SUMMARY OF TOXICOLOGY DATA
LINURON

Chemical Code # 000361, Document Processing Number (DPN) # 00184
SB 950 # 140

Original date: September 18, 1987
Revised date: 3/20/90, 3/22/91, 9/30/93, 6/25/2013, and 09/01/2015

DATA GAP STATUS

Chronic toxicity, rat: No data gap, possible adverse effects
Chronic toxicity, dog: No data gap, possible adverse effects
Oncogenicity, rat: No data gap, possible adverse effects
Oncogenicity, mouse: No data gap, possible adverse effects
Reproduction, rat: No data gap, possible adverse effects
Developmental toxicity, rat: No data gap, no adverse effects
Developmental toxicity, rabbit: No data gap, no adverse effects
Gene mutation: No data gap, no adverse effects
Chromosome effects: No data gap, no adverse effects
DNA damage: No data gap, no adverse effects
Neurotoxicity, hen: Not required at this time

Toxicology one-liners are attached.

All record numbers for the above study types through 285961 (Document No. is 184-0132) were examined. This includes all relevant studies indexed by DPR as of 09/01/2015.

In the 1-liners below:
** Indicates an acceptable study.
Bold face indicates a possible adverse effect.
## indicates a study on file but not yet reviewed.

Toxicology summary was updated by H. Green and M. Silva, 3/20/90; Kishiyama & Silva, 3/22/91; Silva, 9/30/93; Aldous, 6/25/13; and Corlett, 09/01/2015.
NOTE: The following symbols may be used in the Table of Contents which follows:
** = data adequately address FIFRA requirement
† = study(ies) flagged as “possible adverse effect”
N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

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METABOLISM AND PHARMACOKINETICS

184-050 059207 Carter, L. G., “Metabolism of [phenyl-14C(U)] linuron by male and female rats,” E. I. DuPont de Nemours & Co., Wilmington, DE, 3/28/85. Document No. AMR-250-84. Groups of 2 rats/sex were dosed orally with labeled linuron either (1) once with 24 mg/kg, (2) once with 24 mg/kg after 21 days of oral dosing with 100 ppm linuron, or (3) once with 400 mg/kg linuron. Sacrifice was at 96 hrs for 24 mg/kg groups, and 120 hrs for the 400 mg/kg group. One low-dose male was placed in a glass chamber with trapping of respired air for labeled volatiles (no radioactivity was found in the trap). Treatments did not greatly affect metabolism patterns. Most label was found in urine (about 70% of administered dose), and about 20% of dose was found in feces, thus absorption was efficient. Organs and tissues accounted for 1-3% of dose. Generally kidney and liver had the highest concentrations of label, other than occasional high and variable amounts in GI tract and hide. Brain and fat typically had the lowest concentrations. This study used sulfatase, β-glucuronidase, and bacterial proteases to remove conjugates, hence conjugation products were not identified. Identification was by TLC in a system in which highly polar metabolites remained at the origin, and were not identified. These polar materials were typically much more abundant than the most common identified metabolite. Parent linuron constituted 1-6% of fecal samples, but was not found in urine. Dominant metabolites involved ring α-hydroxylation, desmethyl, and desmethoxy products. The desmethyl, desmethoxy product (designated NOR) was the most abundant identified fecal metabolite during the first 24 hrs, after which OH-NOR [4,5-dichloro-2-hydroxyphenylurea] predominated. OH-NOR was the dominant urinary metabolite. Metabolites could not be evaluated in tissues, due to low residues. T1/2 estimates were 21-56 hrs (males having most rapid clearance). Some useful data, but not acceptable or upgradeable. Aldous, 5/24/13.


GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

NOTE: the acute studies summarized below generally reflect end-use product formulations, with the exception of two studies which were performed on technical linuron. The other studies below represent, where possible, accepted studies using either (1) Linex 4L (or Lorox® 4L), both being formulations of about 59% linuron, or (2) Lorox® DF (about 50% linuron). Data in support of some 50% formulations were supported by Linuron 80DF, which assayed at 84.2% technical linuron (see Document No. 184-125, Tab 5). Although the latter product appears not to have been registered in California, data from that formulation have been submitted in support of California registrations, and some data on that product are included below as surrogate information for technical linuron. Aldous, Sept. 1, 2015.
**Acute oral toxicity, rat**

**184-014; 931130; Acute Oral; 811; rat; Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Lab Report No. 101-79; 3/6/79; Lorox 4L (Code Nos. INZ-326-133, NB 7747-142), dosed as a 20% or 25% aqueous mixture; 1000 (10M), 1500 (10F), 1800 (10F), 1850 (10M), 1900 (20M), 1950 (10M), 2000 (30M/10F), 2500 (20F), 3000 (10M), 3500 (10F), 4000 (10M/10F) mg/kg; Mortality- male: 0/10, 0/10, 3/10, 1/20, 0/10, 10/30, 9/10, 9/10, female: 2/10, 1/10, 3/20, 4/10, 6/10; Clinical Observations- included ataxia, lethargy, lacrimation, prostration, salivation, shallow and rapid breathing, cyanosis, diarrhea, eye opacity, humped posture, pallor, piloerection; Necropsy- included lungs heavy, hyperinflated, discolored; liver dark, with prominent lobular markings; GI mucosa sloughing; heart firm; spleen discolored or abnormal in size; foamy exudate in trachea; fluid in thoracic cavity; LD50 (M) = 2437, (F) = 3936 mg/kg; Toxicity Category III; Acceptable. (Duncan, 10/27/94)

**184-104; 138361; Acute Oral LD50; 811; rat; Haskell Laboratory Report No. 292-95; DPX-Z326-222 (Lorox DF) (A I.: 49.31%)- a tan solid; oral dose levels of 3000, 4000 and 5000 mg/kg; 5/sex/dose; mortalities (M) 0/5, 1/5, 3/5 and (F) 1/5, 5/5, 3/5, respectively; clinical observations- lethargic behavior, ruffled fur, hunched over posture, moribundity, ocular discharge, stained eyes, nose and mouth, prostrate posture, high carriage, yellow stained perineum, weakness, exophthalmos and alopecia of the underbody or hindquarters; intermittent weight losses; necropsy revealed no gross lesions resulting from the subject product; LD50 (M & F) = 4220 mg/kg (with a 95% confidence interval of 3400 - 6672 mg/kg); Toxicity Category III; study acceptable. (Kahn 8/25/97)

**184-011; 051965; Acute Oral Toxicity; 811; Rat; Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE, Report No. 123-79, 3/23/79; Lorox 50 DF; 10/sex/dose; doses- males: 4000, 4600, 5000, 5500 mg/kg; females: 3500, 3900, 4600, 5300 mg/kg; mortalities: males: 4/10, 2/10, 5/10, 8/10, respectively; females: 2/10, 4/10, 9/10, 8/10, respectively; observations- eyes half-closed, ataxia, lacrimation, piloerection, chromodacryorrhea, stained face, stained and wet perineal area, moribundity, cyanosis, and weight loss after dosing; necropsy- slightly heavy to heavy livers and lungs with white or gray mottling and a few brown focal areas in 3900-5500 mg/kg dose groups; LD50 (M)=4833 mg/kg, LD50 (F)=4060 (3535-4496) mg/kg; Category III; Acceptable. (de Vlaming, 1/31/86; updated, Corlett, 6/18/93).

