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

003885

8/3/84

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Metolachlor Mouse Oncogenicity Study; EPA Reg. No. 100-537;
Accession Nos. 248722-25; CASWELL #188DD

TO: Richard Mountfort (23)
Registration Division (TS-767)

FROM: D. Stephen Saunders Jr., Ph.D. D. Stephen Saunders Jr.
Toxicologist, Section V 7-30-84
TOX/HED (TS-769)

THRU: Laurence D. Chitlik, DABT LDC 7/30/84
Head, Section V
TOX/HED (TS-769)
and
William L. Burnam WLB 8/3/84
Chief, Toxicology Branch
HED (TS-769)

Action Requested

Review of metolachlor mouse oncogenicity study.

Recommendations

This study has been classified as Core-Minimum data. The following minor points are noted:

1) The study report states that the technical material was used in the study, and that the test compound was analyzed by the registrant at study initiation and every three months thereafter. These data "are on file with Ciba-Geigy", and should be provided to the Agency.

2) The method of sacrifice of test animals was not described in the study report.

If these minor points are clarified, the study can be upgraded to Core-Guideline.

The study is negative, as no increase in tumors was noted at the HDT, 3000 ppm. A decrease in body weight gain of high dose males and females was noted, indicating that the 3000 ppm dose was a Maximally Tolerated Dose (MTD). No other significant chronic effects were noted in this study (see review).

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Study: Carcinogenicty Study With Metolachlor in Albino Mice 003885

Accession No.: 248722

Sponsor/Contracting Lab.: Ciba-Geigy/Hazelton Raltech (Madison, WI)

Study No.: 79026

Report Date/Submitted: 8-13-82/10-2-82

Reviewer: D. Stephen Saunders Jr., Ph.D. DSS 7/30/84

Methods

The methods from the submitted study have been photocopied and are appended. The procedure followed in this study is unremarkable except for the following point:

1) Method of sacrifice of animals not described.

Test Compound

Metolachlor technical, batch no. FL-791174. % a.i. not disclosed in the final report, however it was stated that purity was determined by the sponsor prior to study initiation and at 3-month intervals thereafter. These data are on file with the sponsor. PM team 23 provided a value of 95.0% for the technical material (personal communication).

Results

A. Test diet analysis- Samples of each test diet for weeks 1-4 were analyzed for content of metolachlor. Thereafter, one diet was selected at random each week for analysis of content of the test material. Time-weighted averages of the three test diets indicated that all diets were within 5% of theoretical:

Diet (ppm)	Time-weighted Average (ppm)[a]	Time-weighted %Theoretical
300 (range)	287 (146-351)	96%
1000 (range)	981 (781-1120)	98%
3000 (range)	3087 (2660-3270)	103%

[a]data excerpted from submitted study.

B. Physical signs and Mortality- No significant treatment-related signs were noted. A slight increase in the overall incidence of signs related to the eye were noted as a result of treatment, however several distinct observations, including conjuctivitis, "eyes red", "eyes opaque", and "exudate from

eye", were counted together. No single physical sign was noted in increased frequency that could be related to treatment.

The only group which exhibited a mortality rate that was significantly higher than control or other treatment groups was the high dose females (group 8). This result was considered to be due to a number of deaths in the first weeks of the study that were the result of infection with Sendai virus. If these deaths were factored out of the analysis, no statistically significant differences in mortality existed between any of the groups. For the purpose of this review, these deaths have been considered to be treatment-related: animals in all groups were housed in the same room, and were exposed to the same environment. Since increased susceptibility to infection as a result of exposure to toxic substances is a recognized toxicological endpoint, removal of these deaths from the data base is not considered appropriate by this reviewer.

Dates of death for control and high dose males and females (groups 1, 4, 5, and 8) listed in table 3 of the final report were checked by this reviewer against individual animal pathology sheets, and were accurate. Relative survival was calculated for these groups by the reviewer; one minor error was found (animal #5083 died on test, counted as terminal sacrifice).

Relative survival for all groups is presented below in table 1.

