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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Subject: Toxicology Review for the Reregistration
Eligibility Document on Linuron

To: Flora Chow, Section Head
Reregistration Section
Chemical Coordination Branch
Health Effects Division (7509C)

From: Susan L. Makris, Toxicologist *Susan L. Makris 1-14-94*
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Chemical: Linuron;
3-(3,4-Dichlorophenyl)-1-Methoxy-1-Methylurea

Uses: Herbicide, used on a variety of terrestrial food
and non-food crops

Case/chemical No.: 818791/035506

S44516, D194446



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LINURON

Acute Toxicity

Acute toxicity values and categories for linuron are summarized in the following table.

TEST	RESULTS	CATEGORY
Oral LD ₅₀ - rat	2600 mg/kg	III
Dermal LD ₅₀ - rat	> 2000 mg/kg	III
Inhalation LC ₅₀ - rat	> 218 mg/L/hr	IV
Eye Irritation - rabbit	Slight conjunctival redness at 24 hrs; clear at 72 hrs	III
Dermal Irritation - rabbit	Not an irritant	IV
Dermal Sensitization - guinea pig	Not a sensitizer	

In an acute oral toxicity study conducted in rats, the oral LD₅₀ value for technical (96%) linuron was determined to be 2600 mg/kg (Toxicity Category III) (Consultox Laboratories, Ltd., 1974). In the same study, the dermal LD₅₀ in rats was established at >2000 mg/kg (Toxicity Category III). Inhalation exposure of rats to 96% linuron (Kapp, 1975a) resulted in an LC₅₀ of >218 mg/L per hour (Toxicity Category IV). These acute oral, dermal, and inhalation studies satisfy guidelines §81-1, §81-2, and §81-3, respectively.

Application of 97.4% linuron to the rabbit eye (Shibata, 1992) resulted in slight conjunctival redness at 24 hours, which was clear by 72 hours (Toxicity Category III). No corneal opacity or irritation of the iris was noted. A primary dermal irritation study in rabbits demonstrated that application of 97.4% linuron

produced no irritation (Toxicity Category IV) (Allen, 1993). No dermal sensitization occurred with 95% linuron in guinea pigs (Schulz, 1985). The primary eye and dermal studies and the guinea pig sensitization study satisfy guidelines §81-4, §81-5, and §81-6, respectively.

Subchronic Toxicity

A 3-month subchronic study was conducted with linuron in rats at dietary levels of 80, 400, and 3000 ppm (4, 20, and 150 mg/kg/day). Observations of decreased red blood cell count and increased white blood cell count were noted at 400 ppm. At the high-dose (3000 ppm) growth was retarded. Based upon hematological findings, 400 ppm (20 mg/kg/day) was established as the LOEL; the NOEL was 80 ppm (4 mg/kg/day) (US Government, 1963).

The requirement for a 90-day feeding study in dogs (§82-1) was satisfied by the completion of two acceptable chronic studies conducted with linuron in beagles.

Chronic Toxicity and Carcinogenicity

In a 1-year dog study (Malley, 1988), 96.2% linuron was fed to groups of 4 beagles/sex/dose at dietary levels of 10, 25, 125, and 625 ppm (male: 0.29, 0.79, 4.17, and 18.6 mg/kg/day; females: 0.3, 0.77, 3.49, and 16.1 mg/kg/day, respectively); this study satisfies the §83-1(b) guideline requirement for a chronic canine toxicity study. In a previous 2-year dog study (E.I. du Pont de Nemours and Co., Inc., 1962), linuron was administered in the diet to beagle

