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DATA EVALUATION RECORD

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Oncogenicity Study in Mice

STUDY IDENTIFICATION: Ahmed, F. E., Tegeris, A. S., Seely, J. C. MON-097: 24-month oncogenicity study in the mouse. (Unpublished report No. PR-80-007 prepared by Pharmacopathics Research Laboratories, Inc., Laurel, MD, for Monsanto Agricultural Products Company, St. Louis, MO; dated May 4, 1983.) Accession Nos. 071966-071968.

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Date: August 2, 1985

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

2. TEST MATERIAL: MON-097, purity 94.5%; Lot No. NBP 1737874.

3. STUDY/ACTION TYPE: Oncogenicity study in mice.

4. STUDY IDENTIFICATION: Ahmed, F. E., Tegeris, A. S., Seely, J. C. MON-097: 24-month oncogenicity study in the mouse. (Unpublished report No. PR-80-007 prepared by Pharmacopathics Research Laboratories, Inc., Laurel, MD, for Monsanto Agricultural Products Company, St. Louis, MO; dated May 4, 1983.) Accession Nos. 071966-071968.

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7. CONCLUSIONS:

A. Under the conditions of this study, treatment of random-bred Swiss albino CD-1 mice with MON-097 resulted in a definite increase in tumors of the liver, lung, and uterus with suggestive increased tumors of the ovaries and kidneys:

1. Definite increases based on pairwise comparison using the chi square test or Fisher exact test.

a) liver carcinomas, high-dose males ($p \leq 0.01$)

b) total lung tumors, females at all doses ($p \leq 0.01$)

c) carcinomas of the lung in low and high dose females ($p \leq 0.05$)

d) uterine histiocytic sarcomas, low- and mid-dose females ($p \leq 0.01$) and high dose females ($p \leq 0.05$)

e) Total benign tumors of the ovaries in mid-dose females ($p \leq 0.05$)

2. Only suggestive ~~increases based on linear trend analysis~~ using the Peto method ($p < 0.01$)

a) liver carcinomas, females and males
b) lung carcinomas, females
c) total lung tumors in females
d) ovary benign tumors
e) kidney adenomas, females

Changes in other parameters that appeared to be related to dosing included: 1) an increased mortality in both high-dose males and females; 2) decreased mean body weights in high-dose males and females; 3) decreased red blood cell count, hematocrit, and hemoglobin in high-dose females at terminal sacrifice; 4) increased white blood cell count in high-dose males at terminal sacrifice; 5) increased platelet count in mid- and high-dose females at terminal sacrifice; 6) increased mean liver weights and liver-to body weight ratios at study termination in all dosed groups of males and in high-dose females as well as an increase in liver-to-body weight ratios in all dosed males and females at 12 months; an increase in absolute and relative kidney weights in all dosed groups of males at termination; and an increase in absolute and relative adrenal weights in all groups of males and in high-dose females at study termination; 7) an increase in interstitial nephritis in high-dose males and females.

A NOEL for chronic toxicity could not be established based on increased liver, and kidney, weights at the low-dose level. The LOEL for chronic toxicity of MON-097 in mice was 500 ppm (lowest dose tested)..

Core Classification: Core Minimum.

8. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods:

For details of the author's Materials and Methods see Appendix A of this review.

The test material was MON-097 (CP 55097, NBP 1737874), a maroon liquid with a stated purity of 94.5%. The major component is 2-chloro-N-(ethoxymethyl)-6'-ethyl-ortho-aceto-toluidine. The basic experimental design consisted of the exposure of Swiss albino CD-1 mice to MON-097 in the diet for up to 23 months at dose levels of 0, 500, 1500, and 5000 ppm. Five hundred random-bred Swiss albino CD-1 weanling mice were inspected upon arrival, quarantined for 22-23 days, and randomized by weight into the experimental groups prior to dosing. Twenty mice were sacrificed before the start of dosing to determine baseline gross pathology and histopathology, with the remainder assigned to groups of 60 male and 60 female mice at each dose level. Ten of each group were sacrificed at 12 months so that the long-term study, in effect, consisted of 50 animals per group fed the indicated doses for up to 23 months. The diets were prepared weekly.

Animals were observed twice daily for mortality or other signs of toxicity. Body weights and food consumption were determined once pre-test, weekly during the first 13 weeks, and biweekly thereafter. Terminal body weights were those determined at necropsy or weights taken within 7 days before sacrifice. Organ weights were determined at the interim and the terminal sacrifices on fixed tissues.

Urinalysis, hematology, and blood chemistry values were determined in 10 mice/sex/dose at a 12-month interim sacrifice and at study termination. Blood was pooled from 3-4 mice for chemistry determinations.

Complete gross pathology examinations and histopathological evaluations were performed on each animal.

Body weight and food consumption data were analyzed statistically by one way analysis of variance using F test for comparison of variances and Dunnett's test was used to determine which means were significantly different from controls. Clinical laboratory data and organ weight data were analyzed by a two-sided Student's t-test. Neither the protocol nor materials and methods indicated

that the study author analyzed histopathology data. The study sponsor analyzed the incidence of tumor and nontumor lesions to detect statistically significant ($p \leq 0.01$) dose-related linear trends and differences between control and dosed animal values.

B. Protocol:

See Appendix B for Protocol details.

9. REPORTED RESULTS:

Analysis of Diets: The analytical procedure for MON-097 was validated prior to initiation of the study. The response was linear in the range to be used for the analysis, and diet analyses prior to the study were reasonably reproducible. For nominal values of 500, 1500, and 5000 ppm, the respective reproducibilities were 110.83%, 109.17%, and 88.89%; the respective standard deviations expressed as percent were 9.77, 12.69, and 12.80. Mixing was efficient and test compound was stable in the diet for 14 days. Diet analyses during the study indicated MON-097 was stable in the diets for at least one week (diets were prepared weekly) and was homogeneously mixed with the diets. MON-097 in the diet was analyzed at weeks 1, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 42, 48, 52, 60, 78, and 90. The means and standard deviations for the study, as calculated by our reviewers, were:

Nominal (ppm)	Analytical (ppm)	Coefficient of Variation (%)	Range (ppm)
500	492.06± 37.14	7.5	454.92 - 529.2
1500	1468.71± 93.09	6.3	1375.62 - 1561.80
5000	4894.29±307.90	6.3	4586.39 - 5202.19

Clinical Observations: No unusual clinical signs were observed that were considered to be related to dosing. The most frequently observed signs were alopecia, skin lesions, and distended abdomens; these were random in occurrence.

Mortality: Mortality data at selected intervals are summarized in Table 1. A general increase in mortality began to appear after month 12 in dosed animals as compared with controls. Survival at 18 months ranged from 66-94% in males groups and 60-86% in female groups. The study was terminated at 23 months when survival was 26% in both males and females receiving 5000 ppm (high-dose).

TABLE 1. Mortality and Percent Survival at Selected Intervals in Mice Fed MON-097 for 23 Months[a]

Groups/Dose (ppm)	Mortality (and % Survival) at End of Month				
	1	6	12	18	23
Males					
0	0 (100%)	0 (100%)	0 (100%)	3 (94%)	20 (60%)
500	0 (100%)	3 (94%)	7 (86%)	16 (68%)	25 (50%)
1500	0 (100%)	0 (100%)	2 (96%)	6 (88%)	25 (50%)
5000	0 (100%)	3 (94%)	5 (90%)	17 (66%)	37 (26%)
Females					
0	1 (98%)	1 (98%)	3 (94%)	7 (86%)	19 (62%)
500	0 (100%)	0 (100%)	2 (96%)	9 (82%)	25 (50%)
1500	0 (100%)	0 (100%)	2 (96%)	11 (78%)	33 (34%)
5000	1 (98%)	2 (96%)	7 (86%)	20 (60%)	37 (26%)

[a]Fifty animals/sex/group; animals scheduled for sacrifice at 12 months were not included in mortality calculations.