Table 1. Relative Survival[a]

Dose (ppm)	Week 79 Male	Week 79 Female	Week 105 Male	Week 105 Female
0	41/52[b] (78.8)[c]	44/52 (84.6)	20/52 (38.5)	28/52 (53.8)
300	42/52 (80.8)	37/52 (71.2)	25/52 (48.1)	20/52 (38.5)
1000	43/52 (82.7)	40/52 (76.9)	31/52 (59.6)	24/52 (46.2)
3000	37/52 (71.2)	31/52 (59.6)	28/52 (53.8)	18/52* (34.6)

[a]data excerpted from submitted study.

[b]number alive/total. Total does not include 8 animals/group sacrificed at 12 and 18 months.

[c]percent, calculated by reviewer.

*$p<0.05$

C. Body Weight- Statistically significant reductions in body weight gain were observed for high dose male and female mice. Significant reductions in weight gain were noted for high dose males (group 4) after two weeks of treatment, and this deficit persisted throughout treatment. High dose females (group 8) had significant weight gain deficits beginning with week 32, and at

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23/37 time points measured after this time statistically significant deficits were observed.

Average body weights were recalculated by this reviewer from submitted individual animal data for groups 1, 4, 5, and 8 on weeks 50 and 104; no errors were found.

Body weight data are presented in table 2.

Table 2. Effect of Metolachlor on Body Weight[a]

Dose (ppm)	Week 50 Male	Week 50 Female	Week 104 Male	Week 104 Female
0	40.3±4.1[b]	31.7±4.1	40.5±3.4	35.2±3.8
300	39.8±5.2 (98.8)[c]	31.7±2.9 (100.0)	40.9±4.3 (101.0)	34.3±6.1 (97.4)
1000	39.5±4.6 (98.0)	31.7±2.6 (100.0)	39.7±4.1 (98.0)	34.7±4.6 (98.6)
3000	36.5±3.2** (90.6)	30.3±2.7* (95.6)	37.9±3.6** (93.6)	32.6±3.6 (92.6)

[a]data excerpted from submitted study.

[b]body weight in grams, mean ± std. dev., calculated by reviewer from submitted individual animal data.

[c]percent of control, calculated by reviewer.

*$p<0.05$, **$p<0.01$ by Dunnett's t-test.

D. Feed Consumption and Compound Intake- No differences in food intake were noted between male treatment groups until week 90 of treatment, at which time high dose males ate about 10% less than control. This difference was statistically significant on weeks 98, 102 and 104. No significant effect on food consumption was noted betweem any of the female treatment groups. However, females tended to eat more food than their male counterparts.

Average food consumption for high dose and control male and female mice was calculated by the reviewer from submitted raw data for weeks 50 and 104 and compared to submitted summary data, no errors were found.

Compound intake was calculated by the reviewer based on average food intake and average body weights on weeks 26, 52, 78 and 104. All groups tended to consume less test compound (based on mg/kg body weight) in the latter portion of the study. Based on these calculations, female mice are estimated to have received a dose of metolachlor that was about 15-50% higher than corresponding males. This effect was due to the higher apparent food consumption for females coupled with the lower body weights for females compared to males. Since the effect of the test compound on body weight gain was similar in male and female

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mice, the calculated difference in estimated compound intake is not considered significant.

Table 3 presents the calculated doses of test compound.

Table 3. Calculated Dose of Test Compound[a]

	Group	Diet (ppm)	Week 26	52	78	104
Males	2	300	54[b]	53	46	46
	3	1000	174	185	169	153
	4	3000	539	568	575	421
Females	6	300	55	77	61	54
	7	1000	239	253	226	177
	8	3000	703	852	655	607

[a]data excerpted from submitted study.

[b]dose of metoloachlor in mg/kg body weight, calculated by reviewer based on average food consumption and average body weights.

E. Clinical Pathology- No toxicologically significant effects on hematology, serum chemistries, or urinalyses were noted as a result of treatment with the test compound in any of the treatment groups.

