ATTACHMENT C

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

006571

JAN 29 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of a chronic/oncogencity study in rats with MON 097 (Acetochlor, Harness® and Top-Hand® Herbicides). EPA ID #'s 524-GUI & 3F2966; EPA Record #'s 195381 & 195383; EPA Accession # 400770601; Caswell #3B; Tox Branch Project #7-0702.

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

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 1/29/88
Pharmacologist, Review Section V
Toxicology Branch/HED (TS-769C)

THRU: Quang Q. Bui, Ph.D., D.A.B.T. Quang Bui 1/20/88
Acting Section Head, Review Section V
and
Theodore M. Farber, Ph.D., D.A.B.T.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant: Monsanto Agricultural Products Company
800 N. Lindbergh Boulevard
St. Louis, Missouri 63167

Action Requested: Review a repeat chronic/oncogencity study in rats with MON 097.

Recommendations: Under the conditions of this repeat study, there was evidence of systemic toxicity in the high dose groups (1000 ppm) expressed as decreased body weights and body weight gains in both males and females accompanied by increases in serum gamma glutamyl transpeptidase activity and cholesterol levels in high dose males, increased total bilirubin in high dose females, increased absolute and relative kidney and liver weights in high dose males and increased testicular weights in high dose males (at final sacrifice). There were increases in several non-neoplastic histopathological findings in high dose males and females. Neoplastic histopathological findings were noted in the form of neoplastic nodules of the liver, follicular adenoma/cystadenoma of the thyroids and papillary adenoma of the mucosa of the nose/turbinates in high dose animals.

From the evidence presented in this study, MON 097 is an oncogen in male and female rats at doses of 1000 ppm as evidenced by the findings of neoplastic nodules of the liver, follicular adenoma/cystadenoma of the thyroids and papillary adenoma of the mucosa of the nose/turbinates in high dose animals.

NOEL for Systemic Toxicity = 200 ppm
LOEL for Systemic Toxicity = 1000 ppm

This study is classified as Core-Supplementary Data for chronic toxicity and oncogenicity. The registrant should be directed to supply the data requested in the DER (see Conclusions section). Submission and acceptance of these requested data may permit upgrading of this study.

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Reviewed by: Stephen C. Dapson, Ph.D.
Pharmacologist, Review Section V, Toxicology Branch/HED (TS-769C) 006571
Secondary Review by: Quang Q. Bui, Ph.D., D.A.B.T.
Acting Section Head, Review Section V, Toxicology Branch/HED (TS-769C)

DATA EVALUATION RECORD

STUDY TYPE: Chronic Feeding/Oncogenicity Rodent
Guideline §83-1 and 83-2

EPA IDENTIFICATION NUMBERS: EPA ID NO.: 3F2966 and 524-GUI
EPA ACCESION NUMBER: 400770601
EPA RECORD NO.: 195381 and 195383
SHAUGHNESSY NO.: 121601
CASWELL NO.: 3B
TOX BRANCH PROJECT NO.: 7-0702
DOCUMENT NO.: 006571

TEST MATERIAL: Acetochlor
EHL Substance Identification Code: T830072
Lot No. Dayton RDNT 08001

SYNONYMS: MON 097

STUDY NUMBER(S): Laboratory Project ID: EHL-83107
Report No.: MSL-6119
Study (DMEH Project No.) No.: ML-83-200; EHL #83107

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

TESTING FACILITY: Monsanto Environmental Health Laboratory
St. Louis, Missouri

TITLE OF REPORT: Chronic Feeding Study of MON 097 IN Albino Rats

AUTHOR(S): M.W. Naylor
W.E. Ribelin

REPORT ISSUED: September 25, 1986 (date study completed)

BACKGROUND INFORMATION:

The study reviewed in this DER (Laboratory Project ID: EHL-83107) is a repeat of a previous chronic/oncogenicity study in the rat (Study #PR-80-006, 5/20/83) which was classified as minimum data. A NOEL for systemic effects was not established and a repeat study was requested by the Agency.

The dose levels tested in the initial study were 500, 1500 and 5000 ppm. MON 097 was found to be carcinogenic in the rat (classified as B_2). At the highest dose level there was increased incidence of liver carcinomas and thyroid follicular cell adenomas in males.

Positive trends were noted for hepatic carcinomas in females and thyroid follicular cell adenomas in males (see the Peer Review Document, dated 3/30/87 from R. Engler to R. Taylor).

At the highest dose level there were also increased incidences of polyarteritis of the testes and arteries in the males and liver necrosis and alveolar histiocytosis in females. Further, at the high dose there was increased mortality in females and decreased food consumption in both sexes. A dose-related decrease in body weights were noted in both sexes at the mid and high dose levels and in males at the low dose level. There were systemic effects at the low dose level in the form of organ weight effects and decreased body weights in males, therefore, a systemic NOEL could not be determined.

CONCLUSIONS:

Under the conditions of this repeat study, there was evidence of systemic toxicity in the high dose groups (1000 ppm) expressed as as decreased body weights and body weight gains in both males and females accompanied by increases in serum gamma glutamyl transpeptidase activity and cholesterol levels in high dose males, increased total bilirubin in high dose females, increased absolute and relative kidney and liver weights in high dose males and increased testicular weights in high dose males (at final sacrifice). There were increases in several non-neoplastic histopathological findings in high dose males and females. Neoplastic histopathological findings were noted in the form of neoplastic nodules of the liver, follicular adenoma/cystadenoma of the thyroids and papillary adenoma of the mucosa of the nose/turbinates in high dose animals. From evidence presented in this study, MON 097 is a oncogen in male and female rats.

NOEL for Systemic Toxicity = 200 ppm
LOEL for Systemic Toxicity = 1000 ppm

The registrant is directed to supply the following data. Submission and acceptance of this data may permit upgrading of this study.

1. Summary tables of all reported clinical observations.

2. Tables with actual numbers of tissues examined for each organ/dose level used for histopathological examination.

Classification: Core-Supplementary Data for chronic toxicity and oncogenicity. This study may be upgraded if information requested is submitted and accepted by the Agency.

Special Review Criteria (40 CFR 154.7)

Based on evidence examined by the Toxicology Branch Peer Review Committee (meeting of September 12, 1985, MEMO of March 30, 1987), Acetochlor meets the criteria for Group B2 - Probable Human Carcinogen. Acetochlor is oncogenic in the rat (first study) with evidence of hepatocellular carcinoma in both sexes and thyroid folicular cell adenoma in males. Acetochlor is oncogenic in the mouse with evidence of hepatocellular carcinoma in both sexes, lung carcinoma in females, uterine histiocytic sarcomas, benign ovarian tumors and kidney adenomas in females. Acetochlor is structurally related to known carcinogens and has been shown to be mutagenic.

It should be noted that in this repeat study, papillary adenomas of the mucosa of the nose/turbinates (a neoplastic finding not previously observed) were statistically significantly increased at the 1000 ppm dose level.

A. MATERIALS:

A copy of the "material and methods" section from the investigators' report is appended.

1. Test compound: Acetochlor(MON 097), Description: Amber-Purple Liquid, Lot#: Dayton RDNT 08001, Purity: 96.1%, contaminants: not provided.

EHL Substance Identification Code: T830072
Stated Stability: Stable for > 2 years @ 80°F
Received: Aug. 24, 1983 from Monsanto Agricultural Products Co.

2. Test animals: Species: Albino Rat, Strain: Sprague-Dawley, Age: approximately 26 weeks, Weight: Males:198.0 to 248.0 gms, Females:141.0 to 180.0 gms (at start of study).

Received: September 6, 1983.
The animals were kept under standard animal care conditions (see attached materials and methods.)
Source: Charles River Breeding Laboratory, ~~Portage~~, MI.

B. STUDY DESIGN:

1. Animal assignment

A total of 70 animals per sex per dose group were used. The animals were assigned by computer randomization (EHL KRONIX) to the following test groups:

Test Group	Dose in diet (ppm)	Main Study 24 months male	female	Interim Sac. 12 months male	female
1 Cont.	0	60	60	10	10
2 Low (LDT)	40	60	60	10	10
3 Mid (MDT)	200	60	60	10	10
4 High(HDT)	1000	60	60	10	10

2. Diet Preparation

Diet was prepared "approximately weekly" and stored at room temperature (apparently). Samples of treated food were analyzed for stability at room temperature and when refrigerated. "Dietary Level Verification" was checked on all dietary levels at during first 6 weeks and week 89 and on "one level/week otherwise".

Results - A signed cover sheet for the Appendix (III) containing the chemistry data was provided. Methods for determination were provided.

Test material stability was found to range from 94.6 to 99.8% purity over a 2 year period.

According to the investigators "The homogeneity of the diet mixture was determined to be adequate for study use." They determined the homogeneity on the low and high concentrations prior to study initiation and at week 89. The data provided indicated an adequate mixing of the diet.

