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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

APR 27 1987

SUBJECT: EPA File Symbol 10182-RRO
Prelude Herbicide

FROM: Deloris F. Graham DFG 5/4/87
Technical Support Section
Fungicide-Herbicide Branch
Registration Division (TS-767C)

E 5/4/87

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (TS-767C)

APPLICANT: ICI Americas, Inc.
Agricultural Products
Concord Pike & New Murphy Road
Wilmington, DE 19897

ACTIVE INGREDIENTS:

Paraquat dichloride (1,1'-dimethyl-4,4'-bipyridinium dichloride)	7.86%
Linuron	2.84%
2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide	22.75%
INERT INGREDIENTS:	66.55%

BACKGROUND:

Submitted Acute Oral, Acute Dermal, Acute Inhalation, Eye Irritation, Skin Irritation, and Dermal Sensitization Studies. Studies conducted by ICI Central Toxicology Laboratory and Food & Drug Research Laboratories, Inc. Data under EPA MRID Nos. 400626-01, -02, -03, -04, -05, and -06. Method of support not indicated.

RECOMMENDATIONS:

1. FHB/TSS finds the acute inhalation, skin irritation, and skin sensitization studies acceptable to support conditional registration of this product.

2. The acute oral study is not acceptable due to the fact that only the LD_{50} for one of the active ingredients was determined whereas the study must be conducted on total formulation of product.

3. Due to the number of male animals that died during this acute dermal study, another study to determine LD_{50} for males must be conducted.

4. The eye irritation study must be conducted on total formulation of product to be acceptable for conditional registration, not on dilutions of the formulation.

5. Based on the acute inhalation study, the appropriate signal word is DANGER.

LABEL:

1. The "Keep Out of Reach of Children" statement should precede the signal word.

2. All precautionary statements should precede "Directions For Use."

3. The statement "May cause allergic skin reaction" must be included in precautionary statements.

REVIEW:

(1) Acute Oral Toxicity Study: ICI Central Toxicology Lab.; LAB ID CTL/P/1664; January 9, 1987; EPA MRID No. 400626-01.

PROCEDURE:

Three groups consisting of five male and five female rats each were dosed with one of the following doses: 40, 60, or 120 mg paraquat ion/kg. Observations made once a day up to day 15 after dosing. Necropsy performed on all animals.

RESULTS:

At 40 mg/kg, 1/5 F died; at 60 mg/kg, 2/5 M and 2/5 F died; and at 120 mg/kg, 5/5 M (one animal killed in extremis) and 5/5 F died. Toxic signs reported included activity decrease, miosis, diarrhea, tiptoe gait, chromodacryorrhea, dehydrated, hypothermia, pale, piloerection, salivation, sides pinched in, salivation, stains around mouth and nose, urinary incontinence, thin, upward curvature of spine, irregular breathing, piloerection, reduced stability, and ungroomed. LD_{50} for male rats reported to be 68.1 mg paraquat ion/kg with 95% confidence

limits between 90 and 120 mg paraquat ion/kg. LD_{50} for female rats reported to be 59.4 mg paraquat ion/kg with 95% confidence between 37.5 and 160.7 mg paraquat ion/kg.

STUDY CLASSIFICATION:

Core Supplementary Data. LD_{50} should be on total formulation not on active alone.

(2) Acute Dermal Toxicity Study: Food and Drug Research Laboratories; FDRL Study No. 9328A; December 31, 1986; EPA MRID No. 400626-02.

PROCEDURE:

Five male and five female rabbits with intact skin sites each received a single 2.0 g/kg dose of the test material. Treated sites were placed under occlusive wrap for 24-hour exposure period. Observations made for 14 days postdosing. Necropsy performed on all animals.

RESULTS:

Three out of five males died. Toxic signs reported included anorexia, ataxia, decreased activity, respiratory irregularity, salivation, tremors, blood in litter tray, and coma-like state. Slight to well-defined erythema, slight to moderate edema, and dry and/or cracked skin also reported. Necropsy report revealed dark red fluid in bladder and kidneys; discoloration of kidneys and liver; lungs reddened and ureters swollen. LD_{50} reported to be greater than 2.0 g/kg.

STUDY CLASSIFICATION:

Core Supplementary Data. See Item #3 of Recommendations.

(3) Acute Inhalation Toxicity Study: ICI Central Toxicology Laboratory; LAB ID CTL/P/1681 and CTL/P/1681A; EPA MRID No. 400626-03.

