ATTACHMENT B 14

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004586

EPA: 68-01-6561
TASK: 109
July 29, 1985

DATA EVALUATION RECORD

ACETOCHLOR

Chronic Feeding Toxicity and Oncogenicity Study in the Rat

STUDY IDENTIFICATION: Ahmed, F. E., Seely, J. C. _MON 097: Chronic toxicity and oncogenicity study in the rat. (Unpublished study No. PR-80-006, prepared by Pharmacopathics Research Laboratories, Inc., Laurel, MD, for Monsanto Company, St. Louis, MO; dated May 20, 1983.) Accession Nos. 071962 - 071965.

APPROVED BY:

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Date: 7/26/85

1. CHEMICAL: MON 097, 2-chloro-N(ethoxymethyl)-6'ethyl-ortho-aceto-toluidine, a herbicide (acetochlor).

2. TEST MATERIAL: The test material was from Lot # NBP 1737874 with 94.5% purity. The compound was described as a maroon liquid with a characteristic odor.

3. STUDY/ACTION TYPE: Chronic feeding toxicity and oncogenicity study in the rat.

4. STUDY IDENTIFICATION: Ahmed, F. E., Seely, J. C. MON 097: Chronic toxicity and oncogenicity study in the rat. (Unpublished study No. PR-80-006, prepared by Pharmacopathics Research Laboratories, Inc., Laurel, MD, for Monsanto Company, St. Louis, MO; dated May 20, 1983.) Accession Nos. 07196[illegible]965.

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7. CONCLUSIONS:

A. Under the conditions of this chronic/oncogenicity feeding study with Sprague-Dawley rats, there was increased mortality in females receiving the high dose (5000 ppm). There was a significant ($p < 0.05$) dose-related decrease in the mean body weights of males and females receiving the mid (1500 ppm) and high doses, and a significant ($p < 0.05$) decrease in food consumption by males and females receiving the high dose. A decrease in the mean body weight of males receiving the low dose (500 ppm) also reached a significant ($p < 0.05$) level at the end of the study (weeks 103 to 115). Histopathologic examination of the tissues indicated increased incidences of polyarteritis of the testis and arteries of males and liver necrosis and alveolar histiocytosis in females receiving the high dose ($p < 0.05$). There was also a statistically significant increase in the incidences of liver carcinomas and thyroid adenomas in males receiving the high dose ($p < 0.05$). In addition, a compound-related positive trend ($p < 0.05$) was noted for the incidences of liver carcinomas in males and females and thyroid follicular cell adenomas in males.

Based on body and organ weight data, the LOEL for chronic effects is 500 ppm (LDT).

B. The study is classified as core minimum, although a NOEL for non-neoplastic effects was not established; one must be established in a new chronic study.

8. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods:

A photocopy of the detailed materials and methods used in this study are presented in Appendix A; the following is a brief description:

1. The test material, MON-097, was mixed with the basic diet at specified amounts and provided to the rats ad libitum. Diets were prepared fresh weekly to give dietary levels of 0, 500, 1500, and 5000 ppm.

2. The rats were random-bred Sprague Dawley, Cesarean-derived weanlings purchased from Charles River Breeding Laboratories, Wilmington, MA. Of the 640 rats purchased, 20 were used for baseline studies, 560 were used for the lifetime phase of the study, and the remaining 60 rats were sacrificed on day zero. Animals were acclimatized to laboratory conditions and randomly assigned into four groups, based on body weight; each consisted of 70 males and 70 females.

3. Test diets were analyzed at various intervals throughout the study (weeks 1, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 42, 48, 52, 60, 78, 90, and 104) for MON-097 concentrations, homogeneity and 7-day stability.

4. Clinical observations were performed twice daily, and body weight and food consumption were determined weekly during the first 13 weeks and biweekly thereafter. Clinical chemistry, hematology and urinalysis determinations were performed on 10 males and 10 females per group one week prior to study initiation and at 6, 12, 18, and 24/27 months.

5. All rats that died or that were sacrificed when moribund, sacrificed at month 12 (interim, 10/group/sex), or sacrificed at termination were necropsied and tissues were examined histologically. Organ weights were determined for animals sacrificed at month 12 and at termination.

