2,4-D/TOX

(22)

Releasable

UNIT STATES ENVIRONMENTAL PROTECTION AGENCY

Caswell 323H

3155E

DATE: February 13, 1979

SUBJECT: 464-EUP-55. LONTREL 205 Herbicide. 3,6-Dichloropicolinic Acid. Dowco 290. Dow Chemical Company, Midland, Michigan.

FROM: Roland A. Gessert, D.V.M. Roland A. Gessert 2/15/79
Toxicology Branch

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THRU: Dr. Lamar Dale, Acting Chief, Toxicology Branch

LONTREL 205 Herbicide is a formulation containing:

2,4-Dichlorophenoxyacetic acid, as alkanolamine salts (of the ethanol and isopropanol series)	32.2%
3,6-Dichloropicolinic acid, as alkanolamine salts (of the ethanol and isopropanol series)	8.5%

2,4-D is an "old" chemical, and will not be reviewed separately.
3,6-Dichloropicolinic acid (LONTREL, Dowco 290) is a "new" pesticide chemical, and is reviewed below separately and in the formulation LONTREL 205.
EUP labeled for use in wheat and barley.

CONCLUSIONS AND RECOMMENDATIONS:

1. If the reviews of Chemistry Branch and Ecological Effects Branch so permit, the Experimental Use Permit may be granted. Toxicology data on the formulation are adequate to issue this E.U.P.

2. The complete data were not submitted for the acute studies on technical 3,6-dichloropicolinic acid; only data summaries were submitted. The complete data reports should be submitted for the following studies on the technical chemical when the registration application is submitted:

   a. Acute Oral Toxicity of Dowco 290.

   b. Acute Dermal Toxicity of Dowco 290. (Systemic toxicity)

   c. Primary Skin Irritation of Dowco 290.

   d. Primary Eye Irritation of Dowco 290.

3. In accordance with current policy, the data from the 3-generation Reproduction Study in rats conducted by IBT should be audited by the applicant and verified as valid prior to registration of the formulation.

4. Since only summaries and not complete data reports were submitted for the acute studies on the new technical chemical 3,6-dichloropicolinic acid, these studies cannot at present be classified in accordance with CORE standards, and therefore are considered invalid.

5. Labeling should bear signal word DANGER, based on primary eye irritation.

REVIEW OF DATA:

ACUTE ORAL TOXICITY OF DOWCO 290 (96% technical 3,6-dichloropicolinic acid):

LD_{50} in rats = 4300 mg/kg in females; greater than 5000 mg/kg in males (highest dose tested). Study invalid since only a summary report was submitted.

ACUTE ORAL TOXICITY OF LONTREL 205 Herbicide Formulation (M-3785):

LD50 = 3730 mg/kg in males; 2830 mg/kg in females. Toxicity Category III. 5 rats per sex per dosage level were given 252, 500, 1000, 2000, or 3980 mg/kg of the formulation via single dose oral gavage. The only signs of toxicity noted other than death were lethargy and increased dark secretions around the nose and eye in some animals at the 2000 mg/kg level. This is a CORE Guidelines study.

ACUTE DERMAL TOXICITY OF DOWCO 290 (96% Technical Chemical):

LD_{50} greater than 2000 mg/kg. Four rabbits exposed to 2000 mg/kg as a wet paste on the skin for 24 hours survived. Study invalid since only a summary report was submitted.

ACUTE DERMAL TOXICITY OF LONTREL 205 Formulation (M-3785):

2 male and 2 female rabbits were exposed to 3980 mg/kg of formulation for 24 hours in an acute percutaneous absorption test. All animals survived with no signs of toxicity other than mild topical effects. CORE Minimum data. Toxicity Category III.

PRIMARY SKIN IRRITATION OF DOWCO 290: Prolonged skin contact with 3,6-dichloropicolinic acid would likely result in slight redness and very slight swelling. If the skin was abraded or otherwise irritated, contact might result in slight redness, very slight swelling, and a slight chemical burn. Absorption through skin in acutely toxic amounts is not likely to occur. Study invalid since only a summary report was submitted.

PRIMARY EYE IRRITATION OF DOWCO 290: Eye contact with undiluted 3,6-dichloropicolinic acid would likely result in moderate pain, severe conjunctival inflammation, moderate iritis, and severe corneal injury resulting in possible permanent impairment of vision if eyes are not promptly and thoroughly decontaminated. Study invalid since only a summary report was submitted.

PRIMARY SKIN IRRITATION OF LONTREL 205 Formulation: The formulation was applied on 3 consecutive days to the intact and abraded skin of 6 rabbits in a skin irritation test. Slight erythema resulted. Repeated application to covered, abraded skin sites also produced slight edema and necrosis in some cases. CORE Guidelines Study. Toxicity Category IV.

PRIMARY EYE IRRITATION OF LONTREL 205 Formulation: LONTREL 205 was instilled into both eyes of 6 rabbits in an eye irritation test. One eye was washed after 30 seconds exposure. Corneal cloudiness without opacity and inflammation of the iris and conjunctival membranes were seen in all cases. The eyes of 4 of the 6 rabbits were normal by 7 days. Effects persisted in the other two at 7 days. The washing procedure employed did not modify the response. CORE Minimum Study. Toxicity Category I, in absence of greater detail in data report.