**Acute dermal toxicity**

**184-125 (previously given Document No. 184-241); 137270; Acute Dermal; 812; rabbit; Springborn Institute for Bioresearch, Inc., Spencerville, OH; Lab Study No. 3159.8.2; 6/3/87; Linuron 80 DF (Lot No. 87022401), ground in mortar and moistened with 1 ml water/g test material; 2 g/kg; 5 animals/sex; occlusive wrap, 24-hour exposure; no mortality; Clinical Observations- soft stools, fecal stains, few feces; Necropsy- lungs dark red, white areas on liver; LD50 (M and F) > 2 g/kg; Toxicity Category III; Acceptable. (Duncan, 7/19/95).

**Acute inhalation toxicity, rat (see below)**

Evaluations in response to a Section 3 submission with package ID #156201 did not accept the following study, but noted that the test article was not amenable to a guideline study: see explanation following the 1-liner below.
Acute Inhalation Studies:

**184-241; 137273; Acute Inhalation; 813; rat; Springborn Institute for Bioresearch, Inc., Spencerville, OH; Lab Study No. 3159.8.5; 7/7/87; Linuron 80 DF (Lot No. 87022401), prepared as a 10% aqueous suspension; 0.7 mg Linuron 80 DF/l (estimated gravimetric concentration); 5 animals/sex; liquid aerosol, 4-hour, whole-body exposure; MMAD = 6.8 um (GSD = 1.6); no mortality; Clinical Observations- dark material around nose and eyes, urine and fecal stains, activity decrease, lacrimation, dehydration, labored breathing, unkempt, ataxia, emaciation; Necropsy- no abnormalities; LC50 and Toxicity Category not determined; Study supplemental (test material diluted prior to aerosolization). (Duncan, 7/19/95, revised to supplemental, Moore, 12/8/95)

(Explanation referring to Record No. 137273, above): The acute inhalation toxicity study is supplemental. However, the study results indicate that the test material could not be readily aerosolized and that dilution was the only means available to produce an inhalable atmosphere. The subject product is a similar granular form with a lower active ingredient concentration. In order to produce an inhalable atmosphere, the product would have to be diluted appreciably and would not likely result in a sufficient concentration to be toxicologically significant. The statement, “avoid breathing dust or spray mist,” adequately identifies the acute inhalation toxicity hazard presented by exposure to the subject product.

**Primary eye irritation, rabbit**

**184-082; 124865; Primary Eye Irritation; 814; rabbit; Bozo Research Center Inc., Kannami Laboratory, Japan; Lab Study No. B-2177; 5/8/92; Linuron Technical (Lot No. 90077307; purity = 97.4%), dosed undiluted; 0.1 g/eye; 6 animals unwashed, 3 animals washed after 2-3 mins.; examined at 1, 24, 48, and 72 h (termination); UNWASHED- lid closure and discharge within 6 h after dosing, conjunctival redness of 0-1 at 24 h, clear by 48 h; WASHED- no irritation; Toxicity Category IV; Acceptable. (Duncan, 9/22/93)

**184-011; 051966 (incomplete study) and 051959 (complete study); Primary Dermal Irritation; 815; Rabbit; Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE, Report No. 138-79, 4/12/79; Lorox 50 DF; 6 animals; 2 intact and 2 abraded sites/animal; 0.5 g (moistened with saline)/test site; 24 hr exposure, covered; observations (intact sites)- no edema; erythema (grade 3 in 1/6, grade 2 in 1/6, grade 1 in 4/6) 24 hrs after the initiation of exposure, decreasing to grade 1 in 2/6 72 hrs after the initiation of exposure, clearing in all within 6 days; Category IV; Acceptable. (Originally unacceptable because test report incomplete, de Vlaming,
1/31/86; revised to acceptable on submission of complete test report, Hughett, 4/7/86; updated, Corlett, 6/18/93)

**Dermal sensitization** † (see below)
(Possible sensitizer, based on a study without a DPR review, but for which investigators designated material as a weak skin sensitizer: see 184-0011 051658, below.)

**184-055; 063864; Closed-Patch Repeated Insult Dermal Sensitization Study (Buehler Method) with Lorox 50 DF in Guinea Pigs; E. I. du Pont de Nemours, Newark Delaware, HLR 565-87, 10/18/87; (Lorox 50 DF); 5 animals/sex/dose for the treated dose group (25% test material in distilled water), vehicle control group (distilled water), positive control group (DNCB); 0.4 ml of 50%, 25%, and 10% w/v suspensions of test material in distilled water; occluded patch, exposure period of 6 hours; induction phase- dose administered one a week for 3 consecutive weeks, 2 week rest period then challenge dose administered; 3 animals score of 1 at 48 hours for 3/20 animals at the challenge phase (within range of negative control values); under the test conditions used the material does not appear to be a sensitizer; Acceptable; J. S. Berliner, 1/27/88.

184-0011 51657 “Skin sensitization test of INR-9521-1 in guinea pigs.” This test indicated a mild sensitization, but the test article is not linuron, even though it was included in a volume of linuron studies. Test article was a mixture of two triazines, neither of which resembles linuron. Aldous, Sept. 1, 2015.

184-0011 51957 This is a skin sensitization test with Haskell No. 15,525. This test was negative, but the test article is not linuron, even though it was included in a volume of linuron studies. Aldous, Sept. 1, 2015.