Stability analysis of the "test material/diet mixture" was determined for the low and high dose mixtures at room temperature for 14 days and when refrigerated for 42 days. Provided data indicate that the diet mixtures were stable under both storage conditions.

The investigators also performed weekly analysis of diet concentrations during the first 6 weeks for all the dose levels, one dose level per week after the initial 6 weeks, and for all 3 dose groups at week 89 due to change in batch size. All dose levels tested were slightly less than the target dose but within 10% of the planned level.

3. Animals received food (Ralston Purina rodent Chow No. 5002) and water (St. Louis Public Water Supply) ad libitum.

4. Statistics - According to the investigators' report:

"The following statistical procedures were used to detect statistically significant differences between treated animals and their respective controls":

"Dunnett's Multiple Comparison Test (two-tailed): body weights, food consumption, noncategorical clinical pathology data, absolute organ weights".

"Mann-Whitney Test with Bonferroni Inequality Procedure: Organ weight/body weight ratios".

"Fishers's Exact Test with Bonferroni Inequality Procedure: Incidence of microscopic lesions".

"Generalized Wilcoxin, Generalized Savage Statistics, and life table analysis: Mortality".

"Peto Analysis (one-tailed): Selected microscopic lesions and combinations thereof".

Other statistical procedures used were: "Bartlett's Test to evaluate homogeneity of variances, Analysis of Variance to determine if the sample (group) means could be considered as an estimate of a common population, and Grubb's Test to detect outliers".

5. A Signed "Statement of No Data Confidentiality Claims" was included (no claim of confidentiality made).

A signed "Statement of Compliance" with USEPA-GLP's was included.

A signed "DMEH Quality Assurance Audit Statement" was included.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected twice daily for signs of mortality and moribundity. They were further inspected once weekly for signs of toxicity.

Toxicity/Mortality (survival)

The investigators' provided group mean and individual animal data for mortality. The following Table (1) presents the survival data:

Table 1. Survival Data†

	Sex	Dose Group Control	Low	Mid	High
Survival at termination[a]	M	47	40	37	38
	F	40	43	43	48
Mean survival time (days)	M	681	663	651	670
	F	654	667	634	674

[a] - denominator excludes 10 animals/sex/group sacrificed at 12 months
† = Table appended from the investigators' report (MSL-6119).

No statistically significant differences were noted in the presented data. Inspection of individual data showed that nearly all deaths, either "spontaneous" or sacrifices "in extremis," occurred during the second year of the study. No specific time-to-death pattern was apparent. Gross and non-neoplastic microscopic necropsy observations occurred in similar incidence in all study groups, therefore, no treatment related cause of death could be determined. Neoplastic findings will be discussed later.

Clinical Observations:

The investigators provided a description of clinical signs, however, no effort was made to distinguish between dose groups, except for "Infrequent observations of head tilt, circling movements, somersaulting and dilation of conjunctival blood vessels....primarily in the last one-third of the study and appeared to effect [sic] T-2 and T-3 level rats more than controls (particularly females)." Individual animal data were provided. Inspection of these data reveals a possible dose-response effect on certain observations such as periorbital encrustation and soft stool. The investigators are directed to provide summary tables of all clinical observations.

2. Body weight

Animals were weighed once weekly for 13 weeks, then once every four weeks (following the initial 13 weeks) thereafter.

Table 2 and Figures 1 and 2 for males and females (appended from the investigators' report, only for the first 13 weeks) present body weights and body weight gains at selected intervals. High dose males had lower body weights and body weight gains from day 8 on, statistically significantly lower from days 455 to 678. High dose females also tended to have lower body weights and body weight gains, although values did not obtain statistical significance.

Table 2: Body Weights and Body Weight Gains at Selected Intervals (gm)[a]

	Males											
Day:	0	8	43	91	175	371	399	455	539	623	678	735
Dose (ppm)												
Control	222.7	264.3	443.5	535.0	612.3	752.7	766.7	813.1	813.7	840.4	820.2	744.9
		(41.6)†	(220.8)	(312.3)	(389.6)	(530.0)	(544.0)	(590.4)	(609.0)	(617.7)	(597.5)	(522.2)
40	222.6	272.8	449.1	542.1	615.9	750.5	750.4	795.4	797.4	791.5	780.9	710.1
		(50.2)	(226.5)	(319.5)	(393.3)	(527.9)	(527.8)	(572.8)	(574.8)	(568.9)	(558.3)	(487.5)
200	222.6	273.9*	449.2	536.2	608.9	751.7	762.6	798.8	827.0	814.4	787.5	759.2
		(51.3)	(226.6)	(313.6)	(386.3)	(529.1)	(540.0)	(576.2)	(604.4)	(591.8)	(564.9)	(536.6)
1000	222.6	269.5	439.3	527.1	599.3	719.7	725.9	747.8**	760.8*	732.6**	700.6**	681.7
		(46.9)	(216.7)	(304.5)	(376.7)	(497.1)	(503.3)	(525.2)	(538.2)	(510.0)	(478.0)	(459.1
	Females											
Day:	0	9	44	92	176	372	400	456	540	624	679	736
Control	157.2	176.8	241.5	279.2	318.2	425.7	436.3	455.5	467.3	486.0	505.8	465.1
		(19.6)	(84.3)	(122.0)	(161.0)	(268.5)	(279.1)	(298.3)	(310.1)	(328.8)	(348.6)	(307.9)
40	157.2	177.1	244.4	284.8	326.1	433.2	445.9	467.7	499.0	519.4	522.1	487.6
		(19.9)	(87.2)	(127.6)	(168.9)	(276.0)	(288.7)	(310.5)	(341.8)	(362.2)	(364.9)	(330.4)
200	157.2	177.5	246.3	285.3	326.1	435.2	455.7	475.5	481.7	512.4	527.5	525.7
		(20.3)	(89.1)	(128.1)	(168.9)	(278.0)	(298.5)	(318.3)	(324.5)	(355.2)	(370.3)	(368.5)
1000	157.3	176.1	241.6	281.8	316.9	405.3	412.4	435.2	455.5	469.3	469.6	450.4
		(18.8)	(84.3)	(124.5)	(159.6)	(248.0)	(255.1)	(277.9)	(298.2)	(312.0)	(312.3)	(293.1)

* = $P < 0.05$; ** = $P < 0.01$

† = Body weight gains

[a] = Data extracted from Report MSL-6119, Appendix II, Table 2.

3. Food consumption and compound intake

Food consumption was determined weekly for 13 weeks and then every 4 weeks and mean daily diet consumption was calculated. Food efficiency was calculated from the food consumption and body weight gain data for the first 13 weeks. The investigators supplied group summary and individual animal data for food consumption. They did not calculate compound intake.

Food consumption/Food Efficiency/Compound Intake

Table 3 presents the food consumption data at selected intervals (similar intervals to body weight data). A slight dose-related increase in food consumption in both sexes (high dose) was noted especially during the period when a decrease in body weight and body weight gain was noted. This is indicative of reduced food efficiency.

Table 4 presents the food efficiency data for the first 13 weeks. Reduced food efficiency was observed in both males and females of the high dose during the first 13 weeks of the study.

Table 3: Food Consumption (mean gm/kg body weight/day)[a]

	Males										
Days	1-8	35-43	84-91	168-175	364-371	391-399	448-455	532-539	616-623	672-678	728-735
Dose (ppm)											
Control	80.7	58.4	52.1	42.5	34.6	34.1	33.5	31.3	30.8	33.4	29.2
40	84.9*	58.2	51.4	42.0	35.7*	33.6	33.7	31.3	30.6	34.0	32.8
200	86.1**	59.2	52.6	42.6	36.0**	34.1	33.3	31.9	32.5	32.9	35.8*
1000	85.4**	59.6*	52.6	42.7	36.2**	35.4	34.0	34.3*	33.0	33.3	34.1
	Females										
Days	2-9	36-44	85-92	169-176	365-372	392-400	449-456	533-540	617-624	673-679	729-736
Dose (ppm)											
Control	85.7	69.9	71.8	59.6	46.5	45.3	41.1	40.9	38.3	40.0	36.9
40	86.6	71.1	72.6	60.6	47.1	42.8	41.4	41.5	37.8	37.6	36.2
200	88.7	72.2	71.5	60.8	47.2	43.8	40.0	42.6	37.1	40.4	40.0
1000	89.6**	73.2**	71.6	61.1	47.5	45.8	43.7	41.9	40.6	40.9	37.9

* = P < 0.05 ; ** = P < 0.01

[a] = Data extracted from Report MSL-6119, Appendix II, Table 4.

