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

JUN 13 1985

MEMORANDUM

Releasable

OFFICE OF PESTICIDES AND TOXIC SUBSTANCE

SUBJECT: Toxicological assessment of alternatives to linuron by crop.

TO: Ingrid Sunzenauer, Review Manager
Special Review Branch (TS-767C) Caswell 528

and

Robert Taylor, PM #25
Registration Division (TS-767C)

FROM: for Charles N. Aldous, Ph.D. James N. Rowe 6/12/85
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THRU:

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ACTION REQUESTED: The more practicable alternatives to linuron were to be evaluated for toxicity according to information in the Toxicology Branch "One-liners". It is understood that some studies may not have been reported in the "One-liners", so that the studies reported in the following summary may not contain all available information on the chemicals of consideration.

RECOMMENDATIONS: The reported toxic effects are given below, grouped according to crop uses.

SOYBEANS:

Pre-emergent:

1. METRIBUZIN: A "guideline" mouse oncogenic study was negative at 3200 ppm. No chronic/onco rat study exists. A 2 year dog feeding study found weight reduction, increased mortality, hematological changes, liver and kidney damage at the HDT of 1500 ppm. A systemic LEL of 500 ppm was observed in dogs in a 90 day study (lesion(s) not defined). Systemic LEL values of 500 and 60

ppm were obtained in two 90-day rat feeding studies; lesions were not defined. One acceptable teratology study has been reviewed: no terata were observed in rabbits at the HDT of 135 mg/kg/day in a study which found maternal and fetal toxicity LEL values of 45 mg/kg/day.

SOYBEANS (Continued):

2. DINOSEB: The only data for Dinoseb in the one-liners are several acute studies, all of which are Supplementary or Invalid data. It is known to be an uncoupler of mitochondrial oxidative phosphorylation. Dinoseb was fed to adult rats(0, 75, 150, 225, and 300 ppm for 11 weeks) in a male reproductive study. Dose-related effects on reproductive ability and the testes(atypical spermatozoa, spermatids, spermatogonia, oligospermia,etc.) were noted. An LEL of 225 ppm was determined (based on testicular changes) with a NOEL of 75 ppm(Arch. Environ. Contam. Toxicol. 11:475-485, 1982).

Early Postemergent:

1. DINOSEB: (See above).

Post-emergent:

1. ACIFLUORFEN(Blazer®, Tackle®): 1) Blazer®- NOEL of 60 mg/kg established in rabbit teratology study for both maternal and fetal toxicity. NOEL of 540 ppm(HDT) determined for 3-generation reproduction/teratology study in rats. In a guideline 2 year feeding study in dogs a NOEL of 50 ppm and a LEL of 300 ppm (blood coagulation effects) were determined. A lifetime oncogenic / feeding study in mice was negative for oncogenic effects at 1080 ppm(HDT) and a systemic NOEL of 45 ppm, LEL of 270 ppm (stat. sign. SGOT-SGPT seen at 12 months). A lifetime oncogenic/feeding study in rats was negative for oncogenic effects at 1080 ppm(HDT) and had a systemic NOEL of 90 ppm. A supplementary 24- month feeding/oncogenic study in mice revealed oncogenicity(hepatocellular adenomas/ carcinomas) at 270/1.5 ppm(HDT) but not at 45 or 7.5 ppm (1.5 ppm changed to 270 ppm diet on week 17). Acute oral dermal and inhalation tests indicate a Category III-IV compound and Category I for primary eye irritation. 2) Tackle®- Maternal and fetotoxic NOEL's of> 36 mg/kg/day(HDT) was determined in a rabbit teratology study (gavage) . A guideline teratology study in rats (gavage) produced a maternal NOEL of 90mg/kg/day and a fetotoxic NOEL of 20 mg/kg/day (LDT) as well as a teratogenic NOEL> 180 mg/kg/day (HDT). Two 90 day feeding studies in rats and mice produced NOEL's of 320 ppm with LELs of 1250 ppm (liver cell hypertrophy, fatty infiltration of liver, resp.). An 18 month feeding /onco study in mice resulted in liver tumors at all doses tested (625, 1250, 2500 ppm) in males and 2500 ppm(HDT) in females. A two year feeding/onco study in rats was negative for oncogenic effects at 5000 ppm (HDT) and a systemic LEL of 2500 ppm (elevated BUN and creatinine in males and females; nephritis and pylonephritis of kidneys in males) was observed. A 2 year feeding study in dogs noted a NOEL of 20 ppm(LDT) and LEL of 300

