

REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

RELEASABLE

Chemical: Linuron

CAS #: 330-55-2

Caswell #: 528

Carcinogenicity: Preliminary Classification as Category C (limited evidence)
oncogen (CAG)

Systemic Toxicity: See below.

Preparation Date: 2/19/86

| Endpoint | Experimental Doses | UF | MF | RfD |
|---|---|-----|----|-----------------|
| Hodge (11/12/62) 2-Year Feeding Dog Study | < 25 ppm (0.625 mg/kg/day) (LDT); LEL | 300 | | 0.002 mg/kg/day |

2/6 animals showed
abnormal blood pigment (at 25)
Decreased RBC - females (125 ppm)
Decreased RBC, Hct, Hb - males (625 ppm)

Conversion factor (dog): 1 ppm = 0.025 mg/kg/day

Endpoint and Experimental Doses:

Hodge, H.C., (11/12/62) 2-Year Feeding Dog Study
E.I. du Pont de Nemours and Co., Inc.

Twenty-four beagle dogs were divided into 4 groups of 6 animals each (3 male, 3 female) and administered diets containing 0, 25, 125, and 625 ppm linuron for 2 years. All dogs gained weight except three-two females on 625 ppm and one female, fed 25 ppm of linuron. All males on 625 ppm gained some weight. Body weight data provided no clear information of a possible effect of linuron on body weight. Dogs on 25 ppm showed no significant alterations in RBC counts, hemoglobin values, or hematocrit percentages. Female dogs, fed 125 ppm, had a statistically significant decrease in their mean RBC count. Analyses of bloods revealed an abnormal blood pigment in blood from 3 dogs on 625 ppm. The oxyhemoglobin band was normal for all dogs.

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Uncertainty Factors (UFs):

The UF of 100 includes uncertainties in the extrapolation from laboratory animals to humans and also indicates that there are no data gaps existing for linuron. An additional UF of 3 was used to account for the fact that the NOEL was not established in this study; since the effects at the lowest level are minimal, although dose related the 3 fold UF (i.e., 0.5 log) is considered sufficient. The overall UF thus is 300.

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Modifying Factors (MFs):

None.

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Additional Comments:

Significant increases in interstitial cell adenomas in testes of male rats.

Data Considered for Establishing the RfD

- 1) 2-Year Feeding - Dog NOEL <25 ppm (0.625 mg/kg/day)(LDT) 2/6 animals showed abnormal blood pigment (oxyhemoglobin); decreased RBC - females (125 ppm); decreased RBC, Hct, Hb - males (625 ppm); no core grade
 - 2) 2-Year Feeding/Oncogenic - Rat NOEL=125 ppm (6.25 mg/kg/day), LEL=625 ppm (31.25 mg/kg/day) (Highest level tested) Spleen and bone marrow changes indicative of hemolysis; increased mortality, growth retardation; no core grade
 - 3) 3-Generation Reproduction - Rat Systemic NOEL (adults) =25 ppm (1.25 mg/kg/day), Systemic LEL (adults) =125 ppm (6.25 mg/kg/day)(reduced weights and weight gains of dams prior to mating, reduced dam weights at weaning; reduced body weight gains of both sexes, and alopecia at 625 ppm); Reproductive NOEL=25 ppm (1.25 mg/kg/day), Reproductive LEL=125 ppm (6.25 mg/kg/day)(lower weanling weights; pup weights more consistently reduced at 625 ppm (days 1-21); liver and kidney weights reduced at 625 ppm; liver atrophy at 625 ppm; lower fertility, reduced pup survival on days 0-- 20 625 ppm group); no core grade
 - 4) Teratology - Rat Maternal NOEL=50 ppm (2.50 mg/kg/day)(LDT), Maternal LEL=125 ppm (6.25 mg/kg/day)(decreased food consumption, decreased body weight gain; Fetal NOEL=125 ppm (6.25 mg/kg/day, Fetal LEL=625 ppm (31.25 mg/kg/day) (increased number of absorption sites); Teratogenic NOEL >625 ppm (31.25 mg/kg/day)(HDT); no core grade
 - 5) Teratology - Rabbit Teratogenic NOEL >125 ppm (HDT); no core grade
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Data Gap(s)

Reevaluation of effects on hematology.

Other Data Considered

- 1) 2-Year Feeding/Oncogenic - Rat NOEL <50 ppm (2.5 mg/kg/day) (lowest level tested) (increased MLV, decreased RBC count, possible reticulocytosis; significant increases ($p < 0.05$) in interstitial cell adenomas in testes of male rats receiving 125 and 625 ppm; core grade minimum
 - 2) 90-Day Feeding - Rat NOEL=80 ppm (4.0 mg/kg/day) (LDT), LEL=400 ppm (20 mg/kg/day) (decreased RBC, increased WBC, retarded growth at 3000 ppm); no core grade
 - 3) 30-Day Feeding - Rat NOEL males =60 ppm (3 mg/kg/day), LEL males =300 ppm (15 mg/kg/day) (decreased body weight gain); NOEL female =600 ppm (30 mg/kg/day), LEL females =1200 ppm (60 mg/kg/day); Abnormal blood pigments (not methemoglobin) at 3000 ppm level (M & F), increased mortality, severe growth retardation at 3000 ppm (highest level tested); no core grade
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Confidence in the RfD:

Study: Medium

Data Base: High

RfD: High

The critical study appears to be of good quality and is given a medium rating. Additional studies are supportive and therefore, the RfD is given a high confidence.

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Documentation of RfD and Review:

Registration Standard, June 1984
Special Review PDI

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Agency RfD Review:

U.S. EPA Contact:

First Review: 5/14/86

Primary: Reto Engler FTS 557-7491

Second Review:

Verification Date: 5/14/86

Secondary: George Ghali FTS 557-4382