Table 4: Food Efficiency (mean %[†])[a]

	Males												
Days	1-8	8-14	14-22	22-29	29-35	25-43	43-49	49-56	56-62	62-70	70-77	77-84	84-91
Dose (ppm)													
Control	11.8	30.9	21.6	18.4	15.4	13.5	12.5	9.5	9.1	4.1	5.5	6.0	4.3
40	30.9**	30.2	21.3	17.9	15.7	13.2	12.4	7.3*	11.2	4.5	5.3	6.3	4.1
200	31.0**	28.7	21.3	18.4	14.9	13.3	11.8	9.6	6.2*	5.2	5.9	5.0	4.5
1000	29.1*	29.9	21.2	17.6	13.0**	13.9	11.3	10.6	6.1**	5.8**	6.1	4.0**	5.1
	Females												
Days	2-9	9-15	15-23	23-30	30-36	36-44	44-50	50-57	57-63	63-71	71-78	78-85	85-92
Dose (ppm)													
Control	18.3	12.9	14.0	10.5	6.5	10.3	3.4	8.5	3.0	1.3	5.2	4.5	4.1
40	18.3	12.2	14.7	12.1	5.4	10.6	1.2	9.5	2.2	2.4	5.0	4.3	5.3
200	18.3	15.5*	13.6	11.9	4.5	9.7	1.0*	9.8	2.1	4.0**	5.4	3.2	5.1
1000	16.9	16.9**	13.2	9.8	5.6	8.0*	2.6	8.9	-0.4**	6.0**	4.0	3.5	4.8

* = P < 0.05 ; ** = P < 0.01 (by Dunnett's Test [Two-Tailed])

[†] = mean %, calculated from food consumption and body weight data for the first 13 weeks.

[a] = Data extracted from Report MSL-6119, Appendix II, Table 5.

4. Ophthalmological examinations

Ophthalmic examinations were conducted prior to study initiation and at 6, 12, 18 and 24 months on all animals of the high dose and control (all animals were screened prior to study initiation). The following Table (5) presents the observations.

Table 5: Observed Ophthalmic Lesions[a]

Months	Control Males	High Dose Males	Control Females	High Dose Females
6	2(N=70)	1(N=69)	1(N=70)	2(N=70)
12	4	1	9	9
18	6	9	10	9
24	12(N=30)	13(N=27)	9(N=24)	9(N=30)

[a] = Data extracted from Report MSL-6119, Appendix II, Table 26.

Data for 6, 12 and 18 months may have been provided under clinical observations, but only as individual animal data. At study termination (24 months) the investigators described "senile lens changes and the presence of ocular discharge" as the predominant findings occurring in the control and high dose groups.

5. Blood was collected at approximately six months intervals for hematology and clinical analysis from 10 animals per sex, per dose group. The following parameters were examined.

a. Hematology

Hematocrit (HCT)*
Hemoglobin (HGB)*
Leukocyte count (WBC)*
Erythrocyte count (RBC)*
Platelet count*
Leukocyte differential count*
Mean corpuscular HGB (MCH)
Mean corpuscular HGB conc.(MCHC)
Mean corpuscular volume (MCV)
Reticulocyte count

* Required for chronic studies

Blood clotting measurements were not conducted. The investigators provided group summary and individual animal data. Blood was collected from fasted animals (food withheld 24 hours prior to sampling), from the retroorbital sinus for month 6 and 18 and from the posterior vena cava (under anesthesia) for months 12 and 24. Only occasional differences were noted. There were statistically significant decreases in white blood cell counts in low and mid dose males at 1 year and low dose females at 18 months; a decrease in MCH in low dose females at 1 year and high dose males at 2 years; a decrease in MCHC in high dose males at 1 and 2 years, low dose females at 1 year and mid dose females at 18 months; platelets were increased in mid dose females at 1 year; reticulocyte counts were decreased in low dose females at 1 year; absolute lymphocyte counts were decreased in all male treated groups and mid dose females at 1 year. None of the differences appear biologically relevant as they were not sustained with no dose response apparent and no related pathological changes noted.

b. Clinical Chemistry

Electrolytes:
- Calcium*
- Chloride*
- Phosphorous*
- Potassium*
- Sodium*

Enzymes
- Alkaline phosphatase
- Lactic acid dehydrogenase
- Serum alanine aminotransferase (also SGPT)*
- Serum aspartate aminotransferase (also SGOT)*
- gamma glutamyl transferase

Other:
- Albumin*
- Blood creatinine*
- Blood urea nitrogen*
- Cholesterol*
- Glucose*
- Total Bilirubin*
- Total Serum Protein*
- Direct Bilirubin

* Required for chronic studies

The investigators did not measure magnesium and creatinine phosphokinase, which are required for chronic toxicity studies. The investigators provided group mean and individual animal data. Several measurements achieved statistical significance: decreased glucose levels in low and high dose females at 2 years; decrease BUN levels in mid dose females at 1 year; slightly decreased total protein levels in all dosed males at 1 year; decreased alkaline phosphorus levels in high dose males and females at 6 months; decreased LDH levels in high dose males at 6 months, mid dose males at 1 year, all 3 treated male groups at 18 months, mid and high dose females at 6 months, high dose females at 1 year and low dose female at 18 months; slightly decreased creatinine in high dose females at 6 months; slightly decreased sodium levels in mid dose males at 1 year. None of these differences appear to be related to treatment also, no dose response was apparent. However, several differences were attributable to treatment, (according to the investigators): statistically significant increase in gamma glutamyl transpeptidase in high dose males at 18 months and 2 years (also nonstatistically significant increase in mid and high dose males at 1 year and mid dose males at 2 years); increased cholesterol in high dose males at 2 years (also non-statistically significant increase at 18 months); increased total bilirubin in high dose females at 2 years.

6. Urinalysis

Urine was collected from fasted and "water-withheld" animals at 6, 12, 18 and 24 months. The following parameters were examined.

- Specific gravity*
- pH†
- Bilirubin*†
- Blood*†
- Sediment (microscopic)*
- Protein*†
- Glucose*†
- Ketones*†
- Urobilinogen

* Required for chronic studies

† = Assay with MULTISTIX reagent strips and CLINI-TEK reader.

Urine was collected for 6 hours using "metabolism trays". The investigators did not report appearance or volume of the urine as

required for chronic studies. The only observation of note was a slight increase in specific gravity of the urine of females in all 3 dose groups at 6 months (low dose was statistically significant) and 1 year. However, this observation had no dose response and was not observed in subsequent examinations.

7. Sacrifice and Pathology -

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

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
X	.Salivary glands*	X	.Aorta*	XX	.Brain*†
X	.Esophagus*	XX	.Heart*	X	Periph. nerve*
X	.Stomach*	X	.Bone marrow*	X	Spinal cord(3 levels)*
X	.Duodenum*	X	.Lymph nodes*	X	.Pituitary*
X	.Jejunum*	X	.Spleen*	X	Eyes(optic n.)*
X	.Ileum*	X	.Thymus*		Glandular
X	.Cecum*		Urogenital	XX	.Adrenals*
X	.Colon*	XX	.Kidneys*†	X	Mammary gland*
X	.Rectum*	X	.Urinary bladder*	XX	.Parathyroids*
XX	.Liver*†	XX	.Testes*†(w/epidid)	XX	.Thyroids*(w/parathyroid)
X	.Pancreas*	XX	Epididymides		Other
	Respiratory	X	Prostate	X	Bone*(with marrow)
X	.Trachea*	X	Seminal vesicle	X	Skeletal muscle*
X	.Lung with bronchi*	X	Ovaries*†	X	Skin*
X	Nasal turbinates	X	.Uterus*	X	All gross lesions/masses*
X	Penis			X	Middle ear

* Required for chronic studies
† Organ weights required in chronic studies

a. Organ weight

The investigators supplied group mean and individual animal data for absolute organ weights and organ weights relative to body weights for interim and final sacrifice. Organ weight to brain weight ratios were not calculated. Table 6 presents the mean absolute and relative organ weight data for interim sacrifice and at study termination.

At the interim sacrifice, slight increases in absolute and relative kidney weights were noted in the high dose males along with a slight dose-related increase in absolute and relative liver weights in all treated males. At terminal sacrifice the high dose males had slightly increased absolute and relative kidney weights, a slight increase in absolute and relative (statistically significant in the high dose) liver weights and slightly increased absolute and relative (statistically significant in the high dose) testes weight.

TABLE 6: Absolute and Relative Organ Weights[a]

Organ	Dose (ppm):	Males - Interim Sacrifice Control	40	200	1000	Females - Interim Sacrifice Control	40	200	1000
Adrenals	A[†]	0.055[††]	0.067	0.070	0.060	0.078	0.081	0.079	0.081
	R[†]	0.008	0.009	0.010	0.009	0.019	0.021	0.021	0.022
Brain	A	2.188	2.174	2.171	2.182	2.094	2.048	1.995	1.941*
	R	0.308	0.291	0.305	0.315	0.502	0.534	0.530	0.503
Heart	A	1.908	1.916	1.855	1.861	1.295	1.272	1.261	1.220
	R	0.268	0.254	0.259	0.268	0.307	0.323	0.332	0.311
Kidneys	A	3.796	4.330	3.775	4.327	2.533	2.405	2.573	2.651
	R	0.532	0.575	0.535	0.720	0.606	0.618	0.686	0.675
Liver	A	19.430	19.787	21.184	21.328	11.841	11.113	10.863	11.332
	R	2.721	2.605	2.958	3.050	2.817	2.795	2.827	2.879
Testes	A	5.913	6.602	6.533	6.520	-	-	-	-
	R	0.829	0.867	0.898	0.931	-	-	-	-
Thyroids	A	0.036	0.043	0.040	0.043	0.036	0.040	0.038	0.038
	R	0.005	0.006	0.006	0.006	0.009	0.010	0.010	0.010

* = P<0.05 using Dunnett's Test

† = A = Absolute; R = Relative (mean %)

†† = grams

a = Data extracted from Report MSL-6119, Appendix II, Table 10, 11, 12 and 13.

