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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Linuron Data Call-In, Effect of linuron fed to aged male rats; Caswell 528; EPA I.D. # 035506; Project 7-0132; Record No. 183741

TO: Michael McDavit, Review Manager
Special Review Branch (TS-767C)
and
Robert Taylor, PM #25
Registration Division (TS-767C)

FROM: James N. Rowe, Ph.D.
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Hazard Evaluation Division/HED (TS-769C)

James N. Rowe
11/16/87

THRU: Laurence D. Chitlik, D.A.B.T.
Section Head, Section V.
Toxicology Branch/HED (TS-769C)
and
Theodore M. Farber, Ph.D.
Chief, Toxicology Branch/HED (TS-769C)

Laurence D. Chitlik
1/21/87
Theodore M. Farber
1/22/87

ACTION: Review of Du Pont submission entitled, "Effects of linuron fed to aged male rats" (study #394-86, 1980; MR No. 7351-001) Caswell 528; EPA I.D. # 035506; Project 7-0132; Record no. 183741

CONCLUSIONS/RECOMMENDATIONS:

Linuron produced a statistically significant increase in both testicular hyperplasia and adenomas when the male rats (approximately 12 months of age) were fed dietary linuron for a total of 12 months. These histopathological effects were associated with a depression in weight gain and food consumption which was compound related. Based on these findings, it is evident that linuron is capable of inducing hyperplasia and adenomas of the testes later in the rats life-span and that life-time feeding of this compound is not necessary to induce oncogenic responses in this tissue. It is well known that testicular adenomas are a common observation in older male rats of certain strains such as Fisher 344. Thus, it is possible that linuron is may be accelerating the oncogenic response associated with the aging process. It should be noted that since life-time exposure to linuron in rats is not required for the development of these testicular tumors, linuron may in fact be more potent as an oncogen than previously estimated from the two-year study.

Excerpts of data submitted by DuPont on Linuron are originally attached to this review. (7 pages). These pages may be requested by writing Freedom of Information (A-101), EPA, Washington, D.C. 20460. Requester will be asked to sign an Affirmation of Non-malevolent Status. (see D/7505)

It is recommended 1) that the findings that linuron is capable of inducing hyperplasia and adenomas of the testes in aged rats along with other associated review conclusions for biochemical and statistical data which was submitted concomitantly (see Record Nos. 183738, 184982), be presented to the Toxicology Peer Review Committee for their concurrence and 2) Dupont should submit all relevant historical control histopathology data relating to Cr1:CD®(SD)BR male rat testicular hyperplasias and adenomas (interstitial/Leydig cell).

This data submission is considered scientifically acceptable.

DATA EVALUATION RECORD

STUDY TYPE: Effects of Linuron fed to Aged Male Rats (12 months old)

CHEMICAL: Linuron [3-(3,4-dichlorophenyl) methoxy-1-methylurea]; CAS 330-55-2

TEST MATERIAL: Linuron (INZ-326); purity 94.5%; material submitted by John C. Summers, Agricultural Products Department, E.I. du Pont de Nemours and Company, Wilmington, Delaware 19898

STUDY I.D.:

1. Title: Effects of linuron fed to aged male rats
2. Laboratory: Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware
3. Study #: Haskell Laboratory Report No. 394-86; MR No. 7351-001
4. Date of report: September 24, 1986
5. Study director: Timothy P. Pastoor, Ph.D.
6. Caswell # 528; Accession # 265423; EPA ID # U35506

CONCLUSIONS:

Linuron produced a statistically significant increase in both testicular hyperplasia and adenomas when the male rats (approximately 12 months of age) were fed dietary linuron for a total of 12 months. Treatment for 6 months with normal diet followed by 6 months of dietary linuron did not produce an elevation in testicular hyperplasia but a possible increase in Leydig cell adenomas is suggested. These histopathological effects were associated with a depression in weight gain and food consumption which was compound related. Based on these findings, it is evident that linuron is capable of inducing hyperplasia and adenomas of the testes later in the rats life-span and that life-time feeding of this compound is not necessary to induce oncogenic responses in this tissue. As noted in the study report, this effect may be mediated through an age-related alteration in the testes which may make it more susceptible to an oncogenic response. It is known that testicular adenomas are a common observation in older male rats of certain strains such as Fisher 344. It should be noted that since life-time exposure to linuron in rats is not required for the development of these testicular tumors, linuron may in fact be more potent as an oncogen than previously estimated from the two-year study.

METHODS:

A photocopy of the materials and methods from the report (pages 14-19) is attached. Linuron was administered in the diet of aged male rats (approximately 12 months) at 0 (Group I), 0 (6 mos) + 625 ppm (6 mos) (Group III) and 625 ppm (12 mos) (Group V) which resulted in an average mean daily intake of linuron of 0, 0(days 0-182) + 22 (days 182-364), and 23 (days 0-364) mg/kg/day, respectively. The studies performed in this report are of an experimental nature and are not described in the 1982 EPA Guidelines for pesticide toxicity assessment. Therefore, these studies will be evaluated in terms of their scientific relevance to the issue of linuron's potential carcinogenicity and will not be given a Core grading. Since the data is not a typical chronic study, in terms of animal parameters examined or dosage regimen, the standard chronic study format has not been used.

