

## Linuron; CASRN 330-55-2

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

### STATUS OF DATA FOR Linuron

**File First On-Line 03/31/1987**

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	03/31/1987
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	08/01/1989

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

### I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Linuron  
CASRN — 330-55-2  
Last Revised — 03/31/1987

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of

substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

### I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
<b>Abnormal blood pigment</b>	NOEL: none	300	1	2E-3 mg/kg/day
<b>2-Year Dog Feeding Study</b>	LEL: 25 ppm diet (0.625 mg/kg/day)			
<b>du Pont, 1962</b>				

\*Conversion Factors: 1 ppm = 0.025 mg/kg/day (assumed dog food consumption)

### I.A.2. Principal and Supporting Studies (Oral RfD)

E.I. du Pont de Nemours and Co., Inc. 1962. MRID No. 00018374. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Twenty-four beagle dogs were divided into four groups of six animals each (3 male, 3 female) and administered diets containing 0, 25, 125, and 625 ppm (0, 0.625, 3.125, and 15.63 mg/kg/day) linuron for 2 years. Body weight data provided no clear indication of a possible effect of linuron on body weight; all dogs gained weight except three (two females fed 625 ppm and one female fed 25 ppm). Dogs fed 25 ppm showed no significant alterations in RBC counts, hemoglobin values, or hematocrit percentages. At 125 ppm female dogs had a statistically significant decrease in their mean RBC count. In all dogs fed 625 ppm and 2/3 females fed 25 ppm, blood analysis revealed an abnormal blood pigment (the abnormal pigment was characterized by a band in the 618- to 620- millimicron region, following addition of KCN to the blood). The oxyhemoglobin band was normal for all dogs. Based on the abnormal blood pigment in females, the LEL for systemic toxicity is 25 ppm (0.625 mg/kg/day). A NOEL for systemic toxicity was not established.

### I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The UF of 300 includes uncertainties in the extrapolation from laboratory animals to humans (100-fold) and an additional factor of 3 to account for the fact that the NOEL was not established in this study. Since the effects at the lowest level are minimal, a 3-fold UF is considered sufficient.

MF — None

#### **I.A.4. Additional Studies/Comments (Oral RfD)**

None.

Data Considered for Establishing the RfD:

- 1) 2-Year Feeding - dog: Principal study - see previous description; no core grade (E.I. du Pont de Nemours and Co., Inc., 1962a)
- 2) 2-Year Feeding (oncogenic) - rat: Systemic NOEL=125 ppm (6.25 mg/kg/day); Systemic LEL=625 ppm (31.25 mg/kg/day) (spleen and bone marrow changes indicative of hemolysis; increased mortality, growth retardation; no core grade (E.I. du Pont de Nemours and Co., Inc., 1962b)
- 3) 2-Year Feeding (oncongenic) - rat: Systemic NOEL=none; LEL=50 ppm (2.5 mg/kg/day) (increased MLV, decreased RBC count possible reticulocytosis); core grade minimum (E.I. du Pont de Nemours and Co., Inc., 1980a)
- 4) 3-Generation Reproduction - rat: NOEL (adults)=25 ppm (1.25 mg/kg/day); 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 to 21); liver and kidney weights reduced at 625 ppm; liver atrophy at 625 ppm; lower fertility, reduced pup survival on days 0 to 4 in 625-ppm group]; core grade supplementary (E.I. du Pont de Nemours and Co., Inc., 1984)
- 5) 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 resorption sites); Teratogenic NOEL=625 ppm (31.25 mg/kg/day) (HDT); no core grade (E.I. du Pont de Nemours and Co., Inc., 1979)

6) Teratology - rabbit: Maternal NOEL=5 mg/kg/day; Maternal LEL=25 ppm (depression in maternal body weight; at 100 mg/kg, increase in abortion rate and depression in liver and liver body weight ratio); Developmental NOEL=none; Developmental LEL=5 mg/kg/day (LDT); (decrease in fetal body weights and litter size; statistically significant trend in elevation of total skull alterations; core grade minimum (E.I. du Pont de Nemours and Co., Inc., 1986)