184-0011 051658 “Skin sensitization test in guinea pigs of INR-8260-2 for EPA pesticide registration,” Haskell Laboratory Report 447-85, 8/15/85. This study was examined by a CDFA Medical Toxicology Branch reviewer on Sept. 2, 1986. No worksheet can be found. Test article assayed at 56.47% linuron. Investigators state that substance was a “weak sensitizer.”

**SUBCHRONIC STUDIES**
(Units are mg/kg/day unless specified.)

**Oral toxicity, rat:**

184-009 043461, and 027217. “Oral Toxicity of Linuron in Rats and Dogs” (Fd. Cosmet. Toxicol. 6, pp. 171-183, 1968). Literature review article contains no reviewable data. There is reference on p. 174 to a 90-day feeding study in rats, which found no effects at 80 ppm, reduced RBC counts and reduced hemoglobin along with “erythrogenesis in spleen and bone marrow and haemosiderin deposition in the spleen at 400 ppm, and reduced growth rate and additional hematological toxicity at 2000 ppm. Aldous, 6/14/13.

184-0015 931127, 043459, 043461, 043462, 043464, 027216, 027218 All these records refer to segments of the same 1968 publication by Hodge et al. in the previous paragraph.
Oral toxicity, non-rodent:
There is no study of this type on file.

Dermal toxicity, 21/28-day or 90-day:

0131; 285960; “Linuron- Substance Technical (Code: Hoe 002810 OH ZD96 0003); Repeated Dose Dermal Toxicity Study (21 Applications in 29 Days) with a 14-Day Withdrawal Period” (Simonnard, A., Hoechst AG, Pharma Forschung Toxikologie und Pathologie, Pflanzenschutztoxikologie, Frankfurt am Main, Laboratory Project ID Study No. 3105 TSR, 02/08/1988). 870.3200. Linuron, technical substance (Code: Hoe 002810 OH ZD96 0003, Batch: C0 226-1690, purity = 94.7%), diluted in sesame oil, was applied to the clipped dorsal skin of the trunk of 6 (low-dose and mid-dose groups) or 12 (control and high-dose groups) Sprague Dawley (Crl:CD (SD) BR strain) rats per sex per dose at dose levels of 0 (vehicle only), 10, 30, or 100 mg/kg/dose once daily for 6 hours 5 days per week for a 29-day period (21 applications) using an occlusive wrap followed by a 14-day withdrawal period for 6 animals per sex in the control and high-dose groups. No treatment-related mortalities occurred. No treatment-related clinical signs were observed in the test animals during the treatment and withdrawal periods. No treatment-related effects on mean body weight or mean food consumption were observed. Hematology and urinalysis revealed no toxicologically significant changes. Blood biochemistry revealed no toxicologically significant effects. Increases in mean relative liver (not statistically significant) and spleen weights in males at 100 mg/kg/day were observed; reversibility of these effects was observed in the withdrawal group animals. Macroscopic examination revealed no treatment-related abnormalities. Microscopic examination revealed hyperkeratosis of the treated skin in males at all dose levels and in females at 100 mg/kg/day. No adverse effects. Reported NOEL (M, systemic) = 30 mg/kg/day based on increased mean relative liver and spleen weights, Reported NOEL (F, systemic) = 100 mg/kg/day based on no effects at the highest dose tested, Reported NOEL (M, skin) < 10 mg/kg/day and Reported NOEL (F, skin) = 30 mg/kg/day based on hyperkeratosis of the treated skin. Unacceptable but possibly upgradeable with the submission of an explanation justifying the dose levels selected. (Corlett and Leung, 08/12/2015)

CHRONIC STUDIES

Combined (Chronic and Oncogenicity), rat † **

**184-030/031, 036249, 036250** Kaplan, A. M., “Long-term Feeding Study in Rats With 3-(3,4-Dichlorophenyl)-1-methoxy-1-methyl urea,” Haskell Laboratory Report No. 100-80, 2/14/80. Linuron technical (97% a.i., identification N.B. 7673-8). Groups of 80 Charles River CD rats/sex/group were fed 0, 50, 125 or 625 ppm in the diet. Ten/sex/group were allocated for a 12 month chronic study, while the balance were treated for 24 months. Mean intake for treated lifetime study rats was 2.1, 5.1, and 27 mg/kg/day for males, and 3.1, 7.7, and 48 mg/kg/day for females. Possible adverse effect: testicular interstitial cell adenomas, significantly increased in 125 and 625 ppm males, dose related. There is no clear NOEL for testicular interstitial cell tumors. Interstitial cell tumors were non-significantly elevated also at 50 ppm, with what appears as the low end of a dose-response. NOEL for females = 50 ppm, based mainly on slight body weight decrements. The highest dose achieved an MTD in males (7% body weight decrement at 1 year) and exceeded MTD target in females (high dose females weighed 22% less
than controls at one year). Reductions in RBC parameters, increased hemosiderin deposition in several tissues, and splenic congestion show blood toxicity at 625 ppm in both sexes. Additional treatment effects are tabulated, and the discussion section of this review discusses implications of major findings. Complete, acceptable with several deficiencies noted in DPR review. (C. Aldous, 12/2/85, re-examined by Aldous, 5/23/13).

EPA one-liner (030/031:036249, 036250): Significant increases (p < 0.05) in interstitial cell adenoma in testes of male rats receiving 125 and 625 ppm. NOEL < 50 ppm (increased MLV, decreased RBC count, and possible reticulocytosis). Core grade = Minimum.

184-008, 027208 Summary of 030/031:036249, 036250.


184-046 059704 (Ancillary rat oncogenicity study related to 184-030/031:036249, 036250). Report entitled: “Effects of Linuron Fed to Aged Male Rats” (HLR #394-86). Haskell Labs, 9/24/86. Male Crl:CD(R)BR rats were divided into 3 groups of 25 each. One group was fed control feed and sacrificed at 2 years. One group was fed control feed for 18 months, followed by 625 ppm linuron for 6 months, and then sacrificed. The last group was fed control feed for 1 year, then 625 ppm linuron for 1 year, and was sacrificed. Both linuron treated groups lost significant weight at onset of treatment, and weighed 21 to 23% less than controls at term. There were no major effects on clinical observations, or on mortality. **Possible adverse effect indicated:** Controls, 6-month treated, and 12-month treated groups had testicular interstitial cell (ISC) tumor incidence of 0, 2, and 6, respectively, and ISC hyperplasia incidence of 6, 7, and 14, respectively. Data are consistent with results of the primary rat combined study. (NLH/C. Aldous, 9/4/87).