dogs at 25, 125, and 625 ppm (0.625, 3.13, and 15.63 mg/kg/day); an abnormal pigment was observed in the blood of animals at all dose levels. Decreased red blood cell count, hematocrit, and hemoglobin levels were also noted in males at 625 ppm. Since the abnormal pigment was postulated to be met- and sulphemoglobin, assays for these substances were conducted on the 1-year study. The presence of one or both substances in the blood was confirmed for both sexes in the 125 and 625 ppm dose groups at all intervals tested (3, 6, 9, and 12 months). At 625 ppm, evidence of red blood cell destruction was noted as increased hemosiderin deposition on the Kupffer cells of the liver (male and female), slight decreases in erythrocyte count, hemoglobin, and hematocrit levels at all time periods tested, and a small increase in erythropoietic activity in the bone marrow. Secondary hematological changes at 625 ppm included increased platelet count, leukocyte count, and serum cholesterol levels. In addition, absolute liver weight was increased in males at 625 ppm; relative liver weight was increased in males at 125 and 625 ppm. Based upon hematology changes, the LOEL for systemic toxicity was determined as 125 ppm (4.17 mg/kg/day for males; 3.49 mg/kg/day for females). The NOEL for systemic toxicity is 25 ppm (0.79 mg/kg/day for males; 0.77 mg/kg/day for females).

In a 2-year feeding/carcinogenicity study, linuron (97%) was administered to Crl:CD(SD)BR Sprague-Dawley rats at dietary levels of 50, 125, and 625 ppm (2.5, 6.25, and 31.25 mg/kg/day) (Kaplan, 1980). Testicular interstitial cell adenomas were observed at an

significantly increased incidence in mid- and high-dose males (125 and 625 ppm, respectively). In addition, various indications of blood cell destruction and turnover (increased mean corpuscular volume, decreased red blood cell count, and possible reticulocytosis) were observed in both sexes at 125 and 625 ppm. Analysis of percent hemoglobin to evaluate hematotoxicity (US EPA, 1987) indicated that males were not affected, but percent hemoglobin was decreased for females at 6 and 12 months for the high-dose group, and at 12 months for the mid-dose group. Therefore, based upon hematotoxicity, observed as a decrease in the percent hemoglobin, the LOEL for systemic toxicity for females was 125 ppm (6.25 mg/kg/day). The systemic NOEL for females was 50 ppm (2.5 mg/kg/day), and the systemic NOEL for males was 625 ppm (31.25 mg/kg/day). The requirements for chronic and oncogenicity testing in rodents [guidelines §83-1(a) and §83-2(a)] were satisfied by this study.

In another two-year rat feeding study, in which groups of albino rats were treated with dietary linuron at levels of 25, 125, and 625 ppm (1.25, 6.25, and 31.25 mg/kg/day), the systemic NOEL was determined to be 125 ppm. At the LOEL of 625 ppm (31.25 mg/kg/day), growth retardation was observed. In addition, at that dietary level, hemosiderin content of the spleen was increased for both sexes, marrow fat was reduced for females, the ratio of myeloid-to-erythroid precursors was reduced for males, and the incidence of endometrial hypoplasia was increased for females. These findings were considered to be indicative of hemolysis

(Hodge, 1962).

An 18-month feeding study was conducted in Cr1:CD(SD)BR rats to study the effects of linuron (94.5%) on methemoglobin and sulfhemoglobin blood concentrations (Pastoor, 1985). The dietary levels tested were 25, 125, and 625 ppm (1.25, 6.25, and 31.25 mg/kg/day). Based upon significant changes noted in blood pigments in mid- and high-dose female rats and in high-dose male rats, the LOEL was determined to be 625 ppm (31.25 mg/kg/day) and 125 (6.25 mg/kg/day) for male and female rats, respectively. The corresponding NOELs for male and female rats were 25 and 125 ppm (1.25 and 6.25 mg/kg/day).

In a two-year feeding/oncogenicity study in CD-1 mice (Wood et al., 1982), linuron was administered in the diet at levels of 50, 150, and 1500 ppm (12, 35, and 455 mg/kg/day). This study satisfied the requirement for a guideline §83-2(b) oncogenicity study in a second rodent species. A statistically significant increase in the incidence of hepatocellular adenomas was observed at 1500 ppm for female mice, and border-line statistical significance was attained for hepatocellular adenomas at 50 ppm for male mice. At 1500 ppm, body weight and body weight gain were decreased for both males and females throughout the study. Methemoglobin values were increased at all dietary levels for both sexes. Mean absolute and relative liver weights were increased for females at 1500 ppm. For both males and females at that level, histopathological evaluation identified increased incidences of hemosiderosis of the spleen and hepatocytomegaly, hepatocellular

cytoplasmic alteration, hepatocellular vacuolization, hemorrhage, and necrosis of the liver. A NOEL was not established; the systemic toxicity LOEL, based on increased methemoglobin values, was ≤ 50 ppm (12 mg/kg/day).