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TABLE 6 continued: Absolute and Relative Organ Weights[a]

Organ	Dose (ppm):	Males - Terminal Sacrifice Control	40	200	1000	Females - Terminal Sacrifice Control	40	200	1000
Adrenals	A[†]	0.099[††]	0.100	0.098	0.123	0.113	0.113	0.140	0.109
	R[†]	0.014	0.015	0.014	0.019	0.028	0.024	0.031	0.027
Brain	A	2.358	2.325	2.348	2.304	2.053	2.037	2.031	2.036
	R	0.349	0.352	0.335	0.361	0.502	0.441	0.434	0.515
Heart	A	2.199	2.321	2.238	2.291	1.596	1.521	1.608	1.462
	R	0.321	0.351	0.316	0.354	0.387	0.320	0.343	0.366
Kidneys	A	5.656	5.948	5.441	6.271	3.311	3.201	3.425	3.182
	R	0.839	0.922	0.774	0.967	0.804	0.690	0.708	0.797
Liver	A	20.320	20.842	20.925	22.331	13.910	13.765	14.331	12.652
	R	2.941	3.117	2.908	3.479*	3.260	2.903	2.975	3.096
Testes	A	5.576	5.571	5.756	5.893	-	-	-	-
	R	0.807	0.820	0.790	0.903*	-	-	-	-
Thyroid	A	0.059	0.060	0.056	0.062	0.047	0.051	0.051	0.049
		0.009	0.009	0.008	0.010	0.011	0.011	0.011	0.012

* = P<0.05 using Dunnett's Test

† = A = Absolute; R = Relative (mean

†† = grams

[a] = Data extracted from Report MSL-6119, Appendix II, Table 10, 11, 12 and 13.

2b. Gross pathology

Gross pathological observations during the 1 year interim sacrifice were infrequent and apparently not treatment related. Observations can be seen on Table 7. Observations at 2 years were not significantly different between dose groups (Table 8 presents selected observations). Table 9 presents selected observations of animals dying on study. No biologically relevant differences were noted. Table 10 presents a selected summary of all gross necropsy observations, again no biologically relevant differences were noted.

TABLE 7: Selected Gross Necropsy Observations (1 year)[a]

Dose (ppm):	Control	40	200	1000
#examined m/f	10/10	10/10	10/10	10/10
Observation:				
Adrenals:				
enlarged	0/1	0/1	1/0	0/0
Heart:				
enlarged	3/0	2/0	2/0	1/1
abnormal color	3/0	3/0	2/2	1/1
Kidneys:				
hydronephrosis	0/1	1/0	0/2	0/1
Liver:				
abnormal color	2/2	0/0	1/0	0/0
foci/spots	0/0	0/1	0/0	0/0
Lymph Node				
enlarged	0/0	0/0	1/0	0/0
Nose/Turbinates:				
mass/nodule	0/1	0/0	0/0	0/0
Pitutary:				
enlarged	0/0	0/0	0/1	0/0
hemorrhage	0/0	0/0	0/1	1/0
focus/spots	0/0	0/3	0/2	0/3
Spleen:				
enlarged	0/0	0/0	1/0	0/0
Testes:				
atrophic	0	1	1	1
Thyroids:				
atrophic	0/0	0/0	0/1	0/0
Urinary Bladder:				
urolithiasis	0/0	0/0	0/0	0/1
Uterus:				
thickened walls	0	1	0	0
hydrometra	0	0	1	0

[a] = Data extracted from Report MSL-6119, Appendix II, Table 14.

TABLE 8: Selected Gross Necropsy Observations (2 years)[a]

Dose (ppm):	Control	40	200	1000
#examined m/f	28/24	24/26	22/26	23/30
Observation:				
Adrenals:				
enlarged	7/9	0/6	0/10	2/9
atrophic	0/2	1/0	0/0	0/0
focus(i)	6/11	4/14	5/13	4/13
Brain:				
compressed by pituit.	3/6	1/6	1/9	2/11
Eyes:				
corneal opacity	1/2	0/0	2/4	2/0
Kidneys:				
hydronephrosis	2/0	3/2	0/6	4/0
cyst(s)	1/1	4/1	1/0	3/0
abnormal color	9/3	8/0	4/2	7/0
granular/pitted	6/2	6/1	0/2	6/0
Liver:				
abnormal color	1/5	3/2	4/1	2/2
foci/spots	13/10	4/6	6/-	12/10
mass/nodule	0/2	4/0	1/0	3/4
cyst(s)	0/1	2/2	0/1	2/0
Lymph Node:				
enlarged	3/2	2/0	1/1	3/3
congested	0/3	0/1	0/2	1/0
Nose/Turbinates:				
mass/nodule	0/0	1/0	0/1	0/0
Ovaries:				
cyst(s) [within]	1	1	1	1
paraovarian cysts(s)	3	2	0	0
Pancreas:				
nodule	1/2	2/1	2/1	0/1
Pituitary:				
enlarged	6/11	3/13	6/12	5/13
hemorrhagic	6/3	4/9	1/8	4/7
focus/spots	3/4	3/6	2/4	2/5
mass/nodule	2/4	2/2	3/2	2/5
Spleen:				
enlarged	2/1	2/0	2/0	3/0
mass/nodule	0/0	0/0	1/0	1/1
Testes:				
atrophic	3	6	4	3
growth(s)/mass(es)	0	0	1	0
Thyroids:				
enlarged	0/0	0/0	0/3	0/1
Urinary Bladder:				
urolithiasis	2/0	0/0	1/0	0/0
growths/masses	1/0	0/0	0/0	1/0
Uterus:				
thickened walls	1	1	3	1
hydrometra	0	1	2	2
endometrial polyp(s)	2	3	2	2
cyst(s)	1	0	0	2
Subcutis:				
growth/mass	8/29	5/26	3/27	2/22

a = Data extracted from Report MSL-6119, Appendix II, Table 15.

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TABLE 9: Selected Gross Necropsy Observations (early deaths)[a]

Dose (ppm):	Control	40	200	1000
#examined m/f	32/36	35/34	38/34	37/30
Observation:				
Adrenals:				
enlarged	4/10	5/10	6/8	2/6
atrophic	0/0	0/4	0/2	0/0
focus(i)	8/15	6/10	5/9	8/10
Brain:				
compressed by pituitary	16/22	12/23	20/15	9/18
Eyes:				
corneal opacity	5/3	6/1	8/2	5/3
encrustation	3/5	2/4	1/7	3/5
dicharge	2/11	9/10	4/6	6/5
Heart:				
enlarged	3/0	2/0	2/0	1/1
abnormal color	2/0	3/0	2/1	1/1
Kidneys:				
enlarged	4/1	7/0	5/0	7/1
hydronephrosis	10/4	7/4	7/7	7/3
calculus(i)	1/1	3/2	1/2	0/1
cyst(s)	2/2	6/1	2/0	6/1
abnormal color	12/4	11/3	13/6	12/3
atrophy	0/0	1/0	0/0	0/0
granular pitted	11/1	16/4	17/5	17/3
Liver:				
abnormal color	9/10	20/6	12/10	10/6
foci/sports	9/6	9/11	12/5	8/10
enlarged	0/0	0/0	2/0	1/1
abnormal texture	1/0	0/0	1/2	0/1
pitted/nodular/ granular surface	0/0	0/0	2/0	2/0
mass/nodule	2/1	2/0	2/2	0/1
cyst(s)	1/0	2/1	0/2	0/2
Lymph Node:				
enlarged	0/3	4/3	4/0	1/0
congested	3/0	5/0	3/1	4/1
Lung:				
foci/spots	6/0	3/1	1/3	2/1
congested	7/6	4/5	8/2	6/4
abnormal	3/2	2/3	3/5	2/1
Mammary Gland:				
growth(s)/mass(es)/ nodule(s)	0/1	0/2	1/2	0/0
Nose/Turbinates:				
discharge	5/10	7/7	6/6	6/8
mass/nodule	0/0	1/0	0/0	0/0
Ovaries:				
cyst(s)[within]	0	0	2	1
paraovarian cyst(s)	0	0	1	6
Pancreas:				
nodule	5/0	7/3	4/1	5/2

continued

TABLE 9 continued: Selected Gross Necropsy Observations (early deaths)[a]