184-028, 036240 “Chronic Feeding Studies of Linuron (Herbicide 326) in Rats,” University of Rochester School of Medicine and Dentistry, 11/12/62. Linuron technical (Herbicide 326, purity not indicated), was administered in diet for 2 years at 0, 25, 125 or 625 ppm in 35 rats/group/sex. **Possible adverse effect indicated:** Findings included testicular interstitial cell tumors, hemosiderin pigments in spleen, increased erythroid endometrial hyperplasia: all at 625 ppm. Incomplete, unacceptable, not upgradeable (too few rats/group assigned to study, high incidence intercurrent disease resulting in even fewer available animals/group at study conclusion, and study design lacking many other features expected in a modern lifetime study). Re-examination in 2013 found that the present study, deficient in many respects, provides no endpoints which were not identified in the accepted replacement study (DPR Document Nos. 184-030, 184-031, Record Nos. 36249, 36250), at equivalent or lower dose levels. (DPR review C. Aldous 11/25/85, re-examined by Aldous, 5/29/13).

EPA one-liner (028:036240): NOEL = 125 ppm (Spleen and bone marrow changes indicative of hemolysis; increased mortality, growth retardation). Core grade not stated.

Chronic, dog †  

**184-062 071438**, “Chronic Toxicity Study with IN Z326-118, One-Year Feeding Study in Dogs”, (Haskell Laboratory for Toxicology and Industrial Medicine, report # 181-88, 10/28/88). INZ-326-118 (linuron; 93.3% to 96.2% pure) was fed in the diet for 376 to 380 days at 0, 10, 25, 125 or 625 ppm to 4 Beagle dogs/sex/group. Possible adverse effect. NOEL = 25 ppm (increased relative liver weights were observed in 625 ppm males; elevated concentrations of methemoglobin and sulfhemoglobin were reported in both sexes at 125 and 625 ppm indicating an increase in hemolysis was occurring; increased hematopoietic cells in bone marrow in both sexes were observed at 625 ppm). Acceptable. (Green & Silva, 3/16/90). Peer review with discussion of findings, indicating no change in chronic NOEL, by Aldous, 5/29/13. Peer review suggests that results may have bearing on acute to subacute NOEL’s.

184-029, 036246 “Chronic Feeding Studies of Linuron (Herbicide 326) in Dogs,” Univ. of Rochester School of Med. & Dentistry, 2/1/63. Test article given as H-326, assumed to be technical linuron (not otherwise specified). 0, 25, 125 or 625 ppm in diet of 3 beagles/sex/group for 2 years. Possible adverse effect indicated: Toxicity was primarily blood effects. Pigment accumulation in Kupffer cells, presumed sulfhemoglobin formation. Erythroid cell proliferation in marrow suggest RBC death and increased turnover. Apparent NOEL = 25 ppm. Incomplete, UNACCEPTABLE -Not upgradeable. Aldous peer review on (5/28/13, no new DPR worksheet) found no endpoints which were not equally or better addressed in the accepted study (Record No. 071438, above). That record provided hematol ogy with methemoglobin and sulfhemoglobin on 4 dogs/sex at 4 intervals, far more comprehensive than the present record. In the present record, only once (at termination) was there an examination of all dogs on study for abnormal spectra in blood samples, with 2 of six 25 ppm dogs showing “somewhat abnormal” hemoglobin spectra.

EPA one-liner [ref 029:036246]: NOEL < 25 ppm: 2/6 animals showed abnormal blood pigment (oxyhemoglobin). Decreased RBC in females at 125 ppm. Decreased RBC, Hct, Hb in males at 625 ppm. Core grade not stated.


Oncogenicity, mouse †  

**184-032 036251** Rickard, R. W., “3-(3,4-dichlorophenyl)-1-methoxy-1-methyl urea (Lorox®; Linuron; INZ-326) in mice,” Haskell Report No. 758-82, 12/22/82. Linuron, technical (97%) was administered at 0, 50, 150, and 1500 ppm in the diets of 80 CD-1 mice/group over 24 months. Estimated achieved dose levels were 8, 23, and 261 mg/kg/day in treated males, and 12, 35, and 455 mg/kg/day in females. NOEL = 150 ppm for both sexes. Body weights were clearly reduced by treatment at 1500 ppm in both sexes for most of the study (by 3-4 g in both sexes at 1 year). Possible adverse effect: Females at 1500 ppm had an increase in hepatocellular adenomas. Liver was a key target organ. Hepatocellular adenomas were not elevated in males, and hepatocellular carcinomas were unaffected by treatment in either sex. There was ample evidence of non-neoplastic pathology in livers at 1500 ppm in both sexes. Both sexes showed sharp increases in centrilobular focal hemorrhage, cytomegaly, and
cytoplasmic vacuolation. Incidence of hepatocellular necrosis was conspicuously elevated in high dose males, and hepatocellular fatty change and hepatocellular focal alteration were elevated in females. Splenic hemosiderosis in high dose mice and associated modest but consistent decrease in RBC counts (most evident during the first 6 months of the study) indicate mild but sustained RBC toxicity. Also, methemoglobin was elevated several-fold in high dose males and females at termination. Report is acceptable (missing information noted in first DPR review were addressed in registrant rebuttal of 12/9/86). (DPR reviews 12/4/85 of 9/3/87 and re-examination on 5/24/2013 were performed by C. Aldous).

184-045, 051352 Supplemental data to 032/033:036251, 036252 (individual histopathology and organ weights data as part of registrant rebuttal of 12/9/86). Additional comments in Vol. 044, Tab 7.


**GENOTOXICITY**

**Note:** Both EPA and DPR have found one or more studies acceptable for each of the three categories of mutagenicity studies. In some cases below, gene mutation studies indicate DPR "acceptable", but with the caveat that a given study would not be acceptable by current standards. Usually this was because of lack of a repeat trial. Because there were two negative microbial assays which were individually faulted primarily for lack of a repeat trial, and one mammalian cell study which was fully acceptable to EPA and DPR, failings of the bacterial cell studies accepted previously by DPR constitute a moot issue: the data requirement is filled.

**Gene mutation**


**184-009, 027214 “Mutagenicity Testing on Linuron in Microbial Systems,” Institute of Env. Tox., Tokyo, Japan, no date. Linuron (99. 8%). S. typhimurium at 10, 50, 100, 500 or 1000 µg/plate tested with and without rat liver S-9. Duplicate plates. No adverse effect indicated. Complete, ACCEPTABLE. (DPR review 5/6/85 J. Christopher). (Note: This study would be considered unacceptable by current standards).

