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

002005

MEMORANDUM

DATE: January 24, 1980

SUBJECT: 3125-EUP-RAL and 3125-EUP-RAO. Bayleton 50% Wettable Powder. Request for Experimental Use Permit on Grapes, Apples and Pears and Temporary Tolerances in or on Apples, Fresh Pears, Fresh Grapes

Caswell No. 868 AA

Acc. Nos. 99161, 99162 and 99163

Petition No. O G 2300

FROM: Alex Arce, Toxicology Branch (TS-769)

TO: R. Panebianco, PM Team 21 (TS-767)

THRU: Dr. Adrian Gross, Chief Toxicology Branch (TS-769) W. Butler for Adrian Gross

Registrant: Mobay Chemical Corporation
Agricultural Chemicals Division
Kansas City, Missouri 63120

Action Requested:
a) Experimental Use Permit on Grapes
b) Experimental Use Permit on Apples and Pears
c) Temporary Tolerances in or on Apples, Fresh Pears, Fresh Grapes

Recommendations

a) Tox. B. cannot envision any overt hazard associated with the implementation of the above requested actions

Background Information

Existing Tolerances: There are no existing tolerances for this chemical. The Temporary tolerances proposed are as follows:

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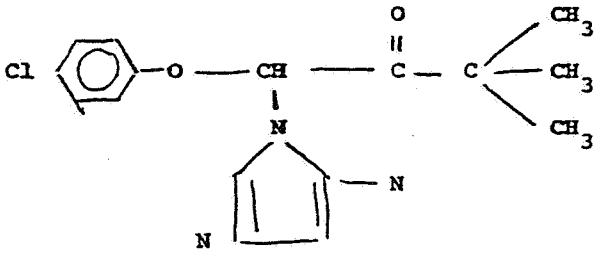
Apples, fresh	0 days interval between last application and harvest	0.75 ppm
Pears, fresh	0 " "	0.75 ppm
Grapes	14 " "	1.0 ppm

Chemical Name 1-(4-chloropehnoxy)-3,3-dimethyl-1-(1H-1,2,4,-triazol-1-yl)-2-butanone

Synonyms Bay-Mab 6447

Chemical Structure $C_{14}H_{16}ClN_3N_3O_2$



Formulation

Bayleton Tech 55.0% Active Ingredient

[redacted]

Inert Ingredients has been cleared under CFR 40 -180.1001 c&e

Uses: Used as a herbicide, to control powdery mildew and cedar-apple rust

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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Summary of all past actions

a) March 22, 1979 — Section 18 exemption emergency use-Washington-perennial ryegrass

b) March 22, 1979 — Section 18 exemption emergency use-Oregon-perennial ryegrass and bluegrass

c) February 16, 1979 — Section 18 exemption-Oregon-perennial ryegrass and Kentucky bluegrass

Summary of Toxicity Data on files

From Memo Dated February 15, 1978 (Doherty to Wilson)

Review of Studies with 50% Bayleton

Acute Oral LD50 (52867) Rats	LD50 = 435 mg/kg. Core minimal
Acute Dermal LD50 (51722) Rats	LD50 > 2000 mg/kg. Core minimal
Acute Inhalation (52870) Rats	No mortality, one dose 20 mg/l. Core minimal
Primary Skin Irritation (51595)	Negative. Core minimal
Primary Eye Irritation (53106)	Corneal damage reversible. Tox. Cat II. Core minimal

Review of Acute Studies with Technical Bayleton

Acute Oral LD_{50}

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 drowsiness. Livers reveal ulcerations.

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Core Minimal. Various LD50's determined

Acute Dermal - Rats - > 1000 mg/kg in acetone. LD50 was not determined. Core minimal.

Acute Inhalation toxicity. Mice, rabbits, Hamsters and Rats concentrations of 174 mg/m^3 and 291 mg/m^3. Core minimal. Toxicity Category III

LC50 > 174 mg/m^3

Primary Skin Irritation - Rabbits. Negative - Core minimal.

Skin Irritation - Humans - Apparently not an irritant for humans.

Eye Irritation - Invalid study. Dose applied is not stated.

Acute Dermal Toxicity - Core minimal LD50 > 2000 mg/kg

Chronic Toxicity

Embryotoxicity and Teratology

Oral Administration to Rats - Positive teratogenic effects at 75 mg/kg. NOEL 50 mg/kg/day - Core minimal

Inhalation Administration effects in Rats - Negative for terata and embryotoxicity at dose of 113.66 mg/m^3 - Core minimal

Oral Administration in Rabbits - Negative effect up to and including 50 mg/kg (highest dose tested) - Core minimal

Mutagenicity

Dominant Lethal Test - Negative for mutagenicity

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Micronucleos Test - Negative for mutagenicity

Ames Test - Negative at doses from 5 to 1000 ug/ml in Salmonella Typhimurium for mutagenicity

The above toxicological data have been found acceptable and can be use on behalf of a petition for an EUP.

