10-25-85

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

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OCT 25 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of a pilot and 1-year dog feeding studies with Thiobencarb (Bolero)
EPA No. 239-2431 Caswell No. 207 DA

TO: Richard Mountford, PM #23
Registration Division (TS-767C)

FROM: Quang Q. Bui, Ph.D. Quang Q. Bui 10/22/85
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Laurence D. Chitlik, D.A.B.T. W. Testers for L. Chitlik 10-23-85
Section Head, Section V
Toxicology Branch/HED (TS-769C)

and

Theodore M. Farber, Ph.D. WMB 10.23.85
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant: Chevron Chemical Company
940 Hensley Street
Richmond, CA. 94804

Action Requested:

Review of a four-week pilot oral toxicity study in dogs (IRDC #415-041) and a one-year subchronic oral toxicity study in dogs (IRDC #415-042) with Technical Thiobencarb (Bolero).

RECOMMENDATION

It is recommended that the pilot oral toxicity study in dogs (IRDC #415-041) be classified as Core Supplementary Data (dose-range finding study). The pilot study is considered as adequate for the selection of dosage levels used in the main study.

The one-year subchronic oral toxicity study in dogs (IRDC #415-042) is presently classified as Core Supplementary Data pending the submission of additional data and clarification by the registrant (see page 6 of this memo).

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STUDY REVIEW

CHEMICAL:	Thiobencarb - Bolero
TEST MATERIAL:	Technical Thiobencarb
STUDY/ACTION TYPE:	Sub-chronic feeding in dogs
STUDY IDENTIFICATION:	"Four-week pilot oral toxicity study in dogs"
Testing Facility:	International Research and Development Corporation Mattawan, Michigan
Final Report No.:	415-041
Final Report Date:	2/17/84
Study Director:	D.E. Johnson
Accession No.:	257362
Reviewed by:	Quang Q. Bui, Ph.D. Section V, Toxicology Branch Hazard Evaluation Division (TS-769C)
Approved by:	Laurence D. Chitlik, D.A.B.T. Section Head, Section V Toxicology Branch/HED (TS-769C)

CONCLUSIONS AND RECOMMENDATION

Under the conditions of this study, oral feeding of Thiobencarb Technical by capsules for 4 weeks in dogs resulted in body weight reductions noted in both males and females of the 64 mg/kg dosage level. Compound-related effects were not apparent in the treated groups relative to ophthalmologic examinations, hematology and clinical chemistry determinations, urinalysis, macroscopic and histopathologic examinations, and organ weights. Compound-related decreases in plasma and RBC cholinesterase levels were observed in the treated males at all dosage levels tested. The plasma cholinesterase levels were also decreased in females treated with 4, 16, or 64 mg/kg. Compound-induced inhibition of brain cholinesterase levels was apparent only in treated females. However, the biological significance of this cholinesterase inhibition is not known with certainty due to the small number of animals used per dosage level.

It is recommended that this pilot dog study be classified as Core Supplementary Data (dose range-finding study).

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MATERIALS AND METHODS

Test Material: Technical Thiobencarb, Lot SX 1381 (unknown purity)
Dosage Levels: 0, 1, 4, 16, and 64 mg/kg/day for 4 weeks
Route of Administration: Daily by capsules
Species tested: Purebred beagle dogs (Ridglan Farms, Wisconsin)
No. animals: 2 per sex per group

PROCEDURES

A copy of the procedures employed in this pilot study is appended. The following comments are noted:

1. The purity of Thiobencarb Technical is unknown.
2. Dosage calculations were not provided with this submission.

RESULTS

1. Body weight (in kg)

The body weight data of all animals are summarized as follows:

