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

005943

JUN 16 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Additional Information on One-Year Dog Study with Acetochlor.
EPA ID Nos. 352966 and 524-GUI, EPA Accession No. 260001
EPA Record Nos. 185605 and 185607 Caswell No. 38,
Tox. Branch Project No. 7-0377

TO: Robert Taylor/Vickie Walters (PM-25)
Herbicide - Fungicide Branch
Registration Division (TS-767C)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 6/15/87
Pharmacologist, Review Section V
Toxicology Branch/HED (TS-769C)

THRU: Quang Q. Bui, Ph.D., D.A.B.T Quang Q Bui 6/16/87
Acting Section Head, Review Section V
and
Theodore M. Farber, Ph.D., D.A.B.T.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Chemical: Acetochlor (MON-097)

Registrant: Monsanto Company
1101 17th Street, N.W.
Washington, D.C. 20036

Action Requested: Review additional data submitted for "A One-Year Feeding Study in Dogs with MON 097"

Recommendations:

The one-year feeding study in dogs is upgraded from Core-Supplementary Data to Core-Minimum Data.

Under conditions of this study, the No Observed Effect Level (NOEL) for systemic effects is 12 mg/kg/day. The Lowest Observed Effect Level (LOEL) for systemic effects is 40 mg/kg/day based on decreased body weight gains in males, decreased terminal body weights in females, testicular atropy with accompanying decreases in absolute and relative testicular weights, increases in absolute and relative adrenal weights in females, increases in relative liver weights in males and females, and increases in SGOT and SGPT levels.

Discussion:

The DER for "A one-year feeding study in dogs with MON 097 (Study No. PR-80-008, PRL # 8006)" generated by Dynamac for the Agency presented the following conclusions and recommendations:

> "Based on the the data presented, there are obvious effects at the high dose level (40 mg/kg): testicular atrophy (6/6) accompanied by decreased ($p<0.05$) absolute and relative (to body weight) testicular weight, decreased ($p<0.05$) body weight gain of males and decreased terminal body weight of females, and increased ($p<0.05$) absolute and relative adrenal weights of females. There is suggestive evidence in the hematological and clinical chemistry data for anemia and hepatotoxicity also at the high dose level; however, a NOEL and LOEL cannot be conclusively determined because of the variability of control data during the study and the wide range of normal values for these parameters established at the testing facility (a copy of the reported normal ranges are attached to this review as appendix 2). Submission of historical control data from the animal supplier and the testing laboratory for a period of two years before and after the time of the in-life phase of the study (1980-1981) may help to resolve these issues.
>
> This study is classified as supplementary data. A NOEL and LOEL for anemia and hepatotoxicity cannot be determined from the reported data. Effects on adrenal weight are strongly suggested also at lower levels in females.
>
> The historical data mentioned above in the 'conclusions' section are requested.
>
> The study is recommended for audit. Particular attention should be given to reproducibility of the analytical chemical procedures and hematological methodology. The durability of capsules prepared on a weekly basis with a liquid test material is questioned. Details of dose preparation were not included in the report. Weighing of dog tissues after fixation is not a customary practice."

In this action, the registrant supplied historical control data for hematology and clinical chemistry, both from Hazleton Research Animals (the animal supplier) and from the testing laboratory (Pharmacopathics Research Laboratories, now called Tegeris Laboratories, Inc.). Only the testing laboratory provided the time period when the data was collected (1970 - 1985).

The memo relative to the Laboratory Data Audit conducted on October 21-25, 1985 (Dated November 1, 1985; from M. Adrian Gross and Roland A. Gessert to John McCann) stated that:

005943

"The hematology and blood chemistry ranges given in the report include values for all control animals for studies conduted in the laboratory. Following submission of the report to Monsanto (and thence EPA), the laboratory had all their historical control data analyzed by MTSC (Science Time Sharing Corporation) in Rockville, MD. The analyzed historical control data, which show standard deviations and a much more reasonable range of normal values, will be provided to Monsanto who may then submit it to EPA for consideration. In examining the data at the laboratory, the analyzed data appear more truly normal.

The methods used were those normally used in a clinical laboratory and have the generally accepted reproducibility."

The historical data provided by the registrant in this action substantiate the above statements, see Table 1 (Clinical Chemistry) and Table 2 (Hematology). When these data are considered, the concurrent control is in an acceptable range, therefore, it is apparent that there is little biological effect of treatment on red blood cell counts (RBC) at time points measured in this study. However, hemoglobin and hematocrit levels are reduced at the high dose level (40 mg/kg/day) during months 7 through 12 in both males and females. Further, clinical chemistry parameters show a dose related increase in SGOT and SGPT levels in males from months 11 to 12 and increases in SGOT and SGPT levels in females at 12 months. There was little biological effect noted on cholesterol, total protein, albumin or globulin levels in either males or females. The changes in SGOT and SGPT levels at the high dose level (40 mg/kg/day) are supported by an increase in liver to body weight ratio (statistically significantly different from control) in both males and females.

Under conditions of this study, the No Observed Effect Level (NOEL) for systemic effects is 12 mg/kg/day. The Lowest Observed Effect Level (LOEL) for systemic effects is 40 mg/kg/day based on decreased body weight gains males, decreased terminal body weights in females, testicular atrophy with accompanying decreases in absolute and relative testicular weights, increases in absolute and relative adrenal weights in females, increased relative liver weights in males and females, and increases in SGOT and SGPT levels.

Relative to the other deficiencies mentioned in the DER, the Laboratory Data Audit Memo (11/1/85) stated that:

"I was assured by more than one person at the laboratory that the capsules containing the liquid chemical were adequately durable to be prepared on a weekly basis; the chemical did not dissolve the capsules. Such stability is checked prior to each study."

Further,

005943

"The Dynamac reviewers criticized the weighing of the tissues after fixation as not being a customary practice. The protocol states, 'the larger organs were weighed fresh while the smaller ones (adrenals, ovaries, thyroids/parathyroids, and pituitary) were weighed after fixation in 10% buffered formalin'. The audit team sees nothing wrong with this practice, as long as they are consistent. This practice may result in better slides because of less autolysis during the time required for trimming and weighing".

