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

TXR 006997

JUN 18 1984

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg# 241-ETG; Arsenal; New herbicide for non-cropland. Caswell #: 221G
Accession #: 251502, -503, -504

TO: Robert Taylor (PM#25)
Registration Division (TS-767)

and

Exposure Assessment Branch
Hazard Evaluation Divison (TS-769C)

FROM: William Dykstra, Ph.D. William Dykstra 5/15/84
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THRU: Christine F. Chaisson, Ph.D. C.F. Chaisson 6/18/84
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REQUESTED ACTION:

Review of submitted data in support of registration.

Recommendation:

1. The submitted studies are acceptable. The registration can be toxicologically supported provided that EAB can conclude that no groundwater contamination will result from use of the herbicide.

Review:

1. Toxicology studies contained in exhibits 1 thru 6 have been previously reviewed in 241-EUP-RNR.

2. Twenty-one day dermal toxicity study with AL 243, 997 in Rabbits (TPS study #18613-301-230-8; 8/8/83)

   Test Material: AL 243,997; Lot #AC4361-97; a beige powdery solid; 93% purity.

1

Randomized groups of 10 male and 10 female NZW rabbits received dermal applications on shaved skin (one half abraded) under an impervions cuff for 6 hours/day. Dosages were 0, 100, 200, and 400 mg/kg/day of test material for five days each week over a three week period. Criteria evaluated were toxic signs, mortality, body weight, food consumption, hematology, clinical chemistry, necropsy findings, organ weights and histopathology. Statistical evaluation of the data was with $P<0.05$ being significant.

Results:

No compound-related effects in toxic signs or mortality were noted. One male rabbit from the high-dose group died on day 13 and one male rabbit of the mid-dose group died on day 16. Both rabbits had gross findings suggestive of pneumonia.

Body weight and food consumption were unaffected by treatment. No compound-related effects in hematology and clinical chemistry values were evident.

Absolute and relative thyroid/parathyroid weights of mid-dose males were significantly lower than controls. However, these findings were not considered compound-related since high-dose values were comparable to control values.

No histopathological findings were present which were considered compound-related. Histologically, treated skin was comparable to untreated skin.

Conclusion:

The systemic NOEL is 400 mg/kg/day (HDT). The NOEL for skin lesions is 400 mg/kg/day (HDT).

Classification: Core Minimum Data

3. Twenty-one day dermal toxicity study with AC 252,925 in rabbits (TPS Study # 187B-301-230-83; 8/15/83)

Test Material: AC 252, 925; Lot #.: AC 4396-77; a greenish brown liquid; Arsenal formulation.

Randomized groups of 10 male and 10 female NZW rabbits received dermal applications on shaved skin (one-half abraded) under an impervious cuff for 6 hours/day. Dosages were 2 ml/kg of sterile saline (0), 25%, 50%, and 100% of test material for five days each week over a three week period.

2

Criteria evaluated were toxic signs, mortality, body weight, food consumption, hematology, clinical chemistry, necropsy findings, organ weights and histopathology.

Statistical evaluation of the data were performed with $p<0.05$ being significant.

Results:

Nine rabbits died during the study due to pneumonia; one control, 4 mid-dose and 4 high-dose rabbits. Decreased body weight and food consumption were present for high-dose male and female rabbits for a three day period ending on day six of the study. No treatment-related effects on body weight and food consumption were noted for the remainder of the study.

Increased platelets were observed at termination for mid- and high-dose female rabbits. Increased GGPT was observed for high-dose males at termination.

Necropsy findings were observed as an increased reddening, scaling, and crusting of treated skin in low-, mid-, and high-dose rabbits.

No compound-related effects on organ weights were noted.

Histopathological findings of treated skin confirmed the necropsy results. An increase in the incidence and severity of skin lesions were observed microscopically in a dose-related manner in treated skin.

Conclusion:

The systemic NOEL is 2 ml/kg of 25% test material. The LEL is increased platelets in mid-dose females. With respect to skin, a dose-related increase in incidence and severity of skin lesions was observed. No NOEL for skin lesions was established.

Classification: Core Minimum Data.

4. Teratology study in albino rats with AC 243,997 (Toxigenic's Study 450-1222; 9/9/83)

Test Material: AC 243,997; Lot #: AC 4361-97; 93% purity; light tan/beige powdery solid

Selection of dosage levels were based on a pilot study. Randomized groups of 25 mated female Sprague-Dawley rats

3

were orally gavaged with 0, 100, 300, and 1000 mg/kg/day of test material during days 6-15 of gestation. Toxic signs and maternal body weight were measured.

All maternal rats were sacrificed at day 20 of gestation and reproductive status was determined.

All fetuses were examined externally. Two-thirds of fetuses from each litter were examined for skeletal anomalies and the remaining fetuses were examined for visceral anomalies by the Wilson free-hand sectioning technique.