7) Teratology - rabbit: Teratogenic NOEL=125 ppm (HDT); no core grade (E.I. du Pont de Nemours and Co., Inc., 1965)

Other Data Reviewed:

1) 90-Day Feeding - rat: NOEL=80 ppm (4.0 mg/kg/day); LEL=400 ppm (20 mg/kg/day) (decreased RBC, increased WBC, retarded growth at 3000 ppm); no core grade

2) 30-Day Feeding - rat: NOEL males=60 ppm (3 mg/kg/day); LEL=300 ppm (15 mg/kg/day)(decreased body weight gain - males only); no core grade; females were not affected at dose levels less than 1200 ppm. At 3000 ppm both sexes showed abnormal blood pigments (not methemoglobin), severe growth retardation and increased mortality.

Data Gap(s): Reevaluation of effects on hematology.

#### **I.A.5. Confidence in the Oral RfD**

Study — Medium

Database — High

RfD — High

The principal study appears to be of good quality and is given a medium rating. The database is fairly complete and additional studies are supportive; therefore, confidence in the database is high. High confidence in the RfD follows.

#### **I.A.6. EPA Documentation and Review of the Oral RfD**

Pesticide Registration Standard, June 1984

Special Review Position Document 1

Agency Work Group Review — 07/22/1985, 05/14/86

Verification Date — 05/14/86

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Linuron conducted in August 2003 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or 202-566-1676.

#### **I.A.7. EPA Contacts (Oral RfD)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (internet address).

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#### **I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)**

Substance Name — Linuron  
CASRN — 330-55-2

Not available at this time.

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## **II. Carcinogenicity Assessment for Lifetime Exposure**

Substance Name — Linuron  
CASRN — 330-55-2  
Last Revised — 08/01/1989

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for

Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

## **II.A. Evidence for Human Carcinogenicity**

### **II.A.1. Weight-of-Evidence Characterization**

Classification — C; possible human carcinogen

Basis — Limited evidence indicated linuron produced increases in both testicular hyperplasia and adenomas in male rats in three separate studies. Hepatocellular adenomas were observed in female mice in a single study at the highest dose group tested; the tumors were benign and showed no progression toward malignancy.

### **II.A.2. Human Carcinogenicity Data**

None.

### **II.A.3. Animal Carcinogenicity Data**

Limited. Charles River Crl:CD rats, 80/sex/dose group, were fed linuron (97% purity) in the diet at 0, 50, 125, or 625 ppm for 2 years (du Pont, 1980). The incidence of interstitial-cell adenoma in the testes was significantly increased in the mid-dose rats (19/64 or 29.7%) and the high-dose rats (37/66 or 56.1%) as compared with the control rats (4/68 or 5.9%). Survival was not affected by the test material as compared to the control group. The MTD was achieved at the high dose in both sexes based on decreased mean body weight and body weight gain, lower hemopoietic activity in both male and female mid- and high-dose groups, and reduced absolute and relative testicular weights in the high-dose males.

In a mouse study conducted by du Pont (1982), Charles River CD-1 mice were fed linuron (97% purity) in the diet at 0, 50, 150, or 1500 ppm for 2 years. The incidence of hepatocellular adenomas was statistically significantly increased in the high dose female mice (20/80 or 25%) compared with the control mice (5/79 or 6.3%). In the low-dose males, the incidence of hepatocellular adenomas was also statistically significantly increased (18/80 or 22.5%) as compared with the controls (7/79 or 11.4%). The incidence of hepatocellular carcinomas was not significantly increased at any dose in either sex. The test substance had no effect on survival. The MTD was achieved at the high dose in both sexes of the mice based on reduced body weight and body weight gain, and increased methemoglobin formation.