Body Weights: Body weights at selected intervals are summarized in Table 2. Significantly ($p \leq 0.05$) lower body weights in dosed animals as compared with controls were observed in the following groups: mid-dose males at 53 and 79 weeks; high-dose males and females at all selected time intervals. The mean body weights of high-dose males and females was approximately 80% of control at study termination. In mid-dose males mean body weights were decreased 6.5% at 18 months but only 3% at 23 months as compared to controls.

Food and Water Consumption: Water consumption was not measured. Food consumption data at selected intervals are summarized in Table 3. Although significant ($p \leq 0.05$) sporadic changes in food consumption were found in both sexes, they were not consistent and there were no changes that were related to dose level.

Food Efficiency: Mean food efficiencies during the first 13 weeks of study are summarized in Table 4. There were no changes in food efficiency that were related to dose level during this early phase of the study. Food efficiency was not studied beyond week 13.

Hematology: Except for a decrease in red cell parameters (RBC, Hmct, and Hb) in high-dose females at month 23, which the authors correlated with anemia, and an increase in white cell count in high-dose males at month 23, which the authors indicated to correlate with hepatocellular carcinoma, other changes were not consistent with time or dose and not considered compound related (authors). The following significant ($p \leq 0.05$) decreases in hematology parameters were observed (Table 5): red blood cell count (RBC) in high-dose females at months 12 and 23; hemoglobin (Hgb) in high-dose females at month 23; hematocrit (Hmct) in high-dose females at month 23 and in mid- and high-dose males at month 12. Significant increases in the following hematology parameters were also observed (Table 5): white blood cell count (WBC) in high-dose males at month 23; RBC in mid-dose females at month 12; platelet count (Plt Ct) in low- and mid-dose males at month 12 and in mid- and high-dose females at month 23.

Clinical Chemistry: For serum alkaline phosphatase (SAP), serum glutamic oxaloacetic transaminase (SGOT), and total bilirubin (TB), some significant increases were observed (Table 6) as follows: SAP in high-dose females at month 12; SGOT in high-dose males at month 12; TB in mid-dose females at month 23. The authors attributed changes in total protein to hemolysis of blood samples. There were no good correlations between SAP, SGOT, SGPT, and TB and histologic findings. Since all values were from pooled blood samples of 3-4 animals, direct animal correlations of chemistry and histologic changes could not be made (CB1 pp 52-57).

TABLE 2. Selected Mean Body Weights for Mice Fed MON-097 for 23 Months

Groups/Dose (ppm)	Body Weights (g) at Week:			
	27	53	79	99
Males				
0	35.683 ± 3.427[a]	37.017 ± 3.895	36.787 ± 3.526	35.500 ± 3.214
500	34.947 ± 2.649	36.547 ± 2.932	36.088 ± 2.843	35.880 ± 3.206
1500	34.950 ± 2.873	35.293[b] ± 3.195	34.386[b] ± 3.059	34.720 ± 3.156
5000	31.386[b] ± 2.527	31.018[b] ± 2.621	30.545[b] ±2.251	29.286[b] ± 2.054
Females				
0	29.441 ± 2.866[a]	30.368 ± 2.932	32.744 ± 2.945	31.545 ± 4.131
500	28.433 ± 2.936	31.069 ± 3.722	33.000 ± 3.413	32.040 ± 2.993
1500	29.267 ± 3.156	30.448 ± 3.039	31.974 ± 2.716	31.750 ± 2.826
5000	25.931[b] ± 2.183	26.830[b] ± 2.293	28.933[b] ± 2.753	28.267[b] ± 3.788

[a] Standard deviation.

[b] Significantly different from control value ($p \leq 0.05$) using ANOVA followed by Dunnett's t-test.

TABLE 3. Selected Mean Food Consumption in Mice Fed MON-097 for 23 Months

Group/Dose (ppm)	Grams of Food/Mouse/Week at Week 13	27	53	79	99
Males					
0	35.2 ±4.6[a]	38.0 ±3.8	37.4 ±4.5	39.0 ±4.4	38.1 ±4.6
500	34.6 ±4.9	38.0 ±3.0	36.7 ±3.6	36.9 ±3.4	35.5 ±3.9
1500	33.2* ±3.2	37.7 ±3.3	36.5 ±3.8	37.0 ±4.8	36.9 ±4.2
5000	35.7 ±4.7	39.2 ±5.4	36.5 ±4.8	36.1* ±4.4	37.0 ±4.6
Females					
0	35.1 ±4.5	40.3 ±5.0	39.4 ±6.0	39.2 ±4.0	36.5 ±5.9
500	32.9* ±3.8	39.7 ±4.4	40.6 ±6.4	40.4 ±3.1	38.7 ±3.2
1500	33.7 ±4.0	40.0 ±4.1	40.1 ±4.8	38.9 ±3.9	37.8 ±4.0
5000	37.9* ±5.1	45.4* ±7.4	41.9 ±8.5	37.4 ±4.6	35.5 ±8.1

[a] Standard deviation

* Significantly different from control value ($p \leq 0.05$) using ANOVA followed by Dunnett's t-test.

TABLE 4. Mean Food Efficiency (Change in Body Weight/Food Consumed/Week) During the First 13 Weeks of a 23-Month Study of MON-097 Oncogenicity[a]

Dose (ppm)	Males	Females
0	0.015[b] ±0.025[c]	0.011 ±0.027
500	0.015 ±0.019	0.011 ±0.023
1500	0.013 ±0.025	0.014 ±0.023
5000	0.008 ±0.022	0.011 ±0.030

[a] Statistical analysis of these data by our reviewers indicated no significant differences in mean food efficiencies between control and dosed groups (ANOVA followed by Duncan's multiple range test) and no dose-related trends (regression analysis).

[b] g body weight/g food consumed/week, mean for first 13 weeks of study.

[c] Standard deviation.

TABLE 5. Determination of Red Blood Cell Count (RBC), White Blood Cell Count (WBC), Hemoglobin (Hgb), Hematocrit (Hmct), and Platelet Count (Plt Ct) in Mice Fed MON-097