Dose (ppm):	Control	40	200	1000
#examined m/f	32/36	35/34	38/34	37/30
Observation:				
Pituitary:				
enlarged	22/31	18/30	24/25	15/24
hemorrhagic	10/15	10/20	16/11	5/10
focus/spots	1/2	11/1	2/2	2/0
mass/nodule	0/1	1/0	0/1	3/0
Prostate:				
atrophy	5	6	7	5
Parathyroids:				
enlarged	4/0	4/0	3/2	5/0
Skin:				
growth(s)/mass(es)	2/1	4/0	3/1	1/0
Spleen:				
enlarged	0/3	2/0	2/3	3/0
atrophic	0/0	0/0	0/2	1/1
mass/nodule	1/0	0/0	1/0	0/0
Seminal Vesicles:				
atrophy	10	9	11	11
enlarged	3	1	1	1
Testes:				
atrophic	10	17	14	13
growth(s)/mass(es)	1	1	0	0
enlarged	0	0	0	1
Thyroids:				
enlarged	2/1	1/0	3/0	6/1
focus	0/0	0/0	1/0	0/0
Urinary Bladder:				
dilated	2/1	6/2	4/1	1/3
urolithiasis	1/0	2/0	1/0	1/1
growths/masses	0/0	0/0	0/0	0/0
thickened walls	0/0	0/0	0/0	0/0
Uterus:				
thickened walls	0	2	2	2
hydrometra	1	0	1	0
endometrial polyp(s)	4	5	5	2
cyst(s)	1	0	0	1
Subcutis:				
growth/mass	4/25	10/30	6/27	7/19

[a] = Data extracted from Report MSL-6119, Appendix II, Table 17.

TABLE 10: Selected Gross Necropsy Observations (all deaths)[a]

Dose (ppm):	Control	40	200	1000
#examined m/f	70/70	69/70	70/70	70/70
Observation:				
Adrenals:				
enlarged	11/20	5/17	7/18	4/15
atrophic	0/2	1/4	0/2	0/0
focus(i)	14/26	10/24	10/22	12/23
Brain:				
compressed by pituitary	19/28	13/29	21/24	11/29
Eyes:				
corneal opacity	6/7	6/1	10/7	7/3
encrustation	4/6	2/4	1/7	3/8
discharge	2/11	9/10	4/6	6/5
Heart:				
enlarged	3/0	2/0	2/0	1/1
abnormal color	3/0	3/0	2/2	1/1
Kidneys:				
enlarged	4/1	7/0	5/0	9/1
hydronephrosis	12/5	11/6	7/15	11/4
calculus(i)	1/1	3/3	1/3	0/1
cyst(s)	3/3	11/3	3/1	9/1
abnormal color	21/7	19/3	17/8	19/3
atrophy	0/0	1/0	0/0	0/0
granular pitted	17/3	22/5	17/7	23/3
Liver:				
abnormal color	12/17	23/8	17/11	12/8
foci/spots	22/16	13/18	18/11	20/20
enlarged	0/0	0/0	2/0	1/1
abnormal texture	1/1	0/0	1/2	1/1
pitted/nodular/ granular surface	0/0	1/0	2/0	2/1
mass/nodule	2/3	6/0	3/2	3/5
cyst(s)	1/1	4/3	0/3	2/2
Lymph Node:				
enlarged	3/5	6/3	6/4	4/3
congested	3/3	5/1	3/3	5/1
Lung:				
foci/spots	6/0	3/2	1/4	2/2
congested	7/6	4/5	8/2	6/4
abnormal color	3/4	2/3	3/5	3/1
nodule(s)	0/0	0/0	2/2	1/0
Mammary Gland				
growth(s)/mass(es)/ nodules(s)	0/1	0/2	1/2	0/1
Nose/Turbinates:				
discharge	5/10	7/7	6/6	6/8
mass/nodule	0/1	2/0	0/1	0/0
Ovaries:				
cyst(s)[within]	1	1	3	1
paraovarian cyst(s)	3	2	1	6
Pancreas:	6/2	9/4	6/2	5/3
nodule				

continued

TABLE 10 continued: Selected Gross Necropsy Observations (all deaths)[a]

Dose (ppm):	Control	40	200	1000
#examined m/f	70/70	69/70	70/70	70/70
Observation:				
Pituitary				
enlarged	28/42	21/43	30/38	20/37
hemorrhagic	16/18	14/29	17/20	10/17
focus/spots	4/6	4/10	4/8	4/8
mass/nodule	2/5	3/2	3/3	5/5
Prostate:				
atrophy	5	7	7	5
Parathyroids:				
enlarged	4/1	4/0	3/2	5/0
Skin:				
growth(s)/mass(es)	4/1	10/2	5/1	3/1
Spleen:				
enlarged	2/4	4/0	5/3	5/0
atrophic	0/0	0/0	0/2	0/1
mass/nodule	1/0	0/0	2/0	1/1
Seminal Vesicles:				
atrophy	10	10	12	11
enlarged	3	2	1	1
Testes:				
atrophic	13	24	19	17
growth(s)/mass(es)	1	1	1	0
enlarged	0	0	1	1
Thyroids:				
enlarged	2/1	1/0	3/3	6/2
atrophic	0/0	0/0	0/1	0/0
Urinary Bladder:				
dilated	2/2	6/2	4/1	1/4
urolithiasis	3/0	2/0	2/0	1/2
growths/masses	1/0	0/0	0/0	1/0
thickened walls	0/0	0/1	0/1	0/1
Uterus:				
thickened walls	1	4	5	3
hydrometra	1	1	4	2
endometrial polyp(s)	6	8	7	4
cyst(s)	2	0	0	3
Subcutis:				
growth/mass	12/55	15/56	9/54	9/41

[a] = Data extracted from Report MSL-6119, Appendix II, Table 17.

c. Microscopic pathology

1) Non-neoplastic

The investigators provided group summary and individual animal data for interim sacrifices, early deaths and final sacrifices. Table 11 presents selected observations from the 1 year interim sacrifice. The major observations were an increase hepatocyte cellular alterations and bile duct hyperplasia in the high dose males and an increase in inflammation of the nasal mucosa in the high dose males and females. Table 12 presents selected observations from animals dying prior to study termination. There was an indication of an increase in hepatocyte cellular alteration, liver bile duct hyperplasia, hepatocyte necrosis and "nodular or diffuse" hyperplasia in the parathyroids of the high dose males. However, the summary data provided did not indicate if the observation listed as "autolysis" changed the number of tissues available for examination. Inspection of the individual data indicates that many of these tissues were not available for microscopic evaluation. Therefore, a thorough evaluation of all animals on study was not possible with the provided summary tables. The investigators' are directed to supply tables indicating the actual number of tissues examined for each organ/dose level used for histopathological examination. Table 13 presents selected observations from the animals at terminal sacrifice (2 years). An interesting observation in these animals and from animals that died prior to the end of the study (Table 12) was that of the brain being compressed by an enlarged pituitary. This occured in roughly equal incidence in all groups, however, an accurate description of the finding was not provided. It is possible that a pituitary tumor could be causing this compression of the brain, this will be discussed later. For the animals sacrificed at study termination, there was an increase in mid and high dose males and high dose females with plasma cell hyperplasia in the lymph node. Also, an increase in high dose males with papillary hyperplasia of the nasal epithelium and "c" cell hyperplasia of the thyroids (statistically significantly different). Table 14 presents a summary of selected observations for all animals on study (again some tissues were autolyzed).

TABLE 11: Selected Microscopic Observations (1 year)[a]

Dose (ppm):	Control	40	200	1000
#animals m/f	10/10	10/10	10/10	10/10
Observation:				
Adrenals:				
hyperplasia/hypertrophy-				
medullary	0/0	0/0	0/0	1/1
cortical nodular	0/0	0/0	0/2	0/1
Brain:				
Compressed by pituitary	0/1	0/0	0/1	0/0
Epididymides:				
epithelial degenerative changes	0	1	1	2
Heart:				
myocarditis	3/0	2/1	2/0	2/0
myocardiolysis	2/0	1/1	3/0	0/0
proliferation of endomysial/ myocyte nuclei	1/0	1/1	1/0	1/0
Kidneys:				
glomerular/periglomerular sclerosis	1/0	1/0	0/0	0/0
chronic nephritis	8/0	8/0	9/0	9/0
hydronephrosis -				
bilateral	0/1	0/0	0/1	0/0
unilateral	0/0	1/0	0/2	0/2
pyelitis	0/1	0/0	1/0	0/1
pelvic epithelium and hyperplasia-				
non-papilliform	0/0	1/0	0/0	0/1
papilliform	0/0	0/0	0/2	0/0
Liver:				
cellular alteration	2/2	2/0	1/0	4/3
hyperplasia-bile duct	1/1	2/2	2/1	4/2
telangiectasis	0/0	0/3	1/0	1/0
nodular hypertrophy/ hyperplasia	0/0	0/1	0/0	0/0
Lymph Node:				
hyperplasia-plasma cell	0/0	0/0	0/2	0/3
mononuclear cell leukemia	0/0	0/0	1/0	0/0
Lung:				
pneumonia	1/0	3/1	2/2	1/2
Nose/Turbinates:				
mucosal lymphoid hyperplasia	6/1	1/0	1/1	1/0
inflammation-				
nasal sinus	1/0	1/0	1/1	0/1
nasal mucosa	1/0	3/1	2/1	4/2
papillary hyperplasia of nasal epithelium	0/0	0/0	2/0	1/0
Pituitary:				
hyperplasia-chromophobe	1/4	2/1	3/4	0/1
Thyroids:				
hyperplasia-"c" cell	0/1	0/0	0/0	0/0
Urinary Bladder:				
hyperplasia-epithelial	0/0	0/0	1/0	0/1

