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

009295

FEB - 4 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id. No.: 053301. Fenthion. Review of a dog chronic feeding study.

TOX CHEM No.: 456F
PC No.: 053301
TOX PROJECT No.: 1-1971
Submission No.: S400714

FROM: John Doherty, PhD. 2/3/92
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: Larry Schnaubelt/Richard King
Product Manager #72
Special Review and Reregistration Division
(H7505C)

THROUGH: Marion Copley, DVM, Section Head Marion Copley 2/4/92
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

I. CONCLUSION

The dog chronic feeding study was reviewed and determined to be CORE GUIDLEINE. The study is acceptable and satisfies the requirement for an 83-1(b) chronic feeding study in a non-rodent species.

II. Action Requested/Comments

The Mobay Chemical Company has submitted a dog chronic feeding study to support the reregistratoion of fenthion, an organophosphate insecticide. The study was reviewed by EPA's contractor Clement International Incorporated. A copy of the DER is attached.

III. Toxicology Branch Comments

1. The NOEL/LEL was based on ChE and AChE inhibition. Toxicology Branch-I (TB-I) concluded that there were no systemic or toxic signs noted. The study report concluded that the high dose group male had an increase in body weight and assigned a NOLE/LEL of 10/50 for systemic effects. TB-I concluded that this apparent increase was related to one dog being larger at the start of dosing and gaining much more weight during the dosing period. The other three dogs in the high dose group had weight gains equialent to the control.

2. There were no indications of any ocular effects or of damage to the nervous system although there were nc special techniques employed.

Study Reviewed

Study	Results
83-1(b) Chronic feeding study - dogs. Mobay Corporation, Stiwell, Kansas, No.: 87-274-01, March 2, 1987. MRID No.: 416328-01 Classification: GUIDELINE. Acceptable.	NOEL/LEL (ChE/AChE) = 2/10 ppm. At 10 ppm: inhibition of plasma ChE (31-41%) and RBC AChE (15% males, 3% females). At 50 ppm: inhibition of plasma ChE (50-77%) and RBC AChE (34% males, 53% females) and brain AChE) (30%, not significant in males and 44% significant in females) at 1 year. NOEL (systemic effects) > 50 ppm. Dose levels tested 0, 2, 10 and 50 ppm equivalent to 0, 0.56, 0.258 and 1.228 mg/kg/day in males and 0.056, 0.262 and 1.182 mg/kg/day in females. Beagle dog.

DOC920062

FINAL

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DATA EVALUATION REPORT

FENTHION

Study Type: Chronic Feeding Dog Study

Prepared for:

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

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

December 2, 1991

Principal Author: John Liccione Date 1/22/92
John Liccione

Reviewer: Wayne Reichardt Date 1-22-92
Wayne Reichardt

QA/QC Manager: Sharon Segal Date 1-22-92
Sharon Segal

Contract Number: 68D10075
Work Assignment Number: 1-21
Clement Number: 91-93
Project Officer: James Scott

EPA Review by: John Doherty, Ph.D.
Review Section 4, Toxicology Branch I,
Health Effects Division

Signature:
Date: 2/5/92

Secondary EPA Review by: Marion Copley, D.V.M.
Section Head, Review Section 4,
Toxicology Branch I, Health Effects Division

Signature:
Date: 2/4/92

DATA EVALUATION REPORT

STUDY TYPE: Chronic feeding dog study

MRID Number: 416328-01

TOX CHEMICAL NO: 456F

TEST MATERIAL: Fenthion

PC NO: 053301

SYNONYMS: Baytex

STUDY NUMBER: 87-274-01

SPONSOR: Mobay Corporation, Agricultural Chemicals Division, Kansas City, Missouri

TESTING FACILITY: Mobay Corporation, Health, Environment, Safety and Plant Management, Corporate Toxicology Department, Stilwell, Kansas

TITLE OF REPORT: Chronic Feeding Toxicity Study of Fenthion Technical (BAYTEX) with Dogs

AUTHOR: W.R. Christianson

REPORT ISSUED: July 31, 1990

STUDY DATES: March 2, 1987 (initiation of study) to March 8, 1988 (termination of study).

CONCLUSIONS:

NOEL (ChE/AChe) = 2 ppm. LEL = 10 ppm. At 10 ppm: reduction of plasma ChE (31-41%) and RBC AChe (15% males and 3% females). At 50 ppm: reduction of plasma ChE (50-77%), RBC AChE (54% in males and 53% in females) and brain AChE (30% but not significant in males and 44%, $p < 0.05$ in females at 1 year).