	Males Dose (ppm)				Females Dose (ppm)			
	0	500	1500	5000	0	500	1500	5000
RBC (x 10^6/mm^3)								
12 months	7.4 ±1.1[a]	7.0 ±0.8	7.3 ±1.0	6.7 ±1.1	7.3 ±0.7	7.7 ±0.6	8.0[b] ±0.5	6.5[b] ±0.9
23 months	5.3 ±1.3	5.0 ±0.6	5.4 ±1.2	4.5 ±0.6	4.8 ±0.6	5.4 ±0.8	5.4 ±1.0	3.8[b] ±0.7
WBC (x 10^3/mm^3)								
12 months	6.9 ±1.7	9.1 ±4.1	7.8 ±2.8	7.8 ±2.8	8.7 ±2.5	9.8 ±4.9	9.3 ±3.1	10.0 ±4.5
23 months	9.7 ±2.4	13.6 ±5.9	12.0 ±3.8	14.5[b] ±3.5	15.2 ±4.4	14.2 ±8.6	13.9 ±4.8	26.0 ±30.0
Hgb (g/dL)								
12 months	12.7 ±0.9	12.7 ±1.0	11.8 ±1.3	11.6 ±1.5	11.9 ±1.9	12.7 ±0.8	12.7 ±1.2	11.7 ±0.7
23 months	12.0 ±2.2	12.0 ±1.2	12.7 ±1.7	10.9 ±1.7	12.0 ±1.5	13.0 ±1.8	12.5 ±2.0	9.3[b] ±2.0
Hmct (pc/dL)								
12 months	40.0 ±3.2	37.9 ±3.0	36.6[b] ±3.4	37.4[b] ±2.2	39.2 ±4.1	39.5 ±2.7	39.5 ±2.2	38.0 ±2.9
23 months	35.8 ±9.6	36.7 ±3.5	37.1 ±4.4	32.6 ±5.5	37.8 ±4.5	38.9 ±5.4	39.5 ±4.0	29.1[b] ±6.4
Plt Ct (x 10^3/mm^3)								
12 months	437 ±262	710 [b] ±180	847 [b] ±153	565 ±242	513 ±303	579 ±261	454 ±187	662 ±168
23 months	456 ±281	408 ±187	547 ±170	478 ±179	302 ±129	309 ±99	484 [b] ±185	482 [b] ±212

[a]Standard deviation.

[b]Significantly different from control value ($p \leq 0.05$) using ANOVA followed by Dunnett's t-test.

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TABLE 6. Serum Levels of Alkaline Phosphatase (SAP), Glutamic Oxaloacetic Transaminase (SGOT), and Total Bilirubin (TB) in Mice Fed MON-097

	Males Dose (ppm)				Females Dose (ppm)			
	0	500	1500	5000	0	500	1500	5000
SAP (IU/L)								
12 months	206 ±42 [a]	212 ±31	211 ±12	199 ±48	167 ±11	182 ±54	183 ±20	195 [b] ±13
23 months	273 [c] ±113	192 ±27	227 ±36	179 ±5	198 ±56	246 ±55	243 ±83	351 [c] ±180
SGOT (IU/L)								
12 months	75 ±8	85 ±14	84 ±18	105 [b] ±7	88 ±16	82 ±13	98 ±1	102 ±7
23 months	116 [c] ±40	77 ±20	106 ±24	103 ±16	82 ±18	61 ±46	109 ±20	85 [c] ±18
TB (mg/dL)								
12 months	0.4 ±0.0	0.4 ±0.1	0.4 0.0	0.4 0.0	0.4 ±0.0	0.5 ±0.2	0.4 ±0.1	0.4 ±0.1
23 months	0.4 [c] ±0.1	0.4 ±0.0	0.6 ±0.1	0.6 ±0.2	0.4 ±0.1	0.5 ±0.3	0.6 [b] ±0.1	0.6 [c] ±0.1

[a] Standard deviation.

[b] Significantly different from control value ($p \leq 0.05$) using ANOVA followed by Dunnett's t-test.

[c] Only 2 pools were analyzed.

Urinalysis: There were no changes in urinary parameters related to dosing.

Organ Weights: At month 12, parallel increases in organ weights and organ-to-body weight ratios were reported for livers (Table 7), and adrenals in dosed females (Table 8). At month 23, parallel increases in organ weights and organ-to-body weight ratios were observed for male livers (Table 7), male and female adrenals (Table 8), male kidneys (Table 9), and female thyroids/parathyroids (Table 10). There were no treatment-related weight changes in the other organs that were examined (brain, pituitary, heart, and gonads).

Gross Pathology: Summary tabulation of gross pathology findings by the report authors (CBI pp II83-II86) did not include the number of animals per group with specific lesions in a particular tissue but tabulated the number of animals with neoplastic or nonneoplastic lesions in an organ system (e.g., digestive, endocrine, reproductive) by dose and sex. Individual pathology data records contained more specific data. Gross observations at necropsy included: 1) an increase in urinary tract lesions in males (scheduled sacrifices for all dose groups; those that died or were sacrificed in moribund condition in the high-dose group) and in the females (scheduled sacrifices for mid- and high-dose groups; those that died or were sacrificed in moribund condition in the high-dose group); 2) an increase in digestive tract (primarily liver) masses in males (scheduled sacrifices for mid- and high-dose groups); 3) an increase in pulmonary masses in females (scheduled sacrifices and animals that died or were sacrificed in moribund condition for all dose groups); and 4) reproductive tract masses in females (scheduled sacrifices for high-dose group). The author stated that a variety of other lesions and masses were observed but were not considered treatment-related.

Histopathology: Table 11 presents a summary of the incidence of neoplastic lesions. If only one animal in any dose group had a tumor, it was not included in the table. The report authors did not indicate any statistical analysis of the data. However, they concluded that there was a dose-related increase in the incidence of the following neoplasms:

- o histiocytic sarcomas of the uterus in low-, mid-, and high-dose females
- o lung adenomas and carcinomas combined in all groups of dosed females
- o lung adenomas in low- and mid-dose groups of males and low-, mid-, and high-dose groups of females
- o hepatic carcinomas in low-, mid- and high-dose groups of males and in high-dose females

TABLE 7. Mean Liver Weights and Liver-to-Body Weight Ratios in Mice Fed MON-097[c]

Dietary Level (ppm)	Males		Females	
	Liver Weight (g)	g Liver / 1000 g body weight	Liver Weight (g)	g Liver / 1000 g body weight
12-Month Sacrifice				
0	1.49 ±0.265[a]	41.964 ±7.865	1.30 ±0.240	48.861 ±7.212
500	1.58 ±0.123	49.636[b] ±6.313	1.45 ±0.235	55.653[b] ±7.245
1500	1.44 ±0.262	52.166[b] ±6.536	1.62[b] ±0.316	60.340[b] ±8.056
5000	1.68 ±0.279	56.324[b] ±12.418	1.53[b] ±0.098	70.994[b] ±5.370
23-Month Sacrifice				
0	1.62 ±0.327[a]	45.507 ±8.169	1.76 ±1.303	54.357 ±30.808
500	2.10[b] ±1.031	58.464[b] ±27.742	1.72 ±0.260	53.886 ±7.989
1500	1.96[b] ±0.451	56.271[b] ±12.167	1.62 ±0.258	50.873 ±7.723
5000	2.52[b] ±0.852	87.088[b] ±32.926	1.92 ±0.311	65.595 ±7.695

[a] Standard deviation.

[b] Significantly different from control ($p \leq 0.05$) using ANOVA followed by Dunnett's t-test; analysis by report authors.

[c] Performance of Bartlett's test by our reviewers indicated inhomogeneous variances for these data; transformation of data to achieve homogeneity of variance was performed by our reviewers prior to reanalysis by ANOVA followed by Duncan's multiple range test. The means and standard deviations are presented as the values before transformation.