Review of Data Submitted in P.P. 3125 EUP 149 received on 12-15-77 Acc. No. 232490

Bayleton™ (Formerly Bay Med 6447) Human Safety, dated June 18, 1977.

Chemagro Agricultural Division, Mobay Chemical Corporation, Kansas City, Mo.

This review includes the studies that were previously submitted on behalf of the various actions already noted, but were not evaluated.

Summary. Product MEB 6447

Subchronic Toxicity Study on Rats (Twelve-week Feeding experiment)	NEL > 2000 ppm
Subchronic Toxicity Study on Dogs (Thirteen-week feeding experiment)	NEL > 2400 ppm

Formulation 6681 (WP) Toxicity Studies Bayleton 25%

Single Oral Administration Rats	LD50 = 4,725 mg/kg

Oral Administrations - Fasted and fed cats	LD50 > 500 mg/kg
Intraperitoneal application - Male and Fem Rats	LD50 = 889 mg/kg m 631 mg/kg f
Dermal Application - rats	No symptoms at 1000 mg/kg
Inhalation Tox-rats	LC50 = 334 mg/m^3
Dermal Irritation - Rabbits (ears)	Negative
Eye Irritation - rabbits	Negative

Product-MEB 6447 Subacute Toxicity Studies (Technical)

30-day Oral Administration - Rats M and F	NEL = 3 mg/kg males 10 mg/kg Females
4 hours Inhalation - Rats	LC50 > 453 mg/m^3
6 hours inhalation exposure Rats	(15 exposures) NEL = 78.7 mg/m^3

Product MEB 6447 Subacute Dermal Cumulative Toxicity Study On Rabbits

Dermal Application for 4 weeks M-F Rabbits	NEL = 250 mg/kg Induced slight erythema and edema in the intact and abraded areas.

Bayleton 25% WP

Dermal Irritancy - Rabbits Primary Irritation Index 0.06

Bayleton™ 50% WP

Subacute Dermal Toxicity to rabbits

3 weeks - 6 to 8 hours per day/500 mg/kg - negative

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Data Review

Subchronic Toxicity Study On Rats (Twelve-week feeding experiment) Product MEB 6447. Report No. R 840a Bayer AG Institut fur Toxikologie Hanover, Nov. 1976

EPA 3521 EUP-149 ACC 232490

Procedure: 150 rats were divided into 5 groups of 15 males and 15 females per group and feed the material incorporated into their diet at the following levels: 0 = control, 50, 200, 800 and 2000 ppm; for 12 consecutive weeks.

Daily physical observations were performed and body weights and food consumption were measured weekly.

Hematology, clinical chemistry and urine analysis were performed prior to dosing, at 6 weeks and at termination.

At the end of the study, autopsies were performed and tissue saved for histopathological examinations.

Results

Mortality: Some animals died while under anesthesia given for exanguination. No animals died due to the administration of the material.

Signs of Toxicity: Unremarkable

Body Weights: Significant difference between the control and highest level treated apparently due to palatability of diet

Food Consumption: Lower at highest level, also due to palatability

Hematology: Difference in the hemoglobin levels of the males at the 12th week, at all levels, was not significant.

Clinical Chemistry: Significant differences in animals in all test groups, but not remarkable when compared to the control animals.

Urinalyses: Unremarkable

Autopsies: Reddened and swollen glandular mucosa of the stomach was observed in the treated groups. Reddening area of the jejunum and a prominent lobular pattern of the liver in the different treated groups. Such signs and other abnormal conditions were observed in the control animals.

Histopathology: Various findings are noted, but they are not related to treatment. Histological confirmation was not obtained for the reddening and swelling of the glandular mucosa of the stomach. NOEL = 2000 ppm Core Minimum Data

Subchronic Toxicity Study on Dogs (Thirteen weeks feeding experiment)

Report No. 5071 Product MEB 6447

Procedure 32 dogs were divided into groups of 4 males and 4 females per group and fed, for 13 weeks, the material incorporated into their diets at levels of 0 = control, 150, 600 and 2,400 ppm. The animals were observed daily for physical appearance and body weights were taken weekly.

Ophthalmoscopic examinations, hematology, clinical chemistry and urinalysis tests were performed prior to dosing at the 6th week and at termination.

Sections of tissue from various organs were fixed for histopathological examination.

Results

Mortality: None

Signs of Toxicity: Decrease in body weight at the highest dose, most likely due to the palatability of the material.

