UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Caswell #33DD

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DATE: February 9, 1979

SUBJECT: File Symbol 353-GON. Lexone DF Weed Killer. Metribuzin. 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one. E. I. duPont deNemours & Co. Wilmington, Delaware.

001145

FROM: Roland A. Gessert, D.V.M.; Toxicology Branch

Roland A. Gessert 2/9/79

TO: Mr. Robert Taylor, Product Manager # 25.

THRU: Dr. Lamar Dale, Acting Chief, Toxicology Branch (TS-769)

Applicant seeks to register subject formulation, a non-dusty, rapidly water dispersible, granular formulation containing 75% metribuzin as the active ingredient. A 50% wettable powder formulation and a liquid formulation previously have been registered.

RECOMMENDATION: LEXONE DF Weed Killer (75% metribuzin) may be registered.

Toxicity studies on subject formulation are as follows. All studies were conducted at the du Pont Haskell Laboratory.

ACUTE ORAL TOXICITY, MALE RATS: LD_{50} = 2795 mg/kg. Toxicity Category III.

10 male rats per dose at 4400, 3400, 3000, 2800, and 2500 mg/kg in corn oil. Toxic signs were dyspnea, weakness, chromodacryorrhea, stained body, pilo-erection, and weight loss. Previous studies on the technical chemical demonstrated no difference between male and female rats in regard to toxicity. CORE Minimum data.

ACUTE DERMAL TOXICITY IN MALE RABBITS: LD_{50} greater than 7500 mg/kg. Toxicity Category III

Six male rabbits were clipped of hair and 7500 mg/kg was applied as a 70% aqueous paste under impervious wrappings for 24 hours. This was the maximum quantity which could be contained under the wrappings. There were no deaths during the 14-day observation period. Mild to moderate skin irritation was observed. Adequate data were submitted for the technical chemical by Chemagro. The quantity applied was limited by the size of the rabbit, and no toxicity was observed. No useful purpose would be served by including 2 lower levels. The registrant undoubtedly was clued to the low dermal toxicity by the previous safety studies of Chemagro on the technical chemical. CORE minimum data.

safety studies of Chemagro on the technical chemical. CORE minimum data.

PRIMARY EYE IRRITATION IN RABBITS: Formulation is an irritant. Toxicity Cat. I

Right eyes of 6 rabbits were treated as per 16 CFR 1500.42, and left eyes served as untreated controls. Eyes were examined with a bright artificial light and a hand-slit lamp at 24, 48, and 72 hours after treatment. A graded response of 1 was obtained for keratitis and conjunctivitis, persisting at 72 hours in some animals. Iritis was not produced. CORE minimum data.

PRIMARY SKIN IRRITATION AND SENSITIZATION TESTS ON GUINEA PIGS.

A range-finding study was conducted with three male albino guinea pigs to test for skin irritation potential. The formulation was a skin irritant as low as 25% in distilled water; it did not irritate the skin at 10%.

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Information which may reveal inert ingredients is not included

The primary irritation test was conducted on ten unexposed guinea pigs by applying and lightly rubbing in 0.05 ml of a 20% and a 2% suspension of the test material in physiological saline on shaved, intact shoulder skin.

The induction phase for sensitization was a series of 4 sacral intradermal injections of 0.1 ml of a 1% solution in physiological saline, one each week beginning 2 days after the test for primary irritation.

After a 2-week rest period, the test animals were challenged for sensitization by applying and lightly rubbing in 0.05 ml of a 20% and a 2% suspension of test material in physiological saline on shaved, intact shoulder skin. At the same time 10 unexposed guinea pigs (controls) of the same age received identical topical applications.

LEXONE 75 DF caused mild to no irritation in 24 and 48 hours when tested as a 20% suspension in physiological saline on the shaved, intact skin on guinea pigs. As a 2% suspension in physiological saline, no irritation was observed. At challenge none of the animals showed a sensitization response.

A preliminary range-finding test showed that this material may be a mild skin irritant. CORE guidelines study.

PRIMARY SKIN IRRITATION IN RABBITS: Toxicity Category IV.

Six rabbits were clipped free of hair on the trunk and lateral areas and placed in stocks. 0.5g solid test material were applied as an aqueous paste to intact and abraded skin under 1" x 1" gauze squares. Rubber sheeting was wrapped around the trunk and secured with adhesive tape. After 24 hours the rabbits were removed from the stocks, the patches removed, and the reactions observed. Observations were also made at 72 hours and scored according to the regulations of the Federal Hazardous Substances Act. LEXONE 75 DF is not a primary skin irritant. CORE minimum data.

INHALATION STUDIES conducted by Chemagro on the technical chemical and on 50% wettable powder at 20 mg/liter exhibited neither symptoms nor mortality. Those data are applicable to this formulation. Toxicity Category IV.