Statistical analysis of the data were performed.

Results:

The number of gravid females obtained from mating were 22, 24, 23 and 22 for the control, low, mid, and high-dose groups, respectively.

No deaths occurred during the study as a result of treatment with the test material. All rats assigned to the study survived to terminal sacrifice.

Salivation was observed in 6 of the 22 gravid females at the high-dose. No other toxic signs considered to be compound-related were noted.

No compound-related effect on maternal body weight was observed during the study.

At necropsy of maternal animals, no compound-related gross findings were observed.

No compound-related effect in corpora lutea, implantations, resorptions, and viable fetuses were observed. Additionally, no effects on sex ration of fetuses, crown-rump length or fetal body weight were observed.

With respect to external anomalies, incidental findings included 2 fetuses (2 litters) with hematoma in the controls. Also in controls was one fetus with micrognathia. Similar findings in test groups of hematomas were present and comparable to controls in numbers. Visceral examination showed one fetus with malpositioned stomach in the mid-dose litters.

The total number of fetuses/litter with abnormal skeletal findings were:

Controls	Number Fetuses	%	Numbers of Litters	%
Control	20/219	(9.1)	9/22	(40.9)
Low	12/238	(5.0)	6/24	(25.0)
Mid	15/222	(6.8)	9/23	(39.1)
High	7/197	(3.6)	5/22	(22.7)

Skeletal anomalies and variants as shown above demonstrated no dose-related or compound-related effects.

Conclusions:

The NOEL for teratogenicity and fetotoxicity is 1000 mg/kg/day .

The NOEL for maternal toxicity is 300 mg/kg/day and the LEL is 1000 mg/kg/day with salivation occuring in 6 of 22 females.

Classification: Core Minimum Data.

5. Teratology pilot study in albino rats with AC 243,997 (Toxigenic's Study 450-1221; 8/2/83)

Test Material: AC 243,997; Lot #: AC 4361-97; 93% purity; light tan/beige powdery solid.

Groups of 5 bred female Sprague-Dawley rats were orally dosed with test material at 0, 250, 500, 1000 or 2000 mg/kg/day during days 6-15 of gestation.

At day 20 of gestation, all females were sacrificed and reproductive status was recorded.

Results:

No deaths occurred in any groups. Toxic signs were present as salivation which occurred in 1/5 at 250 mg/kg/day, 2/5 at 500 mg/kg/day, 3/5 at 1000 mg/kg/day and 5/5 at 2000 mg/kg/day.

No compound-related effects were observed at necropsy.

5

No effects in corpora lutea, implantations, resorptions and viable fetuses were present which were considered compound-related.

Conclusion:

The results of the pilot study are adequate to determine dosage levels in the main teratology study.

Classification: Supplementary Data

6. Teratology Study in albino rabbits with AC 243,997 (Toxigenic's Study 450-1224; 9/21/83)

Test Material: AC 243,997; Lot #: AC 4361-97; 93% purity; light tan/beige powdery solid.

Selection of dosage levels were based on a pilot study. Groups of 18 mated NZW rabbits were orally gavaged with doses of 0, 25, 100 or 400 mg/kg/day of test material during days 6-18 of gestation.

Toxic signs and body weight were recorded during the study.

All females were sacrificed on gestation day 28 and reproductive status was assessed.

Fetuses were examined for external anomalies, weighed, and measured for crown-rump length.

Each fetus was examined for internal development, sexed, and eviscerated. Heads of approximately one-third fetuses/litter were fixed in Bouin's fixative and examined by serial sectioning.

The carcasses of these fetuses as well as all remaining fetuses per litter were examined for skeletal development employing a modified version of Hurley's method.

Statistical analyses of the data were performed with $p<0.05$ being significant.

Results:

The number of resulting pregnancies was 17, 18, and 16 and 17 for the control, low-, mid-, and high-dose groups, respectively.

Two control and two high-dose group rabbits died during the dosing period. Lung effects were noted for these does possibly as a result of gavage. The remaining rabbits survived to final sacrifice.

Body weight of treated does were comparable to controls when corrected for both with and without gravid uterus. Necropsy findings for these does showed primarily lung effects.

No compound-related effects were noted with respect to corpora lutea, implantation sites, early and late resorptions, and viable and dead-fetuses.

Fetal body weight data, sex-ratio, and fetal crown-rump length data did not demonstrate any compound-related effects.

Fetal external examination showed one low-dose fetus with a short tail. Four fetuses (three litters) of the high-dose had one with kinked tail, two with clubbed foot, and one with clubbed foot, spina bifida, and anurous. These findings are not considered compound-related.

With respect to fetal internal findings, a red cyst on the liver was noted for one control fetus and two fetuses (two litters) at the mid-dose. Other internal findings were also as uneventful. Fetal head evaluation showed one high-dose fetus with a malformed brain. No other anomalies were observed in the fetal head evaluation.