Food consumption: Reduced at the high level apparently due to palatability

Body Weights: Reduced at the high level due to decreased food consumption

Hematology: Reduction of Hematocrit value, erythrocyte count and hemoglobin volume at 2,400 ppm

Clinical Chemistry: microsomal enzyme induction in the liver of the dogs fed 2,400 ppm. Alkaline phosphatase increased in comparison with the preliminary values.

Necropsy: Unremarkable

Histophatology: Shows no signs indicative of liver damage. Other tissues were normal.

Conclusion: The administration of MB 6447 at the 4 doses of 0, 150, 600 and 2,400 ppm to male and female dogs for the period of 13 weeks failed to produce obvious signs of toxicity. (NOEL = 2,400 ppm)

Core Minimum Data

Formulation 6681 WP 25%

Toxicological Studies - Oral Administration

255 Male and Female rats were divided in groups of 15 males and 15 females per group and dosed by oral intubation as follows:

Males 100, 250, 500, 1000, 2500 and 5000 ppm and females 100, 250, 500, 1000, 1500, 2000, 2500, 3500 and 5000 ppm. The animals were observed for a period of 21 days post dosing.

Results

Mortality LD 50 Males = 4,725 (3230-6913) mg/kg
Females = 2,140 (1640-2575) mg/kg

Signs of Toxicity such as breathing disorders, cramps, and excitation were observed at autopsy; perforation of the gastric wall was observed in some animals.

Classification: Core Minimum Study

The toxic signs are not clearly defined.

Tox Cat III

Intraperitoneal Administration

255 rats were divided into 8 groups of 15 males per group and 9 groups of 15 females per group and dosed intraperitonealy at the following levels

Males 50, 100, 250, 500, 750, 1000, 1500 and 2000 ppm

Females 50, 100, 250, 350, 500, 750, 1000, 1500 and 2000 ppm

Observations lasted for 21 days

Results

Mortality: LD 50 Males = 889 (670-1149) mg/kg
Females= 631 (524-748) mg/kg

Toxic Signs: Similar to those observed in the oral administration.

Classification: Core Minimum

Dermal Application

The emulsified product was applied to the dorsal skin of shaved rats. It was left in contact for 24 hours, washed with soap and water and observed for 14 days post application.

Results: Negative results after application of a dose of 1000 mg/kg

Classification: Supplementary Data - This was summary data

Inhalation

10 male and 10 female rats were placed in an inhalation chamber and subjected to the product dissolved in a mixture of ethanol/ lutrol (1:1) in a dynamic flow inhalation apparatus for a single run of 4 hours.

The first exposure was 158 mg/m^3 and the second exposure was 354 mg/m^3

Observations lasted for 14 days

Results

None of the rats died. It was stated that, "Brief impairment of the health condition resulted after the exposure to the high dose."

Classification: Supplementary Data

LC50 was not determined

Test for skin irritation (rabbits)

500 mg of the material was applied to the ears of 2 rabbits for 24 hours. Spray prepared from the same formulation was tested in similar manner.

Results

No irritation was observed in either animal

Classification: Supplementary Data

Not enough information submitted. The method was not stated.

Number of animals used is not sufficient.

Test for eye irritation in rabbits

"Approximately 50 mg" of the material was instilled into the conjunctival sac of the eye of each two rabbits

"In similar manner, spray was tested"

Results

No irritation of the eye was observed.

Classification: Supplementary Data

Only two animals used

Method used is unknown.

Dose level not stated

MEB 6447

Subacute Toxicity Studies

Bayer AG Institut Fuer Toxikologie

Report No. 4464 Jan. 25-74

Subacute Oral Administration (Rats)

Male and female rats were divided into groups of 15 animals/group/sex and dosed at 3, 10 and 30 mg/kg body weight for 30 days.

Control animals received a mixture of acetone in oil.

Daily observations were made and at the end of the study the animals were sacrificed and tissues were fixed for Histopathological examinations.

Results

Mortality: All animals survived

Body weights: Unremarkable

Hematology: Unremarkable

Clinical Chemistries and Uranalysis: Unremarkable

Necropsy: Unremarkable

Organ Weights: Liver of animals at the 30 mg/kg level were significantly higher than controls.

Histopathology: Unremarkable

Classification: Core Minimum Data

should be 10 mg/kg/day
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NEL 30 mg/kg

Inhalation Toxicity Experiment

Male and female rats were divided into 3 groups of 10 animals per group/sex and exposed to concentrations of the material at the following levels

(Group 1)

Control - mixture of ethanol/lutrol (1:1)

(Group 2)

78.7 mg/m^3 air

(Group 3)

307 mg/m^3 air

The animals were exposed to the material 6 hours a day for 15 days in a period of 3 weeks.