(1) Hematology- An increase in white blood count was observed for group 2 (300 ppm males) at 18 months, however this result was due to a very high value for one animal (out of 8) (#5171, 78.8 x $10^3/mm^3$). This effect was not repeated at other time points nor was it dose-related. A statistically significant increase in the %neutrophils was also observed at 18 months for group 4 (high dose males). However, this increase was not accompanied by an increase in the WBC count, and, although the increase was statistically significant when compared to concurrent study controls, the values were within the range for normal CD-1 mice (ref. "Representative Historical Control Data", Feb. 1984, Hazelton Laboratories America, Inc.). Other hematology values were not altered.

(2) Serum Chemistries- An increase in average values for AST and ALT was noted at 24 months in high dose males (615.4 ± 901.0 and 306.2 ± 575.7, N = 6, AST and ALT respectively). The increases in average values were due to one animal with abnormally high values (#5275, AST = 2450.6, ALT = 1481.1 IU/L), as reflected by the large standard deviations for the averages. If these values were excluded, the averages were not different from control (AST = 248.3 ± 65.9, ALT = 71.2 ± 14.6; N = 5) and were within the normal range for CD-1 mice (see ref. abcve).

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High dose females (group 8) also had a statistically significant increase in the average for serum AST activity and a decrease in serum uric acid content, both at 12 months. Two animals in the sample had values substantially higher than the other 5 animals in the group, as is reflected by the large standard deviation for the average (414.4 + 258.0, N = 7). However, the average AST activity without the two high values was still significantly higher than control (267.7 + 73.6, N = 5, vs. 168.5 + 69.0, N = 6), and each of the individual values for this group were higher than the average control value. Therefore, even though average AST activity for high dose females was similar to control at 18 and 24 months, the increased activity at 12 months was likely treatment-related. Similarly, the decrease in serum uric acid content in this group at the 12 month interim sacrifice could not be attributed to the influence of out-lying values, and was likely treatment-related.

An approximate two-fold increase in average serum alkaline phosphatase activity was noted in all male treatment groups (groups 2-4) at 24 months. In each group, one animal with an abnormally high value (of 6 or 7 animals per group for which this value was determined) was responsible for the increase in the average. This effect was not dose-related, and only one animal in each group was a responder.

Other serum chemistry values were unremarkable.

(3) Urinalysis- Alterations in average values for protein content were observed, however in each case the increased average could be attributed to the influence of out-lying values. No trends in terms of dose or time-course were apparent. No notable alterations in other parameters were observed.

F. Organ Weights- Statistically significant changes in absolute and organ/body weight ratios were occassionally noted in response to treatment with the test compound. However, organ/brain weight ratios were not significantly altered in any of the treatment groups at any time point. For example, high dose males had statistically significant increases in liver and kidney organ/body weight ratios at 12, 18 and 24 months, and a decrease in the organ/body weight ratio of seminal vesicle at 24 months. These effects could be attributed to decreases in body weight rather than effects on the organs, with the exception of seminal vesicle which had an organ/brain weight ratio that was 55% of control but not statistically significant.

Similarly, effects on the absolute weights and/or organ/body weight ratios were noted in other organs such as kidney, ovaries and uterus, however statistically significant changes in organ/brain weight ratios were not seen in these tissues.

Organ weights for control and high dose male and female rats that were listed in the raw data summaries were compared by the reviewer to the hand-written values that were recorded on individual animal pathology sheets at sacrifice; all values appeared to be recorded accurately. Organ weight ratios were spot-checked, and appeared to have been calculated correctly.

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G. Necropsy Data- (1) Gross findings: No significant treatment-related findings were noted upon macroscopic examination of animals at necropsy. Frequent findings included cortical cysts in the kidneys, enlarged uterus, cystic ovaries, and enlarged seminal vesicles. Other occasional findings included abnormal color or focus in the lung, and abnormal color and/or nodules or masses in the liver. None of these changes occurred in a manner that would suggest a dose-effect relationship with the test compound. There was no significant difference in the distribution of gross observations between animals necropsied at scheduled sacrifice and those that died on test or were sacrificed moribund.

Tabulated summaries of gross findings were compared to individual animal pathology sheets for the 12 and 18 month interim sacrifices; all tabulations appeared accurate. Findings of interest were spot-checked for animals that died on test (including moribund sacrifice) and for final (24 month) sacrifice, and were accurately recorded and tabulated.