RESULTS:

a. Body weights/body weight gains

Administration of linuron throughout the test period produced a statistically significant depression in body weights as compared to the control group within two weeks after the study was initiated which continued during the entire test period (see attached Figure 1). A significant weight depression also occurred within two weeks after Group III was fed dietary feed containing linuron at 6 months into the study. This weight depression continued to study termination.

Body weight gains (g) are summarized below:

<u>Days on test</u>	<u>Grp I</u>	<u>Grp III</u>	<u>Grp V</u>
0-84	86.5	62.1*	-51.7*
84-182	60.0	61.4	44.3
182-364	45.6	-107.8*	10.7
0-364	205.6	18.7*	4.3*

* ANOVA and Least significant difference test (different from control at $p < 0.05$ level of significance); taken from Table 3 (p. 35) of study report

Generally, mean body weight gains were in agreement with mean body weight changes. It is of interest to note that Group III, in which linuron administration was initiated at 6 months into the study, resulted in a precipitous drop in weight gain which was roughly equal to that observed from linuron administration during the entire 12 month period, e.g., mean body weights were 848.5 g(Grp I), 670.1 g(Grp III) and 668.5 g(Grp V) at day 322 on test.

b. Food consumption/food efficiency

Mean daily food consumption and food efficiency data (g) are presented below:

<u>Days on test</u>	<u>Grp I</u>		<u>Grp III</u>		<u>Grp V</u>	
	<u>Food consump.</u>	<u>effic.</u>	<u>Food consump.</u>	<u>effic.</u>	<u>Food consump.</u>	<u>effic.</u>
0-84	27.3	.038	26.5	.028	23.6	-.026
84-182	26.8	.023	26.2	.024	24.3	.019
182-364	28.2	.009	24.2	-.024	23.3	.003
0-364	27.6	.020	25.3	.002	23.6	.000

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Average mean food consumption or mean food efficiency values were not reported as statistically significantly different between the various test groups although both food consumption and food efficiency values were generally lower in both treated groups for the time periods when linuron was administered in the diet, i.e., throughout the entire test period for Group V or from 18 months on in Group III. The fact that the food efficiency values were lower in the treated groups as compared to the controls suggests that linuron is producing significant toxicity and not merely suppressing appetite and, thus, food consumption.

c. Clinical signs

A selected summary of clinical observations is presented below:

<u>Observation</u>	<u>Incidence of observations</u>		
	<u>Group I</u>	<u>Group III</u>	<u>Group V</u>
Alopecia	11 (140) ^a	12 (189)	12 (14)
Diarrhea	20 (140)	12* (77)	6* (56)
Sore tail	4 (7)	8 (315)	11* (28)
Swollen testes	2 (175)	4 (343)	5 (336)

^a the median days-on-test when sign first observed; * statistically different from control group incidence by the Fisher's Exact test with a Bonferroni correction ($p < 0.05$)

Linuron has been reported previously to produce alopecia in males and females (C. Aldous; review of linuron reproduction study; April 23, 1985) but no increase in incidence of alopecia was observed in this study. There was a treatment related decrease in diarrhea as compared to the control animals. This effect does not appear significant to the interpretation of the study. The incidence of sore tail was increased among the linuron treated rats, with Group V being statistically significantly different from controls. The incidence of swollen testes appeared to be minimally elevated in the treated animals versus control values, although not statistically significant. The incidence of swollen testes was associated in all but one animal (Group III) with adenoma and/or hyperplasia.

d. Gross and histopathology

There were no statistically significant increase in grossly observed changes although there appeared to be a treatment-related increase in discoloration of the testes (2/25 = control, 4/25 = 0/625 ppm, 6/25 = 625 ppm). The discoloration did not appear to be consistently associated with either interstitial cell adenoma or hyperplasia.

A summary of selected histopathology data is presented below:

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SELECTED HISTOPATHOLOGY DATA

Rats found dead or sacrificed in extremis:

	<u>Group I (0 ppm)</u>	<u>Group II (0 + 625 ppm)</u>	<u>Group III (625 ppm)</u>
	# in group: 6	# in group: 4	# in group: 4
<u>Testes:</u>			
Adenoma (ISC) ^a	-----	-----	-----
Hyperplasia (ISC)	2 (33) ^b	1 (25)	1 (25)
<u>Adrenal Cortex:</u>			
Adenoma	-----	-----	-----
Hyperplasia	2 (33)		1 (33) [¶]
<u>Adrenal Medulla:</u>			
Pheochromocytoma	-----	-----	-----
Hyperplasia	3 (50)	1 (25)	2 (67) [¶]
<u>Pituitary:</u>			
Adenoma	-----	-----	-----
Hyperplasia	3 (60) [¶]	2 (50)	2 (67) [¶]

