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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: July 9, 1985

SUBJECT: EPA File Symbol 228-RTI
Riverdale Weedestroy Triamine

EPA File Symbol 228-RIR
Riverdale Triamine Lawn Weed Killer

EPA File Symbol 228-RTO
Riverdale Triamine Weed and Feed

EPA File Symbol 228-RIN
Riverdale Three-Way Weed and Feed

FROM: Mary L. Waller
Fungicide/Herbicide Branch/~~TSS~~
Registration Division (TS-767C)

TO: Richard Mountfort
Product Manager (23)
Registration Division (TS-767C)

Applicant: Riverdale Chemical Company
220 East 17th Street
Chicago Heights, IL 60411

228-RTI

ACTIVE INGREDIENTS:

Dimethylamine Salt of 2,4-Dichlorophenoxy acetic acid	16.3%
Dimethylamine Salt of 2-(2-Methyl-4-chlorophenoxy) propionic acid	16.4%
Dimethylamine Salt of 2-(2,4-Dichlorophenoxy)propionic acid	16.2%
Inert Ingredients	51.1%

228-RIR

ACTIVE INGREDIENTS:

Dimethylamine Salt of 2,4-Dichlorophenoxy acetic acid	4.55%
Dimethylamine Salt of 2-(2-Methyl-4-chlorophenoxy) propionic acid	4.58%
Dimethylamine Salt of 2-(2,4-Dichlorophenoxy) propionic acid	4.53%
Inert Ingredients	86.34%

228-RTO

ACTIVE INGREDIENTS:

Dimethylamine Salt of 2,4-Dichlorophenoxyacetic acid	.313%
Dimethylamine Salt of 2-2(Methyl-4-chlorophenoxy) propionic acid	.314%
Dimethylamine Salt of 2-(2,4-Dichlorophenoxy) propionic acid	.310%
Inert Ingredients	99.063%

228-RIN

ACTIVE INGREDIENTS:

Dimethylamine Salt of 2,4-Dichlorophenoxyacetic acid	.156%
Dimethylamine Salt of 2-2(Methyl-4-chlorophenoxy) propionic acid	.157%
Dimethylamine Salt of 2-(2,4-Dichlorophenoxy) propionic acid	.155%
Inert Ingredients	99.532%

Background:

The applicant has submitted an acute oral, an acute dermal, an acute inhalation, an eye irritation, a primary skin irritation and a dermal sensitization study on EPA File Symbol 228-RTI to support the registration of all four products. The data Accession Number is 258479. All studies were conducted by Hazelton Laboratories America, Inc., except for the acute inhalation study which was conducted by American Biogenics Corporation. The method of support is owner submission.

Recommendation:

FHB/TSS has reviewed these data and finds them acceptable to support registration of 228-RTI. In addition, FHB/TSS finds the acute oral, acute inhalation and primary skin irritation studies

acceptable to support registration of 228-RIR. However, the acute dermal, eye irritation and dermal sensitization studies cannot be used to support registration of 228-RIR even though it is a similar product differing only by having a lesser content of active ingredients. Because (for 228-RTI) the eye irritation study is in Toxicity Category I, the acute dermal is in Toxicity Category II, and the dermal sensitization study is positive, FHB/TSS is unable to tell at what point, if any, that the Toxicity categories for these studies may change to a lower category due to the lesser amount of active ingredient in 228-RIR. The Agency is equally concerned that products are not overlabeled as well as underlabeled, therefore, the applicant will have to submit an acute dermal, eye irritation and dermal sensitization study on 228-RIR.

The appropriate signal word for 228-RTI is "DANGER."

Furthermore, the data submitted cannot be used to support registration of 228-RTO and 228-RIN as these products differ substantially from 228-RTI on which the studies were conducted. The applicant must submit a full battery of data on both products (228-RTO and 228-RIN).

In regard to future acute inhalation studies, the Product Manager should inform the applicant of the following: 1) The relative humidity should be calculated in the test chamber; 2) The LC_{50} and 95 percent confidence interval should be determined for each sex; 3) If a test is conducted using an exposure of 5 mg/l (actual concentration of respirable substances) and no deaths occur, then further testing may be unnecessary. However, if deaths do occur at 5 mg/l, then a full study using three dose levels must be conducted and spaced appropriately (between the 10 percent and 90 percent mortality range) to allow for an acceptable determination of the LC_{50}.

The Product Manager should inform the applicant that the observation period for future eye irritation studies should be carried out for 21 days or until all irritation clears.