184-020, 14806 “Mutagenicity Evaluation in Salmonella typhimurium,” Haskell Lab. Report No. 106-83, 2/17/83. S. typhimurium strains TA 1535, TA 1537, TA 98, TA 100. Linuron (95-97%) at 0, 0.5, 0.75, 1.0, 2.5 & 5. 0 µg/plate without activation and 0, 1.0, 5.0, 10.0, 50.0 & 100 µg/plate with activation, duplicate plates; rat liver S-9. Insufficient information for independent adverse effects assessment. Incomplete (missing cytotoxicity data),
UNACCEPTABLE--upgradeable (need justification of dose selection). DPR review J. Christopher 5/7/85.


184-009, 931140 Summary information.

184-035, 36407 Duplicate pages of 020:14806 plus 2 pages of statistical analyses.

184-009, 027212 “Mutagenicity Testing on Linuron in Microbial Systems,” Institute of Env. Tox., Tokyo, Japan, no date. Linuron (99.8%). S. typhimurium strain G46; Host mediated assay with male ICR mice. 0, 50, 200 mg/kg by oral gavage. No adverse effect indicated. Incomplete (missing individual data), UNACCEPTABLE--Not upgradeable (not an accepted protocol). DPR review J. Christopher 5/6/85.

**184-009, 027213 “Mutagenicity Evaluation on Linuron in Microbial Systems,” Institute of Env. Tox., Tokyo, Japan, no date. Linuron (99.8%) at 0, 10, 50, 100, 500 & 1000 µg/plate, duplicate plates; E. coli WP2 her. No adverse effect indicated. Complete, ACCEPTABLE. DPR review J. Christopher 5/6/85. (Note: This study not acceptable by current standards).

**184-020, 014808 “CHO/HGPRT Assay For Gene Mutation,” Haskell Lab., Newark, Delaware, 10/11/83. Chinese Hamster Ovary cells, strain BH4 clone of CHO-K1. Linuron (94.5%) at 0.05, 0.25, 0.35, 0.40, 0.45 & 0.50 mM without activation and at 0.25, 0.50, 0.75, 0.90 & 1.00 with activation; rat liver S-9. No evidence of mutagenicity in the absence of cytotoxicity. Complete, ACCEPTABLE. DPR review 5/7/85 J. Christopher.


**Chromosome damage**

**184-020, 014809 “In Vivo Bone Marrow Chromosome Study in Rats, H #14,703,” Hazleton Lab., Vienna, VA, 9/1/83. Linuron (94.5%) at 0, 100, 300 or 1000 mg/kg to 20 Sprague-Dawley rats/sex/group in a single oral gavage dose. No adverse effect indicated. Complete, ACCEPTABLE. DPR review 5/7/85 J. Christopher.

EPA one-liner (#14809): No increases in aberration frequency. Maximum dosage usable 300 mg/kg. Core grade = acceptable.
DNA damage or miscellaneous effects **

**184-020, 014807 “Unscheduled DNA Synthesis/Rat Hepatocytes In Vitro,” Haskell Lab. Report No. 190-83, Newark, Delaware, 5/13/83. Linuron (94.5%) Trial 1: 10-5 to 50 mM (8 concentrations), Trial 2: 10-2 to 50 mM (5 concentrations); duplicate cultures/level. No evidence of UDS. Complete, ACCEPTABLE. DPR review 5/7/85 J. Christopher.

EPA one-liner (#14807): Negative for unscheduled DNA synthesis. Core grade = acceptable.

184-009, 027215 “Mutagenicity Testing on Linuron in Microbial Systems,” Institute of Env. Tox., Tokyo, Japan, no date. Rec-assay, B. subtilis, Linuron (99.8%) at 20, 100, 200, 500, 1000 or 2000 µg/disk; single plates per dose level. Insufficient information for adverse effects assessment. Incomplete, UNACCEPTABLE--Not upgradeable (no metabolic activation, only one plate per level, strain not characterized). DPR review 5/6/85 J. Christopher.

REPRODUCTIVE TOXICITY, RAT † **

** 184-052, -038 090707, 086709, “Reproductive and Fertility Effects with IN Z326-118 (Linuron) Multigeneration Reproduction Study in Rats”, L. S. Mullin, E. I. Du Pont de Nemours and Co., Haskell Laboratory, HLR Report No. 20-90, 3/29/90). IN Z326-118 (Linuron, purity 96.2%, Batch #: IN Z326-118) was administered in the feed at concentrations of 0 (diet), 12.5, 100, or 625 ppm and fed to 30 Crl:CD®BR, P1 and F1 rats/sex/group (at weaning) and daily until offspring weaning. Parental NOEL = 12.5 ppm (Decreased body weight and food consumption at ≥ 100 ppm was observed for both sexes of P1 & F1). Adverse effects: Reproductive NOEL = 100 ppm (Abnormalities of the testes were observed as: small in size with atrophy, granuloma fibrosis, and hyperplasia. Epididymides were small and deformed, showing arteritis, inflammation/tubular degeneration, lymphoid foci, and oligospermia. In addition, increased estradiol and luteinizing hormone (LH) levels at 625 ppm suggest a potential for antiandrogenic activity of linuron which correlates with decreased fertility for F1 parents at 625 ppm (not statistically significant--72. 4% in control compared with 53. 6% at 625 ppm). Ocular lesions (corneal opacity in 3/30 males and 1/29 females, lens degradation in 3/30 males and 2/29 females, and corneal focal mineralization) occurred in F1 at 625 ppm. ) Pup NOEL = 100 ppm/day (Decreased pup weights, litter size (F2), and pup viability was observed at 625 ppm). ACCEPTABLE (The report is acceptable despite the fact that pages 499-500 are missing. ) (Kishiyama, Silva, 3/7/91).