	Pre-test	After 4 weeks	Weight gain	% of control[a]
MALES (2 animals/dose)				
Control	9.1	10.6	1.5	
1 mg/kg/day	8.8	10.7	1.9	+ 26%
4 mg/kg/day	9.5	11.4	1.9	+ 26%
16 mg/kg/day	8.7	10.4	1.7	+ 13%
64 mg/kg/day	9.2	9.8	0.6	- 60%
FEMALES (2 animals/dose)				
Control	7.1	8.4	1.3	
1 mg/kg/day	7.8	8.7	1.1	- 15%
4 mg/kg/day	7.8	9.3	1.5	+ 15%
16 mg/kg/day	7.9	8.5	0.6	- 54%
64 mg/kg/day	8.1	9.1	1.0	- 23%

(a) Calculated by this reviewer

In the males, decreases in weight gain were observed only at the 64 mg/kg dosage level. However, all treated females had lower weight gains than controls, except for animals in the 4 mg/kg/day group.

2. Food Consumption

Decreases in food consumption were noted in both treated males and females of all dosage levels except for males in the 16 mg/kg group, which had increased food consumption as compared to controls.

The average food consumption for all groups is presented in the next table:

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Average Food Consumption (grams/animal/day)

Dosage levels	Males	Females
Control	304	327
1 mg/kg	273 (-10.2)[a]	227 (-30.6)
4 mg/kg	296 (- 2.6)	270 (-17.4)
16 mg/kg	372 (+22.4)	255 (-22.0)
64 mg/kg	219 (-28.0)	247 (-24.5)

(a) % difference from control values

3. Clinical Observations and Mortality

Compound-related clinical observations were not apparent in any treated group. No deaths occurred throughout the entire investigation.

4. Hematology

Hematologic determinations were performed at study initiation and termination. Significant differences were not observed in any of the 13 parameters measured. However, slight decreases in platelets were noted in all treated males at study termination. The platelet counts (in $10^3/mm^3$) for males of the 0, 1, 4, 16, and 64 mg/kg groups were, respectively, 410, 283, 322, 332, and 372. The biological significant of this finding remains unclear since consistent decreases in platelets were not observed in treated females.

5. Clinical Chemistry

Twenty different clinical chemistry parameters were determined in this study. Compound-related effects were not evident in either treated males or females.

6. Cholinesterase

Plasma and RBC cholinesterase levels were determined in all groups at study initiation and weekly thereafter. Brain cholinesterase levels were investigated at final sacrifice.

In the treated males, inhibition of plasma and red blood cell cholinesterase activity was noted at all dosage levels. However, no compound-related effects were noted in brain cholinesterase activity.

In the treated females, dose-related decreases in plasma cholinesterase activity were noted in the 4, 16, and 64 mg/kg groups. Inhibition of RBC cholinesterase activity was not evident from the data submitted. The brain cholinesterase activity of all dose levels was lower than control, but in the absence of a dose-response relationship, the biological significance of this decrease remains uncertain.

SUMMARY OF CHOLINESTERASE ACTIVITY VALUES AT STUDY TERMINATION †

	Control	1 mg/kg	4 mg/kg	16 mg/kg	64 mg/kg
MALES					
Plasma ChE °	3.5	2.8(-20)[a]	3.3(-6)	1.2(-66)	1.4(-60)
Plasma ChE °°	6.2	4.8(-22)	5.6(-10)	2.0(-68)	1.7(-73)
RBC ChE °	3.4	2.3(-32)	2.6(-24)	2.9(-15)	1.9(-44)
Brain ChE °	2.0	2.3(+15)	2.4(+20)	2.0	1.9(-5)
FEMALES					
Plasms ChE °	3.0	3.0	2.5(-17)	1.6(-47)	1.3(-57)
Plasma ChE °°	5.1	5.0(-2)	4.3(-16)	2.7(-47)	1.7(-67)
RBC ChE °	1.8	1.8	1.7(-6)	2.0(+11)	2.1(+17)
Brain ChE °	2.8	2.1(-25)	2.4(-14)	2.4(-14)	2.7(-4)

(†) Since only 2 animals per sex per dose were used in this pilot study, statistical analysis of the data could not be performed
(a) Mean of 2 animals expressed as uM/ml/min (% inhibition of control values)
(°) Acetyl-Thiocholine as substrate
(°°) Butyryl-thiocholine as substrate

7. Gross observations, histopathologic findings, and urinalysis

Compound-related effects were not apparent from the data submitted.

