UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 0020 3

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DATE: February 15, 1978

SUBJECT: Bayleton, Fungicide for use on azaleas
Caswell No. 862AA

FROM: J. D. Doherty

TO: E. Wilson, Product Manager #21

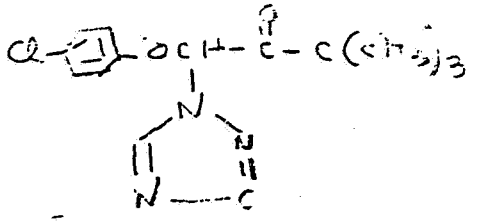
R. Engler E for GEW 5/13/78

Registration Numbers: 03125 00GRI (PA 318)
03125 00GRO (PA 319)
03125 00GEN (PA 320)

Products: Technical Bayleton (8% Inerts)
50% Wettable Powder (50% Inerts)
25% Wettable Powder (75% Inerts)

Registrant: Chemagro Agricultural Division
Mobay Chemical Corporation
Kansas City, Missouri 64120

Chemical:
Active Ingredient:



1-[1,2,4-trizolyl-1]-1-4-chloro-phenoxy-3-dimethylbutanone-2
Inerts are not stated

Recommendations:

Most of the studies presented meet CORE minimal guidlines (see review as follows) However, registration must be withheld until the 50% and 25% formulations are relabelled to conform to toxicity category II on the basis of the eye irritation studies.

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For example, corneal damage, (reversible in 7 days) and conjunctival irritation (not reversed in 7 days) was reported for these formulations. This is criteria for category II.

The eye irritation study on the technical material is unacceptable because the amount instilledin the eye was not stated.

These formulations are otherwise of little hazard to the users who will most likely be homeowners and commercial or public gardeners.

We also request a confidential statement of the formulation and confirmation that the product does not contain nitrosamines.

A. Review of Studies with Bayleton 25%

1) Acute Oral LD_{50} (52868)

i) Chemical Agricultural Division, Mobay Chemical Corporation, March 31, 1977.

ii) 10 male and 10 female Sprague-Dawley rats per dose were treated with doses of 1000, 2000, 4000, 8000 mg/kg of a water suspension of 25% Bayleton. Animals were observed for toxicity for 14 days.

iii) Bayletom was found to be slightly more toxic to males (LD_{50} = 2828 ± 924 mg/kg) then to females (LD_{50} 3668 ± 1252 mg/kg). Signs of toxicity were hyperactivity in cluding increased sexual activity in males, followed by sedation before death.

iv) CORE minimal. Formulation is category III.

2) Acute Dermal Toxicity LD_{50} (52867)
i) Chemical Agricultural Division, Mobay Chemical Corporation, # 76-282 February 25, 1977.

ii) 4 male and 4 female rabbits per group were shaved and abraded and treated with doses of 2000 or 5000 mg/kg of Bayleton 25% and exposure was for 24 hours.

iii) No animals died. One female developed reversible diarrhea. Some rabbits had pale kidneys but no gross lesions were noted.

iv) CORE minimal LD_{50} is greater that 5000 mg/kg.

3) Acute Inhalation (52871)

i) Chemagro Agricultural Division Mobay Chemical Corporation, 68-27, April 20, 1977.

ii) Ten male and 10 female rats were exposed to Bayleton 25% Wettable Powder for 1 hour at a concentration of 20 mg/liter of air. The animals were observed for signs of toxicity and mortality for 14 days.

iii) None of the animals showed signs of toxicity or changes in body weight. Two of 10 females and 3 of the males showed signs of chronic focal pnemonia.

iv) CORE minimal LC_{50} of Bayleton 25% wettable powder is greater than 20 mg/liter of air.

