Appendix J Toxicity Profile (Mammal) of Linuron

There is ample evidence from special studies submitted by the registrant as well as open literature studies which indicate that linuron is an endocrine disruptor. These findings include, in part: (1) competitive androgen receptor antagonist; but not an estrogen receptor antagonist; (2) competitive inhibition of the transcriptional activity of dihydrotestosterone (DHT)-human androgen receptor (hAR) in vitro, decreased anogenital distance and/or an increase in the retention of areolae/nipples in male offspring following in utero exposure to linuron; (3) inhibition of steroidogenic enzymes, and (4) decreased responsiveness of Leydig cells to luteinizing hormone in both immature (22 days) and mature (11 months) male rats treated with linuron, mature rats were less responsive that immature ones; (5) F0 and F1 males had significantly increased levels of estradiol and luteinizing hormone [1].

Oncogenicity studies in the rat and mouse did not show consistent tumor profiles between sexes and species. In the combined chronic toxicity/oncogenicity study in rats, common neoplasms, included pituitary adenomas of the pars anterior in both male and female rats and mammary fibroadenomas in female rats. Testicular adenomas were observed in 6%, 28% and 54%, respectively for control, 125 and 625 ppm dose groups. Decreased incidences of both these tumor types were noted in the high-dose female group. In the mouse oncogenicity study, treatment of up to 104 weeks with 1500 ppm resulted in a significant increase in the incidence of hepatocellular adenomas (control, 6%; 1500 ppm, 25%, $p < 0.05$) in females. Linuron was not mutagenic in bacteria or in cultured mammalian cells. There was also no indication of a clastogenic effect up to toxic doses in vivo. Based on the results of these studies, linuron was classified as an unquantifiable Group C carcinogen (a possible human carcinogen for which there is limited animal evidence) requiring no quantification of human cancer risk [6].

Guideline No. / Study Type	Results	Source Study Classification Dose Levels
Acute Oral (Rat) / 870.1100	LD_{50} = 2600 mg/kg-bw	00027625 Acceptable
Acute Dermal (Rabbit) / 870.1200	LD_{50}> 2000 mg/kg-bw	00027625 Acceptable
Acute Inhalation (Rat) / 870.1300	LC_{50} > 218 mg/L	00053769 Acceptable
Primary Eye Irritation / 870.2400	Slight conjunctival redness at 24 hrs; clear at 72 hrs	42849001 Acceptable
Primary Skin Irritation / 870.2 $_{50}$0	Not an irritant	42849002 Acceptable
Dermal Sensitization / 870.2600	Not a sensitizer	00146868 Acceptable

[1] **HED Chapter for the Linuron Tolerance Reassessment Eligibility Decision**
PC Code: 035506. Case 0047. DP Barcode D271950 FROM: Carol Christensen, Risk Assessor Reregistration Branch II Health Effects Division (7509C)

