

US EPA ARCHIVE DOCUMENT

UNDATED

DER #4

Malathion: 1-Year Chronic Oral Toxicity Study in Dogs. Tegeris  
Laboratories. 1987. MRID 40188501. HED Doc No. 006349.

#8

## DATA EVALUATION RECORD

Study Type: 1-Year Chronic Oral Toxicity Study, Dogs  
OPP Guideline 83-1

P.C. Code: 057701

Tox. Chemical No.: 535

Test Material (purity): Malathion; (95.0% a.i.)

Synonyms O,O-dimethyl dithiophosphate of diethyl mercaptosuccinate; O,O-dimethyl phosphorodithioate of diethyl mercaptosuccinate; diethyl mercaptosuccinate, S-ester with O,O-dimethyl phosphorodithioate; Cythion; AC6,601.

Citation: Tegeris Laboratories, Inc., 1987. One-Year Oral Toxicity Study in Purebred Beagle Dogs with AC6,601. Tegeris Laboratories, Inc., Laurel, MD. Study No. 85010. April 30, 1987. Unpublished.  
MRID 40188501.

Sponsor: American Cyanamid Company, Princeton, NJ.

### Executive Summary:

In a 1-year chronic oral toxicity study in dogs, malathion (95.0% purity) was administered daily in gelatin capsules to groups of 6 male and 6 female Beagle dogs at dose levels of 0 (control), 62.5, 125 or 250 mg/kg/day. Control dogs were given empty capsules. Clinical signs of toxicity, body weights and food consumption were monitored. Ophthalmoscopic examinations, hematology, clinical chemistries (including plasma, erythrocyte and brain cholinesterase determinations) and urinalyses were conducted. At termination of the study at 1 year, gross necropsies, organ weights and histopathological examinations were performed.

No mortalities occurred during the study. No treatment-related clinical signs of toxicity were observed. Differences in body weight and food consumption between treated animals and controls were not observed. Ophthalmoscopic examinations were negative. Increased platelet counts were noted in males and females at all dose levels. At the low dose, platelet counts were increased up to 133% of control levels in males and up to 144% in females. Decreased erythrocyte counts and decreased hematocrit were noted in males and females at the high dose and in females at the mid dose. Decreased creatinine (males and females), decreased SGPT (males) and decreased BUN (males) were observed at all dose levels. In addition, at the high dose, decreased albumin (males and females) and decreased calcium (males and females) were also noted.

Statistically significant treatment-related and dose-related inhibition of plasma and erythrocyte cholinesterase activity were observed in both males and females at all dose levels at all time points. At the low dose, both plasma and erythrocyte inhibition were decreased about 25% compared to the control levels. Brain (cerebrum) and brain (cerebellum) cholinesterase activity were not inhibited at any dose level. Except for red or white foci in the stomach of males and females at the high dose and in females at the mid dose, gross necropsies were unremarkable. Increased liver weights were observed in males and females at all dose levels. At the low dose, the increase in males was 109% and in females was 140% of the control weight. Increased kidney weights were also observed in males and females at all dose levels. At the low dose, the increase in males was 125% and in females was 124% of the control weight. In addition, combined thyroid/parathyroid weights were increased in females at the high dose. Other than increased incidences of inflammation of the lungs in males at the higher dose levels, histopathological examinations did not reveal any adverse findings in males or females at any dose level. No overall cholinesterase NOEL was demonstrated in this study (<62.5 mg/kg/day). The overall cholinesterase LOEL was 62.5 mg/kg/day (LDT) based on inhibition of plasma and erythrocyte cholinesterase activity in both males and females. The NOEL for cholinesterase inhibition for both sexes was <62.5 mg/kg/day (LDT) for plasma and erythrocyte cholinesterase and 250 mg/kg/day for brain cholinesterase. The LOEL for cholinesterase inhibition for both sexes was 62.5 mg/kg/day (LDT) for plasma and erythrocyte cholinesterase and >250 mg/kg/day (HDT) for brain cholinesterase. It was determined by the HED HAZARD ID Committee (9/9/97) that the systemic NOEL in this study for both males and females was 250 mg/kg/day (HDT) and that no systemic LOEL was demonstrated (>250 mg/kg/day). The increased platelet counts, decreased erythrocyte counts, decreased hematocrit, decreased creatinine, decreased albumin, decreased calcium, decreased SGPT and decreased BUN, in the absence of histopathological changes, were not considered adequate to select an endpoint of toxicological concern.