In a multi-generation study (not designed to investigate carcinogenicity) conducted by du Pont (1984), linuron (94.5% purity) was fed to Charles River CrI:CD rats at 0, 25, 125, or 625 ppm. There was an increase in testicular interstitial-cell adenomas and hyperplasia in treated males of both generations compared with controls. The effect was most apparent in the mid- dose group.

In another study conducted by du Pont (1986a) using 12-month-old CrI:CD (SD)BR male rats, linuron (94.5% purity) was fed in the diet at 625 ppm to three different groups. One group received dietary linuron from 12 to 24 months, a second group was fed a normal diet from 12 to 18 months followed by 6 months of dietary linuron, and the third group (control) was fed a normal diet from 12 to 24 months of age. The incidence of testicular adenoma and hyperplasia was statistically significantly increased in the group fed linuron at 625 ppm for a total of 12 months (hyperplasia: 15/25 vs. 8/25 in controls; adenoma: 6/25 vs. 0/25 in controls). No malignant tumors were observed in any group. This finding suggests the effect may be mediated through an age- related alteration of the testes that may make this organ more susceptible to oncogenic response.

#### **II.A.4. Supporting Data for Carcinogenicity**

Gene mutation in CHO cells and Salmonella typhimurium, unscheduled DNA synthesis, and in vivo bone marrow chromosomal aberration assays (du Pont, 1983a,b,c,d, respectively) were negative for linuron.

Based on preliminary data, monuron, a structural analogue, produced kidney and liver tumors in F344/N male rats; other analogues (diuron, propanil, and dimilan) did not produce tumors in rat and mouse oncogenicity studies (propanil was tested in rats only).

Linuron contains two impurities, 3,3',4,4'-tetrachloroazobenzene (TCAB) and 3,3',4,4'-tetrachloroazoxybenzene (TCAOB), which are analogues of 2,3,7,8- tetrachlorodibenzo-p-dioxin (TCDD), classified by the EPA as a B2 carcinogen. TCAB and TCAOB are contained in linuron at levels of approximately 8.8 and <0.05 ppm, respectively (Sundstrom et al., 1978). It has been recommended by the EPA that NTP test TCAB and TCAOB in the 2-year rodent bioassays. Biochemical and histopathologic data (du Pont, 1986b) were presented which suggest that linuron may affect testosterone metabolism in horse testicular microsomes at doses of 11 to 1100 mg. Leydig cells from chronically-dosed male rats (625 ppm) exhibited a hyperactive response to leutenizing hormone (LH) manifested by increased testosterone secretion. In vitro secretion patterns of testosterone suggest that the effects of linuron on Leydig cells of rat testes are age- and dose- related.

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## **II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure**

A quantitative estimate of carcinogenic risk was considered inappropriate.

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## **II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure**

Not available.

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## **II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)**

### **II.D.1. EPA Documentation**

Source Document — U.S. EPA, 1987a,b, 1988

The 1987 Carcinogenicity Assessment for linuron has been reviewed by the Peer Review Committee and the FIFRA Scientific Advisory Panel (SAP) with agreement reached on classification.

### **II.D.2. EPA Review (Carcinogenicity Assessment)**

Agency Work Group Review — 06/15/1988, 02/01/1989

Verification Date — 02/01/1989

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Linuron conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or 202-566-1676.

### **II.D.3. EPA Contacts (Carcinogenicity Assessment)**



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**III. [reserved]**

**IV. [reserved]**

**V. [reserved]**

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## **VI. Bibliography**

Substance Name — Linuron

CASRN — 330-55-2

### **VI.A. Oral RfD References**

E.I. du Pont de Nemours and Company, Inc. 1962a. MRID No. 00018374, 00018376. Available from EPA. Write to FOI, EPA, Washington DC 20460.

E.I. du Pont de Nemours and Company, Inc. 1962b. MRID No. 00018379, 00018381. Available from EPA. Write to FOI, EPA, Washington DC 20460.