Label:

The proposed labeling for 228-RTI must be changed as indicated below.

1. Change on Front Panel - Rearrange the order of the Practical Treatment Statements and include the heading to read as follows:

PRACTICAL TREATMENT

If in Eyes: Flush eyes with water for 15 minutes and get medical attention.
If on Skin: Wash skin with soap and water and get medical attention.
If Swallowed: Get medical attention.

2. Changes on Side Panel - Expand the next to last sentence to read as follows: "Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse."

3. Changes on Side Panel - Include the following sentence in the first paragraph under precautionary statements: "Weedestroy Triamine may cause dermal sensitization reactions."

Additional labeling comments may be necessary for 228-RIR upon submission of an acute dermal, eye irritation and dermal sensitization studies.

Review:

(1) Acute Oral Toxicity Study: Hazelton Laboratories America, Inc., Sample Number 50304968, April 1 to 30, 1985.

Procedure:

Three groups of five male and five female fasted Sprague-Dawley rats were administered one of the following dose levels of undiluted test material by gavage: 1.0 g/kg, 2.0 g/kg and 5.0 g/kg. Animals were observed for toxic effects and mortality at 1, 2.5 and 4 hours. Surviving animals were observed daily thereafter for toxic effects and twice daily for mortality for 14 days. All animals were weighed prior to test material administration, and at 7 and 14 day intervals or at death. Surviving animals were sacrificed and gross necropsy was performed on all animals.

Results:

No deaths occurred at the 1.0 g/kg dose level. At 2.0 g/kg, 2/5 males and 3/5 females died. At 5.0 g/kg, 5/5 males and 5/5 females died. The LD_{50} for males was reported to be 2.3 g/kg with a 95 percent confidence limit of 1.3 to 4.3 g/kg and the LD_{50} for females was reported to be 1.8 g/kg with a 95 percent confidence limit of 1.0 to 3.2 g/kg.

Gross necropsy observations included discoloration of stomach tissue and small intestine, green and tan semifluid substance in the stomach, red/yellow mucoid material in the duodenum and jejunum and red/black mucoid material in ileum.

Study Classification: Core Guideline Data

Toxicity Category: Category III - Caution

(2) Acute Dermal Toxicity Study: Hazelton Laboratories America, Inc., Sample Number 50304968, April 2 to 25, 1985.

Procedure:

Five male and five female rabbits were clipped and treated with 2.0 g/kg of test material applied to the animals backs. Two additional groups each consisting of five females were treated with one dose of 1.0 g/kg or 3.0 g/kg of test material applied to the animals' backs. All test sites were kept under occlusive wrap for 24 hours, and the animals were restrained during this period. After 24 hours, the occlusive wrap was removed and the test sites were washed with warm tap water.

Observations were made at 30 minutes, 1, 2.5 and 4 hours after administration of test material. Observations for toxic effects were also made daily for 14 days and twice daily for mortality. All animals were weighed prior to testing and at 7- and 14-day intervals or at death. Gross necropsy was performed at death or at study termination on all surviving animals.

Results:

The mortality rate was as follows: At 1.0 g/kg, 1/5 females died; at 2.0 g/kg, 2/5 females were sacrificed due to their moribund condition and no deaths occurred among the males; and at 3.0 g/kg, 5/5 females died. The LD_{50} for females were reported to be 2.0 g/kg with a 95 percent confidence limit of 1.3 to 3.2 g/kg. The LD_{50} for males was reported to be > 2.0 g/kg.

Gross necropsy revealed red discoloration of the small intestine which was filled with a green watery fluid, moderate atrophy in the skeletal muscles of all four legs, necrotic areas in the psoas muscles, ulcerations of both stifles, reddened discoloration of skin over spinal column, excess lymph in pericardial sac, dark red discoloration of thymus and skin in treated area diffusely red.

Study Classification: Core Guideline Data

Toxicity Category: Category II - Warning

(3) Primary Skin Irritation Study: Hazelton Laboratories America, Inc., Sample Number 50304968, April 3 to 6, 1985.

Procedure:

Three male and three female albino rabbits were shaved on the back and flank areas 24 hours before testing. Each rabbit received 0.5 ml of test material on the shaven intact skin which was kept under occlusive wrap for 4 hours. Collars were used to restrain the animals during the exposure period, after which, the wrap was removed and the test site was washed with lukewarm tap water.

Observations were made at 4, 24, 48 and 72 hours. Individual body weights were taken just prior to testing and the pH of the test material was determined.