Tabulations of gross lesions and resultant histological diagnoses were checked for lung and liver lesions for all treatment groups against individual animal pathology sheets, and were accurately recorded.

(2) Microscopic- Neoplastic lesions seen in all treatment and control groups included alveologenic tumor, nodular hyperplasia/hepatocellular carcinoma, and lymphosarcoma. No dose-related trends were apparent for any of these lesions when all histopathology data were considered.

The incidences of nodular hyperplasia/hepatocellular carcinoma and lymphosarcoma/reticulum cell sarcoma are depicted in table 6.

An apparent increase in the incidence of alveologenic tumor was observed in male mice at the 18 month interim sacrifice. The difference between group 1 control (0/8) and group 4 high dose (5/8) mice was suggestive of a positive response, and the trend was statistically significant by the method of Peto ($p = 0.02$) and by Fisher's Exact test ($p = 0.02$, see appendix 2). Although suggestive of an effect at 18 months, these data were not confirmed at final (24 month) sacrifice, when the incidences for control (5/20, 25%) and high dose (10/28, 35.7%) males were not significantly different. Addition of data from animals that were sacrificed moribund or died on test also indicated that the data obtained at 18 months were spurious, as evidenced by the lack of a dose-effect relationship for the total incidence of this lesion (table 5). Therefore, the apparent response at 18 months is considered artifactual and of no toxicological significance.

The incidence of alveologenic tumors for all animals (interim and final sacrifices and died on test/moribund sacrifice) is presented in table 5.

Commonly observed non-neoplastic lesions included cystic ovaries and endometrial hyperplasia in females, and lymphoid infiltration and cortical cysts of the kidney in both sexes. The incidences of these and other lesions were not dose-related.

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(3) Correlation between gross and histological observations- Observations recorded at necropsy were compared to microscopic findings and tabulated by the investigators. A number of gross findings at necropsy, principally in the liver, kidney and lymph nodes, had no corresponding microscopic diagnosis and were listed as "not remarkable". Because only positive findings were recorded on the individual animal pathology sheets, it was not possible for this reviewer to independently verify that these gross lesions were actually examined microscopically. However, a tissue inventory was present with each individual animal pathology sheet which indicated the tissues present on each slide. Also, occassional recuts were requested by the study pathologists, apparently in order to locate lesions that were not present on the original slide. Two lung nodules were noted on gross necropsy that were listed as "not remarkable" on microscopic examinations (#5326, group 5, and #5552, group 8; both at final sacrifice). Neither of these nodules, even if they were re-examined and diagnosed as tumors, would change the interpretation of this study.

The remainder of the missing diagnoses were for abnormal color or size of tissues noted at necropsy, with the exception of kidney which included a number of tissues with cortical cysts that were not observed microscopically. For liver, spleen and lymph nodes, the investigators stated in the final report that these tissues "were frequently normal when examined microscopically".

In the case of kidney, the investigators stated that "there was not a good correlation between abnormal observations ... and the corresponding microscopic diagnoses". Most of these disparities were for cortical cysts, which were observed at necropsy, but apparently did not appear on the slide for microscopic examination. Since cortical cysts can be detected by gross observation, and no treatment-related effect on the incidence of this finding was noted, the lack of correlation for this particular lesion is not considered significant.

Table 5. Incidence of Alveologenic Tumors- Males[a]

Group (Dose)	Interim 12 mos.	Interim 18 mos.	Final 24 mos.	Died on test/ Moribund Sac.	Total
1 (0 ppm)	1/8[b] (12.5%)	0/8 -	5/20 (25.0%)	5/28 (17.9%)	11/64 (17.2%)
2 (300 ppm)	1/8 (12.5%)	4/8 (50.0%)	11/25 (44.0%)	6/21 (28.6%)	22/62 (35.5%)
3 (1000 ppm)	0/8 -	2/8 (25.0%)	5/29 (17.2%)	1/20 (5.0%)	8/65 (12.3%)
4 (3000 ppm)	0/8 -	5/8 (62.5%)	10/28 (35.7%)	4/21 (19.0%)	19/65 (27.9%)

