002009

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

MEMORANDUM

DATE: APR 18 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: 1. Bayleton Residue Tolerances on Fresh Grapes and Apples (PP# 1F2474)
2. Bayleton Residue Tolerances in Grape Juice and Wine
3. Bayleton Residue Tolerances on Feeds
PP# 1H5292)
(Reg. No. 3125-320, Acc. No. 099912, Caswell No. 862 AA)

FROM: George Z. Ghali, Ph.D.
Toxicology Branch, HED (TS-769) G. Ghali 4-15-81

TO: Henry Jacoby (PM 21)
Registration Division (TS-767) H. Jacoby 4/15/81

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

Action Requested:
1) Establishment of a tolerance of 2 ppm of Bayleton residues on fresh grapes and 1 ppm on apples.
2) Establishment of tolerances of 2 ppm in grape juice and wine.
3) Establishment of tolerance on seed grass straw and chaff at 30 and 45 ppm respectively.

Conclusions and Recommendations:
1) Toxicology Branch recommends for the establishment of the tolerances for fresh grapes (2 ppm) and apples (1 ppm).
2) The question of residues in grape juice and wine has been addressed before in a memo by G. Ghali to H. Jacoby on June 25, 1981 in reference to PP# 1H5282.
3) Toxicology Branch defers to the RCB the question of residues in feeds as to whether residues would occur in eggs, milk and meat of animals fed on diet containing Bayleton residues at the proposed tolerance levels.
4) The reviewer of this petition considers that the teratology aspects are not adequately delineated until the raw data and background on historical terata incidence in the strain of rats used in this study, are submitted and reviewed as previously requested by Roger Gardner, memo of 4/16/81 to Donald Stubbs. However, an adequate margin of safety (MOS) exists to cover for this toxicity area (teratology) at the highest possible residue tolerance granted on food commodities.

1-312

Existing Tolerances:

There are Tox. approved (unpublished) tolerances for this pesticide, as follows:

Apple, fresh	1.00 ppm	pp#1F2474
Pears, fresh	1.00 ppm	pp#0G2300
Grapes, fresh	2.00 ppm	pp#1E2459, 1F2474
Wheat	0.10 ppm	pp#1G2432
Barley	0.10 ppm	pp#1G2432
Chick Peas	0.10 ppm	pp#1E2459
Tomatoes	0.20 ppm	pp#0E2393
Melons	0.20 ppm	pp#0E2349
Cucumber	0.10 ppm	pp#0E2393

Formulation:

Bayleton technical 55.0% (Active ingredient)

[redacted]

All inert ingredients have been cleared under 40 CFR 180.1001 c and e.

Toxicology Data:

A. Bayleton 50% W.P.:

(memo) by John Doherty dated 2/15/78)

1. Acute oral, rats, LD_{50} 435 mg/kg
2. Acute dermal, rats, LD_{50} > 2000 mg/kg
3. Acute inhalation, rats, LC_{50} > 20 mg/L
4. Primary skin irritation, negative
5. Primary eye irritation, corneal damage, reversible.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

B. Bayleton, technical:

(memo by J. Doherty 1/9/80, A. Arce 1/24/80)

1. Acute oral, rats, LD_{50} 568 mg/kg (male), 363 mg/kg (female), Core minimal.

2. Acute I.P. rats, LD_{50} 293 (female) 321 mg/kg (male).

3. Acute dermal, rats, LD_{50} > 1000 mg/kg, Core minimal.

4. Acute inhalation, mice, rabbits, hamsters and rats. LC_{50} > 174 mg/m^3, Core minimal.

5. Primary skin irritation; rabbits, negative.

6. Skin irritation, human, Not irritant.

7. Eye irritation, invalid study, dose was not reported.

8. Embryotoxicity and teratology:

In an oral administration study in rats, occasionally cleft palates were seen in the groups treated with 75 mg/kg/day and above. These equaled only 4 of the 211 of one experiment and 3 of 183 in another experiment. However, this deformity is seldom seen in this strain. A no-effect level for embryonic and fetal development/teratology was at least 50 mg/kg/day (J. Doherty, 1978).