a = Data extracted from Report MSL-6119, Appendix II, Table 18

TABLE 12: Selected Microscopic Observations (early deaths)†

Dose (ppm):	Control	40	200	1000
#animal m/f	32/36	36/34	38/34	37/30
Observation:				
Adrenals:				
hyperplasia/hypertrophy-				
medullary	5/0	8[a]/1	5/3	7/0
cortical nodular	1/5	2[a]/2	3/3	4/3
Bone Marrow:				
hyperplasia-				
myelocyte/granulocyte	5/10[a]	8[b]/5	5[c]/5	4/6[h]
pancytic	2/4[a]	1[b]/3	0/4	0/2[h]
Brain:				
compressed by pituitary	17/25	20[a]/29	21/23	13/24
Bone:				
fibrotic replacement	4/0	7[b]/0	4[c]/1	9/0
osteolysis	3/0	5[b]/0	2[c]/0	9/0
Epididymides:				
epithelial degenerative				
changes	3	5[a]	4	5
Eyes				
keratitis	8/3	4/0	6/5	4/2
Heart:				
myocarditis	3/3	4[b]/1	4/2[g]	7/4
myocardiolysis	12/5	10[b]/4	12/3[g]	15/4
proliferation of endomysial/				
myocyte nuclei	18/8	22[b]/7	25/9[g]	23/12
myocardial fibrosis	20/8	21[b]/9	22/7[g]	23/11
Kidneys:				
glomerular/periglomerular				
sclerosis	7/3	10[a]/1	14/1	14/1
chronic nephritis	23/15	30[a]/13	34/15	32/18
hydronephrosis -				
bilateral	1/2	2[a]/1	0/2	5/2
unilateral	3/2	4[a]/3	5/6	1/2
pyelitis	2/1	1[a]/2	2/5	2/2
pylonephritis	2/2	2/1	3/1	6/3
pelvic epithelium hyperplasia-				
non-papilliform	1/0	1/2	2/4	2/1
papilliform	0/0	0/1	1/2	2/4
Liver:				
cellular alteration	2/7	3[a]/9	3/2	6/4
hyperplasia-bile duct	7/1	4/3	6/5	10/5
telangiectasis hepatocyte				
necrosis	6/2	7/0	6/1	12/2
nodular hypertrophy/				
hyperplasia	0/3	1/1	2/1	2/1
Lymph Node:				
hyperplasia-plasma cell	1/7	2[b]/9	2/2	0/4
mononuclear cell leuk.	0/0	1/0	0/0	0/0
Lung:				
pneumonia	6/6	8[a]/3	8/11	6/6
edema	2/2	3[a]/1	2/0	6/5
emphysema	3/0	2[a]/2	2/1	1/1
leukemia-				
myclogenous	0/0	0/0	1/0	0/0
mononuclear	0/0	1/0	0/0	0/0

continued

TABLE 12 continued: Selected Microscopic Observations (early deaths)†

Dose (ppm):	Control	40	200	1000
#animals m/f	32/36	36/34	38/34	37/30
Observation:				
Nose/Turbinates:				
mucosal lymphoid hyperplasia	0/0	0/0	0/1	0/0
inflammation				
nasal sinus	0/0	0/0	0/0	0/0
nasal mucosa	2/4	6[a]/4	6/1	6/6
papillary hyperplasia of nasal epithelium	0/0	0/3	0/1	0/3
Pancreas:				
islet cell hyperplasia	1[d]/1	0/2	2[c]/1	0/1
Pituitary:				
hyperplasia-				
chromophobe	1/1[a]	2[b]/0	1/1	4[e]/1
pars intermedia	0/0	0/0	2/0	1[e]/0
Parathyroids:				
hyperplasia-				
nodular(or diffuse)	7[d]/10	14[f]/1[f]	7/39	15[f]/0
Spleen:				
hyperplasia-plasma cell	1/0[b]	0/0	1[c]/0	2/2
Testes:				
hyperplasia-				
interstitial cell	0	1[a]	0	0
Urinary Bladder:				
hyperplasia-epithelial	2[d]/0	49/39	4/1	2/2[h]
Uterus:				
mucosal polyp	2	3	2	1

[a] = 35(#animals); [b]=34; [c]=37; [d]=31; [e]=36; [f]=32; [g]=33; [h]=29.
† = Data extracted from Report MSL-6119, Appendix II, Table 20.

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TABLE 13: Selected Microscopic Observations (2 years)†

Dose (ppm):	Control	40	200	1000
#animals m/f	28/24	24/26	22/26	23/30
Observation:				
Adrenals:				
hyperplasia/hypertrophy-				
medullary	1/2	5/2	4/1	3/2
cortical nodular	3/1	4/2	3/5	1/6
Bone Marrow:				
hyperplasia-				
myelocyte/granulocyte	5/4	2/6	5/3	4/5
pancytic	2/1	0/3	0/2	1/1
Brain:				
compressed by pituitary	11/13	4/11	8/15	8/19
Epididymides:				
epithelial degenerative changes	3	1	3	0
Eyes:				
keratitis	2/2	4/3	1/0	2/0
Heart:				
myocarditis	1/3	1/6	4/5	3/3
myocardiolysis	7/6	5/1	1/2	9/3
proliferation of endomysial/ myocyte nuclei	16/11	16/14	12/16	15/10
myocardial fibrosis	18/11	14/12	12/10	15/11
Kidneys:				
glomerular/periglomerular sclerosis	9/3	12/3	6/4	2/1
chronic nephritis	26/16	24/19	22/18	23/21
hydronephrosis-				
bilateral	0/0	0/1	0/3	2/0
unilateral	2/0	0/2	2/3	4/1
pyelitis	3/2	1/2	1/1	2/2
pyelonephritis	2/3	3/2	1/0	1/0
pelvic epithelium/hyperplasia-				
non-papilliform	0/1	1/3	0/1	1/3
papilliform	2/0	1/6	0/2	2/2
Liver:				
cellular alteration	13/10	9/9	9/12	15/15
hyperplasia-				
bile duct	9/9	7/9	6/5	8/9
telangiectasis	17/2	10/1	11/4	16/3
hepatocyte necrosis	1/4	0/1	0/2	1/1
nodular hypertrophy/ hyperplasia	0/1	4/0	2/2	1/3
Lymph Node:				
hyperplasia-				
plasma cell	0/2	0/0	3/1	4/5
Lung:				
pneumonia	0/4	2/3	0/0	0/3
edema	0/0	0/1	0/1	0/0
emphysema	0/0	2/1	1/1	3/2

continued

TABLE 13 continued: Selected Microscopic Observations (2 years)†

Dose (ppm):	Control	40	200	1000
#animals m/f	28/24	24/26	22/26	23/30
Observation:				
Nose/Turbinates:				
inflammation-				
nasal mucosa	10/4	9/5	2/5	9/4
papillary hyperplasia of				
nasal epithelium	1/1	1/0	2/0	4/1
Pancreas:				
islet cell hyperplasia	1/0	2/1	0/0	0/2
Pituitary:				
hyperplasia-				
chromophobe	5/4	6/2	5/4	2/4
pars intermedia	2/0	2/0	0/0	2/0
Parathyroids:				
hyperplasia-				
nodular (or diffuse)	6[a]/1[c]	8[b]/0	2/1	4[b]/0
Spleen:				
hyperplasia-				
plasma cell	0/0	1/0	0/0	1/1
Testes:				
hyperplasia-				
interstitial cell	1	0	0	2
Thyroids:				
hyperplasia-				
"c" cell	0/2	3/4[d]	1/2	8**[c]/4
Urinary Bladder:				
hyperplasia-				
epithelial	3/0	1/1	1/1	1/1
Uterus:				
mucosa polyp	1	2	0	4

[a] = (#animals) = 27; [b]=21; [c]=22; [d]=25

** = $p<0.01$ by Fisher's Exact Test with Bonferroni inequality.

† = Data extracted from Report MSL-6119, Appendix II, Table 19.