Based on additional data provided by the registrant and the Laboratory Data Audit teams's report, this study can be upgraded from Supplementary Data to Core-Minimum Data.

Table 1. Selected Clinical Chemistry Values for Dogs Administered Acetochlor for 12 Months[†]

Dose(mg/kg/day)	SGOT (IU/I) 8[a]	9	10	11	12	SGPT (IU/I) 8	9	10	11	12	Cholesterol (mg/dl) 8	9	10	11	12
								Males							
Hist.[b]	30.4[c,e]				34.3[d]	35.5[c]				45.0[d]	159.8[c]				158.5[d]
	10.3				14.7	12.0				80.3	30.8				29.4
0	18.0	37.5	37.7	25.8	21.8	18.2	46.5	41.7	47.8	31.2	142.8	127.3	149.3	130.5	133.7
	4.6	6.0	5.6	7.5	9.8	4.5	7.7	4.7	10.9	8.3	25.5	22.0	28.1	18.8	5.1
4	31.3*	37.7	36.7	23.7	33.3*	29.2*	48.8	44.2	53.7	30.0	154.5	137.5	157.7	140.0	148.5*
	5.5	6.0	4.2	8.3	6.9	11.6	8.5	6.7	15.2	13.4	16.6	22.8	16.4	17.8	8.5
12	33.2*	37.0	37.8	25.3	46.7	33.2*	41.2	47.3	52.5	37.5	153.3	129.5	158.2	144.3	148.8*
	3.9	5.8	7.7	6.9	6.9	5.2	10.0	9.2	11.0	8.5	16.6	19.3	28.3	26.9	13.3
40	36.8	41.0	29.3	28.5	41.5*	37.8*	41.2	38.7	59.0	41.2	134.0	147.5	172.0	155.8	154.0
	1.8	8.2	5.9	1.6	6.3	5.3	7.3	8.3	2.6	5.7	21.6	14.5	19.9	14.3	6.3
								Females							
Hist.	32.7[c]				34.6[d]	36.7[c]				38.4[d]	156.9[c]				161.7[d]
	34.2				11.1	17.9				13.8	36.8				36.7
0	32.2	44.5	27.8	31.3	24.0	29.7	40.3	34.0	57.7	33.5	154.8	145.5	159.2	152.0	139.0
	7.6	9.3	8.7	5.3	5.7	6.6	8.0	8.9	12.8	8.1	17.6	10.5	21.7	15.3	12.3
4	34.3	39.5	35.0	28.5	28.3	31.2	44.3	38.2	37.0*	34.0	150.0	126.3*	144.0	131.2*	149.8
	3.7	5.0	3.6	9.5	3.6	11.6	3.4	3.9	9.3	10.4	9.0	8.0	9.0	10.3	18.2
12	33.8	39.2	34.7	28.3	37.5*	37.6	44.2	40.2	44.7	33.3	141.0	133.3*	149.0	144.7	149.5
	3.3	5.0	4.2	6.5	9.1	5.1	9.2	3.5	4.6	3.4	6.8	6.0	18.4	14.1	9.3
40	34.8	35.3	36.2	34.2	37.3*	39.3	42.2	43.3	37.3*	28.7	144.3	128.2*	156.5	153.0	139.5
	3.9	7.4	6.5	3.9	8.6	5.7	6.0	11.3	8.9	11.6	15.3	3.6	8.6	14.6	15.2

Table 1(continued). Selected Clinical Chemistry Values for Dogs Administered Acetochlor for 12 Months[a]

Dose(mg/kg/day)	T. Protein (gm/dl)					Albumin (gm/dl)					Globulin (gm/dl)				
	8[a]	9	10	11	12	8	9	10	11	12	8	9	10	11	12
Males															
Hist.[b]	6.2[c,e]				6.5[d]	3.6[c]				3.6[d]	2.6[c]				3.0[d]
	0.6				0.6	0.4				0.3	0.6				0.6
0	6.4	6.3	6.5	5.5	6.5	3.5	3.6	3.8	3.2	3.6	3.0	2.7	2.7	2.3	2.9
	0.2	0.4	0.4	0.4	0.3	0.1	0.1	0.2	0.2	0.1	0.1	0.4	0.2	0.2	0.3
4	6.0*	6.0	6.3	5.0*	5.8*	3.4	3.4	3.7	3.0*	3.4	2.6	2.6	2.7	2.0*	2.4*
	0.3	0.2	0.4	0.3	0.2	0.1	0.1	0.2	0.2	0.1	0.3	0.2	0.2	0.1	0.1
12	6.3	6.2	6.7	5.4	6.0	3.5	3.5	3.8	3.2	3.5	2.9	2.7	2.9	2.2	2.4*
	0.2	0.1	0.3	0.2	0.3	0.1	0.1	0.1	0.1	0.2	0.3	0.1	0.2	0.1	0.1
40	6.7	5.7*	6.6	4.9*	5.6*	3.5	3.3*	3.8	2.9*	3.3*	3.2	2.4	2.8	2.0*	2.3*
	0.2	0.3	0.4	0.3	0.3	0.2	0.3	0.2	0.2	0.2	0.3	0.1	0.2	0.1	0.1
Females															
Hist.	6.2[c]				6.4[d]	3.7[c]				3.5[d]	2.5[c]				2.8[d]
	0.5				0.7	0.4				0.4	0.5				0.6
0	6.6	6.5	6.3	5.8	6.3	3.6	3.7	3.6	3.4	3.8	3.0	2.8	2.8	2.4	2.4
	0.3	0.1	0.6	0.4	0.2	0.1	0.1	0.2	0.3	0.1	0.2	0.2	0.2	0.2	0.1
4	6.5	6.3	6.4	5.4	6.0	3.6	3.6	3.5	3.2	3.5	2.9	2.7	2.9	2.3*	2.2*
	0.2	0.2	0.3	0.4	0.3	0.1	0.1	0.2	0.2	0.4	0.1	0.1	0.1	0.2	0.1
12	6.4	6.2*	6.7	5.5	6.0	3.5	3.5	3.7	3.2	3.8	2.9	2.7	3.1*	2.3	2.3
	0.3	0.2	0.2	0.2	0.3	0.1	0.1	0.1	0.1	0.2	0.4	0.1	0.1	0.1	0.1
40	6.5	6.2*	6.7	5.7	6.0	3.5	3.6	3.6	3.3	3.7	2.9	2.7	3.1*	2.4	2.3*
	0.2	0.2	0.3	0.3	0.3	0.2	0.1	0.2	0.2	0.2	0.4	0.1	0.1	0.1	0.1