NOEL (systemic effects) > 50 ppm.

Dose levels test 0, 2, 10 and 50 ppm corresponding to 0, 0.056, 0.258 and 1.228 mg/kg/day in males and 0.056, 0.262 and 1.182 mg/kg/day in females.

CORE CLASSIFICATION: Core Guideline. This study satisfies the Guideline Requirements (83-1) for a chronic oral toxicity study in dogs.

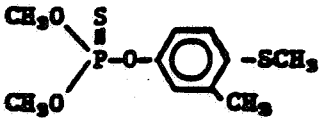
A. MATERIALS, METHODS, AND RESULTS

009295

1. Test Article Description

Name: Fenthion

Formula: O,O-Dimethyl O-[3-methyl-4-(methylthio)phenyl] phosphorothioate



Lot Number: 85R0146I

Purity: 97.1%

Physical property: Amber liquid

Stability: Indefinately in freezer (Sponsor's analysis - data not provided).

2. Test Article Analyses for Purity and Stability

Test diets were prepared by adding an appropriate amount of fenthion to dog chow (Purina Mills Canine Diet 5006-3) and mixing in a Hobart mixer. Corn oil served as a vehicle for the test substance at 1% by weight of the diet. Test diets were prepared weekly and stored frozen at approximately -23°C until used.

Stability of the test diet substance (2 and 50 ppm) in the diets stored at room temperature (22°C) was determined at 0, 1, 3, 7, 10, and 15 days after preparation. Stability of the test substance in the diets stored at freezer temperature (-23°C) was determined at 0, 1, 14, and 22 days after preparation. Homogeneity of the test substance (2 and 50 ppm) in the diet was determined prior to initiation of dosing. For homogeneity analyses, three samples from the top, middle, and bottom layers of each diet mix were obtained. The concentrations of the test substance (2, 10, and 50 ppm) in the diet were determined at weeks 1, 14, 27, 40, and 55.

Results of stability analysis indicated that the test substance, at concentrations of 2 and 50 ppm, was stable in diets stored at room temperature for 7 days or in diets frozen for 22 days. A greater than 15% decline in concentration was noted in the 50-ppm diet stored at room temperature for 10 or 15 days. Mean concentrations of fenthion in the diets at dose levels of 2, 10, and 50 ppm were 94% (cv = 7%) and 91% (cv = 9%) of target dose, respectively. Homogeneity analysis performed on the 2-ppm and 50-ppm diets yielded minimal values of 115% (cv = 4%) and 100% (cv = 3%), respectively.

3. Animals

Dogs (16 males and 16 females, beagle strain) were received from White Eagle Laboratories, Doylestown, Pennsylvania. Dogs were acclimated to laboratory conditions for at least 3 weeks and were not more than 9 months of age at initiation of dosing. Animals were housed individually in stainless steel cages within rooms with the temperature maintained at 16-29°C, a relative humidity of 45-70%, and a 12-hour light/dark cycle. Animals were identified by individual ear tatoo numbers. Water and food (Purina Mills Canine Diet 5006-3) were provided ad libitum.

Prior to initiation of treatment, four males and four females were randomly assigned to the following groups using a computer-generated randomization procedure:

Test Group	Dose in Diet (ppm)	Number of Animals (53 weeks) Males	Females
Control	0	4	4
Low-dose	2	4	4
Mid-dose	10	4	4
High-dose	50	4	4

Dose levels were selected on the basis of the results of a previous 1-year chronic oral toxicity study which was not available for review. As reported in the 1-year chronic study (Mobay Corporation, Agricultural Chemicals Division, Report Number 10853, February 6, 1963), serum and erythrocyte cholinesterase activities were inhibited by 50% and 25%, respectively, throughout the study in dogs receiving 50 ppm. At the 5-ppm dietary level, a 40% depression of serum cholinesterase activity was observed; erythrocyte cholinesterase activity was not inhibited at this level. Cholinesterase inhibition was not seen at the lowest dose tested (2 ppm).

4. Statistics

Continuous data, with the exception of organ weights, were first evaluated by Analysis of Variance (ANOVA) followed by Duncan's Multiple Range Test for parameters that showed a significant F value in the ANOVA. Organ weight data were first evaluated by ANOVA followed by a Student's t-test for parameters showing a significant overall effect in the ANOVA.