In a later memo by Roger Gardner dated 4/16/81 it was concluded that the cleft palates observed in this study may not be attributable to Bayleton treatment. However, the memo also indicated that the raw data and background on the historical terata incidence in this strain of rats are needed to further evaluate the significance of this effect.

From the information available until now, the compound is questionably positive with a clear-cut no-effect level for teratogenic effect of 50 mg/kg/day.

Inhalation administration, rats, negative for terata and embryotoxicity at dose level of 113.6 mg/m^3.

Oral administration, rabbits, negative up to and including 50 mg/kg (highest dose tested).

9. Mutagenicity:

Dominant lethal test, negative for mutagenicity.

Micronucleus test, negative for mutagenicity.

Ames test, negative at doses from 5 to 1000 ug/ml.

10. Subchronic toxicity:

Twelve-week feeding, rats, NOEL > 2000 ppm.

Thirteen-week feeding, dogs, NOEL > 2400 ppm.

11. Subacute toxicity:

Thirty-day oral administration, rats, NOEL 3mg/kg (male), 10 mg/kg (female).

Four-hours inhalation, rats, 15 exposure, NOEL 78.7 mg/m^3.

Cumulative subacute dermal application for four weeks, rabbits, NOEL 250 mg/kg.

12. Chronic Toxicity

(memo by G. Z. Ghali, 3/80)

Two-year feeding (oncogenicity) in rats; NOEL 50 ppm.

Two-year feeding study in dogs, not oncogenic, NOEL 100 ppm.

Multigeneration reproduction study, rats, NOEL 50 ppm.

13. Data Submitted with the Current Petition:

Two-year feeding (oncogenicity) study in mice, not oncogenic, NOEL 50 ppm (review attached).

C. Toxicology Data Gap:

1. An adequate and appropriate metabolism study in mammals.
2. The raw data and background on the historical terata incidence in the strain of rats, used in the teratology study, as requested by Roger Gardner, memo of 4/16/81 to Donald R. Stubbs.

Two-Year Feeding (Oncogenicity) Study in Mice.

Review

Test Chemical: Bayleton (MEB 6447) technical grade (97%), Batch No. 16002/75.

Experimental Animals: This study was conducted on SPF mice (CF_1/ W74 strain), obtained from Winkelmann, Borchen. At the start of the study the animals were 5 to 6 weeks old and weighed about 22g and 20g for males and females respectively. The animals were housed singly and kept under constant conditions throughout the whole experiment. The feeding experiment lasted 24 months.

Testing laboratory: This study was conducted in April 1976 through April 1978 by Bayer AG, Institute fur Toxikologie.

I. Experimental Design:

A. Number of Animals and Dietary Concentrations:

Groups of 50 males and 50 females were maintained for 24 months on diet containing Bayleton (MEB 6447) at concentrations of 0, 50, 300, and 1800 ppm. Additionally, 10 mice per sex per dose were included in the study for laboratory tests and intermediate necropsies.

B. General Checks:

Animals were observed daily for any symptoms. Body weights were recorded on a weekly basis during the first 12 weeks, and at 3 week intervals thereafter. Food consumption was reported.

C. Clinical Laboratory Tests:

These tests were performed on five males and five females of each group at 6 and 12 months after initiation of the experiment, and on 10 males and 10 females of each group at termination. All blood tests were done on blood from anesthetized animals except for blood sugar tests. Blood in all cases was taken from the retroorbital venous plexus.

D. Hematology Tests:

These tests included erythrocyte, leucocyte, thrombocyte and reticulocyte count, hemoglobin content, hematocrit value, differential blood count, and calculation of MCH and MCV values.