[a] Month of study. [b] = Hist = Historical Control; [c] = 6-9 month mean; [d] = 9 month-1 year mean
[e] = One-year mean upper value is the mean, lower value is the standard deviation; n = 6
* Significantly different from control value at $p \leq 0.05$ using Dunnetts' t value.
† = Data from Table 3 of Dynamac Task 109c and PRL Historical Control

TABLE 2. Selected Hematological Values for Dogs Administered Acetochlor for 12 Months†

Dose (mg/kg/day)	RBC ($x10^3/mm^3$) 5[a]	7	9	11	Hgb (g/dl) 5	7	9	11	Hmct (pc/dl) 5	7	9	11
					Males							
Hist.[b]	6.0[c,f]	6.3[d]		6.7[e]	13.8[c]	14.6[d]		15.2[e]	40.5[c]	43.2[d]		44.2[e]
	0.6	0.8		0.6	1.2	1.4		1.4	3.4	4.2		3.6
0	7.1	7.0	6.9	7.0	14.8	14.9	15.4	15.0	42.4	44.0	45.7	45.5
	0.6	0.4	0.4	0.3	1.5	1.0	1.1	0.7	2.7	2.8	1.6	1.9
4	6.8	7.1	6.5	6.8	14.4	14.0	13.8	14.6	41.8	41.3	43.3	43.7
	0.5	0.7	0.4	0.6	1.4	1.5	1.9	1.3	2.7	1.9	3.6	2.7
12	6.5	7.1	6.5	6.9	14.3	14.4	15.0	14.5	42.2	42.3	44.0	44.7
	0.1	0.6	0.6	0.6	1.1	1.5	1.6	1.3	2.5	2.6	4.1	2.7
40	6.2*	6.7	6.4	6.7	14.3	13.5	14.4	13.9	40.7	41.2	42.2	41.0
	0.4	0.5	0.3	0.5	0.9	1.9	1.1	1.1	2.3	3.2	2.6	4.2
	5[a]	8	10	12	5	8	10	12	5	8	10	12
					Females							
Hist.	6.3[c]	6.6[d]		6.8[e]	14.3[c]	15.4[d]		15.5[e]	42.0[c]	45.4[d]		45.2[e]
	0.6	0.8		0.8	1.3	1.4		1.5	3.8	4.0		4.1
0	7.0	7.6	6.8	6.8	14.8	16.3	16.0	15.1	46.3	49.0	47.2	49.0
	0.8	0.5	0.4	0.6	1.3	1.5	1.6	2.1	3.9	2.5	4.0	4.4
4	7.1	7.3	6.3	6.5	15.2	15.0	15.5	15.7	44.5	45.2	48.2	45.8
	0.5	0.7	0.4	0.4	1.2	1.6	1.0	0.7	2.2	4.4	3.8	1.9
12	6.2	7.3	6.7	6.4	14.2	14.7	15.1	14.3	41.2	44.5	43.8	42.8
	0.7	0.8	0.6	0.9	1.1	1.2	1.3	1.0	3.3	3.1	3.4	4.2
40	6.7	6.5	6.7	6.6	14.6	13.7*	15.0	14.2	42.8	41.8*	45.7	43.7
	0.4	0.3	0.5	0.5	0.7	1.4	0.8	1.1	3.4	3.6	3.7	2.8

[a] = Month of study. [b] = Hist = Historical Control; [c] = 4-6 month mean; [d] = 6-9 month mean; [e] = 9 month to 1 year mean; [f] = Upper value is the mean, lower value is the standard deviation; n = 6 .
* = Significantly different from control value at $p \leq 0.05$ using Dunnetts' t value.
† = Data from Table 4 of Dynamac Task 109C and PRL Historical Control.

005943

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

November 1, 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Laboratory Data Audit. Tegeris Laboratories, Laurel, MD.
October 21 - 25, 1985.

FROM: M. Adrian Gross, D.V.M. and Roland A. Gessert, D.V.M.; NLAP

TO: John McCann, Director, National Laboratory Audit Program.

Three long term studies were audited. A chronic toxicity oncogenicity study in rats and a chronic toxicity/oncogenicity study in mice were audited jointly by Dr. Adrian Gross and Dr. Roland Gessert. Dr. Gross will report these two studies.

A chronic one-year study in the dog was also audited jointly by Dr. Gross and Dr. Gessert. Dr. Gessert will report on the dog study.

12-MONTH CHRONIC TOXICITY IN THE DOG. MON 097 (Acetochlor). Pharmacopathic Research Laboratories (Tegeris Laboratories). Study PR-80-008. Conducted for Monsanto Corporation, St. Louis, Missouri.

Study Director	Farid E. Ahmed, Ph.D.
Pathologists	Andrew S. Tegeris, M.D.
	John D. Seely, D.V.M.
Veterinarian	Paul C. Underwood, D.V.M.
Study Coordinator	James Fischer, B.S.
Quality Assurance Coordinator	Joseph H. Lewis, B.S.

Dynamac Corporation (Paul Wennerberg, D.V.M. and Norbert Page, D.V.M.) had reviewed the study for the Toxicology Branch, and had recommended the study for audit, questioning the reproducibility of the analytical chemical and hematological methodology.