6. Food consumption and body weight data were statistically analyzed by one-way analysis of variance (ANOVA) using F-test for variance comparison, and significant differences were further analyzed by Dunnett's test. Clinical chemistry, hematology and organ-weight data were analyzed by the independent, two-sided t-test. The histopathology data were analyzed for statistical significance by the sponsor using the Cochran-Armitage test for linear trend, the chi-square test and the Peto method which utilizes survival and time to tumor information; these analyses utilized a p value of < 0.01 for significance.

9. REPORTED RESULTS:

A. Clinical Observation and Mortality: The most frequently observed clinical signs in both sexes in all groups were opaque eyes and alopecia. Opaque eyes were observed much earlier, i.e., by week 9, and occurred at a higher incidence in males than females; whereas alopecia was observed much earlier and at a higher incidence in females than in males. However, these effects were apparently not compound-related. Skin lesions and tumors were also evident by month 7 for both males and females. The incidences were progressively higher in females than in males, but were similar among dosed and control animals.

Ophthalmology examinations during the study did not reveal any compound-related effects.

Increased mortality was noted in females receiving the high (5000 ppm) dose by month 12 when compared to control animals (Table 1). Due to increased mortality in the high-dose group, all females were sacrificed by week 103 of the study when survival was

TABLE 1. Percent Survival of Rats Fed Diets Containing MON-097 for 24/27 Months

Dietary Level (ppm)	Percent Survival (No. of Dead Animals) at Month			
	12[a]	18	24[b]	27
Males				
Control	98.6(1)	86.7(8)	53.3(28)	31.7(41)
500	100.0(0)	90.0(6)	55.0(27)	33.3(40)
1500	97.1(2)	86.7(8)	65.0(21)	45.0(33
5000	94.3(4)	86.7(8)	58.3(25)	25.0(45)
Females				
Control	98.6(1)	91.7(5)	41.7(35)	--
500	98.6(1)	71.7(17)	31.7(41)	--
1500	97.1(2)	83.3(10)	43.3(34)	--
5000	91.4(6)	68.3(19)	18.3(49)	--

[a] Interim sacrifice animals (10/sex/group) included in percent survival calculations.

[b] Females were sacrificed during week 103 of the study.

18.3% in the high-dose group. There were no compound-related mortalities noted throughout the study in males when compared to controls. By month 24, there were still sufficient males in each group to allow the study to proceed to month 27.

B. Diet Analyses: The concentrations of MON-097 in freshly prepared diets throughout the study were within acceptable limits of the theoretical. Mixing efficiency values ranged between 85 - 113 percent with a few exceptions. Analyses conducted 7 days after diet preparation throughout the study to determine the compound's stability were variable (range 83-118) and no specific pattern, i.e., decrease or increase, compared to day 1 could be detected.

C. Body Weight Determinations: A significant compound-related decrease in mean body weights of males receiving the mid and high doses was noted throughout the study when compared to controls (Table 2). Similarly a significant compound-related decrease in mean body weights of females receiving the high dose was noted during the study when compared to controls. Females receiving the mid-dose (1500 ppm) showed decreased mean body weight between weeks 31 and 103 of the study, but not all intervals were statistically different from control values. There were no significant compound-related effects on body weight in animals receiving the low dose, except in males at study termination. Mean body weights of low-dose males decreased gradually after week 103 of the study and were approximately 14% lower than the control group by termination

D. Food Consumption: Compound-related decreases in mean food consumption were noted at a few time intervals during the study in males and females receiving the high dose. A few isolated incidences of reduced food consumption were also noted for animals receiving the mid dose. There were no other changes noted (Table 3). Feed efficiency data for the first 13 weeks of the study indicated that high-dose animals of both sexes did not utilize feed as efficiently as the other groups. This was in agreement with reduced body weight data. Compound intake data indicated that the amount of compound consumed at the early weeks of the study was higher, as expected, because of the fast rate of growth. The time-weighted average was 22, 69, and 250 mg/kg body weight for males and 30, 93, and 343 mg/kg/body weight for females receiving the low- (25 mg/kg), mid- (75 mg/kg), and high- (250 mg/kg) doses, respectively.

E. Hematology: Females receiving the high dose showed a slight but significant decrease in hemoglobin and hematocrit values for months 6, 12 and 18, but not for month 24 of the study (Table 4). There were no other compound-related changes noted in the parameters investigated for males and females at months 6, 12, 18, or 24/27 of the study.

