

US EPA ARCHIVE DOCUMENT



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: California Department of Food and Agriculture - EPA Toxicology Review for Diuron (Tox. Chem # 410)

FROM: K. Clark Swentzel *K. Clark Swentzel 2/7/89*
Acting Section Head
Toxicology Branch 2 (HFASB)
HED(TS-769C)

THRU: Marcia van Gemert, Ph.D. *Marcia van Gemert 2/7/89*
Acting Branch Chief
Toxicology Branch 2 (HFASB)
HED(TS-769C)

TO: William Burnam, Acting Division Director
Health Effects Division (TS-769C)

The following responses are provided for each specific deficiency identified by the Medical Toxicology Branch of the California Department of Food and Agriculture:

1/ Study Type: Two-year feeding/oncogenic study - rat. October 29, 1985.

Deficiencies: Additional details on ophthalmology and histology methods are needed. No NOEL was obtained.

EPA Response: There is no information in the Toxicology Branch files to indicate that this study was evaluated by the Agency. EPA previously evaluated a 2-year feeding/oncogenicity study in rats (MRID # 00017764, 7/30/64) which was classified core-minimum for chronic toxicity and core-supplementary for oncogenicity.

2/ Study Type: Two-year feeding/oncogenic study - rat. MRID No. 00017764. July 30, 1964.

Deficiency: Inadequate No. of animals at risk

EPA Response: Current guidelines recommend 50/sex/group. The study used 35/sex/group; this is not a major deficiency.

Deficiency: No serum chemistry

EPA Response: TB considers this to be a major deficiency which compromises the study.

WFB

Deficiency: No analysis of diet

EPA Response: This deficiency does not compromise the study. Evidence of compound ingestion included dose-related adverse effects and compound residue levels, measured in urine, feces, muscle, fat, spleen, liver, kidney and blood, which increased in proportion to dosage levels. The NOEL and LEL were, respectively, 6.25 and 12.5 mg/kg based primarily on depressed RBC parameters.

Deficiency: Incomplete histopathology

EPA Response: Although all guideline tissues were not examined, the major organs were included in the examination. These included brain, lungs, heart, liver, spleen, pancreas, kidney, urinary bladder, adrenals, gonads, stomach, large and small intestine, muscle, thyroid gland, femoral bone marrow. TB does not consider this a major deficiency.

Deficiency: Inconsistent sites for harvest of marrow

EPA Response: TB does not consider this a major deficiency. This represents poor laboratory procedure in a supplemental investigation.

Conclusion: Concur with CDFA (data gap for chronic toxicity: primarily because serum chemistry investigations were not included). The Agency previously concluded that this study represents a data gap for oncogenicity.

It should be noted that a recent 2-year chronic toxicity/oncogenicity study in rats has been submitted to the Agency (MRID Nos. 40886501 & 40886502).

Core-classification: Oncogenicity: supplementary (no change)
Chronic toxicity: supplementary (change: previously minimum)

3/ Study Type: Chronic Feeding Study (2-year) - dog. Acc. # 00017763.
July 30, 1964.

Deficiencies: No analysis of diet and no food consumption data.

EPA Response: These deficiencies do not compromise the study since there is adequate evidence of compound ingestion. Dose-related adverse effects were observed. Additionally, compound residue levels, measured in urine, feces, muscle, fat, liver, kidney, spleen and blood, increased in proportion to dosage levels. The NOEL and LEL were, respectively, 0.625 and 3.13 mg/kg (based on abnormal blood pigments). Adverse effects observed at 31.25 mg/kg (HDT) included body weight loss, depressed RBC counts, increased erythrocytic activity in bone marrow, increased liver weight and increased pigment deposition in hepatocytes.

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Deficiency: No ophthalmology examinations

EPA Response: TB agrees that this is a deficiency, however, the rejection of a 2-year dog study, which clearly demonstrated a NOEL, LEL and target organ, is not justified on the basis of this one deficiency.

Conclusion: Non-concur with CDFA (no data gap)

Core classification: minimum (no change)

4/ Study Type: Oncogenicity study - mice

Deficiency: No study on file

EPA Response: CDFA is correct. The 1983 Registration Standard indicated that this study is required.

Conclusion: EPA has independently concluded that an oncogenicity study in mice is required.

Core-classification: not applicable

5/ Study Type: Three-generation reproduction - rat. July 30, 1964.

Deficiencies: No analysis of diet, no food consumption data, single dose administered, inadequate number of pregnant animals, parental animals were not necropsied.

EPA Response: It is TB's opinion that the most serious deficiency was the administration of only 1 dose level (125 ppm) which was predictably ineffective for inducing systemic toxicity in parental generations (ie. LELs in 3-month and 42-day rat studies were 500 and 2,000 ppm, respectively). The only adverse effect from the single dose (125 ppm; 6.25 mg/kg) administered was growth inhibition in the F1a, F2b and F3a offspring, however, this effect was not observed in a second study in which the same dosage level was given. No adverse systemic effects on F1 parental generations were noted in either study.