ACUTE INHALATION STUDY OF LONTREL 205 Formulation: 5 male and 5 female rats were exposed to the aerosolized test formulation diluted 1 part to 8 parts water in an acute inhalation test. Exposure was for 1 hour. All rats survived and showed no signs of toxicity or irritation. The nominal concentration of the aerosol was 5.03 mg/l with over 99% of the particles 7.0 u in number length mean diameter or smaller. No problem is anticipated from a single, short-term exposure to aerosols of the LONTREL 205 Herbicide. CORE Minimum Study. Toxicity Category III.

SUBCHRONIC TOXICITY OF 3,6-Dichloropicolinic Acid in Rats: A 90-day dietary feeding study was conducted in male and female rats at dosage levels adjusted to provide 0, 5, 15, 50, and 150 mg/kg body weight/day of 3,6-dichloropicolinic acid. Parameters evaluated were appearance, mortality, body weight, food consumption, hematologic determinations, urinalyses, clinical chemistry, organ weights, organ to body weight ratios, and gross and histological examination of tissues. No significant differences were detected between rats receiving any dose of 3,6-dichloropicolinic acid and controls. The NEL in rats is 150 mg/kg or greater/day. CORE Minimum study.

180-DAY SUBCHRONIC TOXICITY STUDY IN BEAGLE DOGS: Study conducted by Litton Bionetics. Feeding of 3,6-dichloropicolinic acid to beagle dogs at dietary concentrations corresponding to intakes of 15, 50, and 150 mg/kg/day for a period of 180 days failed to produce detectable evidence of toxic effects. The NEL in Beagle dogs is 150 mg/kg or greater/day. CORE Minimum Study.

TERATOLOGY: A study was conducted to evaluate the effect of 3,6-dichloropicolinic acid on the developing embryo and fetus of rabbits. In a preliminary tolerance study in which the chemical was administered by oral gavage to nonpregnant female rabbits for 13 days, the maximum tolerated dose level was determined to be 250 mg/kg/day. In the teratology study, bred New Zealand White rabbits were given 0, 110, and 250 mg/kg/day on days 6-18 of gestation. Alterations in demeanor or other signs of toxicity were not observed among dams during or after treatment. Examination of fetuses delivered by cesarean section on day 29 of gestation for external and internal (skin, tissue, and skeletal) malformations revealed no evidence of toxicity to the developing embryo or fetus. Thus, administration of 3,6-dichloropicolinic acid to pregnant rabbits at dose levels up to and including the maximum tolerated dose, 250 mg/kg/day was neither embryotoxic nor fetotoxic. A CORE Guidelines study.

METABOLISM: In order to study its metabolism, ^{14}C-labeled 3,6-dichloropicolinic acid was administered as a single oral dose of 10 mg/kg to male and female rats. ^{14}C-3,6-dichloropicolinic acid was rapidly and virtually completely absorbed following oral administration. The compound was ultimately excreted from the body unchanged in the urine, with $92.20 \pm 3.55\%$ of the administered ^{14}C excreted in the urine by 120 hours following administration. Of this quantity of ^{14}C, 96.46% was excreted with a half-life of 3.05 hours and the remainder with a half-life of 24.7 hours. A CORE Supplementary Study.

TWO-YEAR ONCOGENICITY AND CHRONIC TOXICITY FEEDING STUDY IN RATS: No toxicologic effects were associated with ingestion of 3,6-dichloropicolinic acid for two years by Sprague-Dawley rats at dose levels of 0, 5, 15, 50, and 150 mg/kg/day.

Based on the parameters evaluated, which included body weights, food consumption, demeanor, survival, hematology, urinalysis, clinical chemistries, organ weights, and organ-to-body weight ratios, the only finding which may be related to the ingestion of 3,6-dichloropicolinic acid in the diet was a trend toward a decrease in the mean body weight of female rats at the high dose level, 150 mg/kg/day. No gross pathologic or histopathologic alterations attributable to the effect of ingesting the chemical in the diet for up to two years were observed in any of the treated rats examined. Incorporation in the diet did not cause an increased incidence of neoplasms. Thus, in this two-year study in male and female rats, 3,6-dichloropicolinic acid did not have a carcinogenic or an oncogenic effect. A CORE Minimum Study.

18-MONTH ONCOGENICITY FEEDING STUDY IN MICE: Conducted by Biometric Testing, Inc., Englewood Cliffs, New Jersey.

An 18-month mouse oncology study was run with 3,6-dichloropicolinic acid. The compound did not adversely affect body weight, survival, or produce any pathological changes that could be casually related to its administration when fed at levels of 35, 100, and 350 ppm for 13 weeks to parents and for a year and a half to their offspring. A CORE Minimum study.

THREE GENERATION REPRODUCTION STUDY IN RATS: Conducted by Industrial Bio-Test Laboratories, Inc.

A 3-generation reproduction study was conducted employing albino rats fed diets containing 0, 5, 15, or 50 mg of 3,6-dichloropicolinic acid per kg/day. Parental body weights, body weight gains, mortality, and behavior were not affected. Gross and microscopic pathologic studies revealed no deleterious findings among animals fed the compound.

Parameters of reproductive performance, population data and progeny survival indices were not altered. All progeny were judged to be free of external anomalies and displayed normal growth and behavior. A CORE Minimum Study under the existing guidelines. Since this is an IBT Study, the data are subject to audit or verification.

MUTAGENICITY STUDIES: Conducted by Litton Bionetics, Inc. All these studies meet or exceed CORE Guidelines.

A CYTOGENETIC STUDY was conducted in which 3,6-dichloropicolinic acid was administered by gastric intubation to rats at 4, 40, and 400 mg/kg. Bone marrow cells were examined at metaphase, and there were no significant aberrations of the chromosomes at any of the test dosages in both the acute and subacute studies.