The hematology and blood chemistry ranges given in the report include values for all control animals for studies conducted in the laboratory. Following submission of the report to Monsanto (and thence EPA), the laboratory had all their historical control data analyzed by MISC (Science Time Sharing Corporation) in Rockville, MD. The analyzed historical control data, which show standard deviations and a much more reasonable range of normal values, will be provided to Monsanto who may then submit it to EPA for consideration. In examining the data at the laboratory, the analyzed data appear more truly normal.

The methods used were those normally used in a clinical laboratory and have the generally accepted reproducibility.

I was assured by more than one person at the laboratory that the capsules containing the liquid chemical were adequately durable to be prepared on a weekly basis; the chemical did not dissolve the capsules. Such stability is checked prior to each study.

The Dynamac reviewers criticized the weighing of the tissues after fixation as not being a customary practice. The protocol states, "the larger organs were weighed fresh while the smaller ones (adrenals, ovaries, thyroids/parathyroids, and pituitary) were weighed after fixation in 10% buffered formalin. The audit team sees nothing wrong with this practice, as long as they are consistent. This practice may result in better slides because of less autolysis during the time required for trimming and weighing.

Blood chemistry and hematology were checked, as were the body weights and dose calculations.

In all, the dog study appears to have been conducted in a satisfactory manner and as per the protocol.

M. Adrian Gross, D.V.M.

Roland A. Gessert, D.V.M.

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

004586

EPA: 68-01-6561
TASK: 109C
August 2, 1985

005943

DATA EVALUATION RECORD

ACETOCHLOR

One-Year Feeding Study in Dogs

STUDY IDENTIFICATION: Ahmed, F. E. A one-year feeding study in dogs with MON 097. (Unpublished study No. PR-80-008, PRL #8006 by Pharmacopathics Research Laboratories, Laurel, MD, for Monsanto Agricultural Products Co., St. Louis, MO; dated October 14, 1981.) Accession No. 248618 and 248619.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: James R. Plaut for
Date: August 2, 1985

10

005943
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1. CHEMICAL: Acetochlor (MON 097), 2-chloro-N(ethoxymethyl)-6'ethyl-ortho-acetotoluidine.

2. TEST MATERIAL: The test material was MON 097, lot no. NBP 1737874; 94.5% active ingredient. The compound was a maroon liquid having an offensive odor.

3. STUDY/ACTION TYPE: Chronic feeding study in dogs.

4. STUDY IDENTIFICATION: Ahmed, F. E. A one-year feeding study in dogs with MON 097. (Unpublished study No. PR-80-008, PRL #8006 by Pharmacopathics Research Laboratories, Laurel, MD, for Monsanto Agricultural Products Co., St. Louis, MO; dated October 14, 1981.) Accession No. 248618 and 248619.

5. REVIEWED BY:

Paul Wennerberg, D.V.M., M.S.
Principal Author
Dynamac Corporation

Signature: [signature]
Date: 8/1/85

Norbert Page, D.V.M., D.A.B.T.
Independent Reviewer
Dynamac Corporation

Signature: [signature]
Date: 8/2/85

6. APPROVED BY:

William McLellan, Ph.D.
Oncogenicity and Chronic Effects
Technical Quality Control
Dynamac Corporation

Signature: [signature] for
Date: August 2 1985

Quang Bui, Ph.D.
EPA Reviewer

Signature: [signature] for
Date: 8-2-85

Laurence Chitlik, D.A.B.T.
EPA Section Head

Signature: [signature]
Date: 8/5/85

7. CONCLUSIONS:

Based on the data presented, there are obvious effects at the high dose level (40 mg/kg): testicular atrophy (6/6) accompanied by decreased ($p < 0.05$) absolute and relative (to body weight) testicular weight, decreased ($p < 0.05$) body weight gain of males and decreased terminal body weight of females, and increased ($p < 0.05$) absolute and relative adrenal weights of females. There is suggestive evidence in the hematological and clinical chemistry data for anemia and hepatotoxicity also at the high dose level; however, a NOEL and LOEL cannot be conclusively determined because of the variability of control data during the study and the wide range of normal values for these parameters established at the testing facility (a copy of the reported normal ranges are attached to this review as appendix 2). Submission of historical control data from the animal supplier and the testing laboratory for a period of two years before and after the time of the in-life phase of the study (1980-1981) may help to resolve these issues.

8. RECOMMENDATIONS:

This study is classified as supplementary data. A NOEL and LOEL for anemia and hepatotoxicity cannot be determined from the reported data. Effects on adrenal weight are strongly suggested also at lower levels in females. W.T. 3-2-88

The historical data mentioned above in the "conclusions" section are requested.

The study is recommended for audit. Particular attention should be given to reproducibility of the analytical chemical procedures and hematological methodology. The durability of capsules prepared on a weekly basis with a liquid test material is questioned. Details of dose preparation were not included in the report. Weighing of dog tissues after fixation is not a customary practice.

Items 9 through 10 - see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods:

1. The test material, liquid Acetochlor, was added to capsules in unspecified volumes to achieve a dosage of 4, 12, or 40 mg/kg body weight/day. The control group was given empty capsules. No vehicle or diluent was used.

2. Forty-eight, five to six months old, purebred beagle dogs were received from Hazleton Research Laboratories, Inc., Vienna, Virginia.

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[1] Only items appropriate to this DER have been included.

005943

Six dogs/sex/group were administered the appropriate capsule daily for 12 months. Capsules were prepared weekly based on the group mean body weight recorded during the previous two weeks. This practice continued for the first 5 weeks of the study. Starting from week 6 and throughout the study duration, the dose volume was based on the individual dog's weight.

3. All dogs were inspected daily for clinical signs. Body weights were recorded weekly and food consumption daily. Seventeen clinical chemistry, 8 hematology, and 10 urinalysis parameters were measured monthly in all dogs. Each animal had a gross necropsy in which 8 organs were weighed, and about 40 tissues examined histologically.