Linuron was placed in special review for carcinogenesis in 1982. It was later classified as a group C carcinogen with a Q^* of 2×10^{-5} on the basis of a dose-related increase in interstitial cell hyperplasia and adenomas in a two-year rat feeding study (Kaplan, 1980) and hepatocellular tumors that appeared in low-dose male and high-dose female mice in a two-year feeding study (Wood et al., 1982). Subsequent review by the HED peer review committee and the Science Advisory Panel resulted in the elimination of the Q^* , since the weight of evidence suggested that the carcinogenic potential of linuron in humans is weak, and it should not be regulated as a carcinogen (US EPA, 1989).

Developmental Toxicity

In a developmental toxicity study conducted with linuron (97%) in Sprague-Dawley rats, dietary doses of 50, 125, and 625 ppm (5.0, 12.1, and 49.8 mg/kg/day, respectively) were administered on days 6-15 of gestation (Culik, 1979); this study satisfied the guideline §83-3(a) requirement for a developmental toxicity study in rodents. The NOELs for maternal systemic toxicity and developmental toxicity were 125 ppm (12.1 mg/kg/day). The LOEL of 625 ppm (49.8 mg/kg/day) for maternal systemic toxic effects was based upon decreased body weight and food consumption values. The

developmental toxicity LOEL of 625 ppm (49.8 mg/kg/day) was based on increases in postimplantation loss and increases in the litter and fetal incidences of resorptions.

When 96.2% linuron was administered by gavage to New Zealand White rabbits at doses of 5, 25, and 100 mg/kg/day on days 7 through 19 of gestation (Hoberman, 1985), a maternal systemic toxicity LOEL was observed at the 25 mg/kg/day level, based upon reduced maternal body weight, thereby defining the NOEL as 5 mg/kg/day. At the high-dose level (100 mg/kg/day), maternal body weight, food consumption, absolute liver weight, and liver-to-body weight ratios were decreased. The developmental toxicity NOEL was determined to be 25 mg/kg/day, based upon an increased number of abortions, decreased mean number of fetuses per litter, decreased fetal body weight, and increased incidence of fetuses with skeletal variations of the skull at the 100 mg/kg/day level (the developmental toxicity LOEL). This study satisfied the guideline §83-3(b) requirement for a developmental toxicity study in rabbits.

Reproduction

In a two-generation reproductive toxicity study in Sprague-Dawley rats, dietary levels of 12.5, 100, and 625 ppm linuron (96.2%) (males: 0.84, 6.8, and 44.75 mg/kg/day; females: 1.0, 8.3, and 54.1 mg/kg/day) were administered (Mullin, 1990). This study satisfied the requirement for a guideline §83-4 for a multigeneration reproductive toxicity study in rats. Since no evidence of adverse effects on fertility or reproductive

performance was noted, the reproductive toxicity LOEL was undetermined, and the reproductive toxicity NOEL was estimated to be greater than 625 ppm (44.75 and 54.1 mg/kg/day for males and females, respectively). The parental systemic toxicity NOEL was 12.5 ppm, and the systemic LOEL was 100 ppm, based upon decrements in parental body weight gain. In addition, at the 625 ppm level, testicular and epididymal abnormalities (testicular atrophy and intratubular fibrosis; epididymal inflammatory response or oligospermia) and ocular abnormalities (mineralization of the cornea; lens degeneration) were observed at histopathological evaluation of the F1 adults (Stula, 1990). Further evaluation of reproductive organ weight and hormone data from the F1 adults of this 2-generation study combined with an in vitro analysis of the ability of linuron and its metabolites to compete for binding to the androgen receptor resulted in the conclusion that linuron is a weak androgen receptor antagonist (Cook, 1990). These results support the hypothesis that rats exposed to linuron could develop interstitial cell hyperplasia and subsequent adenomas (Leydig cell tumors) of the testicular tissue via a mechanism of sustained hypersecretion of luteinizing hormone induced by the antiandrogenic potential of linuron.