E. Clinical-Chemical Tests:

Alkaline phosphatase (ALP), glutamate-oxalacetate transaminase (GOT), and glutamate-pyruvate transaminase (GPT) activities were measured. Creatinine, blood sugar, cholesterol, bilirubin levels and total protein in plasma were determined.

F. Necropsies:

Mice that died or killed in moribund condition during the feeding experiment were dissected and grossly examined, and tissues were fixed either in Bouin's solution or in a 10% formaldehyde solution.

At intervals of 6 and 12 months after initiation of the test, five of each of the additional males and females from each group were anesthetized with ether, sacrificed and dissected. The thymus, heart, lungs, liver, spleen, kidneys, adrenals and testes were weighed.

At termination of the study all survivors were anesthetized by ether, sacrificed by exsanguination, dissected, and grossly examined. The heart, lungs liver, spleen, kidneys, adrenals and testes were weighed.

At the intermediate and terminal necropsies, these tissues in addition to the brain, pituitary, thyroid, stomach, pancreas, urinary bladder, ovaries, uterus and all macroscopically identified alterations were fixed in 10% buffered formalin.

G. Histopathological Examinations:

Histopathological examinations were performed by Consultox Laboratories, Ltd., London. The following tissues were submitted for examination: brain, pituitary, thyroids, heart, lungs, stomach, liver, spleen, pancreas, kidneys, adrenals, urinary bladder, gonads, uterus and all macroscopically observed alterations.

II. Results:

A. General Checks:

Treated animals did not differ from controls in appearance, behavior and activity during the feeding experiment.

B. Food Consumption and Test Compound Intake:

The data for food consumption was reported as an average per group. No significant difference has been observed between controls and treated groups.

C. Body weights:

Males and females of the 50 and 300 ppm groups made about the same body weight gains as the control except for some occasionally statistically significant difference between these groups and the control that did not appear to be treatment related on a constant basis. However, in the 1800 ppm group, the difference from the control was statistically significant.

D. Mortality:

The test chemical did not have appreciable effect on mortality rate after six months of administration. However, at 12 months, the mortality rate increased for the males at dosage levels of 300 ppm (14.0%) and 1800 ppm (16.0%) and for females at the dosage of 50 ppm (8.0%), 300 ppm (10.0%), and 1800 ppm (6.0%) compared to a maximum mortality of 4.0% and 2.0% for the control males and females respectively. There was no evidence whether this effect is a treatment related, since this effect has not been observed at 18 and 24 months.

E. Clinical Tests:

1. Blood tests:

The blood testing was performed on 5 males and 5 females of each group, after 6 and 12 months. Mice of the 50, 300 and 1800 ppm groups did not show any difference from the controls in respect to erythrocyte count, reticulocyte count, leucocyte count, thrombocyte count, hemoglobin content, hematocrit percent volume, MCH, MCV and differential blood count. There was no alteration in the different blood cell types.

Blood testing performed on 10 males and 10 females of each group at the termination of the experiment showed that both males and females of the 1800 ppm group had statistically significantly higher numbers of erythrocytes than the controls ($P<0.05$). The males of all treated groups had statistically significantly lower MCH values than the controls ($P<0.05$). The females of the 1800 ppm group had statistically significantly higher thrombocyte count ($P<0.05$), hemoglobin levels($P<0.05$), hematocrit levels ($P<0.01$) and MCH ($P<0.05$).

2. Liver function tests:

At 6 months, alkaline phosphatase (ALP), GOT, GPT activities and the levels of bilirubin and total protein in plasma did not show any statistically significant difference from controls in the 50 and 300 ppm groups. However, statistically significantly higher alkaline phosphatase activities were recorded for the males ($P<0.05$) and higher GPT activities for the females ($P<0.01$).

At 12 months, liver function tests did not reveal any toxicologically significant or dose related difference for mice fed dietary concentrations of 50 and 300 ppm. Dietary concentration of 1800 ppm produced a significantly higher GOT activity and lower plasma protein in males ($P<0.05$).

