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

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MEMORANDUM

JUN 16 1982

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TO: Robert Taylor (12)
Registration Division (TS-769)

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

THRU: Orville E. Paynter, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: EPA Reg.#524-316; Alachlor. Review of Monsanto 18-Month
Oncogenic Study in Mice. R.D.#365, Special Report
MSL#1649; Volumes 1 and 2; 6/18/81. Accessions#070168
and #070169. CASWELL#11

Action Requested:

A review is requested for an 18-month oncogenic study in mice submitted by Monsanto Company as a part of the requirement to support registrations and tolerances for Alachlor (2-chloro-2',6' diethyl-N-(methoxymethyl)-acetanilide), a herbicide.

Conclusion:

Classification: Core-Minimum

Alachlor is oncogenic in mice.

*Incidence of animals bearing tumors increased significantly at the high-dose level (260 mg/kg bw/day) in males, $p < 0.05$. The incidence for the combined high-dose male and female animals was also highly significant, $p < 0.01$.

*Lung is the major target organ for oncogenicity. Incidence of lung bronchioalveolar tumors (adenoma + carcinomas) was significant in the high-dose females, $p < 0.05$, and the combined high-dose animals (males and females), $p < 0.05$. The incidence of these tumors was also highly significant, $p < 0.01$, for the high-dose females which died in extremis during the study.

*Incidence of tumors in other organs was also noted to increase at the high-dose level, potentially as a result of Alachlor administration, i.e. liver tumors (adenoma + carcinoma) in the high-dose males and uterine tumors (see description on p. 18) in the high-dose females. The incidence of animals bearing these tumors was not statistically significant.

REVIEWStudy Identification

An 18-month chronic feeding study of Alachlor in mice, BD-77-423, 6/18/81. A final report compiled by R.W. Street, and submitted on 7/1/81 by Monsanto Company, St. Louis, MO. 63166 (Volumes 1 and 2; Accessions#070168 and 070169).

The Study was performed by Bio/dynamics Inc., project#77-2064 (BD-77-423). The final report was dated May 6, 1981 and signed by Ira W. Daly, Ph.D (Study Director) and Geoffrey H. Hogan, Ph.D (Vice President of Toxicology).

In life phase of study was from April 14, 1978 to October 14 to 18, 1979 (550 to 554 days).

Materials and MethodsTest Substance

Alachlor (Lasso[®] technical) material, a clear, brown, slightly viscous liquid, was supplied in two batches by Monsanto. Lot#XHI-167 (92.6% a.i.) was received on 1/5/78 and used from 4/12/78 to 3/6/79; Lot#MHK-6 (92.19% a.i.) was received on 2/8/79 and used from 3/7/79 to termination.

Lot XH7-167 used during the first 11 months of the study was stabilized with 0.5% epichlorohydrin; Lot MHK-6 used during the last 7 months of the study was stabilized [REDACTED] (Ref.: Sec. I, Vol. 1, p. 1).

Study Design

Male and female mice were randomly divided into groups and fed Alachlor continuously in the diet at the following nominal concentrations for the entire duration of the study:

Group	Number of Animals/Sex/Group					
	Dosage mg/kg/day M/F*	Initial M/F	Hematology at 12-month and termination M/F	Necropsy at termination		Histology
				M	F	
I	0	50	10	24	20	All animals
II	26	50	10	16	33	All animals
III	78	50	10	24	23	All animals
IV	260	50	10	22	15	All animals

*M/F represents # males and # females

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Test Animals

Two hundred male (mean body weight 25.65g) and 200 female (mean body weight 20.75 g) CD-1 albino mice were initiated in this 18-month feeding study. The mice were obtained from Charles River Laboratories (Wilmington, Mass.) when 35-days old and then acclimatized for a period of 17 days before treatment. Each mouse was toe-clipped for identification.

The mice were individually housed in elevated stainless steel wire mesh cages and maintained on a 12-hour light/dark cycle, and temperature controlled rooms (monitored twice daily). Control and test diet and tap water were available ad libitum throughout the study.

Preparation of Test Diet

The treated diet was prepared weekly based on body weight and food consumption data. Dietary levels of Alachlor were adjusted weekly for each dosage group so as to provide each group with the designated mg/kg/day intake of test material. Appropriate amounts of Alachlor were dissolved in 100 ml acetone and incorporated into 9 to 12 kg of feed (Purina R-5001 Lab. Chow). Acetone alone was added to the control diet.