TABLE 8. Mean Adrenal Weights and Adrenal-to-Body Weight Ratios in Mice Fed MON-097

Dietary Level (ppm)	Males		Females	
	Adrenal Weight (g)	g Adrenal / 1000 g body weight	Adrenal Weignt (g)	g Adrenal / 1000 g body weight
12-Month Sacrifice				
0	0.01 ±0.004[a]	0.342 ±0.134	0.01 ±0.003	0.420 ±0.131
500	0.01 ±0.005	0.439 ±0.154	0.02[b] ±0.009	0.834[b] ±0.426
1500	0.01 ±0.003	0.411 ±0.167	0.02[b] ±0.005	0.606[b] ±0.219
5000	0.01 ±0.005	0.471 ±0.181	0.02[b] ±0.004	0.831[b] ±0.187
23-Month Sacrifice				
0	0.007 ±0.002[a]	0.191 ±0.068	0.013 ±0.003	0.431 ±0.106
500	0.009[b] ±0.003	0.246[b] ±0.077	0.014 ±0.004	0.443 ±0.106
1500	0.009[b] ±0.003	0.259[b] ±0.105	0.015 ±0.004	0.470 ±0.123
5000	0.010[b] ±0.003	0.360[b] ±0.122	0.016[b] ±0.003	0.556[b] ±0.127

[a] Standard deviation.

[b] Statistically significant from control value ($p \leq 0.05$) using ANOVA followed by Dunnett's t-test.

TABLE 9. Mean Kidney Weights and Kidney-to-Body Weight Ratios in Mice Fed MON-097

Dietary Level (ppm)	Males		Females	
	Kidney Wt. (g)	g kidney / 1000 g body wt.	Kidney Wt. (g)	g kidney / 1000 g body wt.
12-Month Sacrifice				
0	0.73 ±0.108[a]	20.705 ±2.869	0.46 ±0.064	17.403 ±2.485
500	0.89[b] ±0.143	27.762[b] ±4.999	0.54 ±0.105	20.695[b] ±3.483
1500	0.78 ±0.179	28.001[b] ±4.625	0.55[b] ±0.090	20.504[b] ±2.494
5000	0.81 ±0.180	26.983[b] ±5.667	0.41 ±0.047	19.172 ±2.401
23-Month Sacrifice				
0	0.76 ±0.127[a]	21.352 ±2.833	0.55 ±0.099	17.330 ±2.716
500	1.06[b] ±0.183	29.696[b] ±5.254	0.64[b] ±0.084	19.978 ±2.829
1500	1.08[b] ±0.270	31.028[b] ±6.423	0.52 ±0.050	16.283 ±1.397
5000	0.87[b] ±0.178	29.657[b] ±5.696	0.60 ±0.100	20.748[b] ±3.345

[a] Standard deviation.

[b] Significantly different from control ($p \leq 0.05$) using ANOVA followed by Dunnett's t-test.

TABLE 10. Mean Thyroid/Parathyroid Weights and Thyroid/Parathyroid-to-Body Weight Ratios in Mice Fed MON-097

Dietary Level (ppm)	Males		Females	
	Thyroid/ Parathyroids Wt. (g)	g thyroid/parathyroids 1000 g body wt.	Thyroid/ Parathyroids Wt. (g)	g thyroid/parathyroids 1000 g body wt.
12-Month Sacrifice				
0	0.005 ±0.002[a]	0.133 ±0.047	0.005 ±0.003	0.196 ±0.100
500	0.005 ±0.002	0.170 ±0.071	0.005 ±0.002	0.205 ±0.079
1500	0.005 ±0.002	0.191[b] ±0.064	0.007 ±0.002	0.277[b] ±0.069
5000	0.005 ±0.002	0.156 ±0.074	0.006 ±0.002	0.384[b] ±0.083
23-Month Sacrifice				
0	0.007 ±0.002[a]	0.212 ±0.070	0.007 ±0.002	0.212 ±0.071
500	0.009[b] ±0.003	0.253 ±0.092	0.008[b] ±0.002	0.247 ±0.068
1500	0.007 ±0.002	0.206 ±0.065	0.009[b] ±0.002	0.296[b] ±0.089
5000	0.008 ±0.002	0.277[b] ±0.073	0.010[b] ±0.003	0.356[b] ±0.106

[a] Standard deviation.

[b] Significantly different from control value ($p \leq 0.05$) using ANOVA followed by Dunnett's t-test; analysis by report authors.

TABLE 11. Frequently Occurring Neoplastic Lesions in Mice Fed MON-097 for 23 Months[a]

Organ/Lesion	Males/Dose (ppm) 0	500	1500	5000	Females/Dose (ppm) 0	500	1500	5000
No. of animals examined microscopically	60	60	60	60	60	60	60	59
No. of animals with tumors	35	26	43	40[b]	23[c]	31	36[d]	31[e]
- Harderian gland	(60)[f]	(60)	(60)	(60)	(60)	(60)	(60)	(59)
Adenoma	8	7	7	9	3	1	5	4
- Kidneys	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(59)
Adenocarcinoma	0	0	2	1	0	0	0	0
Adenoma	2	1	1	2	0	0	0	3[b]
Sarcoma	0	0	0	0	0	0	0	2
- Total malignant kidney tumors	0	0	2	1	0	0	0	2
- Liver	(60)[f]	(59)	(60)	(59)	(60)	(60)	(60)	(58)
Adenoma	8	4	9	7	2	0	0	4
Carcinoma	6	7	10	22[b,d]	1	0	0	4[b]
- Lungs	(60)[f]	(60)	(60)	(60)	(60)	(60)	(60)	(59)
Adenoma	6	10	12	5	2	6	8[g]	4
Carcinoma	7	3	4	3	0	5[g]	3	7[b,g]
Histiocytic sarcoma	0	0	0	0	0	0	1	0
- Total lung tumors	13	13	16	8	2	11[d]	12[d]	11[b,d]
- Lymphatic System	(60)[f]	(60)	(60)	(60)	(60)	(60)	(60)	(59)
Lymphoma	4	2	2	4	6	7	12	1
- Ovaries	-	-	-	-	(59)[f]	(60)	(60)	(58)
Adenoma	-	-	-	-	0	0	1	0
Granulosa cell tumor	-	-	-	-	0	0	3	2
Luteoma	-	-	-	-	0	0	1	1
- Total benign ovarian tumors	-	-	-	-	0	0	5[g]	3[b]

TABLE 11. Frequently Occurring Neoplastic Lesions in Mice Fed MON-097 for 23 Months[a] (continued)

Organ/Lesion	Males/Dose (ppm) 0	500	1500	5000	Females/Dose (ppm) 0	500	1500	5000
- Pituitary gland	(58)[f]	(49)	(58)	(54)	(58)	(57)	(55)	(51)
Adenoma	0	0	0	1	2	2	0	0
- Uterus	-	-	-	-	(59)[f]	(60)	(60)	(59)
Endometrial stromal polyp	-	-	-	-	1	2	2	2
Histiocytic sarcoma	-	-	-	-	0	6[d]	6[d]	5[g]
Leiomyosarcoma	-	-	-	-	3	0	2	0

[a] Neoplastic lesions that occurred at a frequency of no more than one per dose group were excluded from this table unless significance was noted for total tumors of a given organ.

[b] Statistically significant linear trend ($p \leq 0.01$) using the Peto analysis. It should be noted that the animals scheduled for interim sacrifice at 12 months (10/sex/dose) were included in the above compilation even though they would be at low risk of developing neoplasms by month 12. The sponsors indicated, however, that statistical analysis by the Peto method has the advantage of utilizing survival and time to tumor information.

[c] Corrected value found by our reviewers; this value was reported as 22 by the sponsor.

[d] Statistically significant increase compared to control ($p \leq 0.01$) using the Chi-square test (uncorrected for continuity).