At the end of the feeding experiment, however, significantly higher ALP, GOT, GPT activities were observed for both males and females of the 1800 ppm group.

3. Kidney function tests:

At 6 months the mean urea concentrations measured in the plasma of 5 males and 5 females per group did not exhibit any statistically significantly difference from the control. The mean creatinine concentrations exhibited a significantly lower values ($P<0.05$) in the males of the 50 and 300 ppm groups and in the females of the 1800 ppm group at 12 months.

At 24 months a significantly ($P<0.05$) lower urea and creatinine concentrations have been observed in males of the 50 ppm group while in females significantly lower urea concentrations have been observed in the 50 and 300 ppm groups ($P<0.01$) and in the 1800 ppm groups ($P<0.05$).

4. Blood sugar and cholestrol:

The blood sugar and cholesterol concentrations in plasma were measured in 5 males and 5 females per group at 6 and 12 months ans in 10 males and 10 females per group at 24 months. No significant difference has been observed between the treated groups and the control.

III. Necropsies:

A. Mice died or killed in a moribund condition during the experiment:

No treatment-related pathological alterations were seen in any of the mice fed 50 and 300 ppm. In the 1800 ppm group, there was an increased number of mice with a swollen enlarged liver.

B. Mice sacrificed after 6 and 12 months and at termination:

Gross pathology performed on the mice sacrificed at 6 and 12 months and on termination of the experiment did not reveal any signs of specific damage in the groups fed 50 and 300 ppm.

At the end of the feeding experiment, there was an increased number of mice with swollen livers in the 1800 ppm group. some of the livers were hardened and some were brittle. Liver lobe adhesions were seen in some mice.

C. Organ weights:

The group mean absolute weights of thymus, heart, lung, liver, spleen, kidneys and testes, measured in 5 males and 5 females per group at six months showed that males of the 1800 ppm group had statistically higher liver weights than the controls ($P<0.01$). Females of the same group showed heavier liver weights than the control, however, the difference was not statistically significant.

At 12 months, the absolute mean liver weights of all treated males were significantly lower than those of the controls, although the differences were not dose related. The heart weights of the 1800 ppm males were also significantly lower than those of the controls (P<0.05).

In th males, the absolute mean kidney weights were signi cantly higher at 50 ppm (P<0.01) and lighter at 1800 ppm (P<0.05) ppm than the controls. Additionally, the thymus and heart weight of the females were significantly lower at 300 (P<0.05) and 1800 (P<.01) ppm, and the lung weights were significantly lower at 1800 ppm (P<0.01).

At termination, males of the 1800 ppm group had statistically significantly lighter kidneys than the control (P<0.01). Males of the 50 ppm group also showed significant decrease in kidney weight compared to the controls (P<0.05).

Males and females of the 1800 ppm group showed a significant increase in liver weight (P<0.01).

IV. Histopathological Examinations:

A. Non-neoplastic lesions:

There was no indication of treatment-related effects at dietary levels of 50 and 300 ppm. Dietary level of 1800 ppm was associated with an increase in the incidence of hyperplastic liver nodules in both male and female mice. Other nonneoplastic lesions seen were distributed among all groups (dose-unrelated) as follows:

Lungs

Indications of upper respiratory infection. This was exemlifoed by either pneumonitis or pneumonia and was present in some animals in all groups. No effect of treatment was observed.

Liver

In neither males nor females was there any effect associated with feeding the compound at levels of 50 or 300 ppm. In the high dose groups (1800 ppm), more mice had hyperplastic liver nodules than mice in the other treatment groups or the control groups (15 males and 15 females on 1800 ppm compared with 7 males and 4 females in the control groups). The nodules encountered in all groups were of the type normally found in control mice. Other parenchymal lesions in the liver; necrotic foci or areas of infarction, variation in cell size and other lesions frequently encountered spontaneously in mice were seen in all groups but as with nodules there was some evidence, although not so clear cut that livers in animals on 1800 ppm were more affected than those in the other groups.