Prior to evaluation by the RxC chi-square test and/or Fisher's exact test, frequency data (mortality, pathology findings, etc.) were visually checked for trends that could indicate a compound effect. In this study, no trend was found in the nature of the frequency data that justified additional statistical analysis.

5. General Observations

(a) Mortality/morbidity/survival

There were no deaths during the study.

(b) Clinical observations

Detailed physical examinations for clinical signs of toxicity were repeatedly performed weekly.

No clinical signs attributable to treatment were observed during the study period.

(c) Body weights/food consumption/compound intake

Body weights--Individual body weights were recorded weekly.

Although the study author indicated that the mean body weight gain in high-dose males was significantly increased relative to controls, examination of individual data revealed that the apparent increase in the mean weight gain was attributable to an increase in body weight gain in one high-dose male. This male weighed 9.1 kg at the start of the study and 14.8 kg at week 13 (gain of 5.7 kg) whereas the other dogs were from 6.8 to 7.9 kg and gained from 2.4 to 3.3 kg. The 4 control dogs gained 2.4 to 3.3 kg at week 13. Also, the high dose group dogs were highest in body weight at the start of the study. Weight gain in dogs is not an expected finding for an organophosphate insecticide. Moreover, weight reduction in both sexes was noted in a rat study (Mobay Co. Study No.: 87-271-01, 12/17/90, MRID No.: 417431-01) at 100 ppm. Therefore, the reviewers' do not consider the apparent weight gain to be a response to the test material.

Food consumption--Individual food consumption was determined weekly for each dog for 54 weeks.

Food consumption in all treated animals was similar to controls.

Compound intake--The rate of daily compound intake was calculated by first determining the total amount of fenthion consumed based on weekly mean food consumption values. The total amount of fenthion consumed was divided by the mean number of days on test for each dietary group to yield the mean daily fenthion consumption rate. This daily rate was then divided by the average body weight (mean of weekly body weight means) to yield the mean daily fenthion consumption per kilogram body weight.

Compound intakes in males receiving 2, 10, or 50 ppm during the treatment period were 0.056, 0.258, and 1.228 mg/kg/day.

Compound intakes in females receiving the same doses during the treatment period were 0.056, 0.262, and 1.182 mg/kg/day.

(d) Ophthalmological examination

Ophthalmological examinations were performed prior to study initiation and prior to sacrifice. The pupil reflex, conjunctiva, cornea, and iris were initially examined prior to dilation with a mydriatic (Mydriacyl 1%). Following mydriasis, the lens, vitreous humor, and retina were examined. The examination also included retinal photographs of both eyes taken with a fundus camera.

There were no compound-related ophthalmological findings.

6. Clinical Pathology

Hematological and clinical chemical analyses were performed on all dogs prior to study initiation and at approximately 3, 6, 9, and 12 months on study. Blood was collected by venipuncture; all animals were fasted overnight prior to blood collections. Brain cholinesterase activity was measured only at the twelve month interval. The checked (X) parameters were examined:

(a) Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB concentration (MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)
X	Platelet count*		Coagulation: thromboplastin time (PT)
X	Reticulocyte count (RETIC)		
X	Red cell morphology		

* = Recommended by Subdivision F (November 1984) Guidelines

No effects of biological importance on hematology parameters were seen in dogs dosed with fenthion. A significant ($p<0.05$) increase in MCV and MCH was noted in all treated females at week 14. However, the increases in these hematology parameters occurred at pretest, did not persist over time, was detailed only in one sex, and were within the normal range of values for those parameters.

(b) Blood (clinical) chemistry

The following checked (X) parameters were examined:

Electrolytes		Other	
X	Calcium*	X	Albumin*
X	Chloride*		Albumin/globulin ratio
	Magnesium*	X	Blood creatinine*
X	Phosphorus*	X	Blood urea nitrogen*
X	Potassium*	X	Cholesterol*
X	Sodium*	X	Globulins

Enzymes

X	Alkaline phosphatase (ALP)
	Cholinesterase
X	Creatinine phosphokinase
X	Lactic acid dehydrogenase
X	Serum alanine aminotransferase (SGPT)*
X	Serum aspartate aminotransferase (SGOT)*
X	Gamma glutamyltransferase (GGT)

X	Glucose*
X	Total bilirubin*
	Direct bilirubin
X	Total protein*
X	Triglycerides
X	Plasma cholinesterase
X	Erythrocyte cholinesterase
X	Brain cholinesterase
X	Uric acid