This study is NOT ACCEPTABLE (Supplementary) and DOES NOT SATISFY guideline 83-1 for a chronic toxicity study in dogs because NOELs were not established for inhibition of cholinesterase activity for plasma and erythrocytes in either males or females.

TB997:MALATH18.087

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OPP Guideline 83-1

P.C. Code: 057701

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No mortalities occurred during the study. No treatment-related clinical signs of toxicity were observed. Differences in body weight and food consumption between treated animals and controls were not observed. Ophthalmoscopic examinations were negative. Dose-related increased platelet counts were noted in males and females at all dose levels. At the low dose, platelet counts were increased up to 133% of control levels in males and up to 144% in females. Decreased erythrocyte counts and decreased hematocrit were noted in males and females at the high dose and in females at the mid dose. Decreased creatinine (males and females), decreased SGPT (males) and decreased BUN (males) were observed at all dose levels. In addition, at the high dose, decreased albumin (males and females) and decreased calcium (males and females) were also noted.

Statistically significant treatment-related and dose-related inhibition of plasma and erythrocyte cholinesterase activity were observed in both males and females at all dose levels at all time points. At the low dose, both plasma and erythrocyte inhibition were decreased about 25% compared to the control levels. Brain (cerebrum) and brain (cerebellum) cholinesterase activity were not inhibited at any dose level. Except for red or white foci in the stomach of males and females at the high dose and in females at the mid dose, gross necropsies were unremarkable. Increased liver weights were observed in males and females at all dose levels. At the low dose, the increase in males was 109% and in females was 140% of the control weight. Increased kidney weights were also observed in males and females at all dose levels. At the low dose, the increase in males was 125% and in females was 124% of the control weight. In addition, combined thyroid/parathyroid weights were increased in females at the high dose. Other than increased incidences of inflammation of the lungs in males at the higher dose levels, histopathological examinations did not reveal any adverse findings in males or females at any dose level. **No cholinesterase NOEL was demonstrated in this study (<62.5 mg/kg/day). The cholinesterase LOEL was 62.5 mg/kg/day (LDT) based on inhibition of plasma and erythrocyte cholinesterase activity in both males and females. No systemic NOEL was demonstrated in this study (<62.5 mg/kg/day). The systemic LOEL was 62.5 mg/kg/day (LDT) based on decreased platelet counts, decreased creatinine, decreased BUN, decreased SGPT and decreased liver and kidney weights.**

This study is **NOT ACCEPTABLE** (Supplementary) and **DOES NOT SATISFY** guideline 83-1 for a chronic toxicity study in dogs because NOELs were not established for numerous parameters in the study.

TB997:MALATH18.087



CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OCT 7 1987

006349

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Expedited Review of Malathion Rat Teratology  
and Chronic Dog Studies

FROM: Brian Dementi, Ph.D. *Brian Dementi 10/5/87*  
Review Section #1  
Toxicology Branch/HED (TS-769)

THRU: R. Bruce Jaeger, Section Head *RBJ*  
Review Section #1  
Toxicology Branch/HED (TS-769)

THRU: Theodore Farber, Ph.D., Chief *Theodore Farber*  
Toxicology Branch/HED (TS-769) *10/7/87*

TO: William Miller, PM 16  
Registration Division (TS-767)

Toxicology Branch has reviewed the chronic dog and rat teratology studies on an expedite basis, as requested, for purposes of addressing data requirements for the malathion registration standard (Re: 8/4/87 Memorandum of Edward F. Tinsworth to Anne Barton). Both studies have been classified core supplementary and, hence, will not serve to satisfy guideline requirements. DERs are attached.

