UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

JUN 18 1984

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT 241-EUP-RNR; Arsenal; New herbicide for use on non-cropland. Caswell #221G, Accession #: 252004. (Addendum)

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

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REQUESTED ACTION:

Review of data and label for support of EUP program.

Recommendations:

The EUP program can be toxicologically supported. Data submitted in this request and two teratology studies (rat and rabbit) received in EPA Reg. No. 241-ETG have been reviewed. The teratology studies present no evidence of unacceptable health hazards resulting from the requested use under the described condition. A complete review of the Teratogenicity studies will accompany the response to the registration request.

Review:

1. Arsenal Nomenclature, as stated in the report.

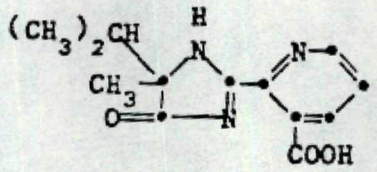
"ARSENAL herbicide has been identified by various designations during the period in which evaluation data included in this application have been accumulated."

"The active ingredient contained in ARSENAL herbicide has been designated as CL 243,997 and AC 243,997. The chemical identity of the active ingredient is 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl) nicotinic acid (IUPAC) and 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-3-pyridine-carboxylic acid (CA)."

"The active ingredient is formulated as the monoisopropylamine salt and the code numbers CL 252,925 and AC 252,925 are the designations for the ARSENAL herbicide formulation. The chemical identity is 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl) nicotinic acid with isopropylamine (1:1) (IUPAC) and 2-[4,5-dihydro-4-methyl-4-(1-mehtylethyl)-5-oxo-1H-imidazol-2-yl]-3-pyridinecarboxylic acid with 2-propanamine (1:1) (CA)."

2. Toxicity Data Report (American Cyanamid Report #A83-24, 7/19/83)

I. Test Material: AC 243,997; sample # 83-62; purity, 93%; Technical Chemical Structure



a. Rat Oral LD_{50}

One group of five male and five female Sprague-Dawley rats were fasted for 18 hours and dosed orally with a 20% W/V corn oil dispersion at a rate of 5000 mg/kg BW. Observations were for 14 days.

Results: No deaths - LD_{50} > 5000 mg/kg (both sexes)

Toxic Signs: None observed.

Body Weight: Survivors gained weight.

Necropsy: No visible lesions.

Toxiciity Category III: Caution.

Classification: Core Minimum Data.

b. Dermal LD_{50} in Rabbits

One group of five male and 5 female NZW rabbits received dermally a dose of 2000 mg/kg on shaved skin under an imprevious cuff for 24 hours. Observation was for 14 days.

Results: No deaths - LD_{50} > 2000 mg/kg (both sexes)

Toxic Signs: None observed.

Body Weight: Survivors gained weight.

Necropsy: Lungs-hemorrhagic in 4/10; Kidney-congested in 1/10; No visible lesions in 5/10.

Toxicity Category III: Caution.

Classification: Core Minimum Data.

c. Primary eye irritation in Rabbits

One group of nine NZW rabbits were used in the study. 100 mg of the test material, as received, was instilled into the conjunctival sac of the right eye, the left eye served as a control. After instillation the lids were held together for 5 seconds and the first 6 animals were returned to their cages. The eyes of the remaining 3 rabbits were flushed with approximately 200 ml of tap water after being exposed to the test material for 20 seconds. At the end of the 24 hour exposure period the treated eyes were rinsed with tap water and examined for irritation with the aid of ultraviolet light and fluorescin. The animals were examined until the irriation, if any, had subsided. Scoring was done using the Draize scale for measuring eye irritation .

Results: Unwashed eyes - No corneal opacity or irtis. Conjunctivitis in 3/3 at 24 hours wich disappeared at 72 hours.

Corneal opacity in 4/6 at 24 hours which were reversible at 72 hours. No iritis. Conjunctivitis in 6/6 at 72 hours which were reversible by day 7.

Toxicity Category III: Caution.

Classification: Core Minimum Data.

d. Primary skin irritation study in Rabbits.

One group of six rabbits each received 0.5 grams/test site on abraded and intact skin under an imprevious cuff for 24 hours. Test sites were scored at 24 and 72 hours according to Draize.

Results: No edema; erythema in 2/6 abraded test sites at 24 hours which cleared at 72 hours.

P.I. = 0.083.

Toxicity Category IV: Caution.

Classification: Core Minimum Data.

II. Test Material: AC 252,925 Arsenal formulation; sample #83-67; 8/25/83.

a. Rat Oral LD_{50}

One group of five male and 5 female Sprague-Dawley rats, fasted for 18 hours, were orally dosed with a 20% W/V dispersion at a rate of 5000 mg/kg BW.

Results: One male rat died - LD_{50} > 5000 mg/kg (both sexes).

Toxic Signs: None observed.

Body Weight: Survivors gained weight.

Necropsy: No visible lesions in any of the survivors. Congestion of liver, kidney and intestinal tract, and hemorrhagic lungs were observed in male that died.

Classification: Core Minimum Data.

b. Dermal LD_{50} in Rabbits

One group of five male and 5 female NZW rabbits were each dermally dosed with 2148 mg/kg BW under an impervious cuff on shaved intail skin for 24 hours. Observation was for 14 days.

Results: One male rabbit died - LD_{50} > 2148 mg/kg

Toxic Signs: None observed.

Body Weight: Survivors gained weight.

Necropsy: Decedent - lungs - pneumonic areas.

Survivors: Liver-mottled and pale 1/9; lung - moderate congestion 1/9; no visible lesions 7/9.

Toxicity Category III: Caution.

c. Primary Skin Irritation Study in Rabbits.