* = Recommended by Subdivision F (November 1984) Guidelines

Table 1 summarizes data on plasma, erythrocyte, and brain cholinesterase activity. Plasma cholinesterase activities of the mid- and high-dose males and females were significantly ($p \leq 0.05$) decreased at every sampling interval. Plasma cholinesterase activity was reduced by approximately 31-41% in the mid-dose animals and by 50-77% in the high-dose animals. The inhibitory effect on cholinesterase activity was somewhat more pronounced in females. A slight and significant decrease in plasma cholinesterase activity was observed in low-dose females only at week 27. The effect on plasma cholinesterase activity was regarded by the study author to be dose related.

Erythrocyte cholinesterase activity was decreased by about 54% and 53% in high-dose males and females, respectively; the reductions were also noted at all time intervals measured. Erythrocyte cholinesterase activity was reduced by about 15% and 3% in the mid-dose males (significant at $p \leq 0.05$) and mid-dose females, respectively, at week 53. Erythrocyte cholinesterase activity was slightly increased ($p \leq 0.05$) in the low-dose males at every sampling interval; the increase in the activity of this enzyme was not considered by the study author to be of any biological significance.

Brain cholinesterase activity was decreased by approximately 30% and 44% in the high-dose males and females, respectively, at week 53, the only sampling interval this enzyme was measured. The depression in brain cholinesterase activity achieved statistical significance ($p \leq 0.05$) only in the high-dose females.

The depression in plasma, erythrocyte, and brain cholinesterase activities was regarded by the study author to be compound related.

While there were several statistically significant changes in noncholinesterase clinical chemistry parameters, there were no consistent time or dose patterns to indicate that any of the changes were of toxicological importance. Elevated uric acid levels and increases in dehydrogenase and gamma-glutamyl

TABLE 1. Representative Results of Cholinesterase Activity (±S.D.) in Dogs Fed Fenthion for 1 Year[a]

	Dose Groups (ppm)							
	Males				Females			
	0	2	10	50	0	2	10	50
Erythrocyte Cholinesterase (IU/mL)								
Pretest	2.29±0.24	2.68±0.21	2.29±0.24	2.38±0.36	2.20±0.24	2.17±0.16	2.61±0.13	2.44±0.36
14	2.23±0.27	2.81±0.23*	2.00±0.28	0.98±0.11*	2.25±0.36	2.12±0.21	2.41±0.24	1.10±0.17*
27	2.33±0.28	2.66±0.08*	2.09±0.25	1.10±0.06*	2.36±0.27	2.46±0.48	2.52±0.22	1.12±0.15*
40	2.41±0.32	2.90±0.19*	2.18±0.22	1.16±0.05*	2.46±0.41	2.47±0.12	2.68±0.36	1.18±0.13*
53	2.34±0.34	2.73±0.14*	2.00±0.18*	1.05±0.10*	2.50±0.31	2.38±0.28	2.43±0.21	1.10±0.20*
Plasma Cholinesterase (IU/mL)								
Pretest	1.21±0.17	1.24±0.20	1.34±0.25	1.60±0.15	1.39±0.08	1.40±0.24	1.42±0.27	1.44±0.25
14	1.37±0.18	1.27±0.16	0.94±0.12*	0.56±0.08*	1.55±0.12	1.53±0.21	1.03±0.12*	0.35±0.06*
27	1.29±0.16	1.25±0.15	0.84±0.15*	0.64±0.07*	1.60±0.19	1.20±0.22*	0.95±0.15*	0.62±0.12*
40	1.27±0.19	1.25±0.21	0.93±0.17*	0.61±0.07*	1.49±0.09	1.38±0.17	0.88±0.23*	0.70±0.12*
53	1.32±0.13	1.16±0.15	0.81±0.15*	0.61±0.06*	1.52±0.17	1.29±0.19	0.93±0.17*	0.57±0.11*
Brain Cholinesterase (IU/g)								
53	5.83±0.50	5.83±0.84	5.05±0.30	4.08±1.53	6.08±0.53	5.93±0.39	5.08±1.41	3.43±0.30*

[a]Data extracted from Study Report, Table CC12 and Appendix CC06.