Conclusion: Concur with CDFA (data gap)

Core-classification: supplementary (change: previously minimum based on ADI Committee report)

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CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DIURON

SB 950-018, Tolerance # 106

December 8, 1986
Revised 8/24/87, 7/12/88

I. DATA GAP STATUS

- Combined (chronic + oncogenicity) rat: Data gap, inadequate study, possible adverse effect indicated
- Chronic dog: Data gap, inadequate study, possible adverse effect indicated
- Oncogenicity, mouse: Data gap, no study on file
- Reproduction rat: Data gap, inadequate study, no adverse effect indicated
- Teratology rat: No data gap, no adverse effect
- Teratology rabbit: No data gap, no adverse effect
- Gene mutation: No data gap, no adverse effect
- Chromosome: No data gap, possible adverse effect
- DNA damage: No data gap, no adverse effect
- Neurotoxicity: Not required at this time

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name T880712

Charles N. Adams
July 12, 1988
J. Parker
7-14-88

II. TOXICOLOGY SUMMARY

012 EPA Registration Standard, September 30, 1983.

COMBINED (CHRONIC + ONCOGENICITY) RAT

035 064725 "Diuron: Study for chronic toxicity and carcinogenicity with Wistar rats (Administration in diet for up to two years)". Institute of Toxicology, Bayer AG, Wuppertal, 10/29/85 (original German report), English translation, 7/14/86. Diuron, 98.7% purity, in feed of Wistar rats for 2 years. Levels of 0, 25, 250, and 2500 ppm for 50 rats/sex/treatment. No NOEL was obtained in this study; hematology parameters (RBC count, Hct, Hgb) and increased reticulocyte count, suggestive of hemolytic anemia (LEL in F = 25 ppm), further substantiated by hemosiderin deposition in spleen and splenic enlargement (LEL in M and F = 25 ppm). Increased erythropoiesis in bone marrow and related signs at higher doses. Transitional epithelial cell carcinomas, especially in urinary bladder, in both sexes at 2500 ppm only. Epithelial cell tumors in renal pelvises of three 2500 males were probably also treatment-related. Marked hyperplasia in bladder and renal epithelium at 2500 ppm in M and F, also to a lesser extent in F at 250 ppm. Erythrocyte and tumor effects constitute possible adverse effects. Report not acceptable, but upgradeable (additional details on ophthalmology and histology methods are needed). Note the related study (034:065390, Bayer AG study T 7018927, 8/1/86), which establishes a NOEL of 10 ppm for hematological effects. This 10 ppm NOEL is an appropriate value for non-oncogenic chronic effects. C. Aldous, 7/8/88.

034 065390 (Subchronic study ancillary to combined study 035:064725) "Diuron: Toxicological study with Wistar rats paying special attention to effects on the blood (Administration in diet for six months)". Institute of Toxicology, Bayer AG, Wuppertal, 8/1/86 (original German report), English translation, 3/27/87. 10 Wistar rats/sex/dosage at 0, 4, 10, and 25 ppm Diuron (98.8%) in diet for 6 months. NOEL = 10 ppm (minor hematological changes, especially in females: increased iron pigment deposition in both sexes at 25 ppm). These data allow a NOEL of 10 ppm for non-oncogenic effects in the associated rat combined study 035:064725. C. Aldous, 7/11/88.

016 036189 to -91, "Chronic Feeding Studies of Diuron in Rats", (Univ. of Rochester School of Medicine and Dentistry, NY, 7/30/64). Two lots of Diuron, 80% a.i., no analysis included; fed to 35/sex/group for 2 years at 0, 25, 125, 250 or 2500 ppm. Decreased body weight gains in 250 and 2500 ppm groups; possible adverse effects of decreased hemoglobin, hematocrit, and erythrocyte counts with associated extramedullary hematopoiesis in the 250 and 2500 ppm females. NOEL = 125 ppm. Unacceptable, not upgradeable (inadequate number of animals at risk, no serum chemistry, no analysis of diet, incomplete histopathology, inconsistent sites for harvest of marrow.) (Martz 12/10/85)

EPA 1-liner: No CORE grade. Systemic NOEL = 25 ppm (slight anemia, enlarged spleens, increased erythrogenic activity in bone marrow and abnormal pigments in the blood.) NOTE: 1983 EPA Reregistration Guidance Document indicates that rodent chronic study data requirement is filled, citing this reference.

001 014740, "Oral Toxicity and Metabolism of Diuron (N-(3,4-Dichlorophenyl)-N,N'-dimethylurea) in Rats and Dogs", (University of Rochester School of Medicine and Dentistry.) Publication: Food Cosmet. Toxicol. 5: 513-531 (1967). Appears to be the same data as in 036189 above.

