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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

CASWELL FILE

DATE: June 26, 1978

SUBJECT: EPA Reg. No. 1023-36 - Amended Registration

PC 031301

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Toxicology Branch, RD (WH-567)

TO: E. Wilson, PM #21
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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

Registrant: The Upjohn Company
Kalamazoo, Michigan 49001

Product: Botran 75W Fungicide
(2,6-dichloro-4-nitroaniline)

Caswell No: 311

The registrant proposes to change the signal word from WARNING to CAUTION.

40 CFR 180.200 has set tolerances for this product for the food items included on the label. BOTRAN is on the Kennedy list (see Ritter memo to D. Campt, Jan. 19, 1978) and is listed in the Mrak report for possible tumorigenic effects. However, since TOX Branch has adequate two-year feeding studies in dogs and rats (D. Ritter opinion, signed by R. Engler, Jan. 19, 1978), no action on this issue is due related to this amended registration.

Recommendation:

TOX Branch cannot approve of the signal word change until an adequate eye irritation study is presented.

Summary of Acute Studies:

Oral LD_{50} (rat)	>4640 mg/kg	III	Core-Minimum
Inhalation LC_{50} (rat)	>21.6 mg/kg	IV	" "
Dermal LD_{50}(rabbit)	>6320 mg/kg	III	" "
Eye effects (rabbit)	Nil	IV	INVALID
Skin effects (rabbit)	Nontoxic	IV	2 tests Invalid, 1 test Core-Minimum

Review of Toxicity Studies Submitted:

A. Acute Oral Toxicity (LD_{50}) in the male albino rat.

International Research and Development Corporation, 400-039, 1/31/67.

Spartan male albino rats weighing from 167 to 200 gms were used. Doses of 100, 215, 464, 1000, 2150 and 4640 mg/kg BOTRAN 75W were used to dose the rats.

All of the animals at each of the lower doses (to 2150 mg/kg) remained essentially normal throughout the observation period and no mortality resulted.

The rats at the highest dose showed signs of bradycardia, bradypnea, hypothermia, and hypoactivity within five hours after treatment. They returned to normal within 2 days.

The LD_{50} was thus considered to be greater than 4640 mg/kg. This test is CORE MINIMUM. Females were not tested and necropsy was not performed on the survivors. But sufficient data with this chemical are available to classify this product as a category III toxicant.

B. Acute Inhalation of BOTRAN 75W

Woodward Research Corporation, June 28, 1965.

5M and 5F albino rats obtained from Charles River Breeding Laboratories were exposed for 1 hour to a dust of BOTRAN 75W at a concentration of 21.6 mg/li of air. A Wright dust feed chamber was used. The range of concentration was 23.6 to 19.6 mg/liter (25% respirable range).

No deaths occurred as a result of this exposure. No changes in internal organs (as revealed by autopsy). Weight gains were normal as were the weight gains of the internal organs.

This test is CORE MINIMUM.

C. Acute Dermal LD_{50} on rabbits

WOODWARD RESEARCH Corporation, July 27, 1965

12 adult albino rabbits were dosed, 4 per group, 2 males and 2 females, with 6,320, 2,000 or 632 mg/kg of BOTRAN 75W. The rabbits were adequataly prepared for a dermal LD_{50} appraisal by both shaving and abrading. 24 hours were allowed for the test material to act.

No compound related death resulted. One rabbit in the low dose group died of apparent acute enteritis. No gross abnormalities were found following autopsy.

This test is CORE MINIMUM. The dermal LD_{50} is greater than 6320 mg/kg.

D. Subacute Dermal Toxicity Study

WOODWARD RESEARCH Corporation, July 27, 1965.

Three groups of albino rabbits were prepared as follows:

Group I	5M, 5F	Skin intact	controls
Group II A	6M, 4F	Skin intact	1500 mg/kg/day
Group II B	5M, 5F	Abraded skin	1500 mg/kg/day
Group III A	5M, 5F	Intact skin	500 mg/kg/day
Group III B	5M, 5F	Abraded skin	500 mg/kg/day

Doses were given 5 days per week for three weeks for 15 treatments. After 21 days, or the day following the last dose, three males and three females from each group were sacrificed. The remaining rabbits were kept under control conditions until day 35 and then sacrificed.

Results

One rabbit in the high dose level (a male) died of apparent pneumonia. The other rabbits were in good condition throughout the study, with only slight erythema evident at the end of the day's exposure.

The treated groups were comparable to the controls in the following parameters.

Mortality, body weight gain, initial and terminal hematological data, hemoglobin and hematocrit values, total leukocyte counts and thrombocyte counts. Initial and terminal clinical chemistry data including SGPT and SGOT, methemoglobin and BUN. No gross pathology at autopsy, at sacrifices on either the 21st or the 35th day. No histopathological findings.

This test is CORE MINIMUM. No consistant or serious abnormalities were found to be attributable to BOTRAN by the dermal route of exposure for a subacute study.

D. Eye irritation

1) An interoffice memo to E.S. Feenstra from R. Johnston, R. Schwikert, M. Fairbanks apparently all employees of the Upjohn Company describes the following experiment. The memo date is Oct. 22, 1964.

"a small amount of test material" was instilled into the left conjunctival sac of each of two rabbits twice daily for 5 days. The eyes were examined daily during the treatment period and two days afterward. Under the conditions of the experiment the occuloirritant property of BOTRAN was very slight.

This test is INVALID. The amount of material instilled is not stated. No method for grading the eye irritation is given. The coding system used in the results is not interpretable. An insufficient number of rabbits were used for the test.

2) A second memo involving the same apparent employees of Upjohn and dated October 21, 1964 describes the following experiment:

"4 drops of the test material (2 lbs/100 gallons of water) were instilled into the left conjunctival sac of two rabbits twice daily for five days."

No occular irritation developed.

This test is CORE INVALID. An insufficient number of animals were used. The method of grading the irritation is not described. A diluted material was used.

E. Skin irritation

1) A memo to E. Feenstra from R. Johnston, R. Schwikert, and M. Fairbanks all apparent employees of the Upjohn Company dated Oct. 21, 1964, describes the following experiment:

BOTRAN 75W was applied to the abraded and unabraded skin of each of two rabbits once a day for five days. There were no essential differences between the control and treated abraded and unabraded skin reported.

This test is INVALID. Not enough rabbits were used, the amount of material applied is not stated.

2) A second memo with the same date describes the following experiment:

BOTRAN (2 pounds/100 gallons) was applied topically to the abraded and unabraded skin of each of two rabbits once a day for five days. The material was possibly slightly irritating to the abraded skin of the back in one rabbit.

This test is CORE INVALID. The amount applied is not sated, insufficient number of rabbits were used. A diluted material was used.

3) A third test was conducted by M.W. Glenn, D.V.M of the Upjohn Company, dated March 10, 1967.

BOTRAN 75W was applied once to the abraded and unabraded skin of each of three rabbits. Skin changes were recorded at 24 and 72 hours after application. Six rabbits were used for this test.

No skin changes were observed at 24 and 72 hours following application of 500 mg of the test material. For example the primary irritation index was 0.

This test is CORE MINIMUM.

R/D Initial GEWhitmore 6/20/78
JD/ccw
E for GEW 6/28/78