4) Primary Skin Irritation (51594)

i) Chemagro Agricultural Division, Mobay Chemical Corporation 76-282, February 1, 1977.

ii) No procedure is given but reference to Federal Hazard Substances Act. Section 191.11 (21 CFR).

iii) At 24 hours, one animal exhibited slight erythema on both intact and abraded sides. The Primary Irritation Index was 0.06.

iv) CORE minimal

5) Primary Eye Irritation (53105)

i) Chemagro Agricultural Division Mobay Chemical Corporation, 76-282, May 10, 1977)

ii) 9 New Zealand White Rabbits were instilled with 50 mg portions of test material. Six rabbits were left unwashed, the remaining three were washed 45 seconds after instillation.

iii) Wash group: Conjunctival irritation was noted that was reversed in 7 days

Unwashed group: 2 of the 6 rabbits showed corneal damage that was reversed in 7 days.

iv) CORE minimal. 2 of the 6 rabbits showed corneal damage, 1/6 showd no reversal of irritation in 7 days this places the chemical in category II and not III as indicated.

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B. Review of Studies with 50% Bayleton

1) Acute Oral LD_{50} (52867)

i) Chemagro Agricultural Division Mobay Chemical Corporation, 76-282, March 31, 1977.

ii) 10 male and 10 female rats were used per dose group and were treated with 259, 500, 1000, 2000, mg/kg of Bayleton 50%.

iii) Signs of toxicity were hyperactivity, biting and antagonism. Some swelling of the head and neck and pilo erection were noted. Males appeared to be sexually stimulated within 24 and 48 hours post treatment. The formulation was found to be more toxic to males (LD_{50} 812±206 mg/kg) them to females (LD_{50} 1470 ± 435 mg/kg).

iv) CORE minimal

2) Acute Dermal LD_{50} (51722)

i) Chemagro Agricultural Division Mobay Chemical Corporation 75-144, February 15, 1977.

ii) Backs of rabbits were shaved and abraded. Formulation was applied to test areas and covered with plastic at 2000 mg/kg.

iii) No signs of toxicity were observed anytime during the study. No gross lesions were noted by necropsy examination.

iv) CORE minimal. LD_{50} is $>$ 2000 mg/kg.

3) Acute Inhalation (52870)

i) Chemagro Agricultural Division Mobay Chemical Corporation 68-22, 76-234, April 20, 1977.

ii) 10 male and 10 female rats were exposed to Bayleton 50% for one hour at a concentration of 20 mg/liter.

iii) No animals died or showed signs of toxicity during the 14 day observation period. No gross pathology could be attributed to this compound.

iv) CORE minimal.

4) Primary Skin Irritation (51595)

i) Chemagro Agricultural Division Mobay Chemical Corporation 75-144, February 1, 1977.

ii) No procedure in given but reference is made to 21 CFR 191.11

iii) No erythema or edema were noted. The Primary Irritation index was 0.0

iv) CORE minimal.

5) Eye Irritation (53106)

i) Chemagro Agricultural Division, Mobay Chemical Corporation 76-282, May 10, 1977.

ii) 9 New Zealand White rabbits were used. 50 mg portions of material were applied to one eye of each rabbit. Three of the rabbits were washed free of the test material 45 seconds after application. The remaining six were not treated with water wash.

iii) Washed Group: Each rabbit showed reversible irritation within seven days in the conjunctiva only.
Unwashed Group: 5/6 rabbits showed corneal damage that was reversed in 4 days. 3/6 rabbits showed iridial damage. All rabbits showed conjunctival irritation, in 4/6 rabbits this was present on 7th day.

iv) CORE minimal. The presence of corneal damage and persistent irritation place this formulation into category II and not III as indicated.

C. Review of Acute Studies with Technical Bayleton.

1) Acute Oral LD_{50}

i) Bayer AG. Institute Für Toxicology # 4416, January 3, 1977

ii) Rats, mice, hamsters, quail, rabbits, dogs and hens were treated for the LD_{50} of Tech. Bayleton.

iii) The following Table summarizes the results.

Animals	Sex	Doses	Animal/Dose	LD_{50}	Route
1) rat	m	25-2500	15	568±61	gavage
2) rat	f	"	15	363±41	"
3) mouse	m	"	15	987±171	"
4) mouse	f	"	15	1071±124	"
5) rabbit	f	100-750	33	500	"
6) dog	f	100-500	2	500	"
7) hen	f	1000-5000	1-5	5000	"
8) quail	f	750-2500	5	1750±2500	"
9) rat	m	10-750	15	321±38	I. P.
10) rat	f	10-500	15	293±22	I. P.