TABLE 2. Selected Mean Body Weights of Rats Fed Diets Containing MON-097 for 24/27 Months

Dietary Level (ppm)	Group Mean Body Weight (g) at Week[a]						
	0	13	27	53	79	103[b]	115
Males							
Control	174.5	511.5	584.0	693.1	752.4	751.8	745.4
	18.4	50.5	67.4	88.2	102.4	130.2	104.1
500	170.6	495.7	568.7	677.8	731.5	721.0	640.9*
	17.5	47.8	62.6	93.9	110.9	117.5	131.4
1500	170.4	472.1*	538.0*	631.0*	678.6*	664.7*	618.7*
	17.1	46.3	49.6	77.3	91.0	111.6	126.1
5000	172.1	418.9*	479.5*	534.5*	545.9*	529.2*	479.8*
	16.6	49.1	49.2	62.9	69.6	67.3	65.1
Females							
Control	147.0	315.1	358.0	450.6	483.6[c]	449.5	--
	14.1	32.6	43.0	77.4	93.5	92.3	
500	144.6	318.7	354.9	445.4	491.2	503.3	--
	12.0	27.7	41.7	75.3	85.1	75.4	
1500	147.9	307.8	342.3	416.6*	437.4*	431.4	--
	10.3	33.2	45.4	75.9	93.9	101.4	
5000	146.5	269.4*	284.0*	302.8*	308.2*	308.1*	--
	11.1	22.8	32.7	48.8	60.5	42.3	

[a] Mean value and standard deviation.

[b] Females were sacrificed during week 103 of the study.

[c] Value corrected by reviewers (original value being 486.5).

* Statistically different from control value ($p < 0.05$).

TABLE 3. Selected Mean Food Consumption of Rats Fed Diets containing MON-097 for 24/27 Months

Dietary Level (ppm)	Mean Food Consumption (g/rat/week) at Week						
	0	13	27	53	79	103[a]	115
Males							
Control	154.1	171.5	170.4	160.4	175.0	180.4	165.6
500	153.6	170.7	163.0	170.6*	181.4	176.0	151.8
1500	156.4	165.6	158.9	166.1	181.0	...7	166.1
5000	124.2*	164.4	162.4	145.8*	159.4*	155.1*	161.1
Females							
Control	131.4	131.2	149.9	160.9	178.4	153.6	--
500	135.1	140.4	147.0	158.7	186.6	151.4	--
1500	133.8	135.4	146.4	155.1	170.2	161.7	--
5000	110.4*	130.1	141.6	119.6*	137.4*	138.9	--

[a] Females were sacrificed during week 103 of the study.

* Significantly different from control value ($p < 0.05$)

TABLE 4. Mean Hemoglobin and Hematocrit Values of Female Rats Fed Diets Containing MON-097 for 24 Months

Dietary Level (ppm)	Mean Hemoglobin (g %) and Hematocrit (pc %) values on months 0		6		12		18		24	
	Hgb	Hct	Hgb	Hct	Hgb	Hct	Hgb	Hct	Hgb	Hct
Control	12.2	39.0	15.0	44.3	14.1	45.0	13.9	41.2	12.9	39.6
500	-	-	14.8	42.7*	14.3	43.5	14.1	41.0	13.3	40.2
1500	-	-	13.9*	43.9	14.3	42.1	13.3	40.5	13.1	40.2
5000	-	-	14.2*	41.6*	12.5*	40.1*	11.4*	34.8*	12.7	39.5

*Statistically different from control value ($p < 0.05$).

F. Clinical Chemistry: There were some isolated significant differences noted in blood chemistry parameters among control and dosed groups. These differences were not consistent over time and were apparently not compound-related.

G. Urinalysis: There were no compound-related changes noted in urine chemistry values and microscopic examination of urine sediments of males and females throughout the study.

H. Gross Examination: Gross pathology findings were summarized for each organ system instead of specific tissues and lesions were not specified, except on individual animal pathology sheets. However, individual animal data indicate that all gross lesions were examined histologically. There was a slight increase in urinary lesions noted in animals receiving the high dose at the 12-month interim sacrifice. For high-dose animals that died or were sacrificed moribund during the second year of the [illegible] an increase in the number of lesions in the following systems was noted: the cardiovascular system of males and females, the endocrine system of males, and urinary and reproductive systems of females. In addition, an increase in the number of lesions of the urinary system of all dosed male groups was observed. At terminal sacrifice, increased lesions were noted in the urinary system of the mid- and high-dose males and high-dose females.