4. Complete Materials and Methods section is in Appendix 1.

12. REPORTED RESULTS:

A. No analytical results were presented for concentration, homogeneity, or stability of the test material.

B. A number of clinical signs were observed. In addition to the observations reported on the pathology records, the following were observed: two control males with bloody diarrhea, one high-dose male with traces of blood in its saliva, and one high-dose male with blood in the feces; all four were treated with chloramphenicol. One control female had a rear leg lameness that was noted 2.5 weeks before study termination.

All dogs survived the duration of the study, and none of the dosed groups of either sex showed a significant difference from controls for mean weekly body weights (Table 1); however, the study author stated that there was a tendency for animals in the high-dose group to show less body-weight gain than the controls.

The author stated that although "there was no persistent statistical decrease between the high-dose group and the control group in either sex, there appeared to be a remarkable decrease [in food consumption] that was considered to be test-compound related." Selected values showing this lack of persistent decrease in food consumption are shown in Table 2. There were only 5 instances of significant decreases in food consumption in males and one in females. Specifically, low-dose males (4 mg/kg/day) were lower at week 13, high-dose males (40 mg/kg/day) were lower at weeks 13, 25, 31, and 44, and high-dose females were lower at week 41.

005943

TABLE 1. Selected Mean Body Weight Values for Dogs Administered Acetochlor for 12 Months

Dosage Level (mg/kg/day)	Mean body weights (kg) at month					Mean body weight gain for the 12 months
	0[a]	3	6	9	12	
Males						
0	8.4[b]	10.0	10.3	10.3	11.3	2.9
	1.1	2.0	1.6	1.5	1.7	1.0
4	9.0	10.7	10.7	11.0	11.6	2.6
	1.2	1.4	1.3	1.6	1.6	1.2
12	8.4	9.6	10.1	10.4	11.5	3.1
	1.5	2.2	2.5	2.6	3.0	1.6
40	8.4	9.1	9.7	9.2	9.7	1.3*
	1.2	1.5	1.5	1.4	1.5	1.1
Females						
0	7.6	8.6	9.4	9.1	10.1	2.5
	1.8	2.0	1.6	1.8	1.9	1.2
4	6.8	8.0	8.6	8.5	9.4	2.6
	0.9	1.0	1.0	1.4	1.3	0.6
12	7.1	8.3	8.7	8.6	9.8	2.7
	0.7	1.4	1.1	1.0	1.2	0.9
40	6.8	7.5	8.2	7.9	8.3	1.5
	0.7	0.6	1.0	0.4	0.7	1.1

[a] Month 0 values were measured at Week -1.

[b] Upper value is the mean, lower value is the standard deviation; n = 6.

* Significantly different from control by ANOVA followed by Duncans test ($p < 0.05$) when analyzed by our reviewers.

TABLE 2. Selected Mean Food Consumption Values for Dogs Administered Acetochlor for 12 Months

Dosage Level (mg/kg/day)	Mean food consumption (g/dog/day) at month				
	0[a]	3	6	9	12
Males					
0	203.8[b] 45.87	327.0 31.50	303.5 42.83	304.2 38.31	352.2 38.59
4	200.7 35.79	319.5 46.33	323.2 49.03	317.5 74.15	342.5 59.00
12	222.3 44.20	343.7 40.98	296.3 43.72	324.0 40.99	350.0 28.45
40	193.8 27.35	304.8 25.19	254.0 35.33	290.5 59.26	297.3 63.93
Females					
0	190.8 69.46	308.7 24.42	284.5 23.86	279.2 23.60	315.2 43.47
4	200.3 89.78	325.3 48.21	254.0 58.19	257.3 39.97	267.2 43.98
12	165.2 58.11	300.0 26.21	228.5 13.95	271.3 44.47	277.3 55.19
40	201.5 43.55	288.2 26.75	226.2 40.40	243.7 57.35	264.8 57.43

[a] Month 0 values were measured at Week -1.
[b] Upper value is the mean, lower value is the standard deviation; n = 6.

Most clinical chemistry parameters of the treated groups were statistically significantly different from the controls during part of the study. Selected parameters from the latter part of the study are in Table 3. The mean high-dose groups which differed significantly from controls included: elevated SGOT values for males during months 1, 8, 12 and females during months 3 and 12; elevated SGPT values for males at 8 months and females at 2 months and a decrease at 11 months; elevated cholesterol levels at month 12 for males and decreased at 9 months in females; depression of total protein values in males at 5, 9, 11, and 12 months and at 2 and 9 months in females; and decreased albumin levels at months 3, 5, 9, 11, and 12 in males and months 2 and 5 in females.

Hematological examinations revealed significant differences in the following parameters between the treated and control groups (Table 4): mean red blood cell counts were decreased for high-dose males at month 5; mean hemoglobin concentrations were decreased for mid-dose females at months 1 and 9 and for high-dose females at month 8; mean hematocrit values were decreased in mid-dose females at month 12 and high-dose females at months 8 and 12. Evaluations of red blood cell morphology revealed nucleated red blood cells, anisocytosis, and polychromasia on occasion in the following number of dogs in the control to high-dose groups: males, 2/6, 4/6, 4/6, 6/6; females, 2/6, 5/6, 6/6, 5/6. These findings were observed in males, primarily after month 7, and in females, after month 4 with the most frequent occurrence in the last 3 months.

There were no compound-related changes in urinary parameters. The primary finding on urinalysis was an increased number of red blood cells. The majority of dogs with this finding were females (equally distributed between all study groups) that were described as being in estrus.

The following significant changes in mean organ weights were reported between treatment and control groups. Low-dose males had an increased gonadal weight and high-dose males had a decreased gonadal weight (Table 5). High-dose females had an increase in adrenal weights. There were several significant organ-to-body weight differences between treated and control groups. High-dose males had an increased relative liver and relative kidney ratios and a decreased gonadal ratio. Low- and high-dose females had an increased adrenal ratio (Table 5).