General health impairment, breathing disorders, signs of excitation, then drowiness. Livers reveal ulcerations.

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iv) CORE minimal. Various LD_{50}'s determined

2) Acute Dermal Application

i) Bayer AG. Institute Für Toxicology # 4416, January 3, 1974.

ii) An Acetone emulsion of 1000 mg/kg was applied to the backs of each of 5 rats and kept in place for seven days.

iii) All rats survived the treatment. Some symptoms intoxication were reported but not sepecified.

iv) CORE mimimal should have used rabbits and determined the LD_{50}, but rats are acceptable because low degree of toxicity is adequately demonstrated.

3) Acute Inhalation Toxicity

i) Bayer AG. Institute Fur Toxicology #4416 January 3, 1974.

ii) A test preparation dissolved in ethanol and lutrol was sprayed into a 3 c. n. inhalation chamber. Exposure was for 4 hours at concentrations of 174 mg/m^3 and 291 mg/m^3.

iii) Mice, rabbits and hamsters in addition to rat were tested at 174 mg/m^3. Neither sex of test animals showed signs of toxicity. At 291 mg/m^3 all exposed animals were affected. 11/20 mice died, but the other animals survived.

iv) CORE minimal. The preparation is a category III toxicant.

4) Primary Skin Irritation

i) Bayer AG. Institute Fur Toxicologie # 4416, June 3, 1974.

ii) The test was carried out by the method recommended by the U. S. Dept. of Agriculture (1969)

iii) Only minimal erythema on intact skin. Moderate erythema and some superficial erosion on the skin of abraded rabbits was seen. It appears that at 72 hours the irritation to the abraded areas was maximal. No additional reservations were made. The overall Draize score was reported to be 1.3/8.0.

iv) CORE minimal. Abraded areas should have been observed until reversal. The test however shows that the compound is not a severe skin irritant.

4A. Skin Irritation on human volunteers

i) Some slight redness of short duration was noted in the skin in 5 out of 30 test subjects. This was reversed within 24 hours.

iv) Apparently not an irritant to humans.

5) Eye Irritation

i) Bayer AG. Institute Fur Toxicologie # 4416 January 3, 1974.

ii) Test carried out as recommended by U. S. Dept. of HEW (1972). The dose of Bayleton was applied to the eye for 5 minute and 24 hours.

iii) Conjunctival redness only was observed at 1 hour after application

iv) Invalid Study. Dose applied is not stated if dose was 0.1 ml core minimal data.

6) Acute Dermal Toxicity

i) Chemagro Agricultural Division Mobay Chemical Corporation.

ii) Backs of rabbits were shaved and abraded and 2000 mg/kg of Bayleton Technical was applied and 24 hours were allowed for exposure.

iii) No signs of toxicity were observed at anytime during the study. Necropsy revealed darkened areas of the kidney but no other gross lesions except for pale kidneys.

iv) CORE minimal. LD_{50} 2000 mg/kg.

7) Embroyotoxicity and Teratology

Test A. Oral Administration to rats

i) Bayer AG. Institute Fur Toxicologie, No. 6294 August 27, 1976.

ii) 22-24 inseminated female rats per test group were used per dose level. Doses were 0, 10, 30 and 100 mg/kg. In experiment 2 the compound given by gavage on days 6 thru 15 of gestation (a total of ten days). A 0.5% aqueous Cemphor emulsion was used to suspend the Bayleton and to treat the controls. On the 20th day of gestation the fetuses were removed by Caesarian section and examined for external and internal malformations.

iii) a. Doses of 30 mg/kg and above resulted in less weight gain by the dams during the treatment period. Only the 100 mg/kg treated dams showed a continued loss in weight at the end of gestation. However, at doses as high as 100 mg/kg there were no detrimental effects on physical appearances and behavioral patterns nor were there any deaths among the dams.

b) A no effect level for embryonic and fetal development/teratology was at least 50 mg/kg/day p.o. At both 75 and 100 mg/kg/day. The average placenta weight was slightly higher than the control groups in the second experiment only at the 100 mg/kg/day level. Occasionally cleft palates were seen in the groups treated with 75 mg/kg and above. These equalled only 4 of the 211 in experiment 1 and 3 of 183 in experiment 2 but this deformity is very seldom seen in this strain. All other parameters measured were within acceptable limits for treated and controls

iv) CORE minimal. The NEL was listed at 50 mg/kg/day based upon the slight effect producing cleft palates. It was not firmly established that BAYLETON produced this malformation.