I. Organ Weights: There were no significant differences in organ weights and organ-to-body weight ratios among control and dosed males at the one-year interim sacrifice. In females, lower mean adrenal weights in mid- (0.13 g) and high-dose (0.10 g) animals (and lower mean adrenal-to-body weight ratios in high-dose animals) were observed when compared to control (0.19 g). However, the authors stated that the mean adrenal weight of the corresponding female control at month 12 was almost twice as high as the value for historical control rats (0.08 - 0.11 g) of that age.

At final sacrifice, the mean brain and heart weights of mid- and high-dose males and the mean brain weight of mid- and high-dose females were lower than the control values. These decreases were accompanied by corresponding increases in organ-to-body weight ratios (Table 5) The mean pituitary, heart, and adrenal weights of high-dose females were lower than the control values, but the organ-to-body weight ratios were similar among control and dosed animals. The mean thyroid/parathyroid weights and organ-to-body weight ratios in all dosed females were significantly higher when compared to control values (Table 5). In addition, the mean relative weights of thyroid in mid- and high-dose males, and the relative weights of liver, adrenals, kidneys, and testis in high-dose males and liver and kidneys in high-dose females were significantly higher than control values.

TABLE 5. Organ Weight Data for Rats Fed Diets containing MON-097 for 24/27 Months

Dietary Level (ppm)	Organ									
	Brain		Thyroid		Heart		Adrenals		Gonads	
	W[a] (g)	RW (%)	W (g)	RW (%)	W (g)	RW (%)	W (g)	RW (%)	W (g)	RW (%)
Males										
Control	2.23	3.03	0.05	0.07	2.12	2.83	0.10	0.14	3.48	4.72
	0.097	0.472	0.020	0.026	0.368	0.371	0.037	0.049	0.522	0.969
500	2.19	3.45*	0.06	0.09	2.01	3.14	0.12	0.19	3.52	5.44
	0.125	0.774	0.034	0.05	0.453	0.898	0.069	0.125	0.761	1.272
1500	2.15*	3.65*	0.05	0.09*	1.87*	3.13	0.20	0.36	3.26	5.41
	0.109	0.835	0.010	0.022	0.324	0.766	0.408	0.788	0.751	1.441
5000	2.11*	4.56*	0.07	0.15*	1.61*	3.42*	0.09	0.20*	4.45	9.85*
	0.115	0.888	0.024	0.053	0.266	0.663	0.018	0.067	3.180	8.522
Females										
Control	2.19	5.01	0.03	0.06	1.66	3.75	0.21	0.48	0.25	0.55
	0.131	1.286	0.007	0.013	0.285	0.912	0.163	0.362	0.407	0.809
500	2.13	4.39	0.04*	0.08*	1.68	3.47	0.17	0.36	0.17	0.35
	0.119	0.690	0.008	0.018	0.324	0.583	0.097	0.220	0.177	0.415
1500	2.09*	5.11	0.04*	0.09*	1.60	3.84	0.17	0.42	0.33	0.68
	0.084	1.058	0.012	0.030	0.441	1.118	0.101	0.249	0.927	1.718
5000	1.99*	6.59*	0.04*	0.12*	1.20*	3.91	0.10*	0.34	0.13	0.45
	0.097	1.150	0.013	0.044	0.231	0.748	0.021	0.100	0.114	0.390

[a] W - weight.
RW - organ-to-body weight ratio.

* Statistically different from control value ($p < 0.05$).

J. Histopathology: At interim sacrifice, an increase in the incidence of prostatitis was noted in males and hemosiderosis of the spleen in females receiving the high dose. There were no other effects noted. A summary of the most frequently observed non-neoplastic lesions at 24/27 months is presented in Table 6. There was a significant increase in the incidence of liver necrosis ($p < 0.05$) and alveolar histiocytosis ($p < 0.05$) in females receiving the high dose. There was also a significant linear trend ($p < 0.05$) in the incidences of peripheral nerve neuropathy, heart thrombosis, and stomach fibrosis. In males, a significant increase in the incidences of polyarteritis of the testes and in polyarteritis of the arteries ($p < 0.05$) was noted in animals receiving the high dose. A significant linear trend ($p < 0.05$) was also noted for these lesions.