Guideline No. / Study Type	Results	Source Study Classification Dose Levels
870.4100 [83-1(b)] 1-Year Feeding Study – Dog	NOAEL= 0.77 mg/kg-bw/day (25 ppm) LOAEL = 3.5 mg/kg-bw/day (125 ppm), based on hematological effects in males and females (increased methemoglobin and sulfhemoglobin levels)	40952601 (1988) Acceptable 0, 10, 25, 125, 625 ppm [males: 0, 0.29, 0.79, 4.2, 19 mg/kg-bw/day females: 0, 0.30, 0.77, 3.5, 16 mg/kg-bw/day]
870.4200 [83-2 (b)] Oncogenicity Study – Mouse	NOAEL= 23 mg/kg-bw/day (150 ppm) LOAEL = 261 mg/kg-bw/day (1500 ppm), based on microscopic liver changes, methemo-globinemia, and deceased body weight gain throughout the study Histopathology: hepatocytomegaly, hepatocellular cytoplasmic alterations, vacuolation, and necrosis in liver, slightly increased incidence of hemosiderosis in spleens of both sexes; significant increase in hepatocellular adenomas in females	0124195 (1981) Acceptable 0, 50, 150, and 1500 ppm [males: 0, 8, 23, and 261 mg/kg-bw/day females: 0, 12, 35, and 455 mg/kg-bw/day]
870.4300 [83-5(a)] Combined Chronic Toxicity/ Carcinogenicity Study – Rat	NOAEL=2.1 mg/kg-bw/day (50 ppm) LOAEL = 5.1 mg/kg-bw/day (125 ppm), based on hematological effects, decreased body weight gains in both sexes, microscopic observations consistent with hemolysis (hemosiderin in Kupffer cells and increased hemosiderosis in bone marrow, spleen, and/or mesenteric lymph nodes) Histopathology: Significant (p = 0.004) increase (27%, 5.7% control) in incidence of benign interstitial cell adenomas in testes.	0029680, 00029679 (1980); 00167411 (1986) Acceptable 0, 50, 125, 625 ppm [males: 0, 2.1, 5.1, 27 mg/kg-bw/day females: 0, 3.1, 7.8, 48 mg/kg-bw/day]
870.3700 [83-3(a)] Developmental Toxicity Study – Rat	Maternal Systemic NOAEL: 12 mg/kg-bw/day (125 ppm) Maternal Systemic LOAEL = 50 mg/kg-bw/day (625 ppm), based on decreased maternal body weight (9%) and food consumption (7-8%). Developmental NOAEL = 12 mg/kg-bw/day (125 ppm) Developmental LOAEL = 50 mg/kg-bw/day (625 ppm), based on increased post-implantation loss and litters with early resorptions.	00018167 (1979) Acceptable/Guideline 0, 50, 125, 625 ppm [females: 0, 5.0, 12, 50 mg/kg-bw/day]
870.3700 [83-3(b)] Developmental Toxicity – Rabbit	Maternal Systemic NOAEL = 5 mg/kg-bw/day Maternal Systemic LOAEL = 25 mg/kg-bw/day, based on decreased maternal body weight gain. Developmental NOAEL = 25 mg/kg-bw/day Developmental LOAEL = 100 mg/kg-bw/day, based on alterations of the bones and skull (irregularly shaped fontanelle, hole in parietals, parietals contain intraparietals, and unossified).	00153867 (1985), 40437201(1985) Acceptable 0, 5, 25, 100 mg/kg-bw/day

Guideline No. / Study Type	Results	Source Study Classification Dose Levels
870.3800 [83-4] 3-Generation Reproduction - Ra	Systemic NOAEL= 2 mg/kg-bw/day (25 ppm) Systemic LOAEL = 9 mg/kg-bw/day (125 ppm), based on decreased body weight gains in males and females and anemia in females. Reproductive NOAEL = 10 mg/kg-bw/day (125 ppm) Reproductive LOAEL = 44 mg/kg-bw/day (625 ppm) based on reduced fertility, decreased pup survival and lower pup body weights. Offspring NOAEL = 9 mg/kg-bw/day (125 ppm) Offspring LOAEL = 44 mg/kg-bw/day (625 ppm), based on decreased pup survival, and lower pup body weights. The offspring toxicity NOAEL is	00146071 (1984); 00155168 (1985) Acceptable 0, 25, 125, 625 ppm [males: 0, 2, 10-11, 48-50 mg/kg-bw/day females: 0, 2, 9, 44-50 mg/kg-bw/day]
870.3800 [83-4] 2-Generation Reproduction – Rat	Systemic NOAEL = 0.74 mg/kg-bw/day (12.5 ppm) Systemic LOAEL = 5.8 mg/kg-bw/day (100 ppm), based on decreased body weight gains in males and females in both generations Reproductive NOAEL = 36 mg/kg-bw/day (625 ppm) Reproductive LOAEL = not established Offspring NOAEL = 0.74 mg/kg-bw/day (12.5 ppm) Offspring LOAEL = 5.8 mg/kg-bw/day (100 ppm), based on decreased pup survival and lower pup body weights of F1a,b and F2a,b litters	41463401 (1990); 41864701 (1991) Acceptable 0, 12.5, 100, 625 ppm [males: 0, 0.74, 5.8, 36 mg/kg-bw/day females: 0, 0.92, 7.3, 45 mg/kg-bw/day]
870.7600 (85-2) Dermal Penetration – Rat	Dermal absorption factor = 16% over 8 to 10 hours.	00163837 (1984) Acceptable ^{14}C (2.35 µCi/mg) 0.12, 1.00, or 7.4 mg/2 in2 2.82, 23.5, or 17.4 µCi
870.7485 (85-1) Metabolism Study – Rate	The biological half-lives ranged from 21 hr in the low dose males to 56 hr in the high dose females. Total recovery of radioactivity was 96% in males and 97% in females, the majority of the administered ^{14}C-linuron was eliminated in the urine (>80%) and, to a lesser extent, in the feces (~15%). Tissue and organ residues were very low (<l%) at both dose levels, and there was no indication of accumulation or retention of linuron or its metabolites. The major metabolites identified in the urine were hydroxy-norlinuron, desmethoxy linuron and norlinuron, and in feces, hydroxy-norlinuron, and norlinuron. Neither hydroxy-3,4-dichloroanaline nor 3,4-dichloroanaline were present in any of the samples. Exposure to linuron appeared to induce mixed-function oxidative enzymes.	00146489 (1985), 40142401 (1985) 41960001 (1991 42006801 (1991) Single doses of ^{14}C-linuron at 24, and 400 mg/kg-bw administered by gavage to male and female rats.