6

7

Reviewed by: Brian Dementi, Ph.D. *Brian Dementi, 10/5/87*  
Section I, Tox. Branch (TS-769C)  
Secondary reviewer: R. Bruce Jaeger, Section Head *RBJ 10/5/87*  
Section I, Tox. Branch (TS-769C)

## DATA EVALUATION REPORT

STUDY TYPE: One Year Dog Chronic Toxicity      TOX. CHEM. NO.: 535

TEST MATERIAL: AC 6.601      MRID NO.: 40188501

SYNONYM: Malathion

STUDY NUMBER(S): 85010

SPONSOR: American Cyanamid Company, Princeton, NJ

TESTING FACILITY: Tegeris Laboratories, Inc., Laurel, MD

TITLE OF REPORT: One-Year Oral Toxicity Study in Purebred  
Beagle Dogs with AC6601

AUTHOR(S): Tegeris Laboratories, Inc.

REPORT ISSUED: April 30, 1987

Special Review Criteria (40 CFR 154.7)

A. MATERIALS:

1. Test compound: AC6601, Description: Clear oily pale yellow liquid, Lot#: W40515-0011, Purity: 95.0%, Contaminants: listed in CBI appendix
2. Test animals: Species: Dog, Strain: Beagle, Age: 5-6 months, Weight: 6.5-7.5 kg, Source: Hazelton Research Products, Inc. Cumberland, VA

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned 6 of each sex to the following test groups:

Test Group	Dose in diet mg/kg/day	Main Study 12 months	
		male	female
1 Cont.	0	6	6
2 Low (LDT)	62.5	6	6
3 Mid (MDT)	125	6	6
4 High(HDT)	250	6	6

2. Diet preparation: Purina Certified Canine Chow, 5072 Meal, Richmond, IN

Test results of general feed and water analyses are on file at Tegeris Laboratories, Inc.

It is noted here that the test compound was administered via capsule in the pure form rather than via the diet. Control animals were administered empty capsules at the time of dosing.

3. Animals received food during a one hour interval daily and were allowed water ad libitum.
4. Statistics - The following procedures were utilized in analyzing the numerical data: one-way analysis of variance (Anova) using F-test for variance comparison. Dunnett's t-test was used to determine means which were statistically different from the control at the 95% confidence interval.
5. Quality assurance: According to the study authors the study was conducted in accordance with good laboratory practice regulations as required by FIFRA. The quality assurance unit manager provided a statement of quality

9

assurance as required under GLP regulations.

Signed by: Thomas Shellenburger, Ph.D. and Leonard Billups, D.V.M., A.C.V.P, 2/11/87.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected twice daily for signs of toxicity and mortality.

Toxicity/mortality (survival): all animals survived to terminal sacrifice and none exhibited any toxicological responses which could be attributed to dosing with the test material. (pp.24-25)

2. Body weight

All dogs were weighed weekly for the duration of the study. There were no statistically significant weight changes in any of the dose groups.

3. Food consumption

Food consumption was determined and mean daily dietary intake was calculated. There was no dose-related effect on this parameter.

4. Ophthalmological examinations

Ophthalmologic examinations were performed on each dog pretest and prior to terminal sacrifice. The examinations did not disclose any compound related effects as affirmed by L. F. Rubin, V.M.D.

5. Blood was collected before treatment and at 1.5, 3 and 6 months and at terminal sacrifice for hematology and clinical analysis from all animals. The CHECKED (X) parameters were examined.

a. Hematology

X	
X	Hematocrit (HCT)*
X	Hemoglobin (HGB)*
X	Leukocyte count (WBC)*
X	Erythrocyte count (RBC)*

X	
X	Leukocyte differential count*
X	Mean corpuscular HGB (MCH)
X	Mean corpuscular HGB conc. (MCHC)
X	Mean corpuscular volume (MCV)

X	Platelet count*	X	Reticulocyte count
	Blood Clotting Measurements (Thromboplastin time) (Clotting time) (Prothrombin time)	X	Erythrocyte Morphology

\* Recommended for subchronic and chronic studies

Among the indicated parameters, platelet count increases were seen at all time intervals and were generally dose related in both sexes. Among females, increases in platelet count seen at the 1-year time interval were significant for all doses. This observation at the 1-year time interval in females is accounted for, in part, by an unexplained somewhat lower platelet count for control animals at this time point. In males, increases were statistically significant for all doses at the 6-week interval. At all other time points, platelet count for males was numerically increased at all doses and significantly so at both higher doses. A NOEL was not established for this parameter.