[e] Reanalysis by our reviewers indicated a statistically significant linear trend ($p < 0.05$) using the Cochran-Armitage test; the analysis reported by the sponsor had used the value of 22 females with tumors at 0 ppm and had reported a significance of $p \leq 0.01$ using the Peto analysis.

[f] Number in parentheses is the number of animals from which tissue was examined histologically.

[g] Significantly different from control by Fisher's exact test $p < 0.05$.

The sponsor provided statistical analysis of incidence of neoplasms using chi-square (without continuity correction), and analysis of linear trend using the Peto analysis. With the chi-square analysis there was a statistically increased incidence ($p \leq 0.01$) in the following:

- o liver carcinomas in high-dose males (22/59) as compared to controls (6/60);
- o total lung tumors in the low- (11/60), mid- (12/60) and high-dose females (11/59) as compared to controls (2/60)
- o histiocytic sarcomas of the uterus in the low- (6/60) and mid-dose (6/60) female groups as compared to controls (0/59).

By the Peto trend analysis there were significant linear trends for the following:

- o females with kidney adenomas (0/60, 0/60, 0/60, and 3/59 in control, low-, mid-, and high-groups groups;
- o males with liver carcinomas (6/60, 7/58, 10/60, and 22/59 in the controls, low-, mid-, and high-dose groups;
- o females with liver carcinomas (1/60, 0/60, 0/60, and 4/58) in control, low-, mid-, and high-dose groups;
- o females with total lung tumors (2/60, 11/60, 12/60, and 11/59 in controls, low-, mid-, and high-dose groups);
- o females with lung carcinomas (0/60, 5/60, 3/60, and 7/59 in controls, low-, mid-, and high-dose groups);
- o females with benign ovarian tumors (0/59, 0/60, 5/60, and 3/58) in control, low-, mid-, and high-dose groups);
- o females with histiocytic sarcomas of the uterus (0/59, 6/60, 6/60, and 5/59 in control, low-, mid-, and high-dose groups).

The incidence of frequent non-neoplastic lesions is summarized in Table 12. The report authors stated that there was a dose-related increased incidence of interstitial nephritis in all dosed groups of males and females.

The sponsor provided statistical analysis of nonneoplastic lesions which indicated significant increases ($p \leq 0.01$) in the incidence of interstitial nephritis compared to controls in both males and females receiving the highest dose Analysis of trend (Peto test) indicated

TABLE 12. Frequently Occurring Nonneoplastic Lesions in Mice Fed MON-097 for 23 Months

Organ/Lesion	Males/Dose (ppm) 0	500	1500	5000	Females/Dose (ppm) 0	500	1500	5000
- Adrenal Gland	(58)[a]	(59)	(58)	(59)	(59)	(60)	(60)	(59)
Amyloidosis	0	2	1	1	1	1	4	1
- Bone Marrow	(60)	(60)	(60)	(60)	(60)	(60)	(59)	(59)
Fibrous Osteodystrophy	0	0	0	0	8	11	6	6
- Cecum	(59)	(56)	(60)	(57)	(56)	(59)	(59)	(58)
Typhlitis	0	3	0	0	0	1	0	1
- Colon	(59)	(56)	(59)	(59)	(57)	(60)	(59)	(59)
Nematodiasis	10	9	1	5	3	1	0	1
- Duodenum	(60)	(56)	(60)	(57)	(57)	(59)	(59)	(58)
Amyloidosis	0	0	0	0	0	1	2	1
Duodenitis	0	2	2	0	0	1	1	3
- Eyes	(60)	(60)	(60)	(59)	(60)	(60)	(60)	(59)
Cataract	3	0	1	0	1	0	1	1
Keratitis	0	1	1	1	2	0	0	0
Panophthalmitis	2	0	0	0	1	0	0	0
Retinal Degeneration	4	3	6	3	2	3	1	8[c]
- Harderian Gland	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(59)
Dacryoadenitis	3	3	0	3	4	1	1	0
- Heart	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(59)
Cardiomyopathy	2	3	1	5	2	1	0	0
Endocarditis	0	2	0	0	0	0	0	0
Myocarditis	0	2	2	2	1	0	2	1
Thrombosis	1	1	3	2	0	2	1	0
- Ileum	(59)	(56)	(59)	(57)	(56)	(59)	(59)	(58)
Amyloidosis	2	0	0	1	2	2	0	2
Ileitis	0	2	0	0	0	0	0	0
- Jejunum	(59)	(56)	(58)	(57)	(57)	(59)	(59)	(58)
Amyloidosis	4	5	3	2	0	2	3	3

[a] Number in parentheses is the number of animals from which tissue was examined histologically.

[c] Statistically significant linear trend ($p \leq 0.01$) using the Cochran-Armitage test; analyses by our reviewers.

TABLE 12. Frequently Occurring Nonneoplastic Lesions in Mice Fed MON-097 for 23 Months (continued)

Organ/Lesion	Males/Dose (ppm) 0	500	1500	5000	Females/Dose (ppm) 0	500	1500	5000
- Kidneys	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(59)[d]
Amyloidosis	1	3	2	1	2	2	4	2
Cysts	5	10	6	2	3	1	0	1
Hydronephrosis	3	1	5	3	2	5	1	6
Infarction	0	6	0	0	1	0	0	0
Interstitial Nephritis	30	35	42	50[b,c]	31	33	31	45[b,c]
Nephrocalcinosis	0	0	0	0	0	1	0	2
- Liver	(60)	(59)	(60)	(59)	(60)	(60)	(60)	(58)
Cell Focus	2	0	0	0	1	1	0	0
Cysts	5	1	3	2	1	1	2	0
Fatty Infiltration	2	0	1	0	0	2	0	0
Hepatitis	3	3	0	2	2	3	5	1
Necrosis	2	5	0	3	5	3	1	4
- Lungs	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(59)
Bronchopneumonia	0	0	0	2	0	0	0	0
Interstitial Pneumonia	5	6	10	3	3	3	4	5
Lymphocytosis	2	1	1	0	4	1	1	2
Precipitate, Alveolar	2	0	0	0	0	0	1	0
- Lymph Nodes	(57)	(55)	(57)	(52)	(55)	(55)	(55)	(51)
Angiectasis	0	1	2	0	4	0	0	0
Congestion	1	2	1	0	2	2	0	1
Lymphadenitis	2	2	1	1	3	0	6	4
Lymphoid Hyperplasia	0	5	2	2	6	0	9	1
- Middle Ear	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(59)
Otitis Media	3	1	1	1	1	1	1	3
- Nose	(60)	(59)	(59)	(60)	(60)	(60)	(60)	(59)
Rhinitis	0	4	3	0	3	2	5	0

[b] Statistically significant increase compared to control ($p \leq 0.01$) using the Chi-square test (uncorrected for continuity).

[d] Correct value determined by our reviewers.

