocol):

[Effective Date: 02 December 2005] The dosage levels for the evaluation of the cholinesterase levels after exposure to Malathion on postnatal day 22 were selected based on a previous study conducted by the Sponsor using postnatal day 12 pups and young adults. At 450 mg/kg, no mortality occurred in the postnatal day 12 pups; however, five of the sixteen pups were observed with tremors prior to being sacrificed at two hours postdosage. No mortality or adverse clinical signs were observed in the young adults.

Dosage Levels, Concentrations and Volumes (page 10 of the protocol):

[Effective Date: 02 December 2005] The dosage levels, concentrations and volumes for the Malathion on postnatal days 12 and 22 were as follows:

Postnatal Day 12

Dosage Group	Number of Pups per Sex	Test Substance	Dosage (mg/kg/day) ^a	Concentration (mg/mL)	Dosage Volume (mL/kg)	Batch Number
I	10	Corn Oil	0 (Vehicle)	0	5	B-TQC00012-A(Day.Month.Year)
II	20	Malathion	150	30	5	B-TQC00012-B(Day.Month.Year)

Postnatal Day 22

Dosage Group	Number of Pups per Sex	Test Substance	Dosage (mg/kg/day) ^a	Concentration (mg/mL)	Dosage Volume (mL/kg)	Batch Number
I	10	Corn Oil	0 (Vehicle)	0	5	B-TQC00012-A(Day.Month.Year)
IV	7	Malathion	50	10	5	B-TQC00012-D(Day.Month.Year)
V	7	Malathion	150	30	5	B-TQC00012-B(Day.Month.Year)
VI	6	Malathion	450	90	5	B-TQC00012-E(Day.Month.Year)

a. The test substance will be considered 100% pure for the purpose of dosage calculations.

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Cholinesterase Assay – Blood and Brain Sample Collection (page 12 of the protocol):

[Effective Date: 02 December 2005] The 0 (Vehicle), 50, 150 and 450 mg/kg dosage levels of Malathion will be sacrificed at 2 hours postdosage and have the RBC and brain cholinesterase levels evaluated as described in the protocol.

Reason for Change:

The above changes are being made to allow for cholinesterase levels to be evaluated after exposure to Malathion on postnatal day 22, rather than cholinesterase levels after repeat exposure as was initially described in the protocol.

4. Number (page 6 of the protocol):

[Effective Date: 02 December 2005] Additional litters, as described below, will be ordered by the Testing Facility to complete the Malathion repeat dose portion of the protocol.

Fo generation population
acclimated:

Seven female rats with litters of ten pups (five male pups and five female pups).

F1 generation population
selected for study:

Six of the above litters (with five male and five female pups) will be evaluated with Malathion. Twenty pups per sex will be dosed with 150 mg/kg/day of malathion for the duration of the dosing period, and the remaining ten pups per sex will be dosed with the vehicle.

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Body Weight and Age (page 6 of the protocol):

[Effective Date: 11 December 2005] The additional litters will be ordered to arrive at the Testing Facility on day 6 postpartum. Actual body weights will be recorded the day after receipt and will be documented in the raw data. The weight range will be included in the final report.

Study Schedule (page 29 of the protocol):

[Effective Date: 02 December 2005] The study schedule for the repeat portion of the Malathion portion of the study will be revised as follows:

13 DEC 05	Dams and Pups Arrive - Acclimation Begins.
19 DEC 05 – 29 DEC 05	Dosage Administration - Pups - Days 12 through 22 postpartum.
29 DEC 05	Dams and Pups Sacrificed on Day 22 Postpartum.
05 JAN 06	Unaudited Letter Report
25 JAN 06	Unaudited Summary Report.

Reason for Change:

This change was necessary because of an insufficient amount of Malathion was available to complete the study as was described in the protocol.

Any revisions to this finalized amendment must be made by subsequent amendment.

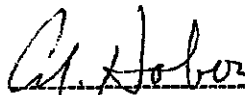

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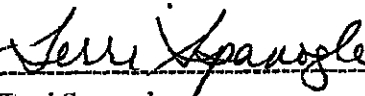
5. Final Report (page 15 of the protocol):

[Effective Date: 15 December 2005] The Testing Facility Quality Assurance Unit will perform a Quality Control check of the cholinesterase data rather than a QAU audit of the cholinesterase data.

Reason for Change:

This change was necessary to clarify the protocol.

	
Alan M. Hoberman, Ph.D., DABT	John F. Barnett Jr., B.S.
Director of Research	Senior Scientist
	Study Director

	
Marjorie B. Vargo, B.A.	Terri Spanogle
Member, Institutional Animal Care and Use Committee	Senior Scientist
	Sponsor's Representative

Any revisions to this finalized amendment must be made by subsequent amendment.

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