Diet analyses were performed on weeks 0, 1, 2, 3, 4, 6, 7, 8, 9, 11, 12, 13, 24, 36, 48, 50, 51, 53, 55, 59, 71 and 72. Technical grade Alachlor was also analyzed to determine its stability during storage. The mice were offered the treated diet at age 53 days and continuously thereafter for 550 to 554 days (from 4/14/78 to 10/14-18/79).

Observations

The animals were observed twice daily for signs of overt toxicity and mortality. Detailed physical examination was performed weekly for signs of local or systemic toxicity, pharmacologic effects and tissue masses.

Body weights and food consumption were measured at pretest, weekly through the first 4 weeks and biweekly from week 16 through week 78 (body weights were also measured terminally after fasting).

Compound intake and food efficiency were calculated; however, food efficiency was calculated weekly for weeks 1-14.

Absolute (ml/interval) and relative (ml/kg/day) water consumption values were determined for 10 mice/sex/group during two 3-day periods on week 75 (month 18) and two 3-day periods on week 78 (termination).

Laboratory Studies

Blood was collected for 10 mice/sex/group at 12 months and at termination (19 months). The mice were fasted overnight prior to blood collection and the blood was obtained via the orbital sinus technique. The same animals were used at both intervals for blood samples when feasible.

The hematological parameters evaluated in this study included hemoglobin concentration, hematocrit value, total erythrocyte counts, total and differential leucocyte counts, and erythrocyte morphology.

Necropsy

All animals were subject to necropsy. Complete gross postmortem examination was performed on all animals dying spontaneously or sacrificed in extremis during the study and on all surviving animals at termination (10/15 to 19/1979). All animals were sacrificed by exsanguination under ether anesthesia.

Brain, adrenal, testes, ovaries, spleen, heart, kidneys, liver and pituitary were weighed at necropsy for animals sacrificed at termination only; and organ to body weight and organ to brain weight ratios were calculated.

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The following tissues were preserved (and histopathologically examined) for all animals dying spontaneously or sacrificed in extremis or at termination:

abdominal aorta
 adrenals
 blood smear¹
 bone and bone marrow (costochondral junction)
 brain (3 sections)
 epididymides
 esophagus
 eyes (with optic nerve and contiguous harderian glands; right eye processed for histopathology)
 gall bladder
 gonads
 head (with entire skull cap)
 heart
 intestine
 cecum
 colon
 duodenum
 ileum
 jejunum
 kidneys
 liver (2 sections)
 lungs (with mainstem bronchi and trachea)
 lymph nodes (mediastinal and mesenteric)
 nerve (right sciatic)
 pancreas
 parathyroid
 pituitary
 prostate
 salivary gland (mandibular)
 skeletal muscle (right biceps femoris)
 skin (with mammary gland)
 spinal cord²
 stomach (3 sections)
 thymus
 thyroid
 urinary bladder
 uterus
 gross lesions
 tissue masses

¹Taken from all animals examined only if anemia, enlarged thymus, lymphadenopathy or hepatosplenomegaly is present.

²Two sections of spinal cord and three coronal sections through the head were taken for 10 animals/sex/group sacrificed at termination. One section of spinal cord was taken for all other animals.

Histopathological Examinations

The eyes with contiguous Harderian glands, testes and epididymides were preserved in Bouin's solution for 48-72 hours, followed by neutral buffered 10% formalin. All other tissues (listed in the above section) were preserved directly in the 10% formalin solution. Hematoxylin and eosin stained sections of these tissues were microscopically examined from all mice.

Statistical Analysis

Statistical analyses of data was performed by using various statistical methods. Statistically significant differences from control were indicated at $p < 0.05$.

RESULTS:

Alachlor Concentrations in Diet

Based on food consumption and body weight data, the calculated compound consumption was found to be as follows:

Group	Dose Level (ppm)	Dose level (mg/kg/day)		
		Week 2 to 4 Male	Female	Week 5 to Termination Male and Female
I	0	0.00	0.00	0.00
II	100	23.96	29.27	26.00
III	300	72.04	83.78	78.00
IV	1000	240.23	280.03	260.00

Chemical analysis of the treated diets indicated that Alachlor was found to be within 81% to 95% (89% average) of the target dosage levels (except for week 12 when the result was 150%).