INERT INGREDIENTS [redacted]

RESIDUE TOLERANCES currently exist as shown on following page:

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RESIDUE TOLERANCES: §180.332 4-Amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5 (4H)-one; tolerances for residues.

Tolerances are established for conbined residues of the herbicide 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5 (4H)-one and its triazinone metabolites in or on raw agricultural commodities as follows:

0.6 part per million in or on potatoes.

0.2 part per million in meat, fat, and meat byproducts of cattle, goats, hogs, horses, poultry, and sheep.

0.1 part per million in or on soybeans, and sugarcane.

0.01 part per million in eggs.

0.01 part per million in milk.

[40 FR 2804, Jan. 16, 1975; 40 FR 11874, Mar. 14, 1975, as amended at 40 FR 55350, Nov. 28, 1975]

PROPOSED LABELING: is in conformity with that previously accepted.

POST HARVEST INTERVALS conform with those recommended by Residue Chemistry Branch.

The PRECAUTIONARY STATEMENTS, after HAZARDS TO HUMANS, KEEP OUT OF REACH OF CHILDREN, should be revised according to requirement set forth in the 40 CFR part 162.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

332

DATE: May 3, 1977

SUBJECT: File Symbol 352-GIE. LEXONE 4L Metribuzin Weed Killer.
4-Amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one
E. I. DuPont De Nemours & Co., Wilmington, Delaware

FROM: Toxicology Branch

001145

TO: Mr. Robert Taylor, Product Manager # 25

This is a liquid formulation of an herbicide already registered by Chemagro as a wettable powder. Chemagro has furnished authorization to refer to their data in behalf of du Pont. Applicant seeks registration for use on soybeans; a residue tolerance of 0.1 ppm for combined residues of 4-amino-6-(1,1-dimethyl-ethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one and its triazinone metabolites in or on soybeans has been established, and is set forth in 40 CFR 180.332. Data indicate the wettable powder and the liquid formulations to be comparable in both safety and efficacy aspects.

Toxicity data for LEXONE 4L are as follows:

Acute Oral Toxicity, rats	LD_{50} = 2390 mg/kg
Acute Dermal Toxicity, rabbits	LD_{50} greater than 7500 mg/kg
Skin Irritation Test, rabbits	Primary Irritation Score = 3.2 Not a primary irritant
Eye Irritation Test, rabbits	Is an irritant

An acute inhalation toxicity test in rats, conducted by Chemagro, revealed an LC_{50} greater than 1920 ug/liter. They were unable to produce signs of toxicity. Chemagro data also indicate the herbicide is not carcinogenic in mice. Rat breeding studies show no effects on fertility, litter size, lactation performance, and growth rate of the offspring at the 35 or 100 ppm levels.

The formulation falls within Toxicity Category III, carrying the signal word, Caution.

RECOMMENDATION: Toxicology Branch has no objections to registration of LEXONE 4L Metribuzin Weed Killer.

Roland A. Gessert 5

Roland A. Gessert, D.V.M.
Toxicology Branch

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

001145

DATE: May 6, 1977

SUBJECT: File Symbol 3125-GRU. SENCOR 4 Flowable.
4-Amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one
Chemagro Agricultural Division of Mobay Corporation

FROM: Toxicology Branch

TO: Mr. Robert Taylor, Product Manager # 25

This is a liquid formulation of an herbicide previously registered as a wettable powder. Applicant seeks registration for use on soybeans; a residue tolerance of 0.1 ppm for combined residues of 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one and its triazinone metabolites in or on soybeans has been established, and is set forth in 40 CFR 180.332. Data indicate the wettable powder and the liquid formulations to be comparable in both safety and efficacy aspects.

Toxicity data for the liquid formulation are as follows:

Acute Oral Toxicity, rats	LD_{50} greater than 500 mg/kg
Acute Dermal Toxicity, rabbits	LD_{50} greater than 20,000 mg/kg (no symptoms or pathology observed)
Acute Inhalation Toxicity, rats	LC_{50} greater than 1920 ug/l (no signs of toxicity observed)
Skin Irritation, rabbits	Did not cause irritation
Eye Irritation, rabbits	- Report showed substance to be corrosive, with effect reversed within 72 hours.

In regard to the eye irritation test, it seems a bit irregular that a substance would produce severe ulceration of the conjunctivae at 1 hour. It also seems irregular that a grade 4 ulceration would be observed in 3 rabbits on day 1, would be cleared up on day 3, but that no effect would be observed on the cornea. Was fluorescein used in any of the examinations?

RECOMMENDATION: Withhold registration pending an explanation for the erratic results obtained in the Eye Irritation Study.

Roland A. Gessert

Roland A. Gessert, D.V.M.
Toxicology Branch