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Table 5. Incidence of Alveologenic Tumors- Females[a]

Group (Dose)	Interim 12 mos.	Interim 18 mos.	Final 24 mos.	Died on test/ Moribund Sac.	Total
5 (0 ppm)	1/8 (12.5%)	2/8 (25.0%)	6/26 (23.1%)	6/25 (23.1%)	15/67 (22.4%)
6 (300 ppm)	1/8 (12.5%)	1/8 (12.5%)	8/20 (40.0%)	5/30 (16.7%)	15/66 (22.7%)
7 (1000 ppm)	0/8 -	4/8 (50.0%)	10/23 (43.5%)	3/28 (10.7%)	17/67 (25.4%)
8 (3000 ppm)	0/8 -	3/8 (37.5%)	4/17 (25.5%)	2/33 (6.1%)	9/66 (13.6%)

[a]data excerpted from submitted study.

[b]number of tumors/number of animals examined.

Table 6. Incidences of Liver and Lymphoid Tumors[a]

	Males				Females			
	Dose (ppm)							
Lesion	0	300	1000	3000	0	300	1000	3000
Nodular hyperplasia	7	8	12	8	1	2	2	2
Hepatocellular carc.	2	0	4	1	1	0	0	0
Total/no. examined	9/63	8/64	16/65	9/64	2/66	2/65	2/65	2/66
Lymphoid Neoplasias[c] -lung	2/64[b]	5/62	2/65	1/65	7/67	6/66	2/67	6/66
-spleen	3/60	3/63	3/64	0/64	7/66	6/66	4/66	7/66
-liver	4/63	4/64	3/65	0/64	6/66	5/65	5/65	7/66
-kidney	5/64	4/63	2/64	0/65	5/66	5/66	4/68	6/66
-mesenteric l.n.	5/58	4/62	3/61	1/63	8/65	4/63	5/63	8/64
no. affected animals	5	5	3	1	11	7	7	12

[a]data excerpted from table 46 of submitted study.

[b]number affected/number examined.

[c]includes lymphosarcoma and reticulum cell sarcoma.

Conclusions

Treatment of mice for 24 months with diets containing 300, 1000 or 3000 ppm of metolachlor failed to produce an increase in tumor incidence. A statistically significant increase in the incidence of alveologenic tumors in males was noted at the 18 month interim sacrifice, however this effect was not confirmed by the 24 month final sacrifice nor by total incidences for all animals. Other neoplastic lesions of the liver and lymphoid system were observed, however were not dose-related.

Animals of the high dose group gained significantly less body weight than did control animals, indicating that the high dose was an MTD.

Effects on organ/body weight ratios were observed in response to treatment with the test compound, particularly in the liver, kidney and ovaries. Although these alterations were statistically significant, similar effects on organ/brain weight ratios were not observed, and no lesions were detected in these organs upon gross and histological examination to suggest a pathogenic process that was dose-related.

Classification: Core-Minimum Method of sacrifice not described; purity of test article not disclosed although report states that purity of the test article was determined by the registrant prior to study initiation and at 3-month intervals during the study.

Not a carcinogen at the HDT (3000 ppm).

Systemic NOEL: 1000 ppm
Systemic LEL: 3000 ppm decreased body weight gain, decreased survival of high dose females.

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Appendix 1. METHODS

Metolachlor toxicology review

Page _____ is not included in this copy.

Pages 12 through 20 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

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

Appendix 2. STATISTICS

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DATE: JULY 11,1984

TITLE: METO.-FEMALES
REMARKS: I.S. AT 18 MO.

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DOSE LEVEL	No. of Animals	OBS. FREQ.	EXP. FREQ
0	8	2	2.5
300	8	1	2.5
1000	8	4	2.5
3000	8	3	2.5

NSUM= 32 OSUM= 10 ESUM= 10 BSUM= 10750 CSUM= 2.5225E+07
T= 2550 V= 9.70042E+06 Q= 1.36688E+07 SD= 3114.55 Z= .818739

p= .2065 79.35% PROBABILITY THAT THE EFFECT IS DOSE RELATED

REMARKS: I.S. AT 18 MO.