ppm (increased leukocyte count and platelet count in males; calcium, cholesterol and creatinine decreased in females). Tackle® was reported negative in mutagenicity studies (rat UDS, rat bone marrow and rat dominant lethal, somatic reversions in Drosophila) but positive in Drosophila Y-chromosome loss and dominant lethal mutations and in yeast genetic recombination studies(with/without met.activ.). Acute oral, dermal and inhalation toxicity were Category III while primary eye irritation was Category I and primary dermal irritation was Category II.

2. BENTAZON: This compound has a small data base. No acceptable chronic or oncogenicity studies are available. Subchronic rat and dog studies suggest modest toxicity (LELs of 200 and 300 ppm, respectively). Testicular degeneration in 2 out of 20 rats at 200 ppm was the basis of the LEL determination. Because there were no such findings at the next dose (800 ppm), the testicular lesions might be artifactual, however the registrant(s) have not yet presented acceptable 90-day or chronic studies to resolve the issue. No acceptable mutagenicity tests have been submitted to date.

Teratology studies submitted to date have been inadequate, however one rat study found teratogenic effects at 200 mg/kg/day (curved, thickened, and shortened extremities). Runting and anasarca were also observed at that level. Another rat teratogenicity study was negative at the same dose level. A rabbit teratology study was negative at the maximum dose of 150 mg/kg/day. One 3-generation study (supplementary) was submitted in which the highest dose was 180 ppm, apparently below the toxic threshold for the compound.

CORN:

Pre-emergent:

1. ATRAZINE: No interpretable rodent feeding/oncogenicity studies were found in 1-liners. A dog 2-year feeding study, although not fully acceptable, found the following systemic toxicity at the HDT (1500 ppm): reduced food intake, decreased body weight, reduced hemoglobin and hematocrit values. An acceptable rat teratology study was negative at the HDT of 1000 mg/kg.

2. SIMAZINE: The data base for simazine is scant. No acceptable chronic or 90-day subchronic tests have been reviewed. No teratogenicity studies have been reported, however one acceptable rat reproduction study has been performed, which indicated a NOEL > 100 ppm. No mutagenicity tests were found. Metabolism studies suggest that test material is not retained long in the body, and is excreted in urine and feces. The disposition of ingested test material is not well understood.

3. PENDIMETHALIN: An LEL of 50 mg/kg/day caused the following in a 2-year dog study: "increase in serum alkaline phosphatase and increased liver weight, hepatic lesions". The NOEL was 12.5 ppm. No valid onco studies are available. A rat teratology study found no terata nor fetotoxicity at the HDT of

500 mg/kg/day. A rabbit teratology study found no effects at the HDT of 60 mg/kg/day. A rabbit pilot study had found maternal deaths and resorptions at 125 mg/kg/day. A rat 3-generation study found reduced litter size, reduced survival index, and reduced pup weights at 5000 ppm, so that the NOEL was 500 ppm.

Post-emergent:

1. AMETRYNE: No valid and core-graded studies exist other than acutes. Existing data do not allow for an evaluation of toxicity. Subchronic studies in dog and rat indicate NOELs of 100-1000 ppm. One rat teratology study has a NOEL of 100 ppm.

2. DICAMBA: The only study other than a series of acutes on dicamba is a 90-day rat feeding study. In that study, the NOEL was 500 ppm and the LEL was 800 ppm ("slight liver cell necrosis and cytoplasmic vacuolization").