Results:

At 4 hours, 2/3 males and 3/3 females exhibited very slight erythema and 1/3 males and 1/3 females exhibited very slight edema. At 24 hours, 1/3 males exhibited very slight erythema. All irritation was gone by 48 hours.

The pH of the test material was reported as 7.7.

Study Classification: Core Guideline Data

Toxicity Category: Category IV - Caution

(4) Eye Irritation Study: Hazelton Laboratories America, Inc., Sample Number 50304968, April 2 to 9, 1985.

Procedure:

Nine albino rabbits selected for the study underwent an ocular examination using sodium fluorescein dye approximately 24 hours before the start of the study. The nine rabbits which exhibited no sign of ocular injury or irritation each received 0.1 ml of test material placed inside the lower eyelid.

The eyelids were held shut for one second. The eyes of 3/9 rabbits were flushed with lukewarm water 30 seconds after test material instillation. The untreated eye of the nine rabbits served as a control.

Observations were made at 24, 48, 72 and 96 hours and at 7 days. The eyes were examined using sodium fluorescein dye at 72 hours and at 7 days. Animals were weighed prior to testing and at study termination.

Results:

The following observations on the animals with unwashed eyes were noted: At 24 hours, corneal opacity (2/6 = 3, 4/6 = 1), area (4/6 = 4, 2/6 = 1), iris irritation (6/6 = 1), redness (6/6 = 3), chemosis (5/6 = 4, 1/6 = 3), and discharge (3/6 = 3, 3/6 = 2); at 48 hours, corneal opacity (1/6 = 4, 4/6 = 3, 1/6 = 2), area (2/6 = 4, 1/6 = 3, 3/6 = 1), iris irritation (6/6 = 1), redness (6/6 = 3), chemosis (6/6 = 4) and discharge (4/6 = 3, 2/6 = 2); at 72 hours, corneal opacity (1/6 = 4, 3/6 = 3, 2/6 = 2), area (1/6 = 2, 5/6 = 1), iris irritation (1/6 = 2, 5/6 = 1), redness (6/6 = 3), chemosis (5/6 = 4, 1/6 = 3), discharge (5/6 = 3, 1/6 = 2) and sodium fluorescein examination (2/6 = 60% positive, 1/6 = 50% positive, 2/6 = 25% positive, 1/6 = 20% positive); at 96 hours, corneal opacity (1/6 = 4, 3/6 = 3, 2/6 = 2), area (6/6 = 1), iris irritation (5/6 = 1, 1/6 = 2), redness (6/6 = 3), chemosis (3/6 = 4, 2/6 = 3, 1/6 = 2), and discharge (3/6 = 3, 3/6 = 2); and at 7 days, corneal opacity (1/6 = 4, 1/6 = 3, 4/6 = 2), area (3/6 = 4, 1/6 = 3, 1/6 = 1), iris irritation (2/6 = 2, 4/6 = 1), redness (6/6 = 3), chemosis (2/6 = 4, 1/6 = 3, 3/6 = 2), discharge (2/6 = 3, 2/6 = 2, 2/6 = 1), and sodium fluorescein examination (1/6 = 90% positive, 1/6 = 40% positive, 2/6 = 30% positive, 1/6 = 10% positive, 1/6 = 5% positive).

The following observations were noted on the animals with washed eyes: At 24 hours, corneal opacity (1/3 = 4, 1/3 = 3, 1/3 = 1), area (1/3 = 4, 1/3 = 3, 1/3 = 1), iris irritation (3/3 = 1), redness (3/3 = 3), chemosis (2/3 = 4, 1/3 = 3) and discharge (2/3 = 3, 1/3 = 2); at 48 hours, corneal opacity (1/3 = 4, 1/3 = 3, 1/3 = 2), area (1/3 = 2, 2/3 = 1), iris irritation (3/3 = 1), redness (2/3 = 3, 1/3 = 2), chemosis (2/3 = 4, 1/3 = 3), and discharge (3/3 = 3); at 72 hours, corneal opacity (2/3 = 3, 1/3 = 2), area (1/3 = 4), 1/3 = 2, 1/3 = 1), iris irritation (1/3 = 2, 2/3 = 1), redness (3/3 = 3), chemosis (2/3 = 4, 1/3 = 3), discharge (2/3 = 3, 1/3 = 2) and sodium fluorescein examination (1/3 = 90% positive, 1/3 = 40% positive, 1/3 = 20% positive); at 96 hours, corneal opacity (2/3 = 2,

1/3 = 2), area (1/3 = 4, 2/3 = 1), iris irritation (3/3 = 1), redness (3/3 = 3), chemosis (2/3 = 4, 1/3 = 2), and discharge (2/3 = 3); and at 7 days, corneal opacity (2/3 = 3, 1/3 = 2), area (2/3 = 4, 1/3 = 2), iris irritation (2/3 = 2), redness (3/3 = 3), chemosis (2/3 = 3, 1/3 = 1), discharge (2/3 = 2) and sodium fluorescein examination (1/3 = 50% positive, 2/3 = 10% positive).