One group of six NZW rabbits received dermally 0.5 ml/test site on the shaved intact and abraded skin for 24 hours under an impervious cuff. Evaluation was at 24 and 72 hours after exposure.

Results: Erythema and edema in abraded sites and erythema in intact skin.

P.I. = 1.29

Toxicity Category IV: Caution
Classification: Core Minimum Data

d. Primary Eye Irritation Study in Rabbits

0.1 ml of the test material, as received, was instilled into conjunctival sac of the right eye, the left eye served as a control. After instillation the lids were held together for 5 seconds and the first 6 animals were returned to their cages. The eyes of the remaining 3 rabbits were flushed with approximately 200 ml of tap water after being exposed to the test material for 20 seconds. At the end of the 24 hour exposure period the treated eyes were rinsed with tap water and examined for irritation with the aid of ultraviolet light and fluorescin. The animals were examined until the irritation, if any, had subsided. Scoring was done using the Draize scale.

Results: Rinsed at 20 seconds:

Conjunctivitis in 3/3 at 24 hours, 1/3 at 48 hours and no irritation at 72 hours.

Eye rinsed at 24 hours:

Corneal opacity in 2/6 at 24 hours (one animal with corneal opacity at 4 days died by day 7) no iritis; conjunctivitis 6/6 at 24 hours; and 0/6 at day 7.

Toxicity Category IV: Caution.

Classification: Core Minimum Data.

3. Acute inhalation toxicity of AC 243,997 (technical) in Sprague-Dawley rats (FDRL Study # 7624; 9/1/83).

Test Material: AC 243,997 (technical), 93% purity.

One group of 10 male and 10 female Sprague-Dawley rats were exposed for 4 hours to an aerosol at a level of 5.1 mg/L, (nominal concentration; 1.3 mg/L, gravimetric concentration). Observation was for 14 days.

Results: No deaths

LC_{50} > 5.1 mg/L (nominal)
LC_{50} > 1.3 mg/L (gravimetric)

Toxic Signs: nasal discharge on day 1

Body Weight: Survivors gained weight

Necropsy: No observable lesions.

Toxicity Category III: Caution.

Classification: Core Minimum Data.

4. Acute inhalation toxicity of AC 252, 925 (Arsenal formulation) in Sprague-Dawley rats (FDRL Study # 7607; 9/1/83).

Test Material: AC 252/925 (Arsenal formulation).

One group of ten male and ten female Sprague-Dawley rats were exposed to an aerosol of test material at a nominal concentration of 5.0 mg/L (gravimetric concentration 0.2 mg/L) for four hours. Observation was for 14 days.

Results: No deaths

LC_{50} > 5.0 mg/L (nominal)
LC_{50} > 0.2 mg/L (gravimetric)

Toxic Signs: No compound-related effects.

Body Weight: Survivors gained weight.

Necropsy: No gross lesions.

Toxicity Category III: Caution.

Classification: Core Minimum Data.

5. Evaluation of the sensitization potential of AC 243,997 technical;(TPS Study #: 186A-201-231-83; 7/20/83) Lot No. AC 4361-97; 93% purity.

A dose range study was conducted using one guinea pig per level at 25, 50, 75 and 100% test material in 0.9% saline to determine the primary irritation effect of the test material.

The results showed that a level of 100% of test material (0.30 grams) could be used in the main study without any erythema or edema present. In the main study, three groups of 10 guinea pigs were used. The control group only received the challenge test material dose. The positive control group received 0.3 gram of DNCB on the shaved back once a week for three weeks for 6 hours per application under an impervious cuff.

The test material treated group of 10 guinea pigs each received 0.3 ml (0.3 gram) of test material on the shaved back once a week for three weeks for 6 hours per application under an impervious cuff.
Twenty-four and 48 hours after each application, the sites were examined for erythema and edema.

Two weeks after the last induction application, all animals received a challenge (0.3 grams) application of their respective compounds.

Results: The positive control guinea pigs exhibited erythema and edema during their induction phase and challenge phase which demonstrates that the skin sensitization potential of the test had been acheived.

No erythema or edema was observed in any of the animals with test material sites during the induction phase and at challenge. This finding demonstrates that the test material was not a skin sensitization agent. The control group showed no erythema or edema at the challenge dose.

Conclusions: AC 243,997 was not a skin senitizer in this study.

Classification: Core Minimum Data.

6. Evaluation of the Sensitization potential of AC 252,925 in guinea pigs (TPS Study # 187A-201-231-83; 7/29/83.

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

A pilot study to determine doses for the main study was conducted on one guinea pig per level using 25, 50, 75 and 100% test material in 0.9% saline to determine the primary irritation effect of the test material.

The results of the pilot study showed that a level of 100% of test material could be used in the main study without any erythema or edema present.

In the main study, three groups of 10 guinea pigs were used. The control group only received the challenge dose of test material. The positive control group received 0.3 gram of DNCB on the shaved back once a week for three weeks for 6 hours per application under an impervious cuff.

The test material treated group of 10 guinea pigs each received 0.3 ml (0.3 gram) of test material on the shaved back once a week for three weeks for 6 hours per application under an impervious cuff.

Twenty-four and 48 hours after each application, the sites were examined for erythema and edema.

Two-weeks after the last induction application, all animals received a challenge application of their respective compounds.

Results: The positive control guinea pigs exhibited erythema and edema during the induction phase and challenge phase which showed that the skin sensitization potential of the test had been acheived.

No erythema or edema was observed in any of the animals with test material sites during the induction phase and at challenge.

This finding demonstrates that the test material was not a skin sentization agent. The control group showed no erythema or edema at the challenge dose.

Conclusion: AC 252-925 was not a skin sensitizer in this study

Classification: Core Minimum Data.