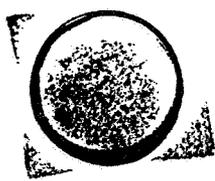


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MEMORANDUM:

SUBJECT: Review of research progress report of studies entitled "LINURON - RELATED INTERSTITIAL CELL ADENOMAS"

TO: Ingrid Sunzenauer, Review Manager
Special Review Branch (TS-767C)

and

Robert Taylor, PM #25
Registration Division (TS-767C)

FROM: Charles N. Aldous, Ph.D.
Section V, Toxicology Branch/HED (TS-769C)

Charles N Aldous 25 Mar 85

THRU: Laurence D. Chitlik, DABT
Section Head, Section V
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for 3/26/85

3/27/85

and

Theodore M. Farber, Ph.D.
Chief, Toxicology Branch/HED (TS-769C)

Three studies were briefly summarized in this report. The goal of these studies was to determine if linuron caused changes in Leydig cell sensitivity or function, or in testosterone clearance rates. Changes seen in these studies would be evaluated in light of a possible relationship with testicular adenoma incidence. An earlier rat chronic/onco study (Accession #241897) found such adenoma incidence to be increased in rats following linuron exposure to 125 to 625 ppm linuron for 2 years.

1. EFFECT OF LINURON ON LEYDIG CELL FUNCTION

The methods were not stated except that "The enzymatic activity of 5 key Leydig cell enzymes were measured in the presense (sic) of 0.5 to 5000 micromolar linuron or any one of four major metabolites of linuron." It is not stated whether the study involved isolated intact cells, a homogenate, or some other test system. Table 1 (photocopied) gives a summary of the results. Some of the enzymes were only generically named, i.e. isomerase, hydroxylase, etc. No consistent linuron-concentration-related decrements in enzyme activities were observed below 500 uM concentration of linuron. The investigators concluded that "the probability of a direct effect of linuron or a metabolite of linuron on the activity of these enzymes is considered negligible".

Table 1. Effect of Linuron or Linuron Metabolites on Testicular Steroidogenic Enzymes In Vitro

Compound	Incubation Conc. (μ M)	Enzyme Activity (nmoles product formed/mg protein)				
		Aromatase	Desmolase	Isomerase	Hydroxylase	Reductase
(A)	0	158.4	106.8	2136	347	85.1
	0.5	140.9	109.6	1716	303*	99.7
	5	140.5	111.3	1729	316	96.9
	50	136.6	89.8	1810	322	102.5
	500	115.4*	56.8*	1656	319	117.3*
	5000	118.2*	9.4*	1755	223*	144.0*
(B)	0	158.4	106.8	2136	347	85.1
	0.5	166.6	93.9	1964	312	99.9
	5	159.1	97.9	2987	340	94.0
	50	156.0	100.4	1987	331	91.3
	500	148.7	87.9	2346	318	92.8
	5000	129.9*	71.9	2275	342	98.4
(C)	0	158.4	106.8	2136	347	85.1
	0.5	168.4	98.1	1997	326	93.7
	5	156.9	98.8	2022	329	88.8
	50	151.4	94.8	2025	308	92.7
	500	139.4	78.8	2080	302	94.9
	5000	131.7	76.5	2489	310	84.0
(D)	0	158.4	106.8	2136	347	85.1
	0.5	158.8	89.6	1976	345	88.6
	5	157.9	104.4	2072	351	88.2
	50	165.2	110.3	1892*	348	91.9
	500	131.2	85.2	2613*	375	92.8
	5000	43.9*	33.9*	833*	104*	158.2*
(E)	0	158.4	106.8	2136	347	85.1
	0.5	167.1	99.3	2140	352	73.9
	5	168.6	105.2	2125	335	81.2
	50	158.2	108.3	2144	350	83.4
	500	128.8*	72.3	2400*	363	82.3
	5000	126.9*	13.1*	2488*	264*	103.0*

(*): Statistically different from control value ($p < 0.5$)

(A): Linuron

(B): Des-methyl linuron (demethylated linuron)

(C): Hydroxy-linuron (ring hydroxylated linuron)

(D): Nor-linuron (O-demethylated and N-demethylated linuron)

(E): Des-methyl-hydroxy-linuron (demethylated and ring hydroxylated)

The information available does not allow an independent evaluation of the appropriateness of the investigators' conclusion. It nevertheless appears that linuron has no potent effect on enzymes tested under assay conditions.

2. EFFECT OF LINURON ON THE METABOLIC CLEARANCE RATE OF TESTOSTERONE

Young adult male rats were dosed for 2 weeks with 200 mg/kg/day linuron. Controls received corn oil vehicle. Animals were castrated and infused at a constant rate with testosterone. Plateau levels of blood testosterone were measured as an indication of the clearance rate. There were no differences between groups, suggesting that linuron did not affect clearance of testosterone. As with the previous experiment, full details of methods and raw data were not given. It can nevertheless be inferred that young rats subjected to short-term exposure to linuron are not affected with respect to testosterone clearance rates.

3. EFFECT OF LINURON ON LEYDIG CELL LH SENSITIVITY

This study tested the hypothesis that linuron or a metabolite reduces the sensitivity of Leydig cells to luteinizing hormone (LH), which results in reduced testosterone production. A subsequent compensatory increase in LH secretion might be expected to hyperstimulate Leydig cells, resulting in Leydig cell hyperplasia.

The experimental design involved three test groups with corresponding controls:

- Young (2 month) rats dosed for 2 weeks with 200 mg/kg/day linuron.
- Old (10-12 month) dosed as above.
- Rats fed 10 months with 625 ppm linuron (age of rats not specified).

Testes from rats were removed, Leydig cells were isolated, and the amount of testosterone generated by Leydig cells in response to stimulation by increasing amounts of LH was assayed. Concentrations of LH employed were not indicated, nor could this be determined from the data presented.

Results from the first two groups did not indicate a linuron effect. Results from the third group were suggestive of an effect, as testosterone levels were much higher in the linuron-fed animals at higher levels of LH applied. Results were not conclusive, however, because control animals were much less responsive to LH than any of the other groups tested (linuron-dosed or controls). This apparent positive result might thus be artifactual.

CONCLUSIONS: The only study in this series which indicated a possible linuron effect was the one evaluating the effect of linuron on Leydig cell LH sensitivity. Leydig cell preparations from chronic-fed rats appeared to produce more testosterone in response to high LH stimulation than did concurrent controls, however data values were not available for independent evaluation. It must be noted that control values were atypical, compared to other control values for older rats. In addition, the reputedly significant values for old chronic linuron fed animals were comparable to values for control and treated animals subjected to different dosing regimes in the same study. For these reasons, results obtained to date are only speculative, and do not offer defensible evidence that linuron-associated testicular adenomas are associated with Leydig cell-hormonal interactions.