Mortality and Observations

The report states that no changes considered to be related to the compound were observed in the general appearance of the animals (individual clinical observations data were not submitted). Periodic findings in some animals include alopecia, lacrimation, hypoactivity and ano-genital staining. In life tissue masses were unremarkable.

The fate of animals at the end of the study (third week of the 19th month) was as follows (initial number of animals: 50 animals/sex/group):

Dosage mg/kg/day	Survivors		Spont. Death		Moribund		Accidental Death	
	M	F	M	F	M	F	M	F
0	24	20	18	23	8	2	0	5
26	16	33	24	16	9	1	1	0
78	24	23	22	18	4	8	0	1
260	22	15	17	29	11	5	0	1

The above table reflects decreased survivability at the high-dose level in females at termination, but survival varied greatly among the test and control groups. However 50% of the animals in each group survived for 15 months of the study period.

Body Weight, Food and Water Consumption

High-dose females had a slightly reduced mean body weight (7%) than the control group during the second year of study (this decrease was statistically significant, $p < 0.05-0.01$, at most of the determination intervals). Mean body weights of all treated male groups and low- and mid-dose females were generally similar to the respective control groups.

Mean body weights at 78 weeks (termination) were slightly reduced in both treated males (2-10%) and females (3-10%) as compared to the respective control groups, see table below:

Dosage Level mg/kg/day	Group Mean Body Weights (grams)	
	Males	Females
0	40.6	37.5
26 (% reduction in bw)	36.4 (10)	36.3 (3)
78 (% reduction in bw)	39.6 (2)	34.9 (7)
260 (% reduction in bw)	37.7 (7)	33.8 (10)

Mean food consumption values were variable for the control and treated animals. However, although statistical differences were found between control and treated groups at some determination intervals, no consistent dose-response relationship was apparent. Food efficiency calculations (determined weekly from weeks 1 through 14) were also variable and inconsistent.

Mean water consumption for the low- and mid-dose animals were similar to the control mice; however the high dose animals (both males and females) reflected a significant increase ($p < 0.05$) in water consumption than the respective control groups.

Ophthalmology

No ophthalmoscopic examination was performed.

Hematology

The 12-month interim data and the terminal hematology data were unremarkable in all animal groups (Note: animal #821, a high-dose female, was removed from these calculations because it was reflecting an unusually low value for all hematology parameters).

Gross Necropsy

Animals killed at termination of study reflected statistically significant increases in mean liver weights (absolute, relative-organ/body and organ/brain) in males and females of the mid- and high-dose levels. Increases were also noted in mean kidney weights (absolute and relative organ/brain weight ratio) for mid- and high-dose males. However in females, mean kidney weights increased at the low-dose, slightly decreased at the high-dose, and were similar to the control group at the mid-dose level, see table below:

Group (ppm)	Measure	Liver		Kidney	
		Males	Females	Males	Females
Control	Absol.	1.53	1.47	0.66	0.49
	Rel./bw	4.51	4.90	1.94	1.65
	Rel./br	3.35	3.20	1.44	1.06
Low	Absol. (%)	1.56(2)	1.59(8)	0.68(3)	0.56*(15)
	Rel./bw (%)	4.81(7)	5.34 (9)	2.08(7)	1.89*(15)
	Rel./br (%)	3.40(2)	3.43 (7)	1.48(3)	1.21(14)
Mid	Absol. (%)	1.75(14)	1.68(14)	0.74*(12)	0.48(2)
	Rel./bw (%)	5.16(14)	6.00*(22)	2.17*(12)	1.70(3)
	Rel./br (%)	3.81(14)	3.75 (17)	1.59*(10)	1.07(1)
High	Absol. (%)	1.90*(24)	1.81*(24)	0.71(9)	0.45(8)
	Rel./bw (%)	6.18**(37)	6.12*(25)	2.23*(15)	1.55(6)
	Rel./br (%)	4.29**(28)	4.11*(28)	1.59*(10)	1.02(4)

*p < 0.05

**p < 0.01

Other Sporadic differences between the mean organ weights of control and treated mice were noted, however no dose-dependent pattern was evident, i.e. pituitary and spleen weights in both sexes, and ovaries weight in females. Also large sporadic differences between individual weights for these three organs were noted in treated animals.