A summary of the most frequently observed neoplastic lesions is presented in Table 7. The incidence of hepatocellular carcinomas was significantly higher (Fisher Exact test) in males receiving 5000 ppm when compared to control and there was a significant dose-related trend. The incidence was also higher in females receiving 5000 ppm, and although there was a significant dose-related trend ($p < 0.05$), the incidence was not significantly different from control using the Fisher Exact test. The data also indicated an increase in the incidence of liver adenomas in the concurrent control (and dosed) males when compared to historical controls from the testing laboratory. The latter were reported to be 2 of 401 (0.5%) at final sacrifice, whereas in concurrent controls the incidence was 3 of 19 (15.8%) males. There was also an increase in the incidence of follicular cell adenoma of the thyroid in males receiving the high dose (Fisher Exact test, $p < 0.05$) and a dose-related trend (Cochran-Armitage test, $p < 0.05$). In addition, an increase in the incidence of interstitial cell tumors of the testes was noted in males receiving the high dose, but the increase was not statistically significant and did not show a linear trend.

10. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The authors concluded that MON-097 fed to this strain of rat caused a statistically significant decrease in food consumption in both high-dose groups, and a decrease in body weights of mid- and high-dose males and females. In addition, dose-related increases in thyroid follicular cell adenomas in mid- and high-dose males, hepatic carcinomas in low-, mid-, and high-dose males and high-dose females, and testicular interstitial cell tumors in all dosed males were observed. These neoplastic changes were considered by the authors to be compound related due to the increased incidences noted when compared to the concurrent and historical control data (see Histopathology Section). Statistical analysis of the histopathology data was not performed by the study authors but was conducted by the sponsor; these analyses are discussed below.

TABLE 6. Summary of Most Frequently Observed Nonneoplastic Lesions in Rats Fed Diets Containing MON-097 for 24/27 Months (continued)

Organ/Lesion		Males				Females			
		0	500	1500	5000	0	500	1500	5000
Peripheral nerve	N[a]	69	67	70	67	66	70	67	63
Neuropathy		1	0	1	1	0	0	0	4[d]
Pituitary	N	68	70	70	70	70	70	70	67
Hyperplasia		3	5	3	3	4	6	6	4
Prostate	N	70	70	70	69	-	-	-	-
Prostatitis		19	18	18	15				
Skin	N	70	69	70	70	70	69	70	70
Granuloma foot-pad		15	17	22	11	19	10	10	0
Spleen	N	70	70	70	70	70	70	70	70
Hemosiderosis		18	13	10	10	20	15	20	27
Stomach	N	70	70	70	70	70	70	70	70
Fibrosis		13	10	13	14	4	5	7	12[d]
Testes	N	70	70	70	70	-	-	-	-
Polyarteritis		7	11	12	17*[b,d]				
Thyroid	N	69	69	70	70	69	69	69	69
C-cell hyperplasia		2	3	2	3	0	0	1	0
Uterus		-	-	-	-	70	70	70	70
Endometritis						10	13	11	5

[a]Number of tissues examined, including interim sacrifice animals.

[b]Statistical analysis conducted by our reviewers, using the Fisher Exact test.

[c]Statistical analysis conducted by the sponsor.

[d]Significant linear trend using the Cochran-Armitage test ($p < 0.05$).

*Statistically different than control values ($p < 0.05$).

TABLE 7. Summary of Most Frequently Observed Neoplastic Lesions in Rats Fed Diets Containing MON-097 for 24/27 Months

Organ/Lesion		Males				Females			
		0	500	1500	5000	0	500	1500	5000
Adrenals	N[a]	70	70	70	70	70	70	70	70
Pheochromocytoma (benign)		4	5	4	1	0	0	0	1
Liver	N	70	70	70	70	70	70	70	70
Hepatocellular adenoma		6	2	5	7	0	2	2	2
Hepatocellular carcinoma		0	2	3	6*[bd]	1	1	1	5[bd]
Hemangiosarcoma		0	0	0	0	1	0	0	1
Mammary gland	N	12	18	10	11	67	69	67	55
Adenoma		0	0	0	0	7	12	7	2
Fibroadenoma		1	0	0	0	50	61	64	39
Adenocarcinoma		0	0	0	0	13	13	13	7
Pancreas	N	69	70	70	70	70	70	70	70
Islet cell adenoma		10	11	10	8	2	1	0	1
Pituitary	N	68	70	70	70	70	70	70	67
Adenoma		23	18	23	19	35	41	34	24
Carcinoma		13	9	5	4	17	6	13	4
Testes	N	70	70	70	70	-	-	-	-
Interstitial cell tumor		2	4	4	7				
Thyroid	N	69	69	70	70	69	69	69	69
C-cell adenoma		7	2	4	4	4	1	1	0
Follicular cell adenoma		0	0	3	5*[bd]	2	0	0	3
Uterus		-	-	-	-	70	70	70	70
Adenocarcinoma						1	0	1	4

[a]Number of tissues examined, including interim sacrifice animals.