	Platelet Count, % of Control @ Low, Medium and High Doses											
	6 Weeks			3 Months			6 Months			1 Year		
	L	M	H	L	M	H	L	M	H	L	M	H
Males	125*	130*	134*	133	147*	149*	123	137*	135*	120	146*	152*
Females	102	127*	128*	115	136*	142*	116	119	126	144*	150*	178*

\* Denotes statistically significant change with respect to control

Erythrocyte count was significantly depressed at the highest dose in both sexes. For females, this parameter was also significantly depressed at the mid-dose at the 3 and 6 month time points. Hematocrit was significantly reduced in high dose males and females at 3 and 6-month time points. Females in addition displayed a significant reduction in this parameter at the mid dose at 3 months. The NOEL in females for the latter two parameters was not clearly identified since at 6 months and one year both parameters were numerically reduced at the low dose, exhibiting a slight trend with those significant changes seen at the higher doses.

#### b. Clinical Chemistry

X

##### Electrolytes:

X	Calcium*
X	Chloride*
	Magnesium*
X	Phosphorous* (Phosphate)
X	Potassium*
X	Sodium*

##### Enzymes

X	Alkaline phosphatase
X	Cholinesterase#

X

##### Other:

X	Albumin*
X	Blood creatinine*
X	Blood urea nitrogen*
X	Cholesterol*
X	Globulins
X	Glucose*
X	Total Bilirubin*
X	Total Serum Protein*
	Triglycerides

X	Creatinine phosphokinase**		Serum protein electrophoresis
X	Lactic acid dehydrogenase	X	Carbon Dioxide
X	Serum alanine aminotransferase (also SGPT)*	X	A/G Ratio (calculated)
X	Serum aspartate aminotransferase (also SGOT)*		
X	Gamma glutamyl transferase (gamma glutamyl transpeptidase) Glutamate dehydrogenase		

\* Recommended for subchronic and chronic studies

# Should be recommended for OP

° Not recommended for subchronic studies

## RESULTS

Parameter most remarkably altered include the following:

**Albumin** - Significantly decreased in animals of both sexes at the high dose, and in females at the low and mid dose as well during the first six weeks; however, effects identified at the low and mid doses are considered due to variability in the control value. Hence, for both sexes LOEL = 250 mg/kg/day; NOEL = 125 mg/kg/day.

**Creatinine** - Significantly reduced in both sexes at all doses at 12 months, and in females at 6 months as well. Also creatinine was significantly reduced in females at the high and mid doses at 6 weeks and 3 months. NOEL < 62.5 mg/kg/day.

**Calcium** - Significantly reduced in females at the high dose at all time points, and in high dose males at the 6-week and 6-month time points only. Also significantly reduced in low dose females at six weeks.

**SGPT** - Significantly inhibited at all dose levels in males, and numerically so in females, at the 6-month and 1-year intervals. NOEL < 62.5 mg/kg/day.

**BUN** - Significantly reduced in males at all doses at the 6-month and 1-year time intervals. In females BUN was significantly reduced at the high dose and numerically so at both lower doses at the 1-year time interval. NOEL < 62.5 mg/kg/day.

Cholesterol and the enzymes alkaline phosphatase and LDH exhibited increased activity at various time points and dose levels, although no consistent significant differences were observed.

## Cholinesterases

The study author does not provide individual results of statistical analysis in the tables of mean values for the various enzymes at the indicated dose levels and time points analyzed (Vol.II pp. 106-111). However, it is apparent from these tabulated mean values that RBC and plasma cholinesterases were inhibited in both sexes at all dose and all time points. Mean plasma cholinesterase values appeared to reach a steady state reduction in male dogs at the lowest dose level and

earliest time point, i.e. there appeared to be no further decrease in activity with either increasing dose or time. This steady state level of activity occurs at about 70-77% of control values. In females there is more evidence of a dose-related (not time-related) trend, where levels of activity decline with increasing dose from about 78% to about 63% of base line value at 1-year.

RBC cholinesterase in both males and females was inhibited to essentially the same extent at all dose and all time points. This steady state level of activity in both sexes under the influence of the test agent was about 75% of the control activity.