018 036196, 036201 and 036202 Summaries of 036189 - 91.

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036189
CMA 7/12/85

CHRONIC DOG

017 036195 "Chronic Feeding Studies of Diuron in Dogs", (Univ. of Rochester School of Medicine and Dentistry, NY, 7/30/64). Diuron, two lots, 80% WP (nominal); 3/sex/group Beagle dogs, except no females at 25 ppm, age not given, were fed 0, 25, 125, 250 or 2500/1250 ppm (high dose was 1250 ppm from week 3 onward) in the diet for two years. No analysis of diet provided; diets prepared weekly. Possible adverse effects include significant decreases in RBC, HGB and HCT in mid- and high-dose males and females, increased liver weight in high dose males, erythroid hyperplasia in marrow and hemosiderin accumulation in reticuloendothelial cells in high dose males and females. Unacceptable, not upgradeable (lack of diet analysis for content and stability under use conditions, no food consumption - both of which prevent determination of actual compound intake for establishment of a NOEL, no ophthalmology exams, other deficiencies as indicated in review by F. Martz. (Martz 12/9/85, C. Aldous 7/11/88).
EPA 1-liner: No CORE grade. Systemic NOEL = 25 ppm (abnormal pigments in the blood.) NOTE: 1983 EPA Reregistration Guidance Document indicates that the dog chronic study data requirement is filled, citing this reference.

018 036200 An interpretative summary of 017:036195, above.

001, 003 041964 Same study as 036195, published in Food Cosmet. Toxicol. 5: 513-531 (1967). J. Schreider noted "insufficient information for assessment", 3/1/85.

ONCOGENICITY RAT

See under Combined Rat above.

ONCOGENICITY MOUSE

No study on file. Such a study is required by EPA, as indicated in the 1983 EPA Reregistration Guidance Document.

REPRODUCTION RAT

016 036192, -93, -97 and -98, "Reproduction Study in Rats Fed Diuron (and Second Reproduction Study in Rats Fed Diuron", (Univ. of Rochester School of Medicine and Dentistry, 7/30/64). Two lots of Diuron, 80%, were fed to 8 males/16 females per group at 0 or 125 ppm. Two studies were performed with the same numbers of animals. No adverse reproductive effect reported in the repeat study but postweaning growth retardation was noted in the first one. The reason for the difference remains undetermined. NOEL cannot be determined because of deficiencies in the reports. Unacceptable, not upgradeable (no analysis of diet, no food consumption, single dose, inadequate number of pregnant animals, parental animals were not necropsied.) (Martz 12/10/85)
EPA 1-liners: No CORE grades. Reproductive NOEL > 125 ppm (single dose tested). In the first study, systemic NOEL < 125 ppm (body weight depression observed at F2b and F3a litters). Systemic NOEL in second > 125 ppm. NOTE: 1983 EPA Reregistration Guidance Document indicates that this study fills the rat reproduction study data requirement.

001 038724 Summary in publication of 036192 and associated records, above. Hodge, H. C. et. al., Food Cosmet. Toxicol. 5: 513-531 (1967).

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TERATOGENICITY RAT

**025 051033, "Developmental Toxicity Study of H-16035 Administered by Gavage to Rats", (Argus Research Laboratories, Inc., Horsham, PA., # HLO 410-86, 6/16/86), H-16035 (diuron) 99.0%, purity and stability contained in sponsor's records; administered in aqueous 0.5% hydroxypropyl methylcellulose by gavage at 0, 16, 80, or 400 mg/kg/day, 25 mated females/group, on days 6 through 15 of gestation (day 0 = sperm and/or plug). Reduced feed consumption, reduced maternal body weight and body weight gain at 80 and 400 mg/kg/day. Reduced fetal body weight and delayed ossification at 400 mg/kg/day. No adverse developmental effects. NOEL (maternal) = 16 mg/kg/day, (developmental) = 80 mg/kg/day. Acceptable. (Carlisle 7/24/87)

001, 020 036209, "Teratogenicity Studies on Pesticidal Formulations of Dimethoate, Diuron and Lindane in Rats", (Publication: Bull. Envir. Contam. Toxicol. 22: 522-529 (1979) by Khera, K. S. et al.). Karmex containing 80% diuron, given in corn oil to 20 female Wistar rats per group by oral gavage, days 6 to 15 of gestation, at 0, 125, 250 or 500 mg/kg/day. Unacceptable, upgradeable (lacking in methods and data). Apparent NOEL < 125 mg/kg. Fetal weight was reduced in the high dose group and wavy ribs were noted in the mid- and high-dose groups. The incidence in the controls was 3 and 7 in each of the mid- and high-dose groups. The number of fetuses examined for skeletal findings was 2/3's of the total number but the actual figure is not given. The number of all fetuses was 199, 164 and 147 in the control, mid- and high-dose groups. No individual data is included for evaluation. Apparent maternal NOEL = 250 (reduced body weight.) (Schreider 3/1/85, Martz 12/10/85)