Gross necropsy observations also reflected a variety of inflammatory, and non-inflammatory alterations, but no compound relationship was evident. However the cause of death in most animals was associated with glomerular amyloidosis (especially renal amyloidosis). Lymphoblastic lymphosarcoma was occasionally noted as a cause of death (i.e. 1, 3, 1 and 4 animals of the control, low, mid and high dose groups respectively were identified with this lesion as the cause of death).

HistopathologyNon-neoplastic lesions

At termination and for animals that died during the study, amyloidosis of different organs, especially the liver and kidney, was noted at a higher incidence in treated animals than the control-rats; this increase was not dose dependent. Other lesions were also noted at higher rates in treated groups. The following table reflects the increase in compound related lesions:

<u>Organs affected</u>	<u>MALES</u>				<u>FEMALES</u>			
	<u>Control</u>	<u>Low</u>	<u>Mid</u>	<u>High</u>	<u>Control</u>	<u>Low</u>	<u>Mid</u>	<u>High</u>
<u>Thyroid</u>	39	39	32	36	36	36	33	36
Amyloid	7	11	7	10	6	10	8	13
Follicular atrophy	1	1	5	6	4	0	5	10
<u>Liver</u>	50	50	50	50	50	50	50	50
Perivascular amyloid	25	28	27	29	19	30	30	36
<u>Kidneys</u>	50	50	50	50	50	50	50	50
Amyloid	29	39	36	33	32	40	42	40
Chronic interstitial fibrosis	1	1	4	6	1	7	5	18
<u>Ovaries</u>					43	47	46	46
Atrophy					10	29	31	31
<u>Eyes</u>	50	49	49	50	50	50	49	50
Retinal atrophy	1	2	2	6	4	6	6	6
<u>Bone marrow</u>	44	46	47	48	45	45	43	46
Hyperplasia	10	25	28	26	-	-	-	-
<u>Lungs</u>	50	50	50	50	50	50	50	49
Amyloid	7	5	20	13	2	10	7	7
Congestion	1	13	13	12	5	5	12	16

--: no difference in female groups

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From the above table it is also noted that incidence of thyroid follicular atrophy increased in the mid- and high-dose males and high-dose females.

Incidence of chronic interstitial fibrosis of the kidneys increased in all treated groups except in the low-dose male group. It is noted that the mean kidney weight values significantly increased ($p < 0.05$) in the mid- and high-dose males and in the low-dose females. The mid-dose female values were similar to the control group. However the high-dose female group (which experienced the highest incidence of kidney fibrosis in this study, see organ weight values, p. 9) reflected a slight decrease in these weight values.

Atrophy of the ovaries was noted in all treatment groups.

The incidence of Retinal atrophy was slightly increased in the treated groups as compared to the control group. This increase was most evident in the high-dose males (6 vs 1 in controls).

The incidence of bone marrow hyperplasia was 2.5 to 2.8 times higher in treated males of any group as compared to controls. No difference was noted in female groups.

Lung congestion increased in all treated male groups and mid- and high-dose female groups. Twenty-five percent of the males and 28% of the females were affected as compared to the control mice (2% M, 10% F).

High incidence of amyloidosis of liver, kidneys and lungs was noted in all animal groups but somewhat greater in treatment groups. The exact relationship between Alachlor administration and amyloidosis in this study is unclear considering that the CD-1 strain of mice (supplier Charles River Laboratories of Wilmington, Mass.) is known to have a high incidence of amyloidosis (JNCI:55 #1, 1975). Thus it is unlikely amyloidosis is compound related in this study.

Neoplastic lesions

The total number of animals bearing tumors increased (almost doubled) in the high-dose group as compared to the control group. The increase was statistically significant for the high-dose males ($p < .05$) and the combined high dose animals, males and females ($p < 0.01$). Increases were also noted in the low- and mid-dose female groups but were not statistically significant. In addition to these findings, the total number of tumors was noted to increase significantly at the high-dose level in both males ($p = 0.05$) and females ($p = 0.009$). However the number of malignant tumors in all treated male and female groups almost doubled.