DISCUSSION

Under the conditions of this study, plasma cholinesterase activity was depressed in males at all dosage levels tested and in females at 4 mg/kg and above. Apparent compound-induced RBC cholinesterase inhibition was noted in treated males but not in females. The brain cholinesterase levels determined at study termination for treated females were suggestive of a compound-related effect. No compound-related effects were evident from the gross and histopathologic examinations, urinalysis, organ weights, hematology and clinical chemistry determinations, and ophthalmologic examinations. Decreased body weight gains were noted in males at the 64 mg/kg dosage level and in females at the 16 and 64 mg/kg dosage levels. Food consumption was decreased in all treated females. However, the small number of animals per group (2/sex/dose) precluded meaningful statistical analysis and assessment of the data submitted.

It is recommended that this dose-range finding study be classified as Core Supplementary Data.

Thiobencarb toxicology review

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The material not included contains the following type of information:

___ Identity of product inert ingredients

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___ Description of the product manufacturing process

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___ Sales or other commercial/financial information

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STUDY REVIEW

CHEMICAL: Thiobencarb - Bolero
TEST MATERIAL: Technical Bolero
STUDY/ACTION TYPE: One year feeding in dogs
STUDY IDENTIFICATION:
" One Year Subchronic Oral Toxicity Study with Thiobencarb Technical in Dogs "

Testing Facility: International Research & Development Corporation
Mattawan, Michigan
Final Report No.: 415-042
Final Report Date: 3/20/85
Study Directors: D.E. Johnson et al.
EPA Accession No.: 257362

Study Reviewed by: Quang Q. Bui, Ph.D.
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Approved by: Laurence D. Chitlik, D.A.B.T.
Section Head, Section V
Toxicology Branch/HED (TS-769C)

CONCLUSIONS AND RECOMMENDATION

Oral administration of Technical Thiobencarb in dogs for one year resulted in significant inhibition of plasma cholinesterase levels in both males and females treated with 8 or 64 mg/kg/day. The decreases in plasma cholinesterase activity were observed in the treated animals at one week after exposure and persisted throughout the entire investigation. Compound-related inhibition of red blood cell cholinesterase was apparent at the 64 mg/kg dosage level. However, no compound-related effects were noted in the brain cholinesterase activity of either treated males or females at any dosage level tested. The plasma cholinesterase NOEL is determined to be 1 mg/kg/day (lowest dose tested).

Signs of systemic toxicity were evidenced by significant decreases in serum protein and albumin found in animals treated with 8 or 64 mg/kg/day. Both males and females in the highest dose group also had significant increases in platelet counts and significant decreases in erythrocyte counts, hemoglobin levels, and hematocrit values. Apparent trend increases in cholesterol values were noted in the treated groups, with statistical significance observed in males at the 64 mg/kg dosage level. The biological significance of this increase at the lowest level could not be ascertained at the present time due to the absence of historical control values for cholesterol (see "Discussion" section).

This is a well conducted one-year subchronic study with adequate investigation of hematology, clinical chemistry, cholinesterase, organ weights, and histopathology parameters. All the supporting data submitted were verified by this reviewer with no major discrepancies found. However, a core classification of Supplementary Data must be assigned to this study since (1) the purity of the test material was not mentioned, (2) in the absence of dosage preparation data, it is unclear as to whether the dose levels used in this study represent the technical material or have been corrected to 100% purity, (3) an apparent error was noted in the alanine aminotransferase of control female #4688 at week 25: A value of 355 IU/L was reported for this animal and resulted in a mean value of 81 $\pm$ S.D. of 134.3 for the control group at week 25, and (4) historical control values for cholesterol are requested to adequately assess the sytemic NOEL. It should be noted that this study may potentially be upgraded depending upon the adequacy of additional information and/or clarification provided by the registrant.