Guideline No. / Study Type	Results	Source Study Classification Dose Levels
Special Study - Leydig cell tumorigenesis in rats	No treatment-related clinical signs of toxicity were observed. Body weight and body weight change were significantly less than controls and decreased accessory sex organ weights for growing and adult rats. Selected animals from the 2-generation reproduction study were used to evaluate changes in serum hormone levels, accessory sex organ weights. Increased serum luteinizing hormone and estradiol levels were observed in F0 and F1 males. High-dose F0 males had decreased absolute epididymides, dorsal lateral prostate, and levator ani muscle weights and increased relative testes, epididymides, and ventral prostate weights. Organ weights were unaffected in the two lower dose groups. These data support the hypothesis that rats exposed to linuron could develop interstitial hyperplasia and subsequent adenomas (Leydig cell tumors) via a mechanism of sustained hypersecretion of luteinizing hormone induced by the antiandrogenic potential of linuron.	41630101 (1990) Acceptable/Nonguideline 0 or 200 mg/kg-bw/day for 14 days to 32 to 33 and 93 day old rats males: 0, 0.74, 5.8, 36 mg/kg-bw/day females: 0, 0.92, 7.3, 45 mg/kg-bw/day in F0 and F1 animals from 2-generation reproduction study (41463401),
Special Study - Cross Mating	The cross-mating results suggest that linuron may cause paternally-mediated effects based on decreased fertility and fecundity as well as maternally-mediated effects based on decreased pup viability and litter survival.	00159846 (1985) Acceptable/Nonguideline 0, 625 ppm %%: 0, 48 mg/ kg-bw/day &&: 0, 44 mg/ kg-bw/day
Special Study - Aged male rats	Linuron induced hyperplasia and adenomas of the testes in aged rats. In addition, life-time feeding was not necessary to induce oncogenic responses in this tissue.	45506501 (1986) Acceptable/Nonguideline 0, 625 ppm 0, 22 mg/ kg-bw/day
Special Study - Biochemical and Histopathological effects	The biochemical and histopathological data presented in this report suggest that linuron may affect testosterone metabolism in horse testicular microsomes for a range of concentrations which overlap the dose levels given rats chronically. However, the net effect of these enzyme changes and the relevance to the rat in vivo are uncertain. Evidence in young and old rats exposed repeatedly (3-7x) or for 11 or 19 months suggests that Leydig cell incubates are differentially altered in their sensitivity to LH. Microscopic lesions in the testes and cervix have been confirmed in other studies.	164093 (1986) Acceptable/Nonguideline 0, 12.5, 100, 625 ppm [males: 0, 0.75, 4.1, 22 mg/kg-bw/day females:: 0, 1.1, 6.1, 37 mg/kg-bw/day]

(a) Source: R. Fricke, Ph.D. January 30, 2002 Memorandum: Linuron (PC Code: 035506) REVISED Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision document. TXR No: 0050429; DP Barcode: D272367.

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