Daily physical inspections were made.

At autopsy, the organs were inspected and blood was collected for hematology and clinical chemistry studies.

Results

Mortality: All animals survived

Signs of Toxicity: Unremarkable

Body Weights: Decrease in body weight at the high dose level

Hematology and clinical chemistry: Unremarkable

Necropsy: Unremarkable

Classification: Supplementary Data

Information regarding the inhalation chamber used and the aerosol was not included.

Subacute Dermal Cumulative Toxicity Study on Rats (4 weeks)

Report No. 6352 Bayer AG Institut Fuer Toxikologie Sept. 13, 1976

Groups of 6 male and six female rabbits were dosed with the material on the shaved backs and flanks for a period of 4 weeks, 5 days a week, 7 hours a day. Half of the animals of each sex had the test areas abraded and the other half intact. A similar control group was also used.

Doses

(Control) = 0 mg/kg, (group 1) = 50 mg/kg (group 2) = 250 mg/kg

The product was emulsified with polyethylene glycol 400 and the dosed animals were immobilized. The treated areas were uncovered.

Hematology, clinical chemistry and urinalysis test were performed.

Autopsies and Histological studies were performed.

Results

Mortality: 3 animals died due to physical injuries caused while being secured in the animal holder but not due to the administration of the material.

Signs of Toxicity: Unremarkable

Body Weights: Not different than the controls

Skin Irritation: Moderate in the intact skin animals, marked in the abraded skin animals.

Hematology, clinical chemistry and urinalysis: Unremarkable

Autopsies: Unremarkable

Histopathology: Unremarkable

NEL = 250 mg/kg

Classification: Core Minimum Data

Bayleton 6447

Chemagro Agricultural Division

The product was tested following instructions from the Federal Hazardous Substances Act, Section 191.11 (21 CFR 191.11)

Acute Dermal Irritancy 25% WP

6 rabbits were tested with the material applied the abraded and intact areas of skin and observed for 48 hours.

Results - Negligible minimal irritation resulted.

Classification - Core Minimal Data

Observations lasted for 48 hours only

Tox Category IV

The Dermal Irritancy of Bayleton 50% WP

6 rabbits were tested with the material applied to the abraded and intact areas of their skins and observed for 48 hours. Dose = 500 mg

Results - The product induced no irritation

Classification: Core Minimal Data - Tox Cat IV

The Acute Dermal Toxicity Oi Bayleton Tech

2 male and 2 female rabbits were dosed with the material applied to the shaved and abraded areas of their backs and observed for 14 days.

Results

Mortality: LD 50 > 2000 mg/kg

Signs of Toxicity: No signs of toxic effects were observed.

Classification: Supplementary Data

Only 4 rabbits were used, and only one dose was applied

The Acute Dermal Toxicity of Bayleton 50% WP

2 male and 2 female rabbits were dosed with the material applied to the shaved and abraded areas of their backs and observed for 14 days.

Results

Mortality: LD 50 > 2000 mg/kg

Signs of Toxicity: None

Classification: Supplementary Data

Only 4 rabbits were used and only one dose was applied.

Subacute Dermal Toxicity to Rabbits 50% W.P.

Twenty rabbits were divided in 2 groups of 5 males and 5 females per group and dosed in the shaved areas of their backs for 6 hours a day, five days a week for 3 weeks.

Daily observations were made and body weights were taken at intervals.

Hematology, blood chemistry and urinalysis tests were performed.

Histopathological examinations were conducted on tissue from all animals.

Doses
5 males and 5 females --- Control

5 males and 5 females --- 500 mg/kg

Results

Mortality: All animals survived

Signs of Toxicity: Unremarkable

Body Weights: Unremarkable

Dermal Irritation: Severe

Hematology, clinical chemistry and urinalysis: Slightly different than controls

Microscopic findings: Unremarkable

Classification: Core Minimum Data

Conclusion

The DataBank accumulated on behalf of this product is sufficient and acceptable for the purpose of granting an EUP.

C. Frick 3/26/80

NO CFR number — Dayleton — 3/26/80

File last updated 3/26/80

ACCEPTABLE DAILY INTAKE DATA 002005

RAT, Older	NOEL	S.F.	PADI	MPI
mg/kg	ppm		mg/kg/day	mg/day/60kg
50.000	1000.00	2000	0.0250	1.5000

Current Action PP0G2300

CROP	Tolerance	Food Factor	mg/day/1.5kg
Apples(2)	0.750	2.53	0.02846
Grapes, not raisins(67)	0.750	0.45	0.00506
Pears(116)	1.000	0.26	0.00383

MPI	THRC	% ADI
1.5000 mg/day/60kg	0.0374 mg/day/1.5kg	2.49

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