PROCEDURE:

Four groups consisting of five male and five female rats each were exposed nose only to one of the following concentrations of paraquat ion: 0.0 (Control), 0.4, 0.8, or 1.2 ug/L. The mean concentrations of paraquat ions in atmosphere was reported to be 0.31, 0.65, and 0.67 ug/L. Temperature reported to range from 19.9 to 20.2 °C and relative humidity from 18.1 to 56.6 percent. Particle size reported to range from 0.5 to 9.8 um. Observations made for 14 days postexposure. Necropsy performed on all animals.

RESULTS:

At 0.8 ug/L, 4/5 M and 5/5 F died; at 1.2 ug/L, 4/5 M and 4/5 F died. Toxic signs reported include chromodacryorrhea, piloerection, red stain around nose, fighting wound on left cheek, wet fur, abnormal respiration, hunched, sides pinched in, subdued, thin, salivation, and increased response to touch. Necropsy report revealed right kidney - moderate pelvic dilatation, thymus - red spots both lobes; lung - dark red, not fully deflated; trachea - exuded froth, lungs - blotchy; thoracic cavity - excess watery fluid. Based on the values of the paraquat ions, the LC_{50} was extrapolated to be 8.032 ug/L (0.008032 mg/L) for females; 10.125 ug/L (0.010125 mg/L) for males; 9.589 ug/L (0.009589 mg/L) for males and females combined.

STUDY CLASSIFICATION: Core Guideline Data.

TOXICITY CATEGORY: I - DANGER.

(4) Eye Irritation Study: ICI Central Toxicology Lab.; Lab ID CTL/P/1699; January 6, 1987; EPA MRID No. 400626-04.

PROCEDURE:

Six rabbits received a 0.1 ml dose of a 1 in 16 dilution of the test material in deionized water. Observations made for 7 days posttreatment.

RESULTS:

At day 1 posttreatment, 6/6 rabbits had conjunctive redness (5/6 = 1, 1/6 = 2); 3/6 chemosis (3/6 = 1) and 4/6 discharge (3/6 = 1, 1/6 = 3). All irritation had cleared by day 7.

STUDY CLASSIFICATION:

Core Supplementary Data. See Item #4 in Recommendations.

(5) Skin Irritation Study: ICI Toxicology Laboratory; Lab ID CTL/P/1686; January 8, 1987; EPA MRID No. 400626-05.

PROCEDURE:

Six rabbits with intact skin sites each received 0.5 ml of the test material undiluted. The treated sites were placed under occlusive wrap for 4-hour exposure period. Observations made for 21 days posttreatment.

RESULTS:

At day 1 posttreatment, 6/6 rabbits had moderate to severe erythema (4/6 = 3, 2/6 = 4) and edema (2/6 = 3, 4/6 = 4). At day 3, moderate to severe erythema (3/6 = 3, 3/6 = 4) and edema (3/6 = 3, 3/6 = 4). Thickening obscuring possible edema noted on day 6. Irritation persisted in a few animals through day 21. Mean irritation score reported to be 3.4.

STUDY CLASSIFICATION: Core Guideline Data.

TOXICITY CATEGORY: II - WARNING.

(6) Skin Sensitization Study: ICI Central Toxicology Laboratory; Lab ID CTL/P/1704; January 9, 1987; EPA MRID No. 400626-06.

PROCEDURE:

Twenty male guinea pigs received three (over a 2-week period) 0.4 ml applications of a 10% (w/v) dilution of the test material in deionized water during the induction phase. Topical patch method of application was used. Two weeks after final induction phase application, a challenge dose was applied using a 3%, 1%, and 0.3% (w/v) dilution of the test material in deionized water. Observations made for 24 and 48 hours after each application. A group of 10 male guinea pigs (control group) were treated in similar manner as previous group except deionized water only was used.

Twenty male guinea pigs (positive control group) were treated with a 50% (w/v) dilution of formaldehyde in deionized water for the first two induction phase applications and a 25% (w/v) dilution for the third induction phase application and at challenge dose. Observations made at 24 and 48 hours after each application.

RESULTS:

Slight to moderate erythema and slight desquamation in test animals during induction phase. At challenge, with 3% (w/v) dilution of test material, scattered mild redness noted in 14/20 guinea pigs of test group and 2/10 of control group. No irritation reported in test or control group at challenge with 1% or 0.3% (w/v) dilutions. It was concluded that due to the response of the animals at challenge with 3% (w/v) dilution, a sensitization reaction was produced.

Severe erythema, thickening, desquamation, necrosis, and hardening reported during induction phase of positive control group; one animal killed following second induction phase

application due to severity of the irritation. Scattered mild redness to intense redness, and swelling reported in 13/19 positive control animals at challenge with a 25% (w/v) dilution of formaldehyde, thereby indicating a sensitization reaction.

STUDY CLASSIFICATION: Core Guideline Data.

TOXICITY CATEGORY: Sensitizing agent.