3. 2,4-D: This compound has been widely used for many years. The data base is incomplete. Additional chronic/oncogenicity studies are being generated currently in response to a recent "data call in".

One teratology study found no teratogenesis at 75 mg/kg (HDT), and delayed ossification at the same dose. A rat reproduction study which was not core-graded found 2,4-D to be "equivocally positive for reduced viability to weanlings at 100 ppm (5 mg/kg)". No other reproduction/teratology studies were acceptable for regulatory purposes.

Two-year dog and rat feeding studies (not core graded) found NOELs of 500 and 1250 ppm, respectively. A supplementary 90-day rat feeding study found "histopathological changes in renal cortical tubules and increased thyroid weight" with a NOEL of < 1 mg/kg.

4. BENTAZON: (See under Soybeans, Post-emergent).

SORGHUM:

Pre-plant Incorporated:

1. TERBUTRYN: This compound was positive in a 2-year rat feeding/ oncogenicity study at 3000 ppm, as follows: Significant increases in thyroid follicular adenomas, mammary gland adenomas and liver adenomas. Borderline statistical significance was found for testicular interstitial cell adenomas. The compound was negative in mice up to 3000 ppm in an oncogenicity study.

Rat teratology studies found no terata up to the HDT of 250 mg/kg/day. A 3-generation rat reproduction study found decreased fertility and decreased body weight gain of both sexes at the HDT of 3000 ppm. A 6-month dog study found increased salivation and agitation at 25 mg/kg/day.

Pre-emergent:

1. ALACHLOR: The recent Alachlor Special Review Position Document 1, quoted in part in this section, indicates that "The Agency has determined that the weight of evidence demonstrates that alachlor is oncogenic to laboratory animals and, it is prudent to treat alachlor as a probable human carcinogen." Dose-related nasal turbinate adenomas were observed in rats of both sexes at dose levels of 42 and 126 mg/kg/day. Rare malignant stomach tumors, most notably mixed carcinomasarcomas, were observed in rats of both sexes fed 126 mg/kg/day and in one female at 42 mg/kg/day. Thyroid follicular tumors (adenomas plus carcinomas) appeared in both sexes at 126 mg/kg/day, and were significantly increased in males. In a second rat study a rare stomach tumor (an undifferentiated sarcoma) was reported in a male at 2.5 mg/kg/day and was judged to be biologically significant. Increased bronchioalveolar tumors were also observed in CD-1 mice fed 260 mg/kg/day alachlor. The presence of epichlorohydrin in the technical material as a stabilizer in the first rat study and in the mouse study may have contributed to the oncogenic responses, but is not likely to to be the sole contributor, as significant nasal turbinate adenomas were observed in the rat study which did not employ epichlorohydrin, also the same study reported the rare aformentioned stomach undifferentiated sarcoma at 2.5 mg/kg/day.

In addition to oncogenic problems, alachlor causes an ocular lesion termed uveal degeneration syndrome. This disease is characterized by free floating pigments derived from the iris or choroid layers, or in severe cases, by degeneration of the iris, diminution of the size of the ocular globe, and secondary cataract formation. The LEL for uveal degeneration syndrome in chronic rat studies was found to be 15 mg/kg/day.

A 3-generation rat reproduction study found an LEL of 30 mg/kg/day, with renal toxicity observed in F_2 adult males and F_3 pups (kidney discoloration, chronic nephritis, and increased relative and absolute kidney weights). A rat teratology study found no teratogenic potential at the maximum dose of 400 mg/kg/day.

2. PROPAZINE: A positive oncogenic response was obtained in rats at 1000 ppm in a two-year feeding/oncogenic study (increase in mammary tumors). Significant body weight decreases were observed at the lowest dose tested (3 ppm). A two-year mouse feeding/oncogenic study was negative to the HDT (3000 ppm) for oncogenicity, at which dose there was increased myocardial fibrosis and myocardial degeneration. An acceptable 3-generation rat reproduction study found a reproductive LEL of 1000 ppm (HDT, reduced mean pup body weights). The only teratology study on record, a rat study which did not meet Core acceptability standards, found no teratogenic effects at the HDT of 600 mg/kg.