TABLE 12. Frequently Occurring Nonneoplastic Lesions in Mice Fed MON-097 for 23 Months (continued)

Organ/Lesion	Males/Dose (ppm) 0	500	1500	5000	Females/Dose (ppm) 0	500	1500	5000
- Ovaries	--	--	--	--	(59)	(60)	(60)	(58)
Amyloidosis	--	--	--	--	2	1	2	0
Cyst, follicular	--	--	--	--	2	2	1	2
Cyst, hemorrhagic	--	--	--	--	11	10	9	7
Cyst, simple	--	--	--	--	29	26	21	19
- Peripheral Nerve	(55)	(46)	(48)	(51)	(54)	(52)	(57)	(57)
Neuropathy	0	0	0	0	2	0	0	0
- Pituitary Gland	(58)	(49)	(58)	(54)	(58)	(57)	(55)	(51)
Hyperplasia	0	0	0	0	1	0	2	0
- Prostate Gland	(60)	(59)	(60)	(60)	--	--	--	--
Prostatitis	3	2	6	3	--	--	--	--
- Salivary Gland	(60)	(60)	(60)	(59)	(60)	(59)	(60)	(57)
Sialoadenitis	3	2	0	2	0	1	3	1
- Seminal Vesicles	(60)	(60)	(60)	(60)	--	--	--	--
Seminal Vesiculitis	3	1	6	1	--	--	--	--
- Skin	(60)	(59)	(60)	(59)	(57)	(60)	(60)	(59)
Dermatitis	4	1	8	3	6	5	2	5
- Spleen	(59)	(56)	(55)	(59)	(57)	(60)	(59)	(57)
Hematopoiesis, Extramedullary	2	0	1	2	4	5	5	4
Hemosiderosis	0	1	0	2	5	4	2	8
- Stomach	(60)	(59)	(60)	(60)	(59)	(60)	(59)	(59)
Adenomatous Hyperplasia	2	8	6	1	2	3	0	4
Gastritis	1	2	3	6	7	4	6	2
- Testes	(60)	(60)	(60)	(60)	--	--	--	--
Atrophy	12	14	14	3	--	--	--	--
Degeneration	1	5	0	3	--	--	--	--
Mineralization	0	2	0	1	--	--	--	--
- Thymus	(50)	(45)	(48)	(45)	(48)	(51)	(49)	(43)
Lymphoid Hyperplasia	0	0	0	0	4	0	1	0

TABLE 12. Frequently Occurring Nonneoplastic Lesions in Mice Fed MON-097 for 23 Months (continued)

Organ/Lesion	Males/Dose (ppm) 0	500	1500	5000	Females/Dose (ppm) 0	500	1500	5000
- Thyroid Gland	(59)	(58)	(58)	(57)	(58)	(58)	(59)	(59)
Cyst, follicular	0	1	0	0	1	2	0	2
Thyroiditis	0	0	0	0	2	0	1	1
- Uterus	--	--	--	--	(59)	(60)	(60)	(59)
Cystic Endometrial Hyperplasia	--	--	--	--	42	30	34	22
Endometritis	--	--	--	--	2	1	4	3
- Vagina	--	--	--	--	(58)	(60)	(59)	(58)
Epidermoid Dysplasia	--	--	--	--	5	6	1	1
Vaginitis	--	--	--	--	2	4	4	4
- Zymbal's Gland	(49)	(56)	(55)	(56)	(58)	(53)	(56)	(55)
Adenitis	3	1	3	0	1	0	1	0

a significant positive trend ($p \leq 0.01$) for interstitial nephritis in males (30/60, 35/60, 42/60, and 50/60 in control, low-, mid- and high-dose groups) and in females (31/60, 33/60, 31/60, and 45/60 in control, low-, mid-, and high-dose groups) and a positive trend ($p \leq 0.01$) for retinal degeneration in females (2/60, 3/60, 1/60, and 8/59 in control, low-, mid-, and high-dose groups). However, analysis by pairwise comparison did not indicate a significant increase ($p < 0.01$) in the incidence of retinal degeneration in high-dose females.

10. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

The authors concluded that when MON-097 was fed in the diet to random bred Swiss albino CD-1 mice at 0, 500, 1500, and 5000 ppm in the diet it was oncogenic under the conditions of the study. It caused a dose-related increase in pulmonary adenomas in males receiving 500 and 1500 ppm and in all female test groups, a dose-related increase in pulmonary carcinomas in all female test groups, an increase in hepatic carcinomas in all female test groups and in high-dose males, and a dose-related increase in uterine histiocytic sarcomas in all female test groups. A dose-related increase in interstitial nephritis was also seen in all test groups of males and females. It caused a persistent decrease in body weight and body weight gain in male and female groups receiving 5000 ppm but not in low- or mid-dose groups. The only clinical laboratory data considered to be compound related was a decrease in RBC, Hgb, and Hmct values in high-dose females at 23 months; the authors considered that "this anemia may be indirectly compound related as it was associated with the presence of tumors, particularly of the liver, and of renal disease." The only changes in organ weight values and organ-to-body weight ratios considered related to treatment were absolute and relative liver and kidney weight ratios in dosed males and absolute and relative kidney weights in dosed females; this was stated to be based on histopathological correlations. Signs of toxicity, food consumption fluctuations, clinical chemistry values in test groups differing from controls and weight changes in adrenals and thyroids were not considered compound related.

A quality assurance statement, signed and dated May 4, 1983, was present

11 REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

We conclude that the experimental design and conduct of this bioassay for the oncogenicity of MON-097 was generally in accord with Pesticide Assessment Guidelines. We classify the study as Core Minimum. Deficiencies are as follows:

1. The mice used in the study were received in three different shipments and were acclimated for different periods of time; however, they were all approximately the same age at study initiation.

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2. Abnormal clinical findings with the date of observation were entered on individual animal disposition records, but summary incidences were not tabulated nor were weekly observation forms available.

3. There was no evidence that blood smears were obtained from 10 animals/sex/dose group at 18 months as suggested by the guidelines.

4. Organ weights were obtained after fixation. It is common practice, however, to weigh organs before fixation.

5. Necropsy findings were summarized by organ systems rather than by individual tissues or organs.

Food efficiency in high-dose males was approximately half of the control value; however, because the variability was so great the difference was not significant (ANOVA α = 0.05, analysis by our reviewers).

Our statistician indicated that it was inappropriate for the study authors to analyze the clinical chemistry, hematology, organ weight, and organ-to-body weight data by the independent, two-sided Student's t-test. However, our statistician's reanalysis of these data by a more appropriate method (ANOVA followed by Duncan's multiple range test) did not change any of the conclusions as to which values in dosed animals were significantly different from control values.

Due to the small size of the blood samples, pooling of 3 to 5 individual samples was necessary for the clinical chemistry analyses at interim and terminal sacrifices; as a result, only 2 or 3 pools were analyzed for each dose group at each sacrifice. We conclude that the availability of only 2-3 values for each clinical chemistry parameter makes the statistical tests (ANOVA, tests to determine differences between means, and trend analyses) of these measurements unstable.

The sponsor concluded that blood chemistry effects indicative of liver damage were observed in dosed animals. This conclusion was based on observations of increased serum alkaline phosphatase in high-dose females at months 12 and 23, increased serum glutamic oxaloacetic transaminase in high-dose males at month 12, and slightly increased total bilirubin in mid- and high-dose mice of both sexes at month 23. The study authors discounted these observations, concluding that these abnormal findings were for the most part randomly distributed and on many occasions lacked any definitive histopathological correlations.

The study authors did not consider effects on organ weights and organ-to-body weight ratios to be test compound-related unless there was correlative histopathology. With this criterion, the study authors considered only liver and kidney weight and organ-to-body weight ratio increases to be test compound-related.

Differences in the accuracy of weighing the adrenals at 12 and 23 months were apparent; the weights of the adrenals were reported to an accuracy of only two digits after the decimal at month 12 (weights were 0.01-0.04 g with most weights being 0.01 or 0.02 g) but were reported to an accuracy of three digits after the decimal at month 23 (most weights were <0.01 g for males and <0.02 g for females). The mean weight of liver in control females at termination that was reported was unusually high and had a large standard deviation (Table 7). Examination of the individual liver weights revealed that one control female (#1508) had a liver weight of 8.57 g which was correlated with hepatocellular carcinoma (4 x 2.2 x 1.8 cm). If this value were omitted the mean was 1.54±0.325 and the high-dose females had a significantly higher ($p \leq 0.05$) mean liver weight than controls.