The following table reflects the tumor incidence in both sexes:

	MALES			
	<u>Control</u>	<u>Low</u>	<u>Mid</u>	<u>High</u>
#of animals examined	50	50	50	50
#malignant tumors (%)	5 (10)	11 (22)	9 (18)	10 (20)
#of tumor bearing animals (%)	14 (28)	14 (28)	14 (28)	25 (50)
total # of tumors	19	17	17	28

	FEMALES			
	<u>Control</u>	<u>Low</u>	<u>Mid</u>	<u>High</u>
#of animals examined	50	50	50	50
#malignant tumors (%)	4 (8)	8 (16)	6 (12)	7 (14)
#of tumor bearing animals (%)	9 (18)	14 (28)	13 (26)	16 (32)
total # of tumors	10	18	14	22

Lungs, liver and uterus appear to be the most affected organs:

°Lung tumor bearing animals increased in all treated female groups (dose-dependent response), and very slightly in mid- and high-dose males. The increase was significant ($p < 0.05$) only at the high-dose level for females and for the combined number of high-dose animals, males and females ($p < 0.01$). Incidences of lung tumors (bronchioalveolar adenoma+carcinoma) in males and females are demonstrated in the table below:

ANIMALS WITH LUNG TUMORS (Bronchiolar-Alveolar, adenoma + carcinoma)

Group				D		T		Total	
Females	D	T	Total ^l	No.	%	No.	%	No.	%
Control	30	20	50	0/30	(0)	3/20	(15)	3/50	(6)
Low	17	33	50	1/17	(6)	4/33	(12)	5/50	(10)
Mid	27	23	50	3/27	(11)	5/23	(21)	8/50	(16)
High	35	15	50	7/35	(23)**	4/15	(27)	11/50	(22)*
Males									
Control	26	24	50	3/26	(12)	6/24	(25)	9/50	(18)
Low	34	16	50	1/34	(3)	5/16	(31)	6/50	(12)
Mid	26	24	50	1/26	(4)	10/24	(42)	11/50	(22)
High	28	22	50	5/28	(18)	7/22	(32)	12/50	(24)

*: $p < 0.05$

** : $p < 0.01$

D: died or sacrificed during study.

T: sacrificed at termination of study.

l: total is based on total number of animals in study.

It is also apparent from the above table that the incidence of lung tumors increased in treated females which died in extremis during the study. This increase was only statistically significant ($p < 0.01$) for the high-dose females.

This reviewer also notes that the incidence of lung tumors in the male control group is unusually high for this strain of mice (JNCI:46 #5, 1971). Consequently the increased incidence of this tumor in treated males may potentially be reduced when compared to the control males.

*The number of liver tumor bearing animals increased in the high-dose male group. However this increase was only significant ($p < 0.05$) for the combined number of affected high-dose males and females, though only 1/50 females was affected.

The table below reflects the incidences of liver tumors in males:

INCIDENCE OF LIVER TUMORS (ADENOMA & ADENOCARCINOMA) IN MALES

Group	D	T	Total	D		T		Total		Malignan	
				No.	%	No.	%	No.	%	No.	(%)
Control	26	24	50	2/26(8)		3/24(13)		5/50(10)		0/50(0)	
Low	34	16	50	2/34(6)		2/16(12)		4/50(8)		3/50(6)	
Mid	26	24	50	0/26(0)		5/24(21)		5/50(10)		1/50(2)	
High	28	22	50	3/28(11)		8/22(36)*		11/50(22)		4/50(8)	

*: $p = 0.06$

The above table indicates that the incidence of liver tumors in the high-dose males is almost statistically significant ($p = 0.06$) in animals sacrificed at the end of the study. The table also reflects an increase in the incidence of adenocarcinoma in all treated males; this increase is not statistically significant.

*Animals bearing uterine tumors increased by a factor of two in the low- and high-dose females. The increase was only significant ($p < 0.05$) for the high-dose females which were sacrificed at the end of the study, see table below:

ANIMALS WITH UTERINE TUMORS^a

<u>Group</u>	<u>D</u>	<u>T</u>	<u>Total</u> ¹	<u>D</u>		<u>T</u>		<u>Total</u>	
				<u>No.</u>	<u>%</u>	<u>No.</u>	<u>%</u>	<u>No.</u>	<u>%</u>
Control	30	20	50	2/30(7)		1/20(5)		3/50(6)	
Low	17	33	50	2/17(12)		6/33(18)		8/50(16)	
Mid	27	23	50	1/27(4)		1/23(4)		2/50(4)	
High	35	15	50	2/35(6)		5/15(33)*		7/50(14)	

*: $p = 0.04$

D: died or sacrificed during study.

T: sacrificed at termination.

1: total is based on total number of animals in study.

a: kind of tumors described on p. 18.