The following observations were made on necropsy. One control male with alopecia of the ventral thorax, one low-dose male with a 1 cm capsular lesion on the spleen, one mid-dose male with a small lesion on its lower lip, and one high-dose male with a consolidated lung lobe. One control female had a small growth on the dorsal surface of the head, one mid-dose female had enlarged lymphoid tissue of the third eyelid, one mid-dose female had a

TABLE 3. Selected Clinical Chemistry Values for Dogs Administered Acetochlor for 12 Months

Dosage Level (mg/kg/day)	SGOT (IU/l)					SGPT (IU/l)					Cholesterol (mg/dl)				
	8[a]	9	10	11	12	8	9	10	11	12	8	9	10	11	12
Males															
0	18.0[b]	37.5	37.7	25.8	21.8	18.2	46.5	41.7	47.8	31.2	142.8	127.3	149.3	130.5	133.7
	4.6	6.0	5.6	7.5	9.8	4.5	7.7	4.7	10.9	8.3	25.5	22.0	28.1	18.8	5.1
4	31.3*	37.7	36.7	23.7	33.3*	29.2*	48.8	44.2	53.7	30.0	154.5	137.5	157.7	140.0	148.5*
	5.5	6.0	4.2	8.3	6.9	11.6	8.5	6.7	15.2	13.4	16.6	22.8	16.4	17.8	8.5
12	33.2*	37.0	37.8	25.3	46.7*	33.2*	41.2	47.3	52.5	37.5	153.3	129.5	158.2	144.3	148.8*
	3.9	5.8	7.7	6.9	6.9	5.2	10.0	9.2	11.0	8.5	16.6	19.3	28.3	26.9	13.3
40	36.8*	41.0	29.3	28.5	41.5*	37.8*	41.2	38.7	59.0	41.2	134.0	147.5	172.0	155.8	154.0*
	1.8	8.2	5.9	1.6	6.3	5.3	7.3	8.3	2.6	5.7	21.6	14.5	19.9	14.3	6.2
Females															
0	32.2	44.5	27.8	31.3	24.0	29.7	40.3	34.0	57.7	33.5	154.8	145.5	159.2	152.0	139.0
	7.6	9.3	8.7	5.3	5.7	6.6	8.0	8.9	12.8	8.1	17.6	10.5	21.7	15.3	12.3
4	34.3	39.5	35.0	28.5	28.3	31.2	44.3	38.2	37.0*	34.0	150.0	126.3*	144.0	131.2*	149.8
	3.7	5.0	3.6	9.5	3.6	11.6	3.4	3.9	9.3	10.4	9.0	8.0	9.0	10.3	18.2
12	33.8	39.2	34.7	28.3	37.5*	37.5	44.2	40.2	44.7	33.3	141.0	133.3*	149.0	144.7	149.5
	3.3	5.0	4.2	6.5	9.1	5.1	9.3	3.5	4.6	3.4	6.8	6.0	18.4	14.1	9.3
40	34.8	35.3	36.2	34.2	37.3*	39.3	42.2	43.3	37.3*	28.7	144.3	128.2*	156.5	153.0	139.5
	3.9	7.4	6.5	3.9	8.6	5.7	6.0	11.3	8.9	11.6	15.3	3.6	8.6	14.6	15.2

TABLE 3. Selected Clinical Chemistry Values for Dogs Administered Acetochlor for 12 Months (Continued)

Dosage Level (mg/kg/day)		T. Protein (gm/dl)					Albumin (gm/dl)					Globulin (gm/dl)				
		8[a]	9	10	11	12	8	9	10	11	12	8	9	10	11	12
Males																
	0	6.4	6.3	6.5	5.5	6.5	3.5	3.6	3.8	3.2	3.6	3.0	2.7	2.7	2.3	2.9
		0.2	0.4	0.4	0.4	0.3	0.1	0.1	0.2	0.2	0.1	0.1	0.4	0.2	0.2	0.3
	4	6.0*	6.0	6.3	5.0*	5.8*	3.4	3.4	3.7	3.0*	3.4	2.6	2.6	2.7	2.0*	2.4*
		0.3	0.2	0.4	0.3	0.2	0.1	0.1	0.2	0.2	0.1	0.3	0.2	0.2	0.1	0.1
	12	6.3	6.2	6.7	5.4	6.0*	3.5	3.5	3.8	3.2	3.5	2.9	2.7	2.9	2.2	2.4*
		0.2	0.1	0.3	0.2	0.3	0.1	0.1	0.1	0.1	0.2	0.3	0.1	0.2	0.1	0.1
	40	6.7	5.7*	6.6	4.9.*	5.6*	3.5	3.3*	3.8	2.9*	3.3*	3.2	2.4	2.8	2.0*	2.3*
		0.2	0.3	0.4	0.3	0.3	0.2	0.3	0.2	0.2	0.2	0.3	0.1	0.2	0.1	0.1
Females																
	0	6.6	6.5	6.3	5.8	6.3	3.6	3.7	3.6	3.4	3.8	3.0	2.8	2.8	2.4	2.4
		0.3	0.1	0.6	0.4	0.2	0.1	0.1	0.2	0.3	0.1	0.2	0.2	0.2	0.2	0.1
	4	6.5	6.3	6.4	5.4	6.0	3.6	3.6	3.5	3.2	3.5	2.9	2.7	2.9	2.3	2.2*
		0.2	0.2	0.3	0.4	0.3	0.1	0.1	0.2	0.2	0.4	0.1	0.1	0.1	0.2	0.1
	12	6.4	6.2*	6.7	5.5	6.0	3.5	3.5	3.7	3.2	3.8	2.9	2.7	3.1*	2.3	2.3
		0.3	0.2	0.2	0.2	0.3	0.1	0.1	0.1	0.1	0.2	0.4	0.1	0.1	0.1	0.1
	40	6.5	6.2*	6.7	5.7	6.0	3.5	3.6	3.6	3.3	3.7	2.9	2.7	3.1*	2.4	2.3*
		0.2	0.2	0.3	0.3	0.3	0.2	0.1	0.2	0.2	0.2	0.4	0.1	0.1	0.1	0.1

[a] Month of study.
[b] Upper value is the mean, lower value is the standard deviation; n = 6.
* Significantly different from control value at $p \leq 0.05$ using Dunnett's t value.