*Significantly different from control value, $p<0.05$.

transpeptidase activities were reported for the high-dose males; however, the changes in these parameters were comparable to historical control values. Other minimal and sporadic differences in clinical chemistry parameters between treated and control groups included decreased sodium levels in low- and high-dose males at week 14, decreased creatine phosphokinase in the low-dose males at week 40, elevated creatinine phosphokinase in the low-dose males at week 40, elevated lactate dehydrogenase in the high-dose females at week 27, decreased glucose levels in the low-dose females at week 40, elevated chloride levels in the low- and high-dose females at termination, and elevated creatinine levels in the low-dose females at termination. -

(c) Urinalysis

Urinalysis was performed on all animals prior to initiation of treatment and at weeks 14, 27, 36, and 52. The CHECKED (X) parameters were examined:

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

* = Recommended by Subdivision F (November 1984) Guidelines

There were no changes of toxicological significance in urinalysis parameters.

7. Sacrifice and Pathology

All dogs were sacrificed after 1 year of treatment, and complete gross necropsies were performed. Tissues were fixed in 10% buffered formalin, except ovaries, eyes, optic nerve, lacrimal gland, testicles, and epididymis which were collected and fixed in Bouin's solution. The checked (X) tissues were collected for histological examination. The double-checked (XX) organs were weighed:

Digestive System		Cardiovascular/Hematologic		Neurologic	
	Tongue	X	Aorta*	XX	Brain
X	Salivary glands*	XX	Heart*	X	Peripheral nerve (sciatic nerve)*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (three levels)
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	XX	Spleen	X	Eyes (optic nerve)*
X	Jejunum*	X	Thymus*		
X	Ileum*				
X	Cecum*	Urogenital		Glandular	
X	Colon*				
X	Rectum	XX	Kidneys*	XX	Adrenals*
XX	Liver*	X	Urinary bladder*		
X	Gallbladder*	XX	Testes*		

11

X	Pancreas*	X	Epididymides	X	Lacrimal gland
		X	Prostate	X	Mammary gland
Respiratory			Seminal vesicle	XX	Thyroids*
		XX	Ovaries	X	Parathyroids*
X	Trachea*	X	Uterus		Harderian glands
XX	Lung*				

Other

X	Bone (sternum and femur)*
X	Skeletal muscle*
X	Skin
X	All gross lesions and masses

* = Recommended by Subdivision F (November 1984) Guidelines

(a) Macroscopic

No gross pathological lesions attributable to administration of fenthion were found. Table 2 summarizes incidental macroscopic findings noted in dogs fed fenthion for 1 year.

(b) Organ weights and body weight ratios

No statistically significant differences were noted in either absolute or relative mean organ weights in either males or females.

(c) Microscopic

Table 3 summarizes the incidence of representative histopathological lesions in dogs fed fenthion for 1 year. However, none of these lesions were attributable to administration of fenthion. The only tumor was a lipoma detected in the mesenteric adipose tissue of one low-dose male; this finding was not considered to be compound-related.

The Reviewer has no other comments regarding the materials and methods sections.

A Good Laboratory Practice Compliance Statement, a Quality Assurance Statement, and a list of Quality Assurance Inspections were included.

B. CONCLUSION

The study is classified as GUIDELINE and support the following "one liner":

NOEL (ChE/AChE) = 2 ppm. LEL = 10 ppm. At 10 ppm: reduction of plasma ChE (31-41%) and RBC AChE (15% males and 3% females). At 50 ppm: reduction of plasma ChE (50-77%), RBC AChE (54% in males and 53% in females) and brain AChE (30% but not significant in males and 44%, $p < 0.05$ in females at 1 year).

NOEL (systemic effects) > 50 ppm.

Dose levels test 0, 2, 10 and 50 ppm corresponding to 0, 0.056, 0.258 and 1.228 mg/kg/day in males and 0.056, 0.262 and 1.182 mg/kg/day in females.

The following minor deviations for the Acceptance Criteria (1989)[1] are noted but are not regarded as sufficient to downgrade the study.

- No signs of toxicity in the high dose group. Although there were no physical signs, there was significant ChE/AChE depression to indicate effects of the chemical.
- Individual animal daily observations not reported. This is not considered critical in the evaluation of this study. The summary provided is considered sufficient.
- Microscopy of the oviduct missing or not performed. This is not considered critical for evaluation of this study.

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[1]See Attachment.