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MATERIALS AND METHODS

Test Material:	Thiobencarb Technical - SX 1381 clear liquid of unknown purity
Test Animals:	Beagle dogs (Ridglan Farms, WI)
Dosage levels:	0, 1, 8, and 64 mg/kg/day by capsule
Number of animals:	6/sex/dose

PROCEDURES:

A copy of the procedures used is appended. The following comments are noted:

The purity of the test material was not indicated. Therefore, it is unclear as to whether the dosage levels stated in the final report represent the technical material or have been corrected to 100% purity. This uncertainty was further deepened by the lack of dosage preparation data.

RESULTS

1. Mortality

One male (#4648) of the high dose group (64 mg/kg) died on day 48. Necropsy data indicated consolidation of the cardiac lobe of the lung and a liver tumor. Microscopic examination revealed multifocal broncho-pneumonia and acute pleuritis. A replacement animal (#4199) from the same supplier was started on study on day 64. All hematology, chemistry, food consumption, and body weight data for this replacement animal were not included in the data analysis for the high dose male group. However, data from this animal were available in the supporting data for review.

2. Clinical Observations

The investigators indicated that male animal #4657 of the 64 mg/kg dosage level had an apparent vestibular or cerebellar dysfunction during week 25 as characterized by tilted head, strabismus, and stiffened neck. Improvement was noted and the animal apparently was normal during the subsequent weeks. The biological significance of this finding remains uncertain. Soft stool diarrhea was noted at a similar frequency in both male and female control and treated dogs.

3. Body Weights

As illustrated in the next table, the body weight gains of the treated animals were not significantly different from those of the controls. Although an apparent dose-related decrease in body weight gain was found in the treated males, comparable findings were not observed in the treated females. The body weight gains of the treated males expressed as percentages of control values are, respectively, -8, -10, and -17 for the 1, 8, and 64 mg/kg groups. The body weight gains of the treated females are +38, -9, and 0% of control gain values for the 1, 8, and 64 mg/kg groups, respectively.

Body Weight Data in kg (†)

	Study Initiation	Study Termination	BW. Gained	%(a)
MALES				
Control	7.9	13.1	5.2	
1 mg/kg	8.3	13.1	4.8	-8
8 mg/kg	8.3	13.0	4.7	-10
64 mg/kg	7.7	12.0	4.3	-17
FEMALES				
Control	6.8	10.2	3.4	
1 mg/kg	6.9	11.6	4.7	+38
8 mg/kg	6.7	9.8	3.1	- 9
64 mg/kg	6.5	9.9	3.4	0

(†) Calculated by this reviewer
(a) Expressed as percentages of control body weight gain

4. Food Consumption

Decreases in food consumption were noted in the 64 mg/kg group only during the first 6 weeks of the study. Isolated incidences of statistically significant differences in food consumption were observed in the treated groups. However, in the absence of persistent effects throughout the entire investigation, a dose-response relationship, and consistent findings between treated males and females, these findings are considered by this reviewer as of questionable biological significance.

5. Ophthalmologic Observations

Evidence of compound-induced effects were not apparent from the data submitted.

6. Hematology

Hematologic determinations were performed on all animals prior to study initiation, and at weeks 4, 8, 13, 25, 38, and 51. Twenty four hematologic parameters were investigated or calculated from each sample. Only findings of interest are discussed in this action.

In the males, significant decreases in erythrocyte count and hemoglobin concentration were found in the 64 mg/kg group at weeks 13 and 38 but not at study termination. Significantly higher platelet counts were noted occasionally in the high dose males. The hematocrit in all treated males was lower than control values with significant differences found at weeks 13 and 38 for the 64 mg/kg group and at week 38 for the 1 mg/kg group.

In the females, slight decreases in hematocrit values were also noted occasionally in treated animals. The platelet counts were significantly increased in females of the 8 and 64 mg/kg groups at weeks 8, 13, and 25. Although these values were still higher than controls at study termination, statistical significance of the differences was not attained. It is interesting to note that high dose females also had significant decreases in erythrocytes and hemoglobin concentration at several intervals during the investigation. However, at study termination, no significant differences were noted between the treated and control animals.