184-065 092520, Additional information to DPR document 052 090707 (HLR 20-90). “Investigation of a Mechanism for Leydig Cell Tumorigenesis by Linuron in Rats”, (J. C. Cook, E. I. du Pont de Nemours and Co., Haskell Laboratory for Toxicology and Industrial Medicine, HL report No. 494-90, 9/10/90). IN Z326 (linuron), purity = 96.2%, was administered by oral gavage at a concentration of 200 mg/kg/day to 10 “growing” (33-46 days of age) and 10 adult (93-107 days of age) male rats for 14 days. Four groups, each with 10 males, served as test article vehicle (Methocel®), positive control vehicle (arachis oil/benzyl alcohol mix), pair-fed, and positive (flutamide) controls, respectively. Data suggest linuron inhibits testosterone. Epididymides, accessory sex organ unit (androgen-dependent tissue), prostate, ventral prostate and seminal vesicles had decreased weights when compared to vehicle controls. The level of
luteinizing hormone (LH) increased and was possibly the triggering mechanism for Leydig cell hyperplasia and/or adenoma formation. In vitro test results indicate linuron is able to compete for and bind to an androgen receptor. (Kishiyama & Silva, 3/10/91).


184-067 089571 Addendum to “Reproductive and Fertility Effects with IN Z326-118 Multi-Generation Reproduction Study in Rats,” (Stula, E. F., E. I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE, 3/29/90). According to the report, the study was performed to more thoroughly examine the eye lesions reported in DPR volume/record #'s: 038 & 052/086709 & 090707. Originally it was reported that eye lesions in F1 male & female rats at 625 ppm might be compound related. After re-evaluation, it appears that ocular effects are compound related in both sexes, but to a lesser degree in females than males (degeneration/basophilia of the cornea & other effects) at 625 ppm. These data are supplemental. Possible adverse effects. NOEL for eye effects = 100 ppm. M. Silva, 9/23/93.

184-034, 036253 “Multigeneration Reproduction Study in Rats With 3-(3,4-Dichlorophenyl)-1-methoxy-1-methylurea (Lorox, Linuron, INZ-326),” Project No. 4581-001, Haskell Lab., 10/26/84. Linuron technical (94.5% purity). 0, 25, 125, 625 ppm in the diet of 20 rats/sex/group. A three generation study with 5 litters. Possible adverse effect indicated: Apparent parental effects NOEL = 25 ppm (weight gain decrements in females at 125 and 625 ppm and in males at 625 ppm). Apparent NOEL for reproduction/lactation parameters = 125 ppm (smaller litters, reduced 24 hour survival of pups, reduced pup weights). Incomplete, UNACCEPTABLE—Not Upgradable (No microscopic evaluation of adult animals, even of those which indicated reproductive toxicity. Insufficient clinical observations). (DPR review 12/6/85 C. Aldous).

EPA one-liner (034:036253): Reproductive NOEL = 25 ppm. Reproductive LEL = 125 ppm (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. Also, lower fertility, reduced pup survival on days 0-4 in 625 ppm groups. Systemic NOEL (adults) = 25 ppm. Systemic LEL (adults) = 125 ppm (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. Core grade = Supplementary.

184-034, 036254 “Cross-mating Study With INZ-326,” Haskell Lab., 8/8/85. Linuron technical (94.5% purity). High dose (625 ppm) and control rats of a previous study (034:36253) cross-mated twice different partners to yield F3B and F3C offspring. Possible adverse effect indicated: Fertility was low in all combinations. Incidence of sperm plugs and percent pregnancy was lower in F3B litters when the treated males were cross-mated with controls than when control males were cross-mated with high-dose females. There was no such difference in F3C litters. Ancillary study does not answer questions raised in 034:36253, and a new reproduction study is required. UNACCEPTABLE—Not upgradeable. (DPR review 12/6/85 C. Aldous).
184-028, 036241 “Reproduction Studies, Herbicide 326,” Univ. of Rochester School of Medicine and Dentistry, 11/12/62. Linuron technical (Herbicide 326, purity not given). Doses tested were 0, 125 ppm in (presumably) Rochester strain rats (Wistar derived). No toxicity observed. Incomplete, UNACCEPTABLE--Not Upgradeable (MTD not achieved, only one dose level). (DPR review 11/25/85 C. Aldous).

EPA one-liner (028:036241): Reproductive NOEL > 125 ppm (Decreased litter weights in F2 & F3. Core grade not stated.


184-046, 051353 [Mechanistic studies related to 184-034:036253 (reproduction) and to 184-030/031, 036249, 036250 (rat combined study)]. Pastoor, T. P. (Study Director): “Biochemical and Pathological Effects of Linuron in Selected Tissues of Male and Female Rats, HLR 643-86,” Haskell Lab., 10/6/86. Small numbers of F1b and F2b male and female CD rat offspring of the principal reproduction study (034:036253) were maintained on respective diets (Control, 25, 125, and 625 ppm) until scheduled sacrifice at 2 years. Organs and tissues closely associated with reproductive function were examined grossly and microscopically in some of these rats. Some in vitro studies were performed to evaluate effects of linuron and four major metabolites on activities of 5 testicular interstitial cell (ISC) enzymes (tested in horse testicular microsomal preparations, at test article concentrations of 0, 0.5, 5, 50, 500, or 5000 µM). Blood clearance of testosterone (infused into femoral artery at 3 or 6 µg/hr) was assessed for 3 hrs in castrated rats, which had been dosed by gavage on 8 of the previous 10 days with 200 mg/kg/day linuron. ISC cell responsiveness to luteinizing hormone (LH) stimulation was estimated in young rats (> 3 weeks) or retired breeder rats (11 months 19 months, respectively, in 2 trials) dosed for either 3 days or 7 days at 200 mg/kg/day linuron. Additional LH stimulation subjects were rats fed chronically (presumably for 2 yrs) at 0, 25, 125, and 625 ppm. In all cases, isolated ISC’s were incubated for 3 hrs with varying concentrations of LH, and testosterone was assayed in supernatant. Results: Major microscopic findings in these aged animals included interstitial cell adenomas and ISC hyperplasia, which were both increased substantially in 125 and 625 ppm males. Uterine findings in females included “cystic endometrial hyperplasia”, which appeared to be dose-related and without an apparent NOEL, and incidence of “cervical cystic hyperkeratosis”, which was apparently elevated at 625 ppm. (Results were similar to those of the combined study (Record No. 036249), but this study was limited by smaller group sizes). In biochemical studies, some ISC steroidogenic enzymes were inhibited by linuron, particularly desmolase (significant change with strong dose-response at 500 to 5000 µM). Some linuron metabolites (nor-linuron and des-methylhydroxy linuron) also showed highly significant desmolase inhibition at 5000 µM only. Activities of other steroidogenic enzymes (aromatase and 17-hydroxylase) were more modestly reduced by linuron. ISC response to LH was decreased by a 7-day regimen of 200 mg/kg/day linuron, however LH response of ISCs increased on chronic exposure of males to linuron at 625 ppm, suggesting a compensatory response to sustained treatment. Blood clearance of infused testosterone in castrated rats was unchanged by linuron, suggesting that enhanced liver metabolism of testosterone was not a major response. Findings appear to support the idea that linuron interferes with testosterone synthesis, leading to compensatory LH production (not tested in this record) and increased LH receptor density. It is not clear whether achieved internal dose of linuron in chronic and reproduction rat studies was
comparable to effective doses in these mechanistic studies, nevertheless data show possible responses to account for linuron effects such as ISC tumors in old rats and oligospermia, hyperplasia, and inflammatory responses in gonadal tissues in younger rats. A metabolism study of limited utility indicated efficient absorption and rapid metabolism and excretion of linuron, but that study was not designed to detail toxicokinetics, which information might assess relevance to effects of linuron on steroid biosynthesis (C. Aldous, 9/8/87, re-examined by Aldous, 5/23/13).