The study authors compiled the gross pathology results into four tables according to whether the animals were sacrificed or found dead or moribund. Two tables were for tumors and the other two for non-tumor lesions. They also reported the microscopic diagnoses by neoplasm and nonneoplastic lesions in different tables. As the gross lesions were tabulated as the number of lesions/sex/dose rather than animals with lesions/sex/dose, the gross pathology results were not amenable to statistical treatment. Our reviewers' examination of the individual animal data records revealed that where tissue masses (suspected tumors) were diagnosed grossly, a microscopic diagnosis was also made and usually confirmed the gross diagnosis with the appropriate cell type. The care with which lesions found grossly were processed through the histology laboratory and presented to the pathologist for microscopic examination appeared to be quite effective. Tables 13 and 14 were prepared by our reviewers to correlate the gross diagnoses with microscopic diagnoses. For practical purposes, the analysis for tumor incidence can appropriately be based solely upon the microscopic diagnoses.

The study authors concluded that dose-related increases occurred only for liver carcinomas (males at all doses and high-dose females), uterine histiocytic sarcomas (females at all doses), pulmonary adenomas (females at all doses and low- and mid-dose males), and pulmonary carcinomas (females at all doses). However, the study authors did not analyze histopathology data statistically. This analysis was provided by the sponsor.

The sponsor concluded that significant ($p \leq 0.01$) dose-related positive trends occurred for liver carcinomas (males and females), liver adenomas (males and females combined), uterine histiocytic sarcomas (females), ovary benign tumors (females), total lung tumors (females), lung carcinomas (females), kidney adenomas (females), malignant kidney tumors (males and females combined), and animals with tumors (males and females). Significantly increased incidences ($p \leq 0.01$) of neoplastic lesions in treated animals as compared to controls were found for liver carcinomas (high-dose males), uterine histiocytic sarcomas (low- and mid-dose females), lung tumors (females at all doses), and animals with tumors (mid-dose females). Although

TABLE 13. Correlation of Reported Gross Pathology (Tissue Masses) and Histopathological Diagnoses of Neoplastic Lesions[a]

LIVER (FEMALES)
- ~gross masses of digestive system in control and all dose groups
- ~carcinomas
  - --significant dose-related positive trend in incidence

LIVER (MALES)
- ~gross masses of digestive system in control and all dose groups
- ~carcinomas
  - --significant dose-related positive trend in incidence
  - --significantly increased incidence at high dose

LIVER (MALES PLUS FEMALES)
- ~gross masses of digestive system in control and all dose groups
- ~adenomas
  - --significant dose-related positive trend in incidence

LUNG (FEMALES)
- ~gross pulmonary masses in control and all dose groups
- ~carcinomas
  - --significant dose-related positive trend in incidence
- ~total lung tumors (including carcinomas)
  - --significant dose-related positive trend in incidence
  - --significantly increased incidence at all doses

KIDNEY (FEMALES)
- ~gross urinary tract masses in mid- and high-dose groups
- ~adenomas
  - --significant dose-related positive trend in incidence

KIDNEY (MALES PLUS FEMALES)
- ~gross urinary tract masses in control and in mid- and high-dose groups
- ~malignant tumors
  - --significant dose-related positive trend in incidence

OVARIES (FEMALES)
- ~gross reproductive tract masses in control and all dose groups
- ~benign tumors
  - --significant dose-related positive trend in incidence

UTERUS (FEMALES)
- ~gross reproductive tract masses in control and all dose groups
- ~histiocytic sarcomas
  - --significant dose-related positive trend in incidence
  - --significantly increased incidence at low and mid doses

TABLE 13. Correlation of Reported Gross Pathology (Tissue Masses) and Histopathological Diagnoses of Neoplastic Lesions[a] (Continued)

TOTAL TUMORS (FEMALES)
-gross tissue masses in control and dose groups
-animals with tumors
--significant dose-related positive trend in incidence
--significantly increased incidence at mid dose.
TOTAL TUMORS (MALES)
-gross tissue masses in control and all dose groups
-animals with tumors
--significant dose-related positive trend in incidence

TABLE 14. Correlation of Reported Gross Pathology (Tissue Lesions) and Histopathological Diagnoses of Nonneoplastic Lesions[a]

EYES (FEMALES)
-gross ocular lesions in control and in mid and high dose groups
-retinal degeneration
--significant dose-related positive trend in incidence
KIDNEYS (MALES AND FEMALES)
-gross urinary tract lesions in control and in all dose groups for both sexes
-interstitial nephritis
--significant dose-related positive trend in incidence for both sexes
--significantly increased incidence at high dose for both sexes

[a] Table prepared by our reviewers.

there are some differences between the study authors' conclusions and those of the sponsor (see Table 15 for tabular presentation), they both unequivocally agree that MON was carcinogenic, causing definite increases in liver carcinomas, lung tumors, and histiocytic sarcomas of the uterus. The sponsors analysis of tumors used a p value of 0.01 for significance. Analysis by our reviewers indicated that in addition to the findings of the sponsor the following neoplasms were significant at a p level of 0.05: carcinoma of lungs in low- and high-dose females, histiocytic sarcoma of the uterus in high-dose females and total ovarian benign tumors of the uterus in mid-dose females.

In addition to total number of tumors occuring in an organ system as related to exposure, an examination as to possible acceleration of tumor development was attempted by our reviewers. This issue had not been addressed by either the sponsor or the study authors. The latency of tumors could only be estimated based upon tumors observed in animals dying during particular time periods. Tables 16 and 17 present a detailed breakdown of the main tumors of concern as related to their observation with time of death and dose level. Tables 18 and 19 present the data in a somewhat different manner allowing a quicker assessment of the early-appearing tumors. Especially notable were the frequencies of high-dose males that died at 20-23 months with liver carcinomas (10/17) (Table 16) and dosed females that died with uterine histiocytic sarcomas at 13-16 months (5/16) and at 17-19 months (4/15) (Table 17).

When we considered the animals that died or were killed before the terminal sacrifice, combining the tumors for all treated groups to assess differences from controls, a slightly different pattern emerged in that tumors of the lung also become prominent. Thirty-six (36) animals (combined males and females) with lung tumors (adenomas plus carcinomas) were observed in 243 early deaths for a 15% incidence versus only 2 out of 59 controls (3%). The number of early uterine sarcomas still remains substantial, 14 of 125 (11%) versus 0 of 29 controls (0%). However, comparing total early liver tumors in the dosed groups with the controls diminishes the evidence for a substantial early development. Based upon these data, it is concluded that earlier-appearing tumors were observed with greater frequency as related to treatment in three organ systems - liver, lungs, and uterus.

A NOEL for chronic toxicity could not be established due to increased liver and kidney weights at the low-dose level. The LOEL for chronic toxicity of MON-097 in mice was 500 ppm in the diet (lowest dose tested).

12. CBI APPENDIX:

Appendix A, Materials and Methods, CBI Vol. I, pp. 9-21.
Appendix B, Protocol, CBI Vol. III, pp. 126-187.