Teratology

Test B. Inhalation administration effects in rats.

i) Bayer Ag. Institute Fur Toxicologic Report No. 6298

ii) 20-22 inseminated females per test group were exposed to an aerosol containing actually 0, 14.03 33.20 and 113.66 mg Bayleton/m^3 of air produced by a dynamic flow apparatus. Treatment was for 10 consecutive days on day 6 thru 15 of gestation for 6 hours daily. Males were not treated.

iii) All dams survived the treatment without an effect on their behavior or physical appearance. There was some statistically significant reduction in weight gain for the dams treated with 33.2 mg/m^3, but dams at higher lower dose did not. Malformations occurred in all groups and were spontaneous rather thru compound related. No teratogenic effect was noted, no cleft palate formation was observed.

iv) Acceptable study, no teratogenic or embryotoxic effect was noted by the inhalation route. Core minimal study, however, not presently required for purposes of registration.

Test C. Oral Administration in Rabbits.

i) Bayer AG. Institute Fur toxicologie No. 6297, August 30, 1976

ii) 10-13 inseminated females per group at dosage levels of 5, 15 and 50 mg/kg of Bayleton were given by gavage to Himaleyan rabbits on days 6 thru 18 (13 dose) of gestation. Males were not treated.

iii) a. The does were not affected by treatment with Bayleton at any level. No deaths attributable to the compound were noted, although one rabbit in the 5 mg/kg and 1 rabbit in the 15 mg/kg group died.

b) There was no indication that BAYLETON had a teratogenic effect at dose levels up to and including 50 mg/kg. No evidence of cleft palate was observed.

iv) CORE minimal. No teratogenic effect noted.

Summary of Teratogenic Studies

The three studies above support the registration of this product and give no indication that embroytoxicity or teratogenesis hazard exists with the use as directed. The occurance of cleft palates in one experiment was small but is not considered serious or proven to be compound related. The low incidence of occurance at the relatively high doses of 75 and 100 mg/kg do not warrant repetition of the study at higher doses.

8) Mutagenicity Test

A. Dominant Lethal Test

i) Bayer AG. Institute Fur Toxicology No. 5837, June 27, 1976

ii) Groups consisting of 20 male and 480 female mice were used. Males were treated with 200 mg/kg of Bayleton. Starting the day of administration of the test material series of 8 meeting at one week intervals were carried out. Females were separated from the males and examined for pregnancy.

iii) The male mice showed no signs of ill effects after administration of the test compound. No detrimental effect on fertilization resulted. It was possible that an increased fertilization quota resulted.

iv) No indication of Bayleton being a mutagenic agent has been demonstrated.

B) Micronucleus Test

i) Bayer AG. Institute Fure Toxicologie, 6622, February 23, 1977.

ii) Groups of 10 mice, (5 males and 5 females) received 2 applicatoons of test material at an interval of 24 hours. Bayleton was administered at the dose of 2 x 10 mg/kg. Erythrocytes (polychromatic) and the incidence of micronuclei in this cell type were scored.

iii) No statistically significant differences between the group treated with Bayleton and the control group with respect to incidence of micronuclei in the polychromatic erythocytes. However, the ratio of polychromatic erythrocytes to monochromatic erythrocytes was 1:66 to 1 in the Bayleton group and 0.93:1 in the control group. This difference was statistically significant. Theotepa gave expected positive results.

iv) The increased polychromates to monochromate erythrocytes was not relavant to proving that Bayleton was a mutagenic agent. This observation may mean that Bayleton causes an increased rate of erythropoiesis.

C. Ames Test

i) Katholike Universiteit Leuven, Laboratorium Voor Hygeine. September 27, 1976.

ii) Bayleton was not demonstrated to be a mutagen or a carcinogen by this test at doses of 5 to 1000 µg/ml in Salmonella Typhimurium and other species of bacteria.

John D. Doherty

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