DOSE LEVEL	No. of Animals	OBS. FREQ.	EXP. FREQ
0	8	2	2.33333
300	8	1	2.33333
1000	8	4	2.33333

NSUM= 24 OSUM= 7 ESUM= 7 BSUM= 3033.33 CSUM= 2.54333E+0
T= 1266.67 V= 908309 Q= 1.22889E+06 SD= 953.053 Z= 1.32906

p= .0919 90.81% PROBABILITY THAT THE EFFECT IS DOSE RELATED

REMARKS: I.S. AT 18 MO.

DOSE LEVEL	No. of Animals	OBS. FREQ.	EXP. FREQ
0	8	2	1.5
300	8	1	1.5

NSUM= 16 OSUM= 3 ESUM= 3 BSUM= 450 CSUM= 135000
T=-150 V= 58500.1 Q= 67500.1 SD= 241.868 Z=-.620173

p= .7324 26.76% PROBABILITY THAT THE EFFECT IS DOSE RELATED

DATE: JULY 11,1984

TITLE: METOLACHLOR-FEMALES
REMARKS: TOT. ALV. CARCENOMA = DOT+IS+MS=TS

DOSE LEVEL	No. of Animals	OBS. FREQ.	EXP. FREQ
0	68	15	16.5
300	68	15	16.5
1000	68	17	16.5
3000	68	19	16.5

NSUM= 272 OSUM= 66 ESUM= 66 BSUM= 70950 CSUM= 1.66485E+0
T= 7550 V= 6.85758E+07 Q= 9.02138E+07 SD= 8281.05 Z= .911721

p= .181 81.9% PROBABILITY THAT THE EFFECT IS DOSE RELATED

REMARKS: TOT. ALV. CARCENOMA = DOT+IS+MS=TS

DOSE LEVEL	No. of Animals	OBS. FREQ.	EXP. FREQ
0	68	15	15.6667
300	68	15	15.6667
1000	68	17	15.6667

NSUM= 204 OSUM= 47 ESUM= 47 BSUM= 20366.7 CSUM= 1.70767E+0
T= 1133.33 V= 6.38139E+06 Q= 8.2511E+06 SD= 2526.14 Z= .448642

p= .3268 67.32% PROBABILITY THAT THE EFFECT IS DOSE RELATED

REMARKS: TOT. ALV. CARCENOMA = DOT+IS+MS=TS

DOSE LEVEL	No. of Animals	OBS. FREQ.	EXP. FREQ
0	68	15	15
300	68	15	15

NSUM= 136 OSUM= 30 ESUM= 30 BSUM= 4500 CSUM= 1.35E+06
T= 0 V= 530000 Q= 675000 SD= 728.011 Z= 0

p= .5 50% PROBABILITY THAT THE EFFECT IS DOSE RELATED

DATE: JULY 11, 1984

TITLE: METO.-MALES
REMARKS: I.S. AT 18 MO

DOSE LEVEL	No. of Animals	OBS. FREQ.	EXP. FREQ
0	8	0	2.75
300	8	4	2.75
1000	8	2	2.75
3000	8	5	2.75