TABLE 14: Selected Microscopic Observations (all deaths)†

Dose (ppm):	Control	40	200	1000
#animals m/f	70/70	70/70	70/70	70/70
Observation:				
Adrenals:				
hyperplasia/hypertrophy -				
medullary	6/2	13[a]/3	9/4	11/3
cortical nodular	4/6	6[a]/4	6/10	5/10
Bone Marrow:				
hyperplasia-				
myelocyte/granulocyte	10/14[b]	11[b]/12	10[a]/9	6/12[a]
pancytic	4/5[b]	1[b]/8	0/6	1/4[a]
Brain:				
compressed by pituitary	28/39	24[a]/40	29/39	21/43
Bone:				
fibrotic replacement	5/0	8[b]/0	5[a]/1	10/1[a]
osteolysis	4/0	6[b]/0	3[a]/0	10/0
Epididymides:				
epithelial degenerative changes	6	7[a]	8	7
Eyes:				
keratitis	11/5	8[a]/3	7/5	6/2
Heart:				
myocarditis	7/6	7[b]/8	10/7[a]	12/7
myocardiolysis	21/11	16[b]/6	16/5[a]	24/7
proliferation of endomysial/ myocyte nuclei	35/19	39[b]/22	38/25[a]	39/22
myocardial fibrosis	38/19	35[b]/21	34/17[a]	38/22
Kidneys:				
glomerular/periglomerular sclerosis	17/6	23[b]/4	20/5	16/2
chronic nephritis	57/33	62[b]/35	65/40	64/45
hydronephrosis-				
bilateral	1/3	2[b]/2	0/6	7/2
unilateral	5/2	5[b]/5	7/11	5/5
pyelitis	5/4	2[b]/4	4/6	4/5
pyelonephritis	4/5	5[b]/3	4/1	7/3
pelvic epithelium/hyperplasia-				
non-papilliform	1/1	3[b]/5	2/5	3/5
papilliform	2/0	1[b]/7	1/6	4/6
Liver:				
cellular alteration	17/19	14[b]/18	13/14	25/22
hyperplasia-				
bile duct	17/11	13[b]/14	14/11	22/16
telangiectasis	23/4	17[b]/4	18/5	29/5
hepatocyte necrosis	4/5	4[b]/4	5/10	7/4
nodular hypertrophy/ hyperplasia	0/4	5[b]/2	4/3	3/4
Lymph Node:				
hyperplasia-				
plasma cell	1/4	2[b]/4	5/6	2[a]/11
mononuclear cell leukemia	0/0	1[b]/0	1/0	0/0

continued

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TABLE 14 continued: Selected Microscopic Observations (all deaths)†

Dose (ppm):	Control	40	200	1000
#animals m/f	70/70	70/70	70/70	70/70
Observation:				
Lung:				
pneumonia	7/10	13[b]/7	10/13	7/11
edema	2/2	3[b]/2	2/1	6/5
emphysema	3/0	4[b]/3	3/2	4/3
leukemia-myelogenous	0/0	0/0	1/0	0/0
Nose/Turbinates:				
mucosal lymphoid hyperplasia	6/1	1[b]/0	1/2	1/0
inflammation-				
nasal sinus	1/0	1[b]/0	1/1	0/1
nasal mucosa	13/8	18[b]/10	10/7	19/12
papillary hyperplasia of nasal epithelium	1/1	1[b]/3	4/1	5/4
reas:				
islet cell hyperplasia	2[a]/1	2[b]/3	2[a]/1	2[b]/3
Pituitary:				
hyperplasia-				
chromophobe	7/9[a]	10[b]/3	9/9	6[a]/6
pars intermedia	2/1	2[b]/0	2/0	3[a]/0
Parathyroids				
hyperplasia-				
nodular(or diffuse)	13[b]/2[d]	22[c]/1[g]	9[d]/4[b]	19[e]/0
Spleen:				
hyperplasia-				
plasma cell	1/0	1[a]/0	1[a]/0	3/3
Testes:				
hyperplasia-				
interstitial cell	2	1[a]	0	2
Thyroids:				
hyperplasia-				
"c" cell	3/3	5[f]/4[a]	4/3	8[a]/4
Urinary Bladder:				
hyperplasia-				
epithelial	5[a]/0	5[f]/4[a]	6/2	3/4[a]
Uterus				
mucosa polyp	3	5	2	5

[a] = 69 (#animals); [b] = 68; [c] = 62; [d] = 66; [e] = 63; [f] = 67; [g] = 64
† = Data extracted from Report MSL-6119, Appendix II, Table 21.

2) Neoplastic

The investigators provided group summary and individual animal data for all reported lesions. Table 15 presents selected observations from the 1 year interim sacrifice. Most lesions were infrequent, however, a lesion of note was the papillary adenoma of mucosa in the nose/turbinates in one female of the high dose. Table 16 presents selected observations at the final sacrifice. Again, most lesions were infrequent and scattered throughout the study groups with the exception of an increase in neoplastic nodules of the liver in the mid and high dose females, follicular adenoma/cystadenoma of the thyroids in high dose males and females and papillary adenoma of muscosa of the nose/turbinates in high dose animals (statistically significantly greater in high dose females). Papillary adenoma of nasal mucosa was also noted in the high dose animals dying prior to the end of the study (statistically significant in both sexes), Table 17. Other lesions present in animals that died early were infrequent and did not reveal any dose-response relationship. Combining observations time of all animals (Table 18) shows an increase neoplastic nodules of the liver in mid and high dose females and a statistically significant increase in the number of papillary adenomas of mucosa in the nose/turbinates in high dose males and females. The high incidence of pituitary adenoma in both sexes of all dose groups may be the reason for the high incidence of the observation "brain compressed by pituitary" noted in gross observations. There were 4 cases of malignant astrocytoma of the brain, 3 in control males and 1 in a high dose female and 2 cases of oligodendroglioma of the brain, 1 each in a control male and a high dose female.

TABLE 15: Selected Neoplastic Observations (1 year)[a]

Dose (ppm):	Control	40	200	1000
#animal m/f	10/10	10/10	10/10	10/10
Observation:				
Pituitary:				
adenocarcinoma	1/0	0/0	0/1	0/0
adenoma	1/4	0/4	5/3	4/3
Mammary Gland:				
adenoma/adenofibroma/ fibroma	0/1	0/0	0/0	0/0
adenocarcinoma	0/0	0/0	0/0	0/1
Nose/Turbinates:				
papillary adenoma of mucosa	0/0	0/0	0/0	0/1

[a] = Data extracted from Report MSL-6119, Appendix II, Table 22.

TABLE 16: Selected Neoplastic Observations (2 years)†

Dose (ppm):	Control	40	200	1000
#animals m/f	28/24	24/26	22/26	23/30
Observations:				
Adrenals:				
cortical adenoma	1/0	0/1	0/0	0/0
pheochromocytoma	3/0	5/1	1/1	5/0
malignant pheochromocytoma	1/0	1/1	0/0	1/0
Brain:				
astrocytoma, malignant	1/0	0/0	0/0	0/1
granular cell tumor	0/0	1/0	0/0	0/0
oligodendroglioma	1/0	0/0	0/0	0/1
Liver:				
neoplastic nodule	1/0	1/1	0/4	1/5
hepatocellular carcinoma	1/1	2/1	1/0	1/1
Mammary Gland:				
adenoma/fibroma	0/12[a]	0/13[b]	0/10	0/10
adenocarcinoma	0/4[a]	0/2[b]	1[c]/3	0/1
Nose/Turbinates:				
papillary adenoma of mucosa	1/0	0/0	0/0	3/9*
Pancreas:				
islet cell adenoma	4/3	3/2	4/2	0/2
Pituitary:				
adenocarcinoma	0/0	0/0	0/0	0/3
adenoma	16/19	16/20	15/21	17/20
Testes:				
interstitial cell tumor	2	3	1	2
Thyroids:				
follicular adenoma/cystadenoma	1/0	0/1[b]	0/1	2[d]/3
"c" cell adenoma	2/2	2/2	0/4	0/1
Subcutis:				
fibrosarcoma	0/-[•]	1[c]/2[f]	0/0	-/0
fibroma	1[f]/-	4[c]/2[f]	0/0	-/0
neurofibroma	1[f]/-	0/0	0/1[g]	-/0

* = $p<0.05$ by Fisher's Exact Test with Bonferroni Inequality

[a] = (#animals) = 22; [b] = 25; [c] = 8; [d] = 22; [e] = 6; [f] = 4; [g] = 3.

[•] = - = no data provided.

† = Data extracted from Report MSL-6119, Appendix II, Table 23.