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SUMMARY OF HEMATOLOGIC DETERMINATIONS

	Control		1 mg/kg		8 mg/kg		64 mg/kg	
	M	F	M	F	M	F	M	F
Erythrocytes (10^6/cm^3)								
Week 13	6.3	6.2	6.0	6.2	5.9	6.0	5.4*	5.7*
Week 38	6.6	6.0	5.9	6.2	6.2	6.1	5.8*	5.8
Week 51	6.8	6.0	5.9*	5.5	6.4	6.1	6.1	6.2
Hemglobin (g/dl)								
Week 13	16.2	16.3	15.7	16.2	14.9	15.8	14.0*	14.6*
Week 38	17.4	15.9	15.6*	16.5	15.9	16.2	15.2*	14.9
Week 51	18.2	15.8	16.0	14.8	17.1	16.6	16.1	16.0
Hematocrit (%)								
Week 13	44.4	44.1	42.7	44.0	40.9	42.4	37.1*	38.9*
Week 38	49.1	45.2	44.1*	46.4	45.5	45.5	42.9*	42.7
Week 51	51.7	45.7	45.4	42.6	48.5	46.6	46.3	46.1
Platelets (10^3/cm^3)								
Week 13	263	282	322	303	293	348*	360	369*
Week 25	281	334	330	350	286	407*	412*	394*
Week 51	656	653	658	623	609	752	717	738

(*) Significantly different from controls, $P < 0.05$

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7. Clinical Chemistry

Biochemical determinations were run concurrently with hematology at the same interval periods.

In the males, significant increases in alkaline phosphatase as well as significant decreases in serum protein, albumin, and alanine aminotransferase were found in the 64 mg/kg dose group throughout the investigation and at study termination. At the 8 mg/kg dosage level, significant decreases in serum protein and albumin were also found at study termination.

Significant decreases in serum total protein and albumin were also noted in treated females of the highest dose group (64 mg/kg) throughout the investigation and at study termination. These findings collectively suggest that the decreases in serum protein and albumin observed in both males and females were compound-related.

SUMMARY OF CLINICAL CHEMISTRY DATA

	Control		1 mg/kg		8 mg/kg		64 mg/kg	
	M	F	M	F	M	F	M	F
Alkaline Phosphatase (IU/L)								
Week 25	28	34	33	35	31	34	51*	34
Week 38	25	30	34	31	29	33	43*	36
Week 51	22	33	27	28	27	28	37*	30
Alanine Aminotransferase (IU/L)								
Week 25	30	81(†)	31	26	27	24	18*	22
Week 38	29	24	45	28	24*	23	18*	19
Week 51	30	25	31	26	28	22	18*	20
Total Protein (g/dl)								
Week 25	5.4	5.0	5.3	5.2	4.9*	5.1	4.9*	4.6*
Week 38	5.5	5.0	5.4	5.4	5.4	5.3	5.1	4.9
Week 51	6.0	5.7	5.7	5.7	5.5*	5.6	5.3*	5.2
Albumin (g/dl)								
Week 25	3.3	3.3	3.3	3.3	3.1	3.3	3.1*	3.1
Week 38	3.5	3.4	3.3	3.4	3.2*	3.4	3.2*	3.2
Week 51	3.5	3.4	3.3	3.4	3.2*	3.3	3.0*	3.0*

(*) Significantly different from controls, $P < 0.05$

(†) A value of 355 IU/L was found for animal # 4688 at week 25 and apparently is a typographical error, which results in a mean of 81 for this group.