2. METOLACHLOR: Acceptable teratology studies found no teratogenic or fetotoxic effects at dose levels up to 360 mg/kg/day in rats and rabbits (HDTs). Respective maternal NOELs were 360 and 120 mg/kg. An acceptable 2-generation reproduction study

found the reproductive NOEL of 300 ppm (reduced pup weights and reduced parental food consumption at 1000 ppm). Oncogenic risk has been identified with metolachlor, as summarized on p. 61 of the Alachlor Special Review Position Document 1, part of which follows:

"Metolachlor has a fairly complete toxicology data base lacking only mutagenicity studies, and a Registration Standard was issued in 1979. Four studies examining the oncogenic potential of metolachlor have been submitted to the Agency. Two of these studies were in the Sprague-Dawley strain of rat and were found to be positive for the induction of neoplastic nodules in the liver at the highest tested dose level of 3000 ppm. The National Academy of Sciences (1980) has concluded that "the neoplastic nodule is a manifestation of the process of hepatocarcinogenesis...It is induced by a variety of hepatocarcinogens but not by noncarcinogenic agents." However, two mouse studies of metolachlor are considered to be negative with respect to oncogenic potential. The potential of metolachlor to cause cancer in laboratory animals, therefore, is substantially less clear than the weight of evidence on the carcinogenic potential of alachlor.

Based on the chronic rat study, the oncogenic potency of metolachlor (as indicated by the Q_1* of 2.1×10^{-3}) appears to be much less than that of alachlor. However, it is noted that the testing of these two compounds was conducted by different laboratories and used different strains of rats. The use patterns, dietary Theoretical Maximum Residue Contributions, applicator exposure patterns and potential for drinking water contamination appear to be similar for the two compounds."

SORGHUM (continued):

Post-emergent:

1. BROMOXYNIL: This substituted phenol contains a nitrile group, which can be cleaved inside the plant and inhibit oxidative phosphorylation. Both the presence of a nitrile and the phenol are potential mammalian toxicological concerns. The compound was found oncogenic in a mouse feeding/ oncogenicity study with a NOEL < 10 ppm. The combined incidence of adenomas and carcinomas in males showed a dose-related trend from the lowest (10 ppm) to the highest dose tested (100 ppm). An evaluation of incidence of total hepatocellular proliferative lesions in males found only the highest dose to be statistically significant compared to controls. Liver hyperplasia was observed in both sexes at the high dose, but was only statistically significant in females. A rat feeding/oncogenicity study, although not meeting EPA acceptance criteria, found no evidence of oncogenicity or systemic effects at the HDT of 100 ppm.

A rabbit teratology study found several teratogenic effects at the HDT of 60 mg/kg/day: hydrocephalus, microphthalmia, anophthalmia, and severe defects in ossification of the skull. A rat teratology study was negative for terata at the HDT of 35 mg/kg.

An acceptable rat reproduction study was negative for reproductive effects at the HDT of 300 ppm.

A battery of mutagenicity tests was performed, and three positive results were obtained:

1. Lymphoma forward mutation assay with metabolic activation.
2. In vitro chromosomal aberration assay (CHO) with metabolic
3. Bacterial DNA repair test with and without metabolic activation.

2. DICAMBA: (See under Corn, post-emergent).

3. 2,4-D: (See under Corn, post-emergent).