TABLE 4. Selected Hematological Values for Dogs Administered Acetochlor for 12 Months

Dosage Level (mg/kg/day)	RBC ($\times 10^3/mm^3$) 5[a]	7	9	11	Hgb (g/dl) 5	7	9	11	Hmct (pc/dl) 5	7	9	11
Males												
0	7.1[b]	7.0	6.9	7.0	14.8	14.9	15.4	15.0	42.4	44.0	45.7	45.5
	0.6	0.4	0.4	0.3	1.5	1.0	1.1	0.7	2.7	2.8	1.6	1.9
4	6.8	7.1	6.5	6.8	14.4	14.0	13.8	14.6	41.8	41.3	43.3	43.7
	0.5	0.7	0.4	0.6	1.4	1.5	1.9	1.3	2.7	1.9	3.6	2.7
12	6.5	7.1	6.5	6.9	14.3	14.4	15.0	14.5	42.2	42.3	44.0	44.7
	0.1	0.6	0.6	0.6	1.1	1.5	1.6	1.3	2.5	2.6	4.1	2.7
40	6.2*	6.7	6.4	6.7	14.3	13.5	14.4	13.9	40.7	41.2	42.2	41.0
	0.4	0.5	0.3	0.5	0.9	1.9	1.1	1.1	2.3	3.2	2.6	4.2
	5[a]	8	10	12	5	8	10	12	5	8	10	12
Females												
0	7.0	7.6	6.8	6.8	14.8	16.3	16.0	15.1	46.3	49.0	47.2	49.0
	0.8	0.5	0.4	0.6	1.3	1.5	1.6	2.1	3.9	2.5	4.0	4.4
4	7.1	7.3	6.3	6.5	15.2	15.0	15.5	15.7	44.5	45.2	48.2	45.8
	0.5	0.7	0.4	0.4	1.2	1.6	1.0	0.7	2.2	4.4	3.8	1.9
12	6.2	7.3	6.7	6.4	14.2	14.7	15.1	14.3	41.2	44.5	43.8	42.8*
	0.7	0.8	0.6	0.9	1.1	1.2	1.3	1.0	3.3	3.1	3.4	4.2
40	6.7	6.5	6.7	6.6	14.6	13.7*	15.0	14.2	42.8	41.8*	45.7	43.7*
	0.4	0.3	0.5	0.5	0.7	1.4	0.8	1.1	3.7	3.6	3.7	2.8

[a] Month of study.
[b] Upper value is the mean, lower value is the standard deviation; n = 6.
* Significantly different from control value at $p \leq 0.05$ using Dunnetts' t value.

TABLE 5. Selected Mean Organ Weight Data for Dogs Fed Acetochlor for 12 Months

Mean Terminal Body Weights, Mean Absolute Organ Weights, and Organ-to-Body Wt. Ratio for Males

Dosage Level (mg/kg/day)	Body Wt. (kg)	Liver		Kidney		Adrenals		Testes	
		Weight (g)	Ratio (g/kg bw)	Weight (g)	Ratio (g/kg bw)	Weight (g)	Ratio (g/kg bw)	Weight (g)	Ratio (g/kg bw)
0	11.2[a]	339	30.65	58	5.31	1.38	0.13	12.36	1.12
	1.66	43.4	3.50	2.6	0.66	0.29	0.03	1.22	0.08
4	11.5	383	33.66	67	5.84	1.37	0.12	14.80*	1.31
	1.57	44.1	2.50	10.3	0.68	0.21	0.02	2.21	0.22
12	11.2	386	34.86	58	5.24	1.40	0.13	11.39	1.03
	2.99	97.0	5.04	11.7	0.79	1.15	0.02	2.74	0.19
40	9.2	335	36.10*	58	6.26*	1.38	0.15	6.09*	0.67*
	1.57	91.2	3.89	12.6	0.75	0.23	0.02	1.23	0.14

Mean Terminal Body Weight, Mean Absolute Organ Weights, and Organ-to-Body Wt. Ratio for Females

Dosage Level (mg/kg/day)	Body Wt.	Liver		Kidney		Adrenals		Ovaries	
		Weight (g)	Ratio (g/kg bw)	Weight (g)	Ratio (g/kg bw)	Weight (g)	Ratio (g/kg bw)	Weight (g)	Ratio (g/kg bw)
0	10.2[a]	305	30.46	57	5.74	1.19	0.12	1.50	0.16
	1.82	39.0	4.18	5.2	1.33	0.21	0.03	0.64	0.08
4	9.1	279	30.85	50	5.54	1.43	0.16*	1.03	0.11
	1.45	42.7	4.53	6.3	0.75	0.21	0.03	0.28	0.02
12	9.7	294	30.12	53	5.40	1.46	0.15	1.60	0.17
	1.15	59.9	3.92	6.1	0.33	0.29	0.02	0.40	0.04
40	8.0*	291	36.44	52	6.44	1.64*	0.21*	1.23	0.15
	0.57	44.9	6.23	8.8	0.93	0.20	0.03	0.28	0.03

[a] Upper value is the mean, lower value is the standard deviation; n = 6.
* Significantly different from control value at $p \leq 0.05$.

1.5 cm cyst on the dorsal surface of the head, and one high-dose female had an irregular surface on its kidneys with several small cysts; these kidneys also weighed considerably less than those of other females in the same group.

005943

A number of findings were made on histological examination (Table 6). The primary finding was diffuse atrophy of the testes in all 6 high-dose dogs.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The following are the study author's conclusions.

"From the data presented above we conclude that MON-097, when fed to the dogs under the conditions of this study caused a remarkable decrease in feed consumption and body weight at the high-dose level (40 mg/kg bd.wt./day) in both sexes and a biologically meaningful decrease in testicular weight that was borne out histopathologically."

"No compound-related effects were observed in the mid-dose (12 mg/kg bd.wt./day) or the low-dose (4 mg/kg bd.wt./day) levels in either sex."