The following table identifies further the incidence of individual tumors according to tissue of origin.

Individual Number of Animals with Tumors

<u>Organs</u>	<u>Males</u>				<u>Females</u>			
	<u>C</u>	<u>Low</u>	<u>Mid</u>	<u>High</u>	<u>C</u>	<u>Low</u>	<u>Mid</u>	<u>High</u>
<u>Blood & Hemato- poietic system</u>								
<u>Spleen</u>	50	50	50	50	50	50	50	50
Hemangioendothelioma	1	0	0	0	1	0	0	0
Lymphosarcoma	0	1	0	0	0	0	0	0
Myelosarcoma	0	0	0	0	1	2	0	0
Hemangioma	0	1	0	0	0	0	0	0
<u>Lymph Nodes</u>	50	50	50	50	50	50	50	50
Lymphosarcoma	0	1	1	1	1	2	1	2
<u>Bone Marrow</u>	50	50	50	50	50	50	50	50
Myelogenous Leukemia	1	0	0	0	0	0	0	0
Granulocytic sarcoma	0	1	1	1	0	0	0	0
<u>Liver</u>	50	50	50	50	50	50	50	50
Adenoma	5	1	4	7	0	0	0	1
Adenocarcinoma	0	3	1	4	0	0	1	0
Hemangioma	0	0	0	0	1	0	1	0
<u>Lungs</u>	50	50	50	50	50	50	50	50
Bronchiolar-alveolar adenoma	6	1	4	10	2	4	7	10
Bronchiolar-alveolar adenocarcinoma	3	5	7	2	1	1	1	1
Fibrosarcoma	0	0	0	0	0	0	0	1
<u>Brain</u>	50	50	50	50	50	50	50	50
Astrocytoma	0	0	0	1	0	0	0	0

	Females			
	C	Low	Mid	High
<u>Uterus</u>	50	50	50	50
Hemangioma	1	1	0	0
Hemangiosarcoma	0	1	0	0
Endometrial carcinoma	0	1	0	0
Leiomyoma	0	2	0	0
Leiomyosarcoma	1	0	2	3
Granular cell myoblastoma	0	0	0	1
(Fibrovascular endometrial polyp)	1	3	0	3

Note: Data were collected from appendices 21-22 and table 19A.

The denominators in the above table and in the table on page 10 (non-neoplastic lesions) differ occasionally. However these differences are minimal and have no impact on the statistical evaluation of the above listed tumors.

As noted in the above table, the total number of lymphosarcoma of the blood and hematopoietic system increased slightly in treated animals of all groups, i.e. 1, 4, 2, and 3 in the combined male and female control, low-, mid- and high-dose groups respectively. One brain astrocytoma (a rare tumor) was noted in a high-dose male. Bone marrow granulocytic sarcomas were noted only in treated males. (it is important to state here that incidences of bone marrow hyperplasia almost doubled in each of the treated male groups as compared to the control group, see p. 11).

Conclusions:

This study indicates that Alachlor is oncogenic in mice.

°Lung is the major target organ for oncogenicity. Incidence of lung bronchioalveolar tumors (adenoma + carcinoma) was significant at the high-dose level (260 mg/kg bw/day) in females, $p < 0.05$, and the combined high-dose animals (males + females), $p < 0.05$. The incidence of these tumors was also highly significant, $p < 0.01$, for the high-dose females which died in extremis during the study.

This reviewer notes that the decreased significance of the lung tumors in males may be due to a high incidence of this tumor in the male control group, an incidence which is unusually high for this strain of mice (JNCI: 46 #5, 1971).

°Incidence of uterine tumors (see p. 17 for description) was only significant in the high-dose females (28% above control) which were sacrificed at the end of the study, $p < 0.05$.

°Incidence of liver tumors (adenoma + adenocarcinoma) increased in the high-dose males (12% above control). This increase was not statistically significant ($p = 0.06$ for animals sacrificed at the end of the study, and $p = 0.086$ for all high-dose males in the study).

°The incidence of animals bearing tumors increased significantly at the high-dose level in males (22% above control), $p < 0.05$. The incidence of animals bearing tumors increased in all treated female groups (8-14% above control), however these increases were not statistically significant except when the high-dose female data were combined to the high-dose male data, $p < 0.01$.

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TS-769:th:AMahfouz:6-4-82:TOX/HED:card 5