NSUM= 32 OSUM= 11 ESUM= 11 BSUM= 11825 CSUM= 2.77475E+0
T= 6375 V= 1.01854E+07 Q= 1.50357E+07 SD= 3191.46 Z= 1.99752

p= .0229 97.71% PROBABILITY THAT THE EFFECT IS DOSE RELATED

REMARKS: I.S. AT 18 MO

DOSE LEVEL	No. of Animals	OBS. FREQ.	EXP. FREQ
0	8	0	2
300	8	4	2
1000	8	2	2

NSUM= 24 OSUM= 6 ESUM= 6 BSUM= 2600 CSUM= 2.18E+06
T= 600 V= 824348 Q= 1.05333E+06 SD= 907.936 Z= .66084

p= .2544 74.56% PROBABILITY THAT THE EFFECT IS DOSE RELATED

REMARKS: I.S. AT 18 MO

DOSE LEVEL	No. of Animals	OBS. FREQ.	EXP. FREQ
0	8	0	2
300	8	4	2

NSUM= 16 OSUM= 4 ESUM= 4 BSUM= 600 CSUM= 180000
T= 600 V= 72000 Q= 90000 SD= 268.328 Z= 2.23607

p= .0127 98.73% PROBABILITY THAT THE EFFECT IS DOSE RELATED

NAME: LACAYO
TITLE: METOLACHLOR-MALES
REMARKS: TOTAL=DOT+MS=+IS+TS=ALL ALV. CARCENOMA

DATE: JULY 10,1984

DOSE LEVEL	No. of Animals	OBS. FREQ.	EXP. FREQ
0	68	11	14.9451
300	68	22	14.9451
1000	68	8	14.9451
3000	69	19	15.1648

NSUM= 273 OSUM= 60 ESUM= 60 BSUM= 64923.1 CSUM= 1.52774E+08
T= 6676.92 V= 6.46233E+07 Q= 8.25236E+07 SD= 8038.86 Z= .83058

P= .2031 79.69% PROBABILITY THAT THE EFFECT IS DOSE RELATED

REMARKS: TOTAL=DOT+MS=+IS+TS=ALL ALV. CARCENOMA

DOSE LEVEL	No. of Animals	OBS. FREQ.	EXP. FREQ
0	68	11	13.6667
300	68	22	13.6667
1000	68	8	13.6667

NSUM= 204 OSUM= 41 ESUM= 41 BSUM= 17766.7 CSUM= 1.48967E+07
T=-3166.67 V= 5.7795E+06 Q= 7.19778E+06 SD= 2404.06 Z=-1.31722