Brain cholinesterase activity as measured in the cerebrum was not inhibited in either sex. As measured in the cerebellum there was in both sexes a slight numerical reduction in activity at the highest dose. However, in view of the wide standard deviation for this parameter evident not only in this particular study but in supplemental information submitted by Tegeris Laboratories<sup>1</sup>, the noted numerical reductions are considered to be of questionable meaning.

The study author indicates that "Plasma and RBC ChE were inhibited in all dose levels at all time intervals. There was no apparent dose-response relationship in the RBC enzyme. Brain ChE was not inhibited at any dose level. The NOEL for brain ChE inhibition was 250 mg/kg/day, the highest dose tested". p.54

#### Conclusion:

Plasma ChE	LOEL = 62.5 mg/kg/day (LDT)
	NOEL < "
RCB ChE	LOEL = "
	NOEL < "
Brain* ChE	NOEL = 250 mg/kg/day (HDT)

\* cerebrum and cerebellum only

Examination of cholinesterase activity in the cerebrum and cerebellum does not constitute evaluation of brain cholinesterase activity per se (i.e. in other areas and nuclei of the brain). The study as submitted contained insufficient discussion of the preparation of the brain and analyses of brain enzyme. However, the sponsor subsequently provided, upon request, the detailed procedure employed in the assay of brain cholinesterase<sup>1</sup>. Although we do not question the analytical procedure employed, Toxicology Branch does not believe examination of these portions of the brain constitutes an examination of cholinesterase activity in the whole brain. Toxicology Branch encourages further discussion of this particular aspect of cholinesterase activity evaluation.

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1 "Cholinesterase Activities In Beagle Dogs Using An Automated Enzyme Analyzer" B.J. Quinn, T.E. Shellenberger and A.S. Tegeris, 86

6. Urinalysis

Urine was collected from animals at pretest, week 6, months 3 and 6 and terminal. The CHECKED (X) parameters were examined. 006349

X	X	Appearance*	X	X	Glucose*
		Volume*		X	Ketones*
X		Specific gravity*		X	Bilirubin*
X		pH		X	Blood*
		Sediment (microscopic)*			Nitrate
X		Protein*		X	Urobilinogen

- \* Recommended for chronic studies
- ° Not recommended for subchronic studies

Results: Among parameters examined, there were no remarkable findings for either sex.

7. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue		.Aorta*	(X)X	.Brain*†
	.Salivary glands*(X)X	(X)X	.Heart*		Periph. nerve*‡
	.Esophagus*		.Bone marrow*		Spinal cord (3 levels)*‡
X	.Stomach*	X	.Lymph nodes*		.Pituitary*
X	.Duodenum*	(X)X	.Spleen*		Eyes (optic n.)*‡
	.Jejunum*	(X)X	.Thymus*		Glandular
	.Ileum*		Urogenital	(X)X	.Adrenals*
X	.Cecum*	(X)X	.Kidneys*†		Lacrimal gland‡
	.Colon*		.Urinary bladder*		Mammary gland*‡
	.Rectum*	(X)X	.Testes*†	(X)X	.Parathyroids*††)Combined
(X)X	.Liver*†		Epididymides	(X)X	.Thyroids*†† ) weight
X	Gall bladder*‡		Prostate		Other
	.Pancreas*		Seminal vesicle		Bone*‡
	Respiratory	(X)X	Ovaries*†		Skeletal muscle*‡
	.Trachea*	X	.Uterus*	X	Skin*‡
(X)X	.Lung*	X	Vagina		All gross lesions
	Nose°				and masses*
	Pharynx°				
	Larynx°				

Note: Those not marked with X may have been examined - report is not clear. See vol. II pp. 124-125 and vol. III p.7

- \* Recommended for subchronic and chronic studies
- ° Recommended for chronic inhalation
- ‡ In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
- † Organ weights recommended in subchronic and chronic studies
- †† Organ weight recommended for non-rodent studies

RESULTS

- A) Gross Pathology - Gross pathologic findings as reported in TABLE T-4.11.1 (pp. 124-126) reveal, among males of the high dose group and females of the high and mid dose groups, red or white foci of the stomach not observed in animals of the control and low dose group. Otherwise, no dose related gross pathology was identified.
- B) Organ Weight Data - Liver and kidney weights were increased in both males and females at all doses, generally in a dose-related manner, whether expressed on the basis of absolute organ weight, organ weight/body weight or organ weight/brain weight.