Rats sacrificed by design:

	# in group: 19	# in group: 21	# in group: 21
<u>Testes:</u>			
Adenoma (ISC) ^a	-----	2 (10)	6 (29)*
Hyperplasia (ISC)	6 (32)	7 (33)	14 (67)*
<u>Adrenal Cortex:</u>			
Adenoma	-----	1 (5)	-----
Hyperplasia	5 (26)	6 (29)	6 (29)
<u>Adrenal Medulla:</u>			
Pheochromocytoma	2 (11)	2 (10)	1 (5)
Hyperplasia	5 (26)	6 (29)	6 (29)
<u>Pituitary:</u>			
Adenoma	7 (37)	6 (29)	
Hyperplasia	6 (32)		

(continued on next page)

Group I (0 ppm) Group III (0 + 625 ppm) Group V (625 ppm)

All rat observations:

	# in group: 25	# in group: 25	# in group: 25
<u>Testes:</u>			
Adenoma (ISC) ^a	-----	2 [†] (8)	6 [†] (24)*
Hyperplasia (ISC)	8 (32) ^b	8 (32)	15 (60)*
<u>Adrenal Cortex:</u>			
Adenoma	-----	1 (4)	-----
Hyperplasia	7 (28)	4 (16)	2 (8)¶
<u>Adrenal Medulla:</u>			
Pheochromocytoma	2 (8)	2 (8)	1 (4)¶
Hyperplasia	8 (32)	7 (28)	8 (33)¶
<u>Pituitary:</u>			
Adenoma	10 (42)¶	8 (32)	9 (38)¶
Hyperplasia	6 (25)¶	8 (32)	5 (21)¶

^a ISC = interstitial cell; ^b percent of total; ¶ reflects loss of one tissue for evaluation; * denotes a treated-group incidence which is statistically significantly different from the control incidence using Fisher's Exact Test ($p < 0.05$); [†] both hyperplasia and adenoma were reported for some of these animals: 1) Group III: rat # 380457, 2) Group V: rat #s 380486 and 380490-492

Linuron did not appear to increase the incidence of hyperplasia or adenoma in the adrenal cortex, adrenal medulla or pituitary gland based on an examination of tissues from all animals (found dead, sacrificed in extremis, or sacrificed by design) for either treatment group as compared to control values.

For animals sacrificed by design at the end of the study, there appeared to be a dose-related increase in testicular adenomas which was statistically significant for animals treated for the entire test period of 12 months [0/19 = control, 2/21 = 0 + 625 ppm, 6/21 = 625 ppm ($p < 0.050$)] for rats sacrificed by design. Hyperplasia did not appear elevated except at the "high dose" (continuous treatment group) where it was statistically significantly different from the control group [6/19 = control, 7/21 = 0 + 625 ppm, 14/21 = 625 ppm ($p < 0.05$)]. Combining all rat observations for testicular hyperplasia did not make any apparent difference in the general dose-response effect observed or the statistical analysis. Based on these results, it would appear that linuron can produce oncogenic or pre-oncogenic effects* later in the rats life-span, and lifetime feeding is not necessary to induce this toxicological change.

[*note: Generally speaking, hyperplasia does not necessarily progress to tumors, but it can progress to this state. However, tumors are usually not observed without the presence of hyperplasia (personal communication from L. Kasza; 12/10/86)]

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DISCUSSION/CONCLUSIONS:

The stated purpose of this study was, "...to determine whether or not 625 ppm dietary linuron, given to rats at 12 or 18 months of age until sacrificed at 24 months of age, would induce an increase in the incidence of testicular interstitial cell (Leydig cell) hyperplasia and adenomas. This study was conducted to test the hypothesis that these testicular effects, which were observed after 15 months on test in a two-year study, were due to a late-life initiating event."

Linuron has produced a statistically significant increase in both testicular hyperplasia and adenomas when the male rats (approximately 12 months of age) were fed dietary linuron for a total of 12 months. Treatment for 6 months with normal diet followed by 6 months of dietary linuron did not produce an elevation in testicular hyperplasia but a possible increase in Leydig cell adenomas is suggested. These histopathological effects were associated with a depression in weight gain and food consumption which was compound related. Based on these findings, it is evident that linuron is capable of inducing hyperplasia and adenomas of the testes later in the rats life-span and that life-time feeding of this compound is not necessary to induce oncogenic responses in this tissue. As noted in the study report, this effect may be mediated through an age-related alteration in the testes which may make it more susceptible to an oncogenic response. It is known that testicular adenomas are a common observation in older male rats of certain strains such as Fisher 344. It should be noted that since life-time exposure to linuron in rats is not required for the development of these testicular tumors, linuron may in fact be more potent as an oncogen than previously estimated from the two-year study.