COTTON:

1. ACIFLUORFEN: (See under Soybeans, post-emergent).

2. METRIBUZIN: (See under Soybeans, pre-emergent).

3. CYANAZINE: Negative for oncogenicity in mice at the HDT of 1000 ppm. The systemic NOEL was < 10 ppm (LDT, decreased body weight in both sexes). Rat and dog chronic studies have been performed and no untoward effects were observed below 100 ppm (this dose caused reduced growth rates and liver weights in female dogs). The latter chronic studies were submitted in 1970, were not "Core Graded", and it is not known if they would meet present standards for EPA submissions. A 3-generation reproduction study reported no effects up to the HDT of 80 ppm. A rat teratology study found no terata nor fetotoxicity at the HDT of 30 mg/kg/day. A rabbit teratology study found increased post-implantation losses and decreased numbers of live fetuses per dam at 2 mg/kg, so that the the NOEL for fetotoxicity and/or teratogenicity would be 1 mg/kg/day The same study found increased incidence of anomalies at the HDT of 4 mg/kg/day, including 4 cases (2 litters) of domed head. From the available data, the fetotoxicity/teratology findings at 2 mg/kg/day dosage level are the findings of most immediate concern.

4. DIURON: Blood effects observed are similar to those of linuron. In a 2-year rat feeding/onco study, the following was reported at 125 ppm: "Slight anemia, enlarged spleens, increased erythrogenic activity in bone marrow and abnormal pigments in the blood". The systemic NOEL was 25 ppm. The oncogenic NOEL was > 2500 ppm (HDT). In a 2-year dog study, the systemic LEL was 125 ppm (abnormal pigments in the blood). The NOEL was 25 ppm. A 90-day rat study found growth retardation and methemoglobinemia at 500 ppm, so that the NOEL was 50 ppm. Additionally, a 42 day rat feeding study reported "decreased RBC counts and hemoglobin values in females". No reproductive effects were observed at the only dose tested of 125 ppm in a 3-generation rat study (this test could not meet EPA standards because of the design limitations). An 80% formulation was tested for teratogenicity in rats and found negative for terata at the HDT of 500 mg/kg/day. Some fetotoxicity was noted at 500 mg/kg/day, so that

the NOEL would be 125 mg/kg/day.

POTATOES:

1. METRIBUZIN: (See under soybeans, pre-emergent)

ASPARAGUS:

Over one year old root stocks:

1. METRIBUZIN: (See under soybeans, pre-emergent).

2. SIMAZINE: (See under corn, pre-emergent).

3. DIURON: (See under cotton).

4. CHLORAMBEN (Amiben): Technical material yielded no terata and was not maternally toxic to rats at the HDT of 4500 ppm. The fetotoxic LEL was 1500 ppm (delayed ossification). A 1966 era reproduction study (not core graded) determined the systemic and reproductive NOELs to be 4500 ppm (HDT). An acceptable 2-year dog feeding study determined the systemic NOEL to be > 10,000 ppm (250 mg/kg), the highest dose tested. A NCI carcinogenic bioassay of technical grade Chloramben was conducted in feed to Osborne-Mendel rats and B6C3F1 mice (10,000 or 20,000 ppm). The report states that in both male and female mice, the incidences of heptocellular carcinoma showed significant dose-related trends as compared to pooled controls and was classified as an animal carcinogen. This study is currently being audited by the Laboratory Data Integrity Program, EPA's OPTS.

The ammonium salt of amiben has been tested for teratogenic effects in rabbits, and the NOEL for terata could not be determined from the data due to the unsatisfactory health of the animals,e.g., coccidial infections, insignificant maternal weight gains, congested lungs, etc., and technical errors including faulty dosing period and mishandling of animals(gavage errors). In one study(dosage levels=0, 25, 50, 75 mg/kg), the maternal and fetotoxic NOEL's were < 25mg/kg, and in a second study (dosage levels=0, 10, 30, 60 mg/kg) the maternal NOEL was 10 mg/kg (based on body wts.) and the fetotoxic NOEL was < 10 mg/kg (increased skeletal variations).

Transplanted, first year:

(No alternatives available).

Directed seeded:

1. CHLORAMBEN: (See asparagus, over one year old).

RIGHTS OF WAY:

Pre-emergent:

1. SIMAZINE, ATRAZINE: (See under corn, pre-emergent).

Post-emergent:

1. DALAPON: No core-graded studies are listed. Major studies include one rat teratology study, 2 rat reproduction studies, a dog reproduction study, a 1-year dog feeding study, two 2-year rat chronic/onco studies and several subchronic feeding studies. No terata were found at the highest dose tested (1500 mg/kg/day). An old 3-generation rat study found a NOEL of 3000 ppm. The chronic dog study established a NOEL of 100 mg/kg. The lowest NOEL recorded for a 2-year rat feeding study was 300 ppm.