An apparent trend increase in cholesterol levels was noted in the treated groups as depicted in the next table:

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CHOLESTEROL LEVELS (mg/dl)

	Control	1 mg/kg	8 mg/kg	64 mg/kg
MALES				
Week 25	143 ± 15.4	164 ± 20.2 (+12.8%)[a]	165 ± 27.3 (+15.4%)	192* ± 27.8 (+25.5%)
Week 38	141 ± 14.5	169 ± 33.9 (+16.6%)	174 ± 27.5 (+23.4%)	201* ± 30.8 (+42.5%)
Week 51	157 ± 26.2	191 ± 43.7 (+21.6%)	190 ± 30.7 (+21.0%)	227* ± 41.7 (+44.6%)
FEMALES				
Week 25	151 ± 28.3	202 ± 85.7 (+33.8%)	207 ± 89.1 (+37.1%)	207 ± 47.3 (+37.1%)
Week 38	157 ± 46.0	172 ± 24.4 (+9.6%)	164 ± 35.3 (+4.4%)	226* ± 41.7 (+43.9%)
Week 51	173 ± 30.5	232 ± 63.1 (+34.1%)	243 ± 113.1 (+40.5%)	281 ± 77.4 (+62.4%)

All values are expressed as Mean ± S.D.
(*) Significantly different from controls, $P < 0.05$
(a) Percentage of controls, calculated by this reviewer

Evident from the above table are both compound- and dose-related increases in cholesterol levels in both treated males and females. However, consistent statistically significant differences were noted only in males of the 64 mg/kg group. The lack of statistical significance in other dose groups apparently was due to marked variations among the small number of samples (6 animals per group). The biological significance of this finding is discussed in the "Discussion" section.

8. Cholinesterase Determinations

Plasma and RBC cholinesterase determinations were performed at several intervals during the study using both acetyl-thiocholine and butyryl-thiocholine as substrates. Brain cholinesterase levels were measured in all animals at study termination.

The following tables summarize the findings:

PLASMA CHOLINESTERASE (uM/ml/min); Acetyl-Thiocholine as substrate

	Control		1 mg/kg		8 mg/kg		64 mg/kg	
	M	F	M	F	M	F	M	F
Week 0	3.3	2.9	(-3)[a]	(+3)	(- 3)	(+ 7)	(- 9)	(- 9)
Week 4	2.8	2.7	(0)	(0)	(-32)*	(-30)	(-71)*	(-67)*
Week 8	3.2	3.2	(-3)	(-3)	(-34)*	(-28)	(-56)*	(-53)*
Week 13	3.4	3.0	(-6)	(+3)	(-35)*	(-23)	(-62)*	(-60)*
Week 25	3.1	2.7	(-13)	(+4)	(-42)*	(-22)	(-61)*	(-48)*
Week 51	3.1	3.0	(-10)	(-7)	(-42)*	(-33)*	(-61)*	(-57)*

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PLASMA CHOLINESTERASE (uM/ml/min); Butyryl-Thiocholine as substrate

	Control		1 mg/kg (a)		8 mg/kg (a)		64 mg/kg (a)	
	M	F	M	F	M	F	M	F
Week 0	6.4	6.1	(- 2)	(+ 3)	(+ 5)	(+ 7)	(- 9)	(+ 5)
Week 4	5.6	5.5	(- 4)	(- 4)	(-40)*	(-38)*	(-86)*	(-82)*
Week 8	6.4	6.3	(- 2)	(- 2)	(-38)*	(-32)	(-77)*	(-65)*
Week 13	6.5	5.9	(- 3)	(0)	(-36)*	(-31)	(-78)*	(-73)*
Week 25	6.3	5.6	(-11)	(+ 4)	(-43)*	(-25)	(-71)*	(-63)*
Week 51	6.1	6.0	(-11)	(- 2)	(-48)*	(-35)	(-77)*	(-70)*

RED BLOOD CELL CHOLINESTERASE (uM/ml/min); Acetyl-Thiocholine as substrate

Week 25	2.9	2.9	(+ 3)	(+ 3)	(0)	(+ 7)	(-20)	(-10)
Week 51	2.8	2.8	(- 4)	(-11)	(- 4)	(- 4)	(-21)	(-18)