TABLE 2. Representative Gross Lesions in Dogs Fed Fenthion for 1 year[a,b]

Organ/Finding	Dietary Level (ppm)							
	Males				Females			
	0	2	10	50	0	2	10	50
Brain								
Dilation	0	1	0	0	0	0	0	0
Kidney								
Discoloration	0	0	1	0	0	0	0	0
Lymph node (mesenteric)								
Discoloration	0	0	0	1	0	0	0	0
Lymph node (cervical)								
Discoloration	0	0	0	0	1	2	0	2
Spleen								
Raised zone	0	1	0	0	0	0	0	0
Discolored zone	0	0	0	0	0	1	0	0
Ovary								
Enlarged	-	-	-	-	0	1	0	0

[a]Data extracted from Table GPI-SUM of the report.
[b]Based on 4 dogs/sex.

TABLE 3. Representative Histopathologic Lesions in Dogs Fed Fenthion for 1 year[a,b]

Organ/Finding	Dietary Level (ppm) Males 0	2	10	50	Females 0	2	10	50
Adrenals								
Vacuolar degeneration	1	1	2	1	4	4	2	4
Brain								
Vacuolization	2	2	0	3	1	0	0	2
Gliosis	1	0	0	0	0	2	0	0
Eyes								
Cyst	1	1	1	3	2	1	2	2
Kidneys								
Mineralization	2	2	3	2	3	3	4	3
Larynx								
Lymphoid hyperplasia	1	1	3	0	2	2	0	1
Liver								
Vacuolar degeneration	4	2	3	4	1	3	1	4
Pituitary								
Cyst	2	0	2	1	0	0	0	0
Thyroid								
C-cell hyperplasia	2	2	0	0	0	0	1	1

[a]Data extracted from Table MPI-SUM of the report.
[b]Based on 4 dogs/sex.

009295

Fenthion
HOBAY # 87-274-01
MRID # 416328-01

83-1 Chronic Feeding in the Rodent and Nonrodent

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 20 rodents or 4 nonrodents/sex/group (3 test groups and control group).
3. ✓ Dosing duration in rodents minimum 12 month nonfood use, 24 months food use; in nonrodents minimum 12 months[3].
4. NO Doses tested include signs of toxicity at high dose but no lethality in nonrodents or a limit dose if nontoxic (1,000 mg/kg).
5. • ✓ Doses tested include a NOEL.
6. • ✓ Analysis for test material stability, homogeneity and concentration in dosing medium
7. NO Individual daily observations.
8. ✓ Individual body weights.
9. ✓ Individual or cage food consumption.
10. • ✓ Opthalmoscopic examination (at least pertest and at term) control and high dose.
11. ✓ Clinical pathology data for all nonrodents and at least 10 rodents/group consisting of 12, 13 & 14.
13. ✓ Hematology at 6 month intervals consisting of at least;
    - ✓ Erythrocyte count
    - ✓ Hemoglobin
    - ✓ Hematocrit
    - ✓ Leucocyte count
    - • ✓ Differential count
    - ✓ Platelet count (or clotting measure)
14. ✓ Clinical chemistry at 6 month intervals consisting of at least;
    - ✓ Alkaline phosphatase
    - ✓ Aspartate aminotransferase
    - • ✓ Creatinine kinase
    - ✓ Lactic dehydrogenase
    - ✓ Glucose
    - ✓ Bilirubin
    - ✓ Cholesterol
    - • ✓ Creatinine
    - ✓ Total Protein
    - ✓ Albumin
    - ✓ Urea
    - ✓ Inorganic phosphate
    - ✓ Calcium
    - • ✓ Potassium
    - ✓ Sodium
    - • ✓ Chloride
15. ✓ Urinalysis at 6 month intervals consisting of at least;
    - ✓ Blood
    - ✓ Protein
    - ✓ Ketone bodies
    - ✓ Appearance
    - ✓ Glucose
    - ✓ Total bilirubin
    - • ✓ Urobilirubin
    - ✓ Sediment
    - ✓ Specific gravity (osmolality)
    - • ___ Volume
16. ✓ Individual necropsy of all animals.
17. ✓ Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

Criteria marked with a • are supplemental and may not be required for every study.

[redacted]

eyes	bone marrow	kidneys†
caecum	liver†	esophagus
colon	lung†	ovaries†
duodenum	lymph nodes	oviduct
brain†	stomach	pancreas
skin	mammary gland	rectum
heart†	spleen†	spinal cord (3x)
testes†	musculature	thyroid / parathyroids
pituitary	epididymis	salivary glands
ileum	adrenals†	thymus
trachea	uterus	urinary bladder

† organs to be weighed

[redacted]

Criteria marked with a * are supplemental and may not be required for every study.