Fetal skeletal development did not show any compound-related anomalies or variants.

The total number of fetuses/litter with abnormal skeletal findings were as follows.

Dose	Number of Fetuses	%	Number of Litters	%
Control	2/100	1.9	2/13	15.4
Low	10/152	6.6	6/17	35.3
Mid	9/147	6.1	8/16	50.0
High	2/144	1.4	2/16	12.5

Clearly the data are not dose-related and therefore are not considered compound-related.

Conclusion:

The test material was not teratogenic or fetotoxic at dosages up to 400 mg/kg/day (HDT). The maternal toxic NOEL is also 400 mg/kg/day. However, based on the maternal toxicity noted in the pilot study, the dosages in this study have been properly chosen.

7

Classification: Core Minimum Data.

7. Teratology pilot study in albino rabbits with AC 243,977 (Toxigenic's study 450-1223; 8/2/83)

Test Material: AC 243,997; Lot #: AC 4361-97; 93% purity; light tan/beige powdery solid.

Groups of five bred female NZW rabbits were orally gavaged with 0, 250, 500, 1000 or 2000 mg/kg/day of test material during gestation days 6-18. Surviving animals were sacrificed at gestation day 28. Reproductive status of female rabbits was determined.

Results:

Two of the five 250 mg/kg/day group rabbits, 4 of the five 1000 mg/kg/day group rabbits, and all 5 of the 2000 mg/kg/day rabbits died before final sacrifice. Necropsy examination revealed stomach ulcers, and gastrointestinal lesions which can be considered compound-related.

Toxic signs and body weight data of surviving (day 28 of gestation) does were comparable between control and treated animals.

Corpora lutea, implantation sites, resorption sites and viable fetuses were comparable between control and treated surviving animals. Necropsy of surviving does revealed no compound-related lesions.

Conclusions:

Dosages used in this pilot study showed that at 1000 and 2000 mg/kg/day, maternal death resulted from exposure. The findings at 250 and 500 mg/kg/day showed that these doses are appropriate for the main teratology study.

Classification: Supplementary Data.

8. Bacterial/Microsome Reverse Mutation (Ames) Test on AC 243,997 (Cyanamid project # 0493; 6/17/83).

Test Material: AC 243,997; Lot #: AC4361-97; 93% purity positive controls: 2-nitrofluorene (2-NF), 9-aminoanthracene (2-AA), N-methyl-N-nitro-N-nitrosoguaridine (MNNG).

The assay employed both the plate and disc methods. S. typhimurium strains TA-98, TA-100, TA-1535, TA-1538 and E. coli WP-2-UVRA were used.

8

Dosages of test material were 0, 50, 158, 500, 1581 and 5000 (HDT) micrograms/plate both with and without S-9 metabolic activattion and 1000 micrograms/disc both with and without activation. The plate assay was conducted in triplicate twice to confirm initial results and the disc test was repeated to confirm initial results. Positive controls were used for each tester strain in the appropriate metabolic system at every assay.

Results:

The test material did not produce a mean number of revertants which was twice the number found on solvent control plates and no plate containing a disc impregnated with test material showed a ring of revertants around the disc. Positive controls showed the expected results which demonstrated the mutagenic assay was functional.

Conclusion:

AC 243,997 was not mutagenic in the Ames assay.

Classification: Acceptable.

9. Herbicide AC 243,997; the absorption, excretion, tissue residues and metabolism C^{14}-labeled AC 243,997 in the rat (AC Project # 0493; 6/6/83)

One group of 15 male Sprague-Dawley rats were used in the study. Three rats were control animals and 12 rats were treated animals. Each treated rat received a single oral dose of C^{14}-label AC 243,997 equal to 1.1 mg (33 microcuries). Based on body weight of the rats (approximately 225 grams), this dose was 4.4 mg/kg.

Three treated rats were sacrificed at days 1, 2, 5 and 8. One control rat was sacrificed on day 5 and two were sacrificed on day 8.

Urine and feces were collected daily. At each sacrifice interval, blood was collected and liver, kidney, muscle and fat were removed. All metabolism cages housing treated rats were rinsed with water and methanol and collected.

Results:

At day 1, 55.3% of the dose was excreted in the urine and 31.9% was excreted in the feces. Excretion was essentially complete by day 6 and was 95.1% of the total dose. Overall recovery of cage washes and excretion was 98.0% at day 8.

9

Using TLC and mass spectrometry, the radiolabeled organic extracted material in feces and urine at day 1 was parent compound.

At day 1, kidney and liver cotnained 0.03 and 0.02 ppm, respectively and less than 0.01 ppm on day 8.

Muscle, fat and blood had less than 0.01 ppm at both days 1 and 8.

Conclusion:

The half-life of AC 243,997 was less than one day. No significant radiolabelled compound in the rat was present from tissue residues.

Classification: Core Minimum Data.