BRAIN CHOLINESTERASE (uM/ml/min); Acetyl-Thiocholine as substrate

Week 51	2.1	2.0	(- 5)	(0)	(- 5)	(+ 5)	(- 5)	(+ 5)

(*) Significantly different from controls, $P < 0.01$
(a) Expressed as percentage inhibition of control values

Using both butyryl-thiocholine and acetyl-thiocholine as substrates, the plasma cholinesterase levels were biologically depressed (greater than 20% inhibition) in males and females of the 8 and 64 mg/kg groups throughout the entire investigation. Decreases in RBC cholinesterase levels were found in both 64 mg/kg males and females. However, no changes in brain cholinesterase activities were noted in either males or females at study termination.

9. Urinalysis

No compound-related effects were evident from the data submitted.

10. Organ Weights

Although statistical significance was not found for any changes in absolute organ weights, trend increases in kidney and liver were evident from the data submitted. The increases in absolute kidney and liver weights were associated with significant increases in relative liver and kidney weights at the 64 mg/kg dosage level. In the treated males, the decrease in terminal body weight as compared to controls may have contributed to this increase in relative weights. However, since the 64 mg/kg female body weights were comparable to those of the controls, the effect noted for this sex may well be a compound-related effect.

Although the mean relative and absolute testis weights of the treated groups were not significantly different from controls, all treated males apparently had lower testis weights. The biological significance of this observation remains uncertain.

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ORGAN WEIGHT DATA (grams)

	Control		1 mg/kg		8 mg/kg		64 mg/kg		
	Abs	Rel	Abs	Rel	Abs	Rel	Abs	Rel	(¶)
Males, left kidney	25.4	2.01	23.9	1.88	26.2	2.11	28.6	2.51*	
right kidney	25.3	2.01	23.5	1.85	25.3	2.03	29.1	2.55*	
Females, left kidney	20.6	2.08	21.4	1.90	22.3	2.35	24.2	2.54*	
right kidney	20.1	2.02	21.3	1.88	21.3	2.25	24.3	2.57*	
Males, liver	309	2.46	320	2.54	311	2.47	331	2.86	
Females, liver	240	2.44	284	2.54	270	2.82	297	3.10*	
Males, left testis	9.2	7.20[a]	8.9	6.94	8.3	6.62	8.3	7.25	
right testis	9.6	7.48	8.7	6.82	8.6	6.88	8.1	7.04	

(¶) Abs = absolute weight; Rel = relative weight (organ/body weight)
(a) Relative weight expressed as % x 10^2
(*) Significantly different from controls, $P < 0.05$

11. Gross Observations

Gross observations performed at final sacrifice did not suggest any evidence of a compound-induced effect.

12. Histopathology

Findings of interest are summarized in the next table:

SUMMARY OF HISTOPATHOLOGIC FINDINGS (a)

	Control		1 mg/kg		8 mg/kg		64 mg/kg	
	M	F	M	F	M	F	M	F
Kidney, chronic inflammation	1	0	0	1	0	0	3	1
Lung, interstitial pneumonia	0	0	4	1	0	0	1	2
Pituitary craniopharyngeal cyst	0	0	1	1	2	2	2	2

(a) Six animals per sex per dose

Chronic inflammation of the kidney cortex (unilateral, mild, focal) was found in one control and 3 high-dose males and in 1 female each in the 1 and 64 mg/kg group. Apparently, chronic inflammation of the kidneys partly contributed to the increased absolute weights mentioned earlier, at least in the males. Craniopharyngeal cyst of the pituitary was found only in the treated groups, affecting 1, 2, and 2 males and females each in the 1, 8, and 64 mg/kg groups, respectively. These pituitary cysts were described as trace (1 male, 4 females), mild (2 males, 1 female)

and moderate (1 male). The severity of the pituitary craniopharyngeal cysts was not dose-related. Although no pituitary craniopharyngeal cyst was found in the control, its presence in the treated groups is unlikely to be compound-related due its common occurrence in dogs.
(In consultation with Louis Kasza, D.V.M., Ph.D., Tox. Branch Pathologist) L. K.