B. A signed quality assurance statement stated that the study was reviewed several times during the course of the study and that the report was checked to accurately reflect the raw data.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. The study author's conclusions that body weight gain and food consumption values decreased in the high-dose group of both sexes when compared to controls were supported by the data. Our analyses showed that males had a significantly decreased weight gain over the 12 months (Table 1) and the report showed that the terminal body weights for females were significantly decreased (Table 5). We believe that the decrease in body weights may have been the result of the decrease in food consumption. Specifically, in the high-dose males and females at twelve months, the mean male body weight was 86% (9.7/11.3) of control and the mean food consumption was 84% (297.3/352.2) of control while the mean female body weight was 82% (8.3/10.1) of control and the mean food consumption was 84% (264.8/315.2) of control values.

005943

TABLE 6. Incidence of Histopathologic Findings in Dogs Administered Acetochlor for One Year

	Dosage Level (mg/kg/day)							
	Males				Females			
	0	4	12	40	0	4	12	40
Pituitary								
Cyst, Rathke's pouch	1	1	0	0	1	0	2	0
Thyroid								
Chronic thyroiditis	1	1	0	0	0	0	0	0
Severe thyroiditis	1	0	0	0	0	0	0	0
C-cell hyperplasia	0	1	0	0	1	0	0	0
Spleen								
Focal siderosis	0	1	0	0	0	0	0	0
Liver								
Fatty infiltration	0	0	1	1	0	0	0	0
Kidney								
Infarcts, multiple	0	0	0	0	0	0	0	1
Cystitis	0	0	0	0	0	1	0	0
Skin								
Histiocytoma	0	0	1	0	0	0	0	0
Epidermal cyst	0	0	0	0	0	0	1	0
Squamous papilloma	0	0	0	0	1	0	0	0
Testes								
Atrophy	0	0	0	6*	-	-	-	-
Eye								
Conjunctivitis	0	0	0	0	0	0	1	0
Lung								
Bronchopneumonia	0	0	0	1	0	0	0	0

* Significantly different from control value at $p < 0.05$ using Fishers' exact test when analyzed by these reviewers.

The author did not consider the changes in clinical chemistry parameters to be of biologic importance since the values were all within the laboratory's normal historical range. However, the ranges exceed values available in the veterinary literature[a]. While variation is to be expected between laboratories and animal populations, the study's wide range for historical normal values might obscure biologically significant changes. There is also a relationship between increases in SGOT, SGPT, and cholesterol, decreases in albumin, and total protein in high-dose males and the increased incidence of fatty infiltration of the liver and increased liver-to-body weight ratio.

The report author did not consider changes in hematology parameters to be of biologic importance. However, decreases in RBC count, hematocrit, and hemoglobin suggest compound-related anemia in high-dose female dogs. Our reviewers noted that there was also an increased incidence of abnormal red cell morphology which may have been dose related. When we analyzed the incidence of altered red blood cell morphology (nucleated red blood cells, anisocytosis, and polychromasia) using Fisher's Exact test ($p < 0.05$), the incidence of 6/6 was significantly greater than 2/6. The complete data for the incidence of altered red blood cell morphology from control to high-dose groups were 2/6, 4/6, 4/6, and 6/6 for males and 2/6, 5/6, 6/6, and 5/6 for females. There was a positive trend for males using the Cochran-Armitage Trend test ($p < 0.05$) but not for the females. All of these hematological parameters together indicate anemia.

B. The author stated that "the only biologically meaningful change" in organ weight or organ-to-body weight ratio was in the testes. This significant decrease in both mean absolute and relative testes weight in males receiving 40 mg/kg/day was accompanied by testicular atrophy seen on histopathological examination in all males of this group. Since circulating hormone levels were not measured, this aspect of the testicular atrophy cannot be evaluated. There were significant increases in the relative weight of kidneys and liver in high-dose males, but no changes in mean absolute weights when compared with controls. Both changes can be accounted for by the decreased mean body weights. Two male dogs, however, (one mid dose and one high dose) were diagnosed as having fatty infiltration of the liver.

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[a] Duncan, J.R., Prasse, K.W. Veterinary Laboratory Medicine. 3rd printing, 1979. The Iowa State University Press, Ames, Iowa. pp. 188, 189.

Andersen, A.C. ed. The Beagle as an Experimental Dog. 1st edition, 1970. The Iowa State University Press, Ames, Iowa. p. 282.

A significant increase in adrenal weight and adrenal-to-body weight ratio in females receiving 40 mg/kg/day was also noted. It is difficult to assess the biological importance of this change. Dose-related changes in testicular and adrenal weights could possibly be accompanied by changes in immune function since gonadotropins and sex hormones and also adrenalcorticoids can be cytotoxic to some lymphocyte subsets and cause immunosuppression. However, in this study no correlations can be made since there were no electrophoretic analyses of globulins, analyses of circulating hormone levels, or performance of immune function tests.

Our assessment of the study is that the data strongly support a compound-related effect (atrophy of the testes); there is also suggestive evidence of anemia and liver toxicity; however, it is not possible to assess endocrine or immune system changes from the data reported. and other effects as noted above wt. 8-2-85

The resolution of the differences between the author and our reviewers would involve a reevaluation of their normal range values, especially for the clinical parameters previously discussed. This could be accomplished with the submission and subsequent evaluation of historical control data from both the animal supplier and testing laboratory. Endocrine and immune system involvement could be investigated through measurement of hormone levels, characterization of serum globulins, and reexamination of histopathological specimens for evidence of hypertrophy.

C. There were several deficiencies in the study design and conduct:

- the dogs did not receive eye examinations; wt. 8-2-85
- dosing capsules containing a liquid were prepared on a weekly basis; and
- some tissues were weighed after fixation.

In addition, we utilized various nonparametric statistical tests to analyze the continuous data based on the low sample size (6 dogs/sex/group) and unequal variances; however, the results were not different from those reported.

Item 15 - see footnote 1.

16. CBI APPENDIX:

Appendix 1 (Materials and Methods), CBI pp. 6-18.

APPENDIX 1

(Materials and Methods)
CBI pp. 6-18

ACETOCHLOR

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Page_____ is not included in this copy.

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____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.