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Kidney

Cysts have been observed in both males and females. These did not appear to be related to other renal disease such as glomerulonephrosis. It was seen principally in male mice and has a high incidence in both low and medium treatment groups and the Control group. However, only two males on 1800 ppm had the condition. Fewer females were affected and no effect of treatment was observed.

Uterus

Cystic endometrialhyperplasia was common in the female mice but again no effect of treatment was observed. Again fewer animals were affected in the high dose group.

To summarise treatment did not appear to have adverse effect on the incidence of various lesions other than liver parenchymal nodules.

B. Neoplastic lesions:

The tumor profile provided no indication that Bayleton had any influence on total tumor incidence, on the number of mice with tumors or on incidence of single tumor types.

Comparison of the individual histopathological findings with the gross pathology findings for mice that died during the experiment shows that the treatment also had no influence on the time of tumor occurance.

Few liver adenomas were observed in all dose groups. The incidence did not vary markedly being almost identical in the four male groups (2/control group, 2/50 ppm, 1/300 ppm, 2/1800 ppm) and occuring at a similar level in the low (1) and high (2) treatment group in females. In no animal was there any sign of gross malignancy or metastasis.

Adenomas of the lung formed the orther principal type of benign tumour encountered. The incidence was not affected by treatment in either male or female groups. Nomalignant lung tumour was seen.

The few other benign neoplasms at various sites were distributed unrelated to the treatment.

Apart from an adenocarcinoma of the mammary gland seen in a male mouse on 300 ppm, lymphosarcomas and reticulum cell neoplasms formed the only malignant tumcurs seen in this study.

These neoplastic lesions of the reticulo-endothelial system are common in mice. The incidence in female mice varied from 9 in the control group to 16 in the low (50 ppm) group and dropped to 7 in the medium group and 10 in the high dose group.

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Treatment thus had no significant effect on incidence. Similarly in the male mice there was no dose response in the incidence of lymphosarcomas and reticulum cell neoplasms and differences bewteen control and treatment groups were not significant (1/0 ppm, 4/50 ppm, 2/300 ppm, 3/1800 ppm).

There is no evidence that treatment with Bayleton affected the types and frequencies of benign or malignant neoplasms.

V. Conclusion:

1. The type, localization, incidence and time of occurance of the tumors seen provided no indication of Bayleton having oncogenic effects.

2. Dietary concentration of up to 50 ppm was tolerated by male and female mice, except for some variable and toxicologically insignificant effects.

3. The NOEL can be established at 50 ppm. although mean creatinine ... exhibited a significant ... value in ... this level would be considered as a NOEL.

VI. Classification:

Core-Minimum.

NC Case Number Bayleton 7/9/81

002009

File last updated 7/9/81

ACCEPTABLE DAILY INTAKE DATA

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

Unpublished, Tox Approved 0G2300,1G2432,0E2393,1E2459,0F2349

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Apples(2)	0.750	2.53	0.02646
Pears(116)	1.000	0.26	0.00383
Barley(8)	0.100	0.03	0.00005
Wheat(170)	0.100	10.36	0.01554
Cucumbers,not pickl(47)	0.100	0.34	0.00051
Tomatoes(163)	0.200	2.87	0.00862
Grapes, not raisins(67)	2.000	0.45	0.01349
Melons(92)	0.200	2.00	0.00601
Chick peas (214)	0.100	0.03	0.00005

MPI	THRC	% ADI
1.5000 mg/day(60kg)	0.0766 mg/day(1.5kg)	5.10

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Current Action - PP# 0G2300 - revised Sec F

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Eggs(54)	0.010	2.77	0.00042
Milk&Dairy Products(93)	0.010	28.62	0.00429
Meat,inc poultry(89)	0.010	13.85	0.00208

MPI	THRC	% ADI
1.5000 mg/day(60kg)	0.0833 mg/day(1.5kg)	5.56

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