TABLE 15. Analysis of Neoplastic Response

	MALES							
	Study Author				Sponsor			
	Trend	L	M	H[a]	Trend	L	M	H
Liver adenoma					X[b]			
Liver carcinoma		X	X	X	X			X
Lung adenoma		X	X					
Lung carcinoma								
Total lung tumors								
Kidney adenoma								
Malignant kidney tumors					X[b]			
Total animals with tumors					X			

	FEMALES							
	Study Author				Sponsor			
	Trend	L	M	H	Trend	L	M	H
Liver adenoma					X[b]			
Liver carcinoma				X	X			
Lung adenoma		X	X	X				
Lung carcinoma		X	X	X	X			
Total lung tumors					X	X	X	X
Kidney adenomas					X			
Malignant kidney tumors					X[b]			
Uterine histiocytic sarcomas		X	X	X	X	X	X	
Benign ovary tumors					X			
Total animals with tumors					X		X	

[a] L, low dose; M, mid dose; H, high dose.

[b] Indicates statistics performed using combined male and female groups.

TABLE 16. Frequencies of Tumors in Males as Related to Time of Death[a]

	0-12 Months				12 Month Sacrifice				13-16 Months				17-19 Months				20-23 Months				23 Month Sacrifice			
Dose Level (ppm)	0	500	1500	5000	0	500	1500	5000	0	500	1500	5000	0	500	1500	5000	0	500	1500	5000	0	500	1500	5000
No. of Animals Examined	0	7	2	6	10	10	10	10	3	5	3	6	2	5	5	8	15	9	15	17	30	24	25	13
No. of Tumors Observed	0	0	0	0	2	0	2	2	0	4	2	7[b]	1	3	10	7	13	5	8	19	25	22	25	20
Harderian Gland																								
Adenoma	0	0	0	0	0	0	1[c]	0	0	1	0	1	1	0	1	2	1	1	2	2	6	5	3	5
Kidneys																								
Adenocarcinoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	0
Adenoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	2	0	1	1	0
Liver																								
Adenoma	0	0	0	0	1	0	0	1	0	0	0	1	0	0	2	0	3	0	1	1	7	4	6	4
Carcinoma	0	0	0	0	0	0	0	0	0	1	0	1	0	1	2	3	5	1	2	10	1	4	6	8
Lungs																								
Adenoma	0	0	0	0	0	0	1	0	0	1	0	1	0	1	1	1	0	0	2	1	6	8	8	2
Carcinoma	0	0	0	0	0	0	0	0	0	0	1	1	0	1	3	0	2	2	0	1	5	0	0	1
Histiocytic Sarcoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lymphatic System																								
Lymphoma	0	0	0	0	1	0	0	0	0	1	1	2	0	0	1	1	3	1	0	1	0	0	0	0
Pituitary Gland																								
Adenoma	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

[a] Table prepared by our reviewers.
[b] Total number of tumors may exceed the number of animals examined due to multiplicity of tumors in some animals.
[c] Number of animals in which a given tumor type was found upon histopathological examination.

TABLE 17. Frequencies of Tumors in Females as Related to Time of Death[a]

	0-12 Months				12 Month Sacrifice				13-16 Months				17-19 Months				20-23 Months				23 Month Sacrifice			
Dose Level (ppm)	0	500	1500	5000	0	500	1500	5000	0	500	1500	5000	0	500	1500	5000	0	500	1500	5000	0	500	1500	5000
No. of Animals Examined	3	3	2	6	10	10	10	10	2	3	5	8	5	6	4	5	9	13	22	18	31	25	17	12
No. of Tumors Observed	0	0	2	1	1	1	2	0	0	2	2	4	2	5	9[b]	5	4	10	16	12	10	12	11	15
Harderian Gland																								
Adenoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2[c]	0	0	0	1	2	2	1	2	2
Kidneys																								
Adenocarcinoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Adenoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0
Liver																								
Adenoma	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	3
Carcinoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	1	0	0	1
Lungs																								
Adenoma	0	0	0	0	0	0	1	0	0	0	0	0	0	1	3	1	0	2	3	1	2	3	1	2
Carcinoma	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	2	0	2	0	3	3	3
Histiocytic Sarcoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lymphatic System																								
Lymphoma	0	0	2	1	0	0	1	0	0	0	1	0	2	2	2	0	2	3	6	0	2	2	0	0
Pituitary Gland																								
Adenoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	0	0
Ovaries																								
Adenoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Granlosa Cell Tumor	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	0	0	0	1	1
Luteoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0
Uterus																								
Endometrial Stromal Polyp	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	1	2
Histiocytic Sarcoma	0	0	0	0	0	0	0	0	0	1	1	3	0	2	1	1	0	0	4	1	0	1	0	0
Leiomyosarcoma	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	2	1	0	1	0	1	0

[a] Table prepared by our reviewers.
[b] Total number of tumors may exceed the number of animals examined due to multiplicity of tumors in some animals.

TABLE 18. Summary of Males With Tumors as Related to Time of Death

	Months						
	0-12	12	13-16	17-19	20-23	23	Total
Liver Adenoma							
Control	-	1	-	-	-	7	8
L	-	-	-	-	-	4	4
M	-	-	-	2	1	6	9
H	-	1	1	-	1	4	7
	0	2	1	2	2	21	28
Liver Carcinoma							
Control	-	-	-	-	5	1	6
L	-	-	1	1	1	4	7
M	-	-	-	2	2	6	10
H	-	-	1	3	10	8	22
	0	0	2	6	18	19	45
Lung Adenoma							
Control	-	-	-	-	-	6	6
L	-	-	1	1	-	8	10
M	-	1	-	1	2	8	12
H	-	-	1	1	1	2	5
	0	1	2	3	3	24	33
Lung Carcinoma							
Control	-	-	-	-	2	5	7
L	-	-	-	1	2	-	3
M	-	-	1	3	-	-	4
H	-	-	1	-	1	1	3
	0	0	2	4	5	6	17
Kidney Adenoma							
Control	-	-	-	-	2	-	2
L	-	-	-	-	-	1	1
M	-	-	-	-	-	1	1
H	-	-	-	-	2	-	2
	0	0	0	0	4	2	6

L = low dose
M = mid dose
H = high dose

TABLE 19. Summary of Females with Tumors as Related to Time of Death

	Months 0-12	12	13-16	17-19	20-23	23	Total
Liver Carcinomas							
Control	-	-	-	-	-	1	1
L	-	-	-	-	-	-	0
M	-	-	-	-	-	-	0
H	-	-	-	-	3	1	4
	0	0	0	0	3	2	5
Lung Adenomas							
Control	-	-	-	-	-	2	2
L	-	-	-	1	2	3	6
M	-	1	-	3	3	1	8
H	-	-	-	1	1	2	4
	0	1	0	5	6	8	20
Lung Carcinoma							
Control	-	-	-	-	-	-	-
L	-	-	-	-	2	3	5
M	-	-	-	-	-	3	3
H	-	-	1	1	2	3	7
	0	0	1	1	4	9	15
Lymphomas							
Control	-	-	-	2	2	2	6
L	-	-	-	2	3	2	7
M	2	1	1	2	6	-	12
H	1	-	-	-	-	-	1
	3	1	1	6	11	4	26
Uterus Hist. Sarcomas							
Control	-	-	-	-	-	-	0
L	-	-	1	2	-	1	4
M	-	-	1	1	4	-	6
H	-	-	3	1	1	-	5
	0	0	5	4	5	1	15

L = low dose
M = mid dose
H = high dose