% of Control Values @ Low, Medium and High Doses

	<u>Organ Wt.</u>			<u>Organ Wt./Body Wt.</u>			<u>Organ Wt./Brain Wt.</u>		
	L	M	H	L	M	H	L	M	H
<u>Kidney</u>									
Male	119	125*	147*	120	123*	158*	120	132*	158*
Female	118	124*	155*	115	125*	178*	114	122*	155*
<u>Liver</u>									
Male	109	121	123	111	118	133*	111	129*	132*
Female	140*	131	141*	134*	131*	151*	135*	128	141*

\* Denotes statistically significant change with respect to control

It is noted that among females, thyroid/parathyroid combined weight, on the basis of all three modes of expression, exhibited a dose-related upward trend which, on the body weight basis, was statistically significant at the high dose. This parameter was numerically increased in males at all doses and by all three modes of expression.

*St. P. 8/24/72*

c. Microscopic pathology

1) Non-neoplastic

Examination of the study for non-neoplastic microscopic findings disclosed no adverse findings in males or females, with the exception of inflammation of the lungs in the high-dose male groups. (T-4.12.1 Vol.II pp. 127-130)

15

CONCLUSIONS

1. There was no clear histopathologic evidence of an adverse effect of the test substance. It is noted that gross pathology did disclose red or white foci of the stomach in males and females at the two higher doses, particularly evident at the highest dose. While microscopic and gross pathology did not disclose much evidence of an adverse effect of malathion, such effects were evident in organ weight data where liver and kidney weights were elevated in both sexes at all dose levels. Also, in females the combined thyroid/parathyroid weight was increased, being statistically significant at the high dose and exhibiting a dose-related trend with numerical increases at the mid and low doses. Among males this parameter was numerically increased at all dose levels.
2. Among hematologic parameters, platelet count was significantly elevated in both sexes at the mid and high doses, and questionably so at the low dose; erythrocyte count was significantly reduced at the high dose in both sexes, and was significantly reduced in females at the mid dose at two time points. Hematocrit was similarly affected except that the consistent decreases seen at the high dose in both sexes were statistically significant only at two time points. For females, decreases were seen in hematocrit at the mid dose, but was statistically significant at only one time point.
3. Clinical chemistry parameters altered include: creatinine, which was significantly reduced in both sexes at all doses at the point of termination of the study; BUN was significantly reduced in males at all doses at the 6-month and 1-year time intervals, females exhibited significantly reduced BUN at the high and mid doses at 6-months and only at the high dose at 12-months; SGPT was inhibited at all dose levels, significantly so in males at 6 and 12 months ; albumin was significantly decreased in dogs of both sexes at the high dose level; calcium was significantly reduced in females at the high dose and sporadically so in males at the high dose.
4. There were no apparent symptoms of cholinesterase inhibition. Plasma and erythrocyte cholinesterases were inhibited at all doses. The extent of inhibition was approximated 25%, i.e. these enzymes retained about 75% of control activity. Erythrocyte cholinesterase did not exhibit a dose response, while plasma cholinesterase displayed only a modest dose response. A NOEL was not identified for either of these latter two enzymes; LOEL < 62.5 mg/kg/day.

16

A unifying explanation for the observed changes in relation to administration of the test material cannot be offered at this time. There were no marked dose response relationships apparent (possibly excepting kidney weight changes) among the parameters for which significant changes were observed, cholinesterase included. Elevations in platelet count quite possibly could be explained as a cholinergic effect, since via  $\alpha$ -receptor stimulation the spleen capsule will contract, resulting in reduced platelet storage capacity. It is possible that the other observed changes were the result, directly or indirectly, of cholinesterase inhibition, and that more pronounced dose responses would have been observed had there been more substantial dose related effects on cholinesterase.

Classification: core - supplementary

The NOEL was not identified for the following parameters:

- 1) Increased liver and kidney weights
- 2) Elevated platelet count
- 3) Decreased creatinine in both sexes
- 4) Decreased BUN in males
- 5) Inhibition of SGPT in males
- 6) Inhibition of erythrocyte and plasma cholinesterases in both sexes

17