[b]Statistical analysis conducted by our reviewers, using the Fisher Exact test.

[c]Statistical analysis conducted by the sponsor.

[d]Significant linear trend using the Cochran-Armitage test ($p < 0.05$).

*Statistically different than control values ($p < 0.05$) using the Fisher Exact test.

For other parameters investigated in this study, the sponsor was in agreement with the conclusions of the authors except for some hematology results. The study authors considered that only the statistically significant decrease at month 18 in the mean hemoglobin count in females receiving the high-dose was compound-related, whereas, the sponsor indicated that the decrease in both hemoglobin and hematocrit values in this group at months 6, 12, and 18 was compound-related.

B. Quality assurance inspections were performed periodically throughout the study.

11. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

Our evaluation of the results of this chronic toxicity/oncogenicity study with MON-097 in rats indicates that it was adequately conducted and reported yet there were some deficiencies noted e.g., summarizing gross examination data by systems, rather than by organ or tissues, weighing organs after fixation and use of a $p < 0.01$ rather than 0.05 for statistical significance of histopathologic data. The conclusions of the authors are supported by the data.

The results indicate increased mortality in females receiving 5000 ppm of test material in the diet (high dose). However, adequate numbers of animals were alive after month 18 to allow for evaluation of late-developing tumors. There was also a compound-related decrease in the mean body weights of males and females receiving 1500 and 5000 ppm of test material, although the decrease in mid-dose females was less pronounced. In addition a decrease in the mean body weights of males receiving the low dose by about week 103 was noted; this effect appears to be biologically significant and compound-related. Decreased food consumption and food efficiency was also observed in males and females receiving the high dose throughout the study. There were no compound-related effects in clinical signs and eye examinations, hematology, blood chemistry, and urinalysis noted in dosed animals, except for lower hemoglobin and hematocrit values in females receiving the high dose at months 6, 12, and 18, but not month 24. Changes in organ weights and organ-to-body weight ratios were usually associated with lower body weights of dosed animals. However, it should also be noted that the organs were weighed after fixation in 10% buffered formalin. Consequently, these changes could not be definitively related to compound administration, except for the liver, thyroid, and testis, where the animals exhibited histopathologic changes.

Individual animal data indicate that all gross lesions were further examined histologically. There were some compound-related effects

noted during histologic examination of the tissues. Based on statistical analysis conducted by these reviewers, nonneoplastic lesions included increased incidences of polyarteritis of the testes and arteries of males and liver necrosis and alveolar histiocytosis of females receiving the high dose ($p < 0.01$). In addition, the statistical analyses of the data by the sponsor indicated significant linear trends for these lesions ($p < 0.01$) as well as significant increases in the incidences of liver necrosis and alveolar histiocytosis and inflammation of the tongue in females receiving the high dose.

Neoplastic lesions were also noted and the data were analyzed statistically by our reviewers. A significant increase ($p < 0.05$) in liver carcinomas and thyroid follicular cell adenomas was noted in males receiving 5000 ppm using the Fisher Exact test. A statistically significant increase in the incidences of liver carcinomas in the females receiving the high dose was not observed by our reviewers using either the Fisher Exact test or the Peto method at a $p < 0.05$. However, a significant positive trend (Cochran-Armitage test) in the incidences of liver carcinomas in females ($p < 0.05$) as well as in the incidence of liver carcinomas and thyroid follicular cell adenomas in males ($p < 0.05$) was noted.

The statistical analyses of neoplastic lesions conducted by the sponsor indicated only a linear trend in the incidence of liver carcinomas for both sexes combined ($p < 0.01$) and a significant increase in the incidence of liver carcinomas for both sexes combined using the Peto method ($p < 0.01$). In addition, a positive trend was noted for the thyroid follicular cell adenomas. It should be noted, however, that the sponsor utilized a p value of 0.01 instead of 0.05 which is more commonly accepted, and is an EPA policy.

The following deficiencies were noted: organs were weighed following fixation in 10% buffered formalin and necropsy data were reported as the number of lesions per organ system.

Based on body weight data and organ weight data the LOEL for chronic effects is 500 ppm (LDT) of test material in the diet, and a NOEL cannot be established.

12. CBI APPENDIX: Appendix A, Materials and Methods, CBI, pp. 9-22.