NOTE: Dr. Schreider noted "possible adverse effect" (effects of possible "borderline significance"), however both he and Martz noted "insufficient information for assessment" or "information supplementary only". The subsequent submission of an acceptable study (025:051033, above), which demonstrated that developmental effects were not observed until a definitively maternally toxic dose was achieved, removes concerns about developmental toxicity in this study. (C. Aldous, 7/12/88)

EPA 1-liner: Supplementary. Teratogenic NOEL > 500 mg/kg (HDT). Fetotoxic NOEL < 125 mg/kg (developmental toxicity).

TERATOGENICITY, MOUSE

003, 020 036208, "Teratogenicity of Pesticides". Chapter 8. Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health. US EPA, December, 1969. (Publication, 1969). Only data are in Table 3 in which diuron is stated to be negative in 6 litters at 215 mg/kg. Unacceptable. (Schreider 3/4/85, Martz 11/25/85)

TERATOGENICITY, RABBIT

**026 51034, "Developmental Toxicity Study of H-16035 Administered by Gavage to New Zealand White Rabbits", (Argus Research Laboratories, Inc., Horsham, PA., # HLO-332-86, 5/6/86), H-16035 (diuron) 99.0%, in aqueous 0.5% hydroxypropyl methylcellulose administered by gavage on days 7 through 19 of gestation to artificially-inseminated females, 23, 24 or 25/group, at 0, 2, 10, or 50 mg/kg/day. Maternal toxicity (decreased feed consumption and weight gains and 1 abortion) at 50 mg/kg/day. No adverse developmental effects. NOEL (maternal) = 10 mg/kg/day, (developmental) > 50 mg/kg/day. Acceptable. (J. Carlisle, 7/24/87)

Handwritten notes: CCA 7/12/89, with initials and a large number 7.

MUTAGENICITY, GNMU

Microbial Systems

**019, 013 036206, "Mutagenicity Evaluation in Salmonella typhimurium", (Haskell Lab, Report No. 471-84, 11/9/84) Diuron, 98%; tested in Salmonella strains TA1535, TA97, TA98 and TA100 with rat liver activation at 0, 10, 25, 50, 100 or 250 ug/plate and without activation at 0, 0.5, 1, 2.5, 5 or 10 ug/plate in duplicate, two trials; no increase in reversion rate reported; cytotoxicity with TA1535; acceptable. (Schreider 3/1/85, Remsen (Gee) 12/16/85)

Mammalian cells

** 019 036204, "Mutagenicity Evaluation of Diuron in the CHO/HGPRT Assay", (Haskell Labs, Report No. 282-85, 6/28/85.), Diuron, 98.19%; tested in CHO cells at 0, 0.01, 0.5, 1.0, 1.125, 1.25 or 0.5 mM; 18-20 hours without activation, 5 hours with rat liver activation; duplicates, 3 trials; no increase in mutation frequency. Acceptable. (Remsen (Gee) 12/11/85)

MUTAGENICITY, CHROMOSOME

** 019 036205, "In vivo Assay of Diuron for Chromosome Aberrations in Rat Bone Marrow Cells". Haskell Labs, Report No. 366-85, 6/26/85. Sprague-Dawley rats. Diuron, 98.19%, given by oral gavage in a single dose of 0, 50, 500 or 5000 mg/kg to 15/sex/group; 5/sex/group were sacrificed at 6, 24 or 48 hours; 50 metaphases per rat scored; at high dose, weight loss, mitotic index decreased and average number of aberrations increased in the 48-hour sampling - no difference at 6 hours, questionable effect at 24 hours. Acceptable. (J. Remsen (Gee) 12/11/85)

MUTAGENICITY, DNA/OTHER

**019, 025 036207, 051032, "Assessment of Diuron in the In vitro Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes", (Haskell Labs, Report No. 349-85, 7/10/85), diuron technical 98.19%, lot # T-50906; dissolved in DMSO and tested at 0, 0.001, 0.010, 0.1, 0.33, 1.0, or 20 mM with 5x10⁵ rat hepatocytes/well, 6 wells/plate/dose; 2 trials; positive control DMBA. Cytotoxicity at 0.33 mM and above with a decrease in cytoplasmic grain counts and an increase in nuclear grain counts. No UDS reported. Initially reviewed by J. Remsen (Gee), 12/11/85 as unacceptable with insufficient information to assess. Re-reviewed by J. Carlisle, 7/24/87. Additional information (025 051032) led to change in status to acceptable with no adverse effects.

NEUROTOXICITY

Not required at this time.

J. Carlisle 7-4-87
Coca 7/12/87