E.I. du Pont de Nemours and Company, Inc. 1980a. MRID No. 00029680. Available from EPA. Write to FOI, EPA, Washington DC 20460.

E.I. du Pont de Nemours and Company, Inc. 1984. MRID No. 00146071. Available from EPA. Write to FOI, EPA, Washington DC 20460.

E.I. du Pont de Nemours and Company, Inc. 1979. MRID No. 00018167. Available from EPA. Write to FOI, EPA, Washington DC 20460.

E.I. du Pont de Nemours and Company, Inc. 1986. MRID No. 00153867. Available from EPA. Write to FOI, EPA, Washington DC 20460.

E.I. du Pont de Nemours and Company, Inc. 1965. MRID No. 00018170. Available from EPA. Write to FOI, EPA, Washington DC 20460.

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## **VI.B. Inhalation RfC References**

None

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## **VI.C. Carcinogenicity Assessment References**

E.I. du Pont de Nemours and Company, Inc. 1980. EPA Accession No. 241897. Available from EPA. Write to FOI, EPA, Washington DC 20460.

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E.I. du Pont de Nemours and Company, Inc. 1984. EPA Accession No. 255829. Available from EPA. Write to FOI, EPA, Washington DC. 20460.

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Rinde, E. 1987. U.S. EPA, Scientific Mission Support Staff. Memorandum to Addressees: U.S. EPA, Toxicology Branch, Peer Review Committee. Draft Document on Linuron.

Sundstrom, G., B. Tonsson and L. Renberg. 1978. Determination of the toxic impurities 2,2',4,4'-tetrachloroazoxybenzene in commercial Divron, Linuron and 3,4-dichloroaniline samples. Chemosphere. 12: 973-979.

U.S. EPA. 1987a. Carcinogenicity Assessment of Linuron. Prepared by the Office of Pesticide and Toxic Substances, Office of Pesticide Programs, Hazard Evaluation Division, Toxicology Branch, Washington, DC.

U.S. EPA. 1987b. Scientific Advisory Panel (SAP) Open Meeting, Arlington, VA, September 23rd.

U.S. EPA. 1988. Linuron: Preliminary determination to conclude the special review. Federal Register. 53(159): 31262.

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## VII. Revision History

Substance Name — Linuron  
CASRN — 330-55-2

Date	Section	Description
08/01/1989	II.	Carcinogen summary on-line
10/28/2003	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

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## VIII. Synonyms

Substance Name — Linuron

CASRN — 330-55-2

Last Revised — 03/31/1987

- 330-55-2
- AFALON
- AFALON INURON
- APHALON
- CEPHALON
- 3-(3,4-DICHLOR-FENYL)-1-METHOXY-1-METHYLUREUM
- 3-(3,4-DICHLORO-FENIL)-1-METOSI-1-METIL-UREA
- 3-(3,4-DICHLOROPHENYL)-1-METHOXYMETHYLUREA
- 3-(3,4-DICHLOROPHENYL)-1-METHOXY-1-METHYLUREA
- 1-(3,4-DICHLOROPHENYL)3-METHOXY-3-METHYLUREE
- 3-(3,4-DICHLOR-PHENYL)-1-METHOXY-1-METHYL-HARNSTOFF
- 3-(4,5-DICHLORPHENYL)-1-METHOXY-1-METHYLHARNSTOFF
- DU PONT 326
- GARNITAN
- HOE 2810
- LINEX 4L
- LINOROX
- LINUREX
- Linuron
- LOREX
- LOROX
- METHOXYDIURON
- 1-METHOXY-1-METHYL-3-(3,4-DICHLOROPHENYL)UREA
- N'-(3,4-DICHLOROPHENYL)-N-METHOXY-N-METHYLUREA
- N-(3,4-DICHLOROPHENYL)-N'-METHYL-N'-METHOXYUREA
- PREMALIN
- SARCLEX
- SCARCLEX
- SINURON
- UREA, 3-(3,4-DICHLOROPHENYL)-1-METHOXY-1-METHYL-