Table 17: Selected Neoplastic Observations (early deaths)†

Dose (ppm):	Control	40	200	1000
#animals m/f	32/36	36/34	38/34	37/30
Observation:				
Adrenals:				
cortical carcinoma	0/0	0/2	1/2	0/0
cortical adenoma	2/1	2[a]/0	5/1	3/0
pheochromocytoma	0/1	0/1	0/0	0/0
malignant pheochromocytoma	0/0	0/0	0/0	1/0
Brain:				
astrocytoma, malignant	2/0	0/0	0/0	0/0
granular cell tumor	0/0	0/0	0/1	0/0
Liver:				
neoplastic nodule	0/2	1[a]/1	1/1	0/1
hepatocellular carcinoma	0/1	0/0	0/0	0/0
Mammary Gland:				
adenoma/adenofibroma/ fibroma	0/14	0/10[c]	2[b]/13[d]	0/8[e]
adenocarcinoma	0/4	0/3[c]	0/3[d]	0/4[e]
Nose/Turbinates:				
papillary adenoma of mucosa	0/0	0/0	0/0	9*/9*
adenocarcinoma of submucosal gland	0/0	0/0	0/1	0/0
Pancreas:				
islet cell adenoma	0/0	5[f]/5	4[g]/1	1[a]/2
islet cell carcinoma	0/0	0/0	0/1	0/0
acinar cell adenoma	1[d]/0	0/0	1[g]/0	0/0
acinar cell carcinoma	0/0	1[f]/0	0/0	0/0
Pituitary:				
adenocarcinoma	0/2[a]	0/1	1/3	0/3
adenoma	27/28[a]	27[f]/32	27/24	22[h]/22
Testes:				
interstitial cell tumor	0	0	0	1
Thyroids:				
follicular adenoma/ cystadenoma	0/1	1[i]/1	1/1	0/1
"c" cell adenoma	1/5	3[i]/0	0/1	2/1
Subcutis:				
fibrosarcoma	2[j]/0	1[k]/0	0/2[l]	1[m]/1[m]
fibroma	1[j]/0	3[k]/1[n]	1[n]/0	0/0
neurofibroma	0/1[n]	0/0	0/1[l]	0/0

* = $p<0.05$ using Fisher's Exact Test with Bonferroni Inequality

a = (#animals) = 35; b=11; c=29; d=31; e=28; f=34; g=37; h=36; i=33; j=3; k=6; l=5; m=1; n=2.

† = Data extracted from Report MSL-6119, Appendix II, Table 24.

TABLE 18: Selected Neoplastic Observations (all deaths)†

Dose (ppm):	Control	40	200	1000
#animals m/f	70/70	70/70	70/70	70/70
Observation:				
Adrenals:				
cortical carcinoma	0/0	0/2	1/2	0/0
cortical adenoma	1/1	0/2	0/0	0/0
pheochromocytoma	5/1	7[a]/1	6/2	8/0
malignant pheochromocytoma	1/0	1[a]/1	0/0	2/0
Brain:				
astrocytoma, malignant	3/0	0/0	0/0	0/1
granular cell tumor	0/0	1[a]/0	0/1	0/0
oligodendroglioma	1/0	0/0	0/0	0/1
Liver:				
neoplastic nodule	1/2	2[a]/2	1/5	1/6
hepatocellular carcinoma	1/2	2[a]/1	1/0	1/1
Mammary Gland:				
adenoma/adenofibroma/ fibroma	0/27[b]	0/23[c]	2[d]/23[e]	0/18[b]
adenocarcinoma	0/8[b]	0/5[c]	1[d]/6[e]	0/6
Nose/Turbinates:				
papillary adenoma of mucosa	1/0	0/0	0/0	12*/19*
adenocarcinoma of submucosal gland	0/0	0/0	0/1	0/0
Pancreas:				
islet cell adenoma	4[a]/3	8[b]/7	8[a]/3	1[b]/4
islet cell carcinoma	0/0	0/0	0/1	0/0
acinar cell adenoma	1[a]/0	0/0	1[a]/0	0/0
acinar cell carcinoma	0/0	1[b]/0	0/0	0/0
Pituitary:				
adenocarcinoma	1/2[a]	0/1	1/4	0/6
adenoma	41/51[a]	43[b]/56	47/48	43[a]/45
Testes:				
interstitial cell tumor	2	3[a]	1	3
Thyroids:				
follicular adenoma/ cystadenoma	1/1	1[f]/2[a]	1/2	2[a]/4
"c" cell adenoma	3/7	5[f]/2[a]	0/5	2[a]/2
Subcutis:				
fibrosarcoma	2[g]/0	2[h]/2[i]	0/2[i]	1[k]/1[l]
fibroma	2[g]/0	7[h]/3[i]	1[m]/0	0/0
neurofibroma	1[g]/1[k]	0/0	0/2[i]	0/0

* = $p<0.05$ using Fisher's Exact Test with Bonferroni Inequality.
[a] = (#animals) = 69; [b]=68; [c]=64; [d]=21; [e]=65; [f]=67; [g]=7; [h]=12; [i]=6; [j]=8; [k]=1; [l]=2; [m]=3.
† = Data extracted from Report MSL-6119, Appendix II, Table 25.

D. DISCUSSION:

Acetochlor administered in doses of 40, 200 and 1000 ppm did not appreciably affect mortality or time-to-death. The clinical observation data were not presented in an adequate form for evaluation. Inspection of the individual animal clinical signs data reveals a possible dose-response in some observations. Body weight and body weight gain data showed a decrease in high dose males from day 8 on (statistically significant from days 455 to 678). High dose females also had a slight, but not statistically significant decrease in body weight and body weight gain. Food consumption was slightly decreased in the high dose animals. Food efficiency was reduced in animals of the high dose group (data was only presented for the first 13 weeks). No treatment related opthalmic observations were noted.

No biologically relevant or dose-related observations were noted in hematological parameters at 6, 12, 18 or 24 months.

The investigators did not conduct several clinical chemistry analyses, especially magnesium determinations, which can reveal several defects. Of the parameters measured, those attributable to treatment were statistically significant increases in gamma glutamyl transpeptidase in high dose males at 18 months and 2 years (mid and high dose males at 1 year showed slight increases as did mid dose males at 2 years). Also, cholesterol levels were increased (statistically significant) in high dose males at 2 years (a slight increase was noted at 18 months) and total bilrubin was increased in high dose females at 2 years. The observations of increased levels of gamma glutamyl transpeptidase and cholesterol may be indicative of liver toxicity.

No biologically relevant observations were noted in urinalysis data.

Organ weights determined at the interim sacrifice showed a slight increase in absolute and relative kidney weights in high dose males and a slight, dose-related increase in absolute and relative liver weights in treated males. This continued to final sacrifice where similar observations were noted including a statistically significant increase in relative liver weight of high dose males and an increase in absolute and relative testicular weight (statistically significant) in high dose males. Females were not similarly affected.

The gross pathological observations revealed no biologically relevant differences.

Microscopic observations for non-neoplastic findings at one year consisted of an increase in hepatocyte cellular alterations and liver bile duct hyperplasia in high dose males (1000 ppm) and an increase in inflammation of the nasal mucosa in high dose males and females. Of those animals dying prior to the end of the study, there was an apparent increase in hepatocyte cellular alteration, liver bile duct hyperplasia, hepatocyte necrosis and "nodular or diffuse" hyperplasia in the parathyroids of high dose males. However, tissue availability was not presented and since many organs had the observation "autolysis" with no indication if the autolysis involved the whole organ or just a defined area, a thorough evaluation of microscopic observations was not possible. At terminal sacrifice there was an increase in mid and high dose males and high dose females with plasma cell hyperplasia of the lymph node along with an increase in high dose males with papillary hyperplasia of the nasal epithelium and "C" cell hyperplasia of the thyroids (statistically significant). In the previous study (Study #PR-80-006, 5/20/83) with MON 097, there were increased histopathological observations in the liver and kidney in the high dose group (5000 ppm), see following discussion on neoplastic findings.

Neoplastic findings at the 1 year interim sacrifice were minimal with one incidence of a papillary adenoma of the mucosa in the nose/turbinates of a female in the high dose (1000 ppm) A statistically significant increase in this observation was noted in high dose males and females that died prior to study termination. At final sacrifice this observation was also increased where a statistically significant increase in high dose female and increase in high dose males of the observation of papillary adenoma of the mucosa in the nose/turbinates was noted. Other observations consisted of liver neoplastic nodules in high dose males and females at final sacrifice and early deaths and follicular adenoma/cystadenoma of the thyroids in high dose animals. These latter observations are similar to those observed in the earlier study (Study #PR-80-006, 5/20/83). In the earlier study, the high dose level (5000 ppm) caused increased incidence of liver carcinomas and thyroid follicular cell adenomas in males along with positive trends of increased hepatic carcinomas in high dose females (5000 ppm) and thyroid follicular cell adenomas in high dose males.

Based on the observations of decreased body weight gain, clinical chemistry observations, non-neoplastic findings and the neoplastic finding of an increase in papillary adenoma of the mucosa of the nose/turbinates in the males and females of the high dose group, it is apparent that the MTD (Maximum Tolerated Dose) was achieved in this study. This study is therefore acceptable for the chronic/oncogencity data requirement for Acetochlor (MON 097), however, the study is classified as supplementary data which possibly can be upgraded if requested data is submitted and accepted by the Agency.