2. TRICHLOROACETIC ACID (TCA): The one-liner data consists only of 4 acute studies. Formulations containing 8.6% TCA presented low acute and dermal toxicity. Primary eye irritation testing found persistent (7 days minimum) corneal opacity. Primary dermal irritation studies found necrosis as might be expected of a protein denaturing agent.

3. PICLORAM (Tordon): An NCI "Report on Bioassay of Picloram for Possible Carcinogenicity" was published in the Federal Register Volume 43, No. 26, dated Feb. 7, 1978. A dose-related trend was observed in females for benign hepatic neoplastic nodules in the low (7,437 ppm) and high dose (14,875 ppm) groups. A memo from Dr. Louis Kasza dated May 1, 1980 states "We agree with NCI's conclusion: 'It is concluded that under the conditions of the bioassay, the findings are suggestive of the ability of the compound to induce benign tumors in the livers of female Osborne-Mendel rats'". To date, no valid feeding/oncogenic studies have been received from registrants and reviewed to either confirm or contradict the NCI findings. However, it is known that Picloram is contaminated with HCB, an animal carcinogen and teratogen (H. Spencer, Pers. comm.). Rat reproduction and teratology studies, although not acceptable under present EPA guidelines, do not suggest positive findings.

4. 2,4-D and DICAMBA : (See under corn, post-emergent).

CARROTS, PARSNIPS:

STODDARD SOLVENT(Sd.Sv.): (Information obtained from industry submissions to Chemical Screening Branch, Office of Toxic Substances; or Casarett and Doull ;1975). Five performance tests in 2 groups of 7 male humans(2 hr inhalation exposure; 625 mg/m^3 increased at 1/2 hr intervals to 1250, 1875, and 2500 mg/m^3) produced no effect(during exposure or after 7-day exposure-free period.) 8/14 men exposed to 400 mg/m^3 for 50 minutes produced prolonged reaction time and probably impairment of short term memory. A lifetime skin painting study(C3H/HeJ male mice;50 animals;positive control; solvent-cutback type rust preventive with 90.9% by vol. Sd. Sv., Ca soap and petroleum sulfonate, mixt. 6.6% by vol., ethylene glycol monobutyl ether, 2.5% by vol.) produced squamous cell carcinoma in 6/49 animals compared with 48/50(10% catalytically

cracked oil) and 0/50 in negative controls(white mineral oil). Pregnant rats (25/dose; 0,100, 400 ppm for 6 hrs/day, days 6-15 gestation) exposed via inhalation produced no adverse compound-related effects. Inhalation exposure of male rats (1,2,4 mg/l;3 ,8, and 13 wks; 6 hrs/day, 5/7 days/wk) resulted in a dose-dependent increase in incidence and severity of kidney regenerative tubular epithelium and tubular dilatation(only slightly increased at 1 mg/l). Dogs treated similarly with the same regimen and sacrificed at 13 weeks were not reported to differ significantly from controls. Ingestion may result in pneumonititis, pulmonary edema and hemorrhage of lungs. Dermatitis is the most common industrial problem associated with its use.

CELERY:

STODDARD SOLVENT: (See under carrots and parsnips).

PROMETRYN:

PROMETRYNE: A 2-year rat feeding/oncogenic study was performed on a formulation (50W). No systemic toxicity or oncogenic response was obtained up to 1250 ppm (HDT). A 2-year dog study was performed with another formulation (80W). In this case, degenerative changes in the liver and renal tubules, and bone marrow atrophy were observed at the HDT of 1500 ppm. The technical material was negative for teratogenesis in rats at the HDT of 250 mg/kg in an acceptable study.