Observations noted that continued through day 7 included the following: hypopyon, petite hemorrhaging, blanching, purulent discharge, pannus, corneal epithelial damage (peeling), keratoconus, hair loss around eye, necrotic areas of the conjunctivae and corneal neovascularization.

Study Classification: Core Minimum Data

See comments in recommendation.

Toxicity Category: Category I - Danger

(5) Dermal Sensitization Study: Hazelton Laboratories America, Inc., Sample Number 50804968, April 2 to May 6, 1985.

Range Finding Study:

Four guinea pigs were administered two concentrations of test material as follows: undiluted, 25 percent, 50 percent and 75 percent w/v in deionized water. Based upon the results, the test material used in the main study was administered undiluted in the sensitization phase and as a 75 percent w/v mixture in deionized water for the challenge dose.

Main Study

Procedure:

Twenty-four male albino guinea pigs maintained under appropriate laboratory conditions were shaved prior to treatment. Induction treatments were administered to the left flank. The positive control group consisting of four animals received one 0.4 ml dose per week for 3 weeks of 2,4-dinitrochlorobenzene (DNCB) at a concentration of 0.3 percent w/v in 80 percent ethanol/distilled water. A test group of 10 animals received one 0.4 ml dose of 75 percent test material in a w/v mixture of deionized water. A previously untreated control group of 10 animals were also treated with the test material in the same manner as the test group. The positive control group received a 0.4 ml dose of DNCB at a concentration of 0.1 percent w/v in acetone.

Observations were made at 24 and 48 hours following sensitizing and challenge applications in order to score the degree of erythema and edema. Animals were also observed once daily during study to note general behavior and appearance. Body weights were taken at study initiation, at weekly intervals and at study termination.

Results:

Animals treated with test material during the induction phase exhibited slight to severe dermal irritation. Following the challenge dose of test material, 9/10 animals exhibited slight to severe dermal irritation. Four out of 10 naive control animals exhibited slight nonconfluent erythema after receiving only the challenge dose of test material. The dermal reaction of 6/10 test animals exceeded the highest reaction of the naive control animals. Therefore, the test material was considered a sensitizer.

All four of the animals in the positive control group reacted to the sensitizing and challenge doses. The positive control animals were considered to have been sensitized because of the slight to severe reactions exhibited in response the challenge dose of 0.1 percent w/v concentration of DNCB in acetone.

Normal weight gains were recorded for all animals throughout the study except during the last 3 days when two test animals, six naive control animals, and one positive control animal exhibited a slight weight loss of 5 to 22 g.

(6) Acute Inhalation Study: American Biogenics Corporation, Study Number 420-2114, June 19, 1985.

Procedure:

Two groups of five male and five female rats each received whole-body exposure for 4 hours to an aerosol atmosphere of test material in a stainless steel and glass inhalation chamber. The temperature was measured in the test chamber and the humidity was measured in an empty chamber run concurrently with the test chamber. The gravimetric concentration and particle size was calculated for each exposure. Animals were observed once daily for 14 days and mortality checks were conducted twice daily. Animals were weighed prior to exposure and on the 7th and 14th observation day or at death. Gross necropsy was performed on all animals.

Results:

In group I, which was exposed to an average gravimetric concentration of 4.87 mg/l for 4 hours, 1/5 males and 2/5 females died. In group II, which was exposed to an average gravimetric

concentration of 6 mg/l, 4/5 males and 3/5 females died. Based on the raw data used to determine the average gravimetric concentration, the LD_{50} is between 4.87 mg/l and 6 mg/l.

Observations revealed the following toxic symptoms: irregular breathing, crusty eyes and muzzles, lethargy, damp fur, gasping, lacrimation, swollen muzzle, squinting, salivation, prostration, and poor coat quality. Gross necropsy revealed abnormalities of the stomach, small intestine, lungs, stomach, liver, and bronchii.

Study Classification: Core Minimum Data

Toxicity Category: Category III - Caution.