DEVELOPMENTAL TOXICITY

Rat **

**184-020/035, 014805, 036411 “Teratogenicity Study of 3-(3,4-Dichlorophenyl)-1-methoxy-1-methylurea in Rats,” Report No. 33-79, Haskell Lab., 5/8/79. Linuron (97%), 0, 50, 125 or 625 ppm in the diet days 6-15 of gestation to 27 mated rats/group. Maternal effects NOEL = 125 ppm (reduced body weight gain: also possible maternal treatment effects limited to the 625 ppm group included one dam with chromodacryorrhea and one with a total litter loss). Developmental toxicity NOEL = 125 ppm (slight increases in minor skeletal anomalies: thoracic bipartite centra and asymmetrical sternebrae). No apparent adverse health effects indicated, as maternal toxicity and minor developmental effects were observed at the same dosage. Study not accepted by J. Christopher for 6 concerns listed in his 5/8/85 review. Study found ACCEPTABLE by C. Aldous on 9/3/87 upon examination of additional data submitted in the 12/9/86 du Pont rebuttal response. [Note: EPA accepted this as a “Guideline” study. EPA review in Vol. 044, Tab 2.]

184-044, 051351 Rebuttal comments and some additional data to 020:014805 submitted 12/9/86 (see above). Major concerns of the 5/8/85 DPR review were addressed.

111-068/084, 014778 “Teratogenicity Studies on Linuron, Malathion and Methoxychlor in Rats,” Toxicol. Appl. Pharmacol. 45, 435-444 (1978). Technical linuron (95.1%) at 0, 12.5, 25, 50, 100 or 200 mg/kg. Two linuron formulations each containing 50% linuron (L2 & L3); L2 tested at 0, 50, 100 & 200 mg/kg; L3 tested at 1, 25, 50, 100 & 200 mg/kg. Oral gavage to 20 mated Wistar rats/group days 6-15 of gavage. Decrease in maternal weight gain at high dose reported, however data does not support this. Insufficient information for independent adverse effects assessment. Incomplete UNACCEPTABLE (lacks analysis of dosing solutions, individual data). DPR review 5/6/85 by J. Christopher.

Rabbit **

**184-035, 036412; Christian, M. S. and A. M. Hoberman, “Developmental Toxicity Study of INZ-326 Administered Via Gavage to New Zealand White Rabbits,” Argus Research Lab., 9/16/85. Linuron (purity 96.2%) was administered by gavage at 0, 5, 25, 100 mg/kg/day on days 7-19 of gestation to groups of 25 New Zealand rabbits. Maternal and developmental toxicity NOEL = 25 mg/kg/day. High dose was associated with decreased maternal food consumption and decreased maternal weight gain (with rebound in both cases after cessation of treatment), increased liver weight, and increased abortions. The only fetal alteration was increased
incidence of irregularly shaped fontanelle at high dose. There were no malformations, and no ossification delays. Complete, acceptable. (Review 12/9/85 by C. Aldous: re-examined with additional data tables by Aldous, 5/29/13).

184-009, 027218 and 43459 “Oral Toxicity of Linuron in Rats and Dogs,”Fd. Cosmet. Toxicol. 6, 1968, pp. 171-183. Literature review article which contains a summary of a teratology study in New Zealand rabbits. Linuron (a 50% WP formulation) at 0, 25 or 125 ppm in the diet, 8 mated does/group. Insufficient information for adverse effects assessment. Incomplete (no individual data), UNACCEPTABLE--Not Upgradeable (only 2 dose levels, no evidence of maternal toxicity). DPR review 5/6/85 by J. Christopher.
EPA one-liner (#027218): Teratogenic NOEL > 125 ppm. Core grade not stated.

NEUROTOXICITY

Acute neurotoxicity, rat **

**184-127  271092, Herberth, M. T., “An oral (gavage) acute neurotoxicity study of linuron in rats,” WIL Research Laboratories, LLC, April 1, 2013. WIL-851008. Ten Crl:CD(SD) rats/sex per group were dosed with Linuron technical, 99.4% purity, Lot No. 1012A3876, by gavage at nominally 0, 20, 100, or 500 mg/kg. Achieved dose levels, based on suspension assays, were 21, 104, and 585 mg/kg in treated rats. This was a standard acute neurotoxicity study, with all rats subjected to clinical observations, FOB and motor activity assessments [pre-test, day 0 (peak response time), and at days 7 and 14], and with 5/sex perfusion-fixed rats of control and high dose groups examined for neurohistopathology at termination. NOEL = 21 mg/kg, based on reduced motor and locomotor activities, with strong dose-response in both sexes at 104 and 585 mg/kg; also on reduced rearing behavior in 104 and 585 mg/kg males. Many findings were observed at the highest dose level [in both sexes unless indicated below]. These include clinical signs of “prostrate” behavior (only in females) and “hypoactivity”, “body cool” or “limbs cool”, “dried red material around nose,” and several instances of “dried red material around eyes” and chromodacryorrhea. These signs almost always were associated with the day of first dosing or occasionally on the next day. Death of one high dose female in extremis was preceded several of these signs. Body weight gains were significantly depressed in males at 585 mg/kg/day during days 0-7. All FOB findings of interest were meaningfully elevated only on day 0, and except for reduced rearing in males, were limited to 585 mg/kg. These included FOB home cage findings of “sitting, head held low” and “drooping eyelids (half-closed).” Red deposits or crusty deposits on the nose were noted on handling. Open field observations found impaired mobility, ataxia or tiptoe gait, impaired gait, “stuporous” arousal state, and reduced rearing. Sensory responses found some rats with reduced responses to approach, touch, startle, or tail pinch. Air righting reflex was commonly compromised. There were several cases of failed hindlimb extension. Strength assessments showed reductions in day 0 high dose males and females for forelimb and hindlimb grip strength. High dose rats sustained markedly reduced time on the rotarod. Hindlimb foot splay was reduced significantly for both sexes. Catalepsy time (assessed as time the rat spent in position after being placed with its four feet on four separate raised platforms) was increased. Body temperature was decreased by 3-4 °C. Neurohistopathology and brain dimensions were unaffected. Study is acceptable, with no adverse effects. Aldous, 6/25/13.
90-day neurotoxicity, rat

There is no study of this type on file.