P= .9061 9.39% PROBABILITY THAT THE EFFECT IS DOSE RELATED

EMARKS: TOTAL=DOT+MS=+IS+TS=ALL ALV. CARCENOMA

OSE LEVEL	No. of Animals	OBS. FREQ.	EXP. FREQ
0	68	11	16.5
300	68	22	16.5

SUM= 136 OSUM= 33 ESUM= 33 BSUM= 4950 CSUM= 1.485E+06
= 1650 V= 566501 Q= 742501 SD= 752.662 Z= 2.19222

= .0142 98.58% PROBABILITY THAT THE EFFECT IS DOSE RELATED

Meto-Lachlor

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Input Program

ct fisher def

```
//LHEX2CL JOB (WMJ1,352,A),LACAYO
/*CNTL NEG1DZT,SHR
// EXEC FORVLKGO,LIBDISK=FILE02,
// LIBNAME='NEG1DZT.STAT.LOAD'
//LOAD.SYSLIN DD *
  INCLUDE SYSLIB(C2X2)
  ENTRY MAIN
//GO.FT01F001 DD *
1 -1 1
.025 .025
-1
METOLACHLOR-MALES,CONTROL VS ALL DOSES AT 18 MO
0,8 11,24
-1
METO.-MALES,CONTROL VS ALL DOSES AT 24 MO.
5,20 26,84
-1
METO.-FEM,CONTROL VS ALL DOSES AT 18 MO
2,8 8,24
//
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Meto-Fem, Control vs all doses at 24 mo.

6,28 21 23,61

1

DIAGNOSTIC MESSAGE DIRE

IEW0201 WARNING - OVERLAY STRUCTURE CONTAINS ONLY ONE SEGMENT — OPTION CANCELED.

1

0IFY215I VCVTH - ILLEGAL DECIMAL CHARACTER (0)
0**** START OF BUFFER CONTENTS ****
0,8 11,24
0**** END OF BUFFER CONTENTS ****
0TRACEBACK OF CALLING ROUTINES; MODULE ENTRY ADDRESS=00145DA8
IFYVCVTH(0015A978) CALLED BY VLDIO# (00153168) AT ISN ** OFFSET).
NO ARGUMENTS PASSED TO SUBROUTINE
VLDIO# (00153168) CALLED BY MAIN (00145DA8) AT ISN ** OFFSET).
NO ARGUMENTS PASSED TO SUBROUTINE
MAIN (00145DA8) CALLED BY (OP/SYS)
0 STANDARD CORRECTIVE ACTION TAKEN, EXECUTION CONTINUING.
METOLACHLOR-MALES,CONTROL VS ALL DOSES AT 18 MO

TABLE(S):

0 8
11 13

TABLE(S) REORIENTED TO PREVENT ALL ODDS RATIOS BEING INFINITE

TABLE(S):

11 13
0 8

ODDS RATIO(S):

0.0000

ASYMPTOTIC MAXIMUM LIKELIHOOD ESTIMATE OF PSI= 0.0000

ASYMPTOTIC TEST FOR MAIN EFFECT, P=0.2849E-01

*** WARNING, LOWER LIMIT MUST BE 0;
PROBABILITY REQUESTED FOR LOWER LIMIT INCLUDED IN UPPER LIMIT **

95.0% LIMIT PSI < 0.744307

CONDITIONAL MAXIMUM LIKELIHOOD ESTIMATE OF PSI= 0.0000

EXACT TEST FOR MAIN EFFECT, P=0.1935E-01

EXACT CONFIDENCE LIMITS FOR PSI

BEST AVAILABLE COPY

*** WARNING, LOWER LIMIT MUST BE 0.

95.0% LIMIT PSI < 9.682947

*** SINGLE/COMBINED 2X2 TABLE PROGRAM JAN/16/84 *** CPU TIME=
SEC.
1

003885

METO.-MALES,CONTROL VS ALL DOSES AT 24 MO.

TABLE(S):

5 15
26 58

ODDS RATIO(S):

1.3448

ASYMPTOTIC MAXIMUM LIKELIHOOD ESTIMATE OF PSI= 1.3448

ASYMPTOTIC TEST FOR MAIN EFFECT, P=0.4014

95.0% LIMITS 0.398443 < PSI < 4.771767

CONDITIONAL MAXIMUM LIKELIHOOD ESTIMATE OF PSI= 1.3411

EXACT TEST FOR MAIN EFFECT, P=0.4097

EXACT CONFIDENCE LIMITS FOR PSI

95.0% LIMITS 0.406236 < PSI < 5.225135

*** SINGLE/COMBINED 2X2 TABLE PROGRAM JAN/16/84 *** CPU TIME=
SEC.
1

METO.-FEM,CONTROL VS ALL DOSES AT 18 MO

TABLE(S):

2 6
8 16

ODDS RATIO(S):

1.5000

ASYMPTOTIC MAXIMUM LIKELIHOOD ESTIMATE OF PSI= 1.5000

ASYMPTOTIC TEST FOR MAIN EFFECT, P=0.5000

95.0% LIMITS 0.192134 < PSI < 13.827908

CONDITIONAL MAXIMUM LIKELIHOOD ESTIMATE OF PSI= 1.4818

EXACT TEST FOR MAIN EFFECT, P=0.5118

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EXACT CONFIDENCE LIMITS FOR PSI

*** SINGLE/COMBINED 2X2 TABLE PROGRAM JAN/16/84 *** CPU TIME=
SEC.
1

METO.-FEM, CONTROL VS ALL DOSES AT 24 MO

003885

TABLE(S):

6	22
22	39

ODDS RATIO(S):

2.0684

ASYMPTOTIC MAXIMUM LIKELIHOOD ESTIMATE OF PSI= 2.0684

ASYMPTOTIC TEST FOR MAIN EFFECT, P=0.1295

95.0% LIMITS 0.660090 < PSI < 6.725539

CONDITIONAL MAXIMUM LIKELIHOOD ESTIMATE OF PSI= 2.0523

EXACT TEST FOR MAIN EFFECT, P=0.1274

EXACT CONFIDENCE LIMITS FOR PSI

95.0% LIMITS 0.671158 < PSI < 7.144249

*** SINGLE/COMBINED 2X2 TABLE PROGRAM JAN/16/84 *** CPU TIME=
SEC.
0 MESSAGE SUMMARY: MESSAGE NUMBER - COUNT
0 215 1

[illegible]