A three-generation reproductive toxicity study in Sprague-Dawley rats (Pastoor, 1984), was conducted with 94.5% linuron at dietary levels of 25, 125, or 625 ppm (approximately 1.25, 6.25, and 31.25 mg/kg/day). Parental systemic effects observed included reduced pre-mating body weight in females of all three generations

at 125 and 625 ppm, reduced body weights at weaning for 125 ppm dams, and alopecia in both sexes for the F0 and F1b adults at 625 ppm. Based upon the findings at the mid-dose level, the systemic LOEL was determined to be 125 ppm (6.25 mg/kg/day), and the systemic NOEL was 25 ppm (1.25 mg/kg/day). The reproductive toxicity NOEL was 25 ppm (1.25 mg/kg/day) and the reproductive toxicity LOEL was determined to be 125 ppm (6.25 mg/kg/day), based on the following findings. Fertility was reduced in generations F2a through F3a. Pup survival was consistently decreased for pups at 625 ppm, with most deaths occurring in the first 24 hours postpartum, and a trend for decreased viability from days 1-4. Weanling body weights were decreased for F1b and F2b male and female pups. Absolute liver and kidney weights of weanlings (both sexes) were decreased, and histopathology of the F2b weanlings identified a frequent incidence of liver atrophy (decreased cytoplasmic clear spaces of hepatocytes). This study was flawed by the lack of histopathological data on the adult animals; however, the systemic study results are considered to be supportive of those obtained from the two-generation study on linuron (Mullin, 1990).

Mutagenicity

Technical linuron did not produce gene mutation in an Ames assay (Russell, 1983), in which Salmonella typhimurium bacteria were tested without activation up to 5.0 µg/plate and with activation up to 100 µg/plate. In an in vitro assay using CHO cells (McCooley, 1983), linuron did not produce gene mutations when

tested up to 0.50 mM in a nonactivated system and up to 1.0 mM in an S9-activated system. Similarly, linuron did not induce bone marrow chromosome aberrations in vivo (Farrow et al., 1983), and in other tests for genotoxicity, linuron did not induce unscheduled DNA synthesis in isolated rat hepatocytes (Chromey et al., 1983). These studies met the mutagenicity testing requirements for guidelines §84-2(a), §84-2(b), and §84-4 (gene mutation, structural chromosomal aberration, and other genotoxic effects).

Metabolism

The metabolism and tissue distribution of [phenyl-¹⁴C](U) linuron was studied in male and female Sprague-Dawley rats. The results of several metabolism studies and communications containing supplemental information were combined to satisfy the requirements for a §85-1 metabolism study. In the first study, labeled linuron was administered as a single gavage dose to 2 rats/sex/dose at 24 mg/kg and 400 mg/kg and also as a single 400 mg/kg gavage dose following dietary pretreatment at 100 ppm (approximately 10 mg/kg) to 2 rats/sex/dose (Carter, 1985a; Carter, 1985b). To further elucidate the metabolic pathway of linuron, a second study was conducted in which a single oral dose of 400 mg/kg of ¹⁴C-linuron was administered by gavage to five Sprague-Dawley rats per sex (Hundley, 1991; Brown, 1991; Brown, 1992). The results from these studies indicate that linuron was extensively metabolized by male and female rats at both the low- (24 mg/kg) and high-dose (400 mg/kg) levels when administered by gavage. The majority of the

administered ^{14}C -linuron was eliminated in the urine and, to a lesser extent, in the feces, within 96-120 hours. In general, tissue and organ residues were very low (<1%) 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 and feces were hydroxy-norlinuron and norlinuron. Approximately 4-5% and 6-8% of the urinary and fecal metabolites, respectively, remained unidentified. Exposure to linuron appears to induce mixed function oxidative enzymes.

Reference Dose (RfD) for Chronic Oral Exposure

The RfD for linuron was determined to be 0.0077 (0.008) mg/kg bodyweight per day. This was based on results of a one-year chronic dog study (Malley, 1988) in which hematological changes demonstrated LOELs of 4.17 and 3.49 mg/kg/day for males and females, and NOELs of 0.79 and 0.77 mg/kg/day. The RfD calculation was based upon the NOEL of 0.77 mg/kg/day and used an uncertainty factor of 100 to account for inter-species extrapolation and intra-species variability.

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