Developmental neurotoxicity, rat

There is no study of this type on file.

Delayed neurotoxicity, hen

There is no study of this type on file.

IMMUNOTOXICITY **

**184-128  271093  Smiraldo, P. G., “A 28-day oral (dietary) immunotoxicity study of linuron in male Wistar Han rats,” WIL Research Laboratories, LLC, 4/20/12.  Project ID: WIL-851006.  Groups of ten male rats/sex/group were dosed in diet with Linuron technical, 99.4% purity, for 28 days in two separate immunotoxicity studies: (1) antibody-forming cell assay (AFC), and (2) natural killer (NK) assay.  Initial linuron dose levels were 0, 150, 500, and 1500 ppm.  The latter dose was reduced to 1000 ppm on day 10 due to excessive toxicity for both assays.  Mean achieved dose levels were 13, 43, and 107 mg/kg/day for the AFC assay and 13, 42, and 107 mg/kg/day for the NK assay.  Positive controls received 4 consecutive daily ip injections of cyclophosphamide monohydrate on study days 24-27 (for AFC assay), or a single iv injection of 1 ml of a reconstituted suspension of anti asialo GM1 on the day prior to necropsy (for the NK assay).  All AFC groups received a single iv injection of 2 x 10^8 sRBC’s on day 24.  Spleen and thymus weights were taken at necropsy.  For the AFC assay, spleen cell suspensions were assessed for IgM antibodies against sRBC (plaque assay, based on enhanced lysis of sRBC’s in spleen cell preparations in immunized rats).  For the NK assay, YAC-1 cells labeled with ^51Cr were incubated in spleen cell suspension, and radiolabel in supernatant was counted as an indicator of NK killing of YAC-1 cells.  Necropsy was uneventful.  Absolute spleen weights were elevated at 500 ppm linuron, and relative spleen weights were elevated in all linuron groups.  Relative thymus weights were constant over linuron dose range.  Spleen cell numbers rose 21% at 500 ppm linuron in the NK assay, roughly proportional to the elevation in absolute spleen weights in that group.  There were no significant changes in specific activity to sRBC cells in the AFC plaque assay.  Total spleen activity was non-significantly elevated in all linuron groups compared to concurrent controls.  AFC positive control suppressed specific activity and total spleen activity to sRBC’s to unquantifiable levels.  Natural killer cell activity did not change systematically with dose.  Positive controls reduced activity to less than 50% of untreated controls.  Study is acceptable, with no adverse effects.  Aldous, 6/19/13.

ENDOCRINE DISRUPTOR STUDIES

There is no study of this type on file.
SUPPLEMENTAL STUDIES


0132; 285961: “Linuron- Substance Technical Code Hoe 002810 OH ZD96 0003 Testing for Subchronic Inhalation Toxicity (21 Applications within 29 Days) in Male and Female Wistar Rats” (Hofmann, T., Pharma Research Toxicology and Pathology, Hoechst Aktiengesellschaft, Frankfurt am Main, Laboratory Project ID 86.0892, Study No. 874, 04/14/1989). Linuron, technical substance (Code: Hoe 002810 OH ZD96 0003, Batch: CO 226-1690, purity = 94.6%) was aerosolized (dust aerosol) and administered in a nose-only manner to 15 Wistar (Hoe: WISKf(SPF71)) rats per sex per dose (except for the low-dose where 10 animals per sex were used) at dose levels (mean gravimetric concentrations) of 0 (air only), 0.013, 0.070, and 0.35 mg/L (mean (range) MMADs of 4.2 (3.3-5.0), 4.0 (3.3-4.7), and 4.7 (3.8-5.4) μm, respectively) for 6 hours per day 5 days per week for a 29-day period (21 exposures). 10 animals per sex per dose were sacrificed after 29 days of treatment; the remaining 5 animals per sex per dose (no low-dose animals) were sacrificed following a recovery period of 29 days. No deaths occurred during the study. No clinical signs were reported at mean gravimetric concentrations of 0.013 and 0.070 mg/l. At the 0.35 mg/l concentration, the animals exhibited uncoordinated gait and ruffled fur (in males from day 13 and in females from day 12 of the study); no clinical signs were reported during the recovery period. A treatment-related decrease in mean body weight was observed in males at the high-dose (0.35 mg/L); this effect was not observed in the 0.35 mg/L recovery group animals. No treatment-related effects on mean female body weight or on mean food consumption in either sex were observed. Hematological investigations revealed a treatment-related decrease in the mean erythrocyte level and a treatment-related increase the mean reticulocyte level in both sexes at the 0.35 mg/L dose level; these effects were not observed in the recovery group animals. Serum chemistry investigations revealed treatment-related increases in mean total bilirubin, mean total lipids, and mean alanine aminotransferase levels in both sexes at 0.35 mg/L, a treatment-related increase in the mean aspartate aminotransferase level in females at 0.35 mg/L, and a treatment-related decrease in the mean glucose level in both sexes at 0.070 and 0.35 mg/L; none of these effects were observed in the recovery group animals. Urinalysis revealed no treatment-related effects. A treatment-related increase in mean relative liver weight was observed in females at 0.35 mg/L; this effect was not observed in the recovery group animals. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. Possible adverse effect indicated: uncoordinated gait in high-dose animals. NOEL (M/F) = 0.070 mg/L based on increases in mean relative liver weight, and mean reticulocyte, mean total bilirubin, mean total lipids, and mean alanine aminotransferase levels, and decreases in mean erythrocyte and mean glucose levels. Supplemental study (the animals were treated for 29 days rather than the guideline-required 90 days). (Corlett and Leung, 08/20/2015)