DISCUSSION

Administration of Technical Bolero at 64 mg/kg/day by capsule for one year did not result in increased mortality or observational signs of toxic effect. Decreased weight gain was found in treated males (-17% of control values) of the 64 mg/kg dosage level but not in treated females. The food consumption data measured throughout the entire investigation did not reveal any evidence of a compound-related effect. The mean relative kidney and liver weights in both males and females of the 64 mg/kg dosage level were significantly increased as compared to controls. Positive trend increases in absolute liver and kidney weights were also noted in both males and females. The increases in relative liver and kidney weights, at least in females, apparently were compound-related. Cortical inflammation of the kidneys was noted in 1, 0, 0, and 3 males and in 0, 1, 0, 1 females in the groups receiving 0, 1, 8, and 64 mg/kg, respectively. The presence of kidney inflammation in 3 high-dose males may have contributed, in part, to the increase in absolute kidney weights observed in this group. Craniopharyngeal cyst of the pituitary was noted only in the treated groups, being present in 1, 2, and 2 males, and 1, 2, and 2 females in the 1, 8, and 64 mg/kg groups, respectively. In the absence of a dose related increase in severity coupled with the fact that they are a common finding in dogs, the pituitary cysts were considered as sporadic findings in the treated animals.

Decreased erythrocyte counts and hemoglobin levels associated with a reduction in hematocrit were noted in both males and females of the highest dose group (64 mg/kg/day). Increases in platelet counts were found in both males and females at this dosage level. Significant decreases in alanine aminotransferase levels were found for animals in the 64 mg/kg group. Compound-related effects were evidenced by significant decreases in serum total protein and albumin levels in both males and females of the 8 and 64 mg/kg groups. Apparent trend increases in cholesterol values were found in the treated groups. However, statistically significant differences were noted only in the 64 mg/kg males. The lack of statistical differrences for cholesterol levels at other doses may be attributed to the large variations found and the small number of animals per group (6 per sex/dose). It is well known that cholesterol is synthesized mainly in the liver. However, the use of cholesterol as an index of liver function and toxicity is handicapped by the technical difficulties of the test itself and the considerable variation in measurement. Therefore, it is difficult to know if the increase observed in this study is genuine or not in the absence of historical data for this measurement collected from the testing facility. It is recommended that the historical control data (and range) of cholesterol values from the testing facility be submitted for consideration in establishing a systemic NOEL for Bolero.

Plasma cholinesterase activities were determined using two substrates: acetyl-thiocholine and butyryl-thiocholine. The plasma cholinesterase activities were depressed ($P < 0.01$) in both males and females in the 64 mg/kg group for both substrates. Male dogs apparently were more affected than females as demonstrated by significant decreases in plasma cholinesterase activities ($P < 0.01$) at the 8 mg/kg dosage level. Plasma cholinesterase activities were also depressed in the

8 mg/kg females (inhibition greater than 20% of controls) although significant differences ($P < 0.01$) were noted only after 51 weeks of exposure. Inhibition of plasma cholinesterase occurred in the 8 and 64 mg/kg males and 64 mg/kg females at 1 week after exposure and persisted throughout the entire investigation. The decreases in plasma cholinesterase observed in the 1 mg/kg group did not attain biological significance (not more than 13% inhibition at any interval). Inhibition of RBC cholinesterase activity was apparent only in animals treated with 64 mg/kg. No statistically and/or biologically significant differences in brain cholinesterase activity were noted between the treated and control groups.

Under the conditions of this study, the plasma cholinesterase NOEL is determined to be 1 mg/kg/day (lowest dose tested). A systemic NOEL cannot be established at the present time pending the submission of historical control data for cholesterol.

This is a well conducted one-year dog study with adequate investigation of all necessary parameters. However, it is recommended that this study be classified as Core Supplementary Data pending the submission of additional information and/or clarification as listed on page 6 of this memo. It should be noted that this study may potentially be upgraded depending upon the adequacy of additional data provided by the registrant.

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