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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: JUN 25 1981

SUBJECT: Request for the establishment of a tolerance of 0.2 ppm of Bayleton (MEB 6447) in/on grapes "fresh" and 0.2 ppm in/on melons imported into the United States. (EPA Reg. 3125-318, Acc. # 099412-13, Caswell # 862 AA, Petition # 0F2349).

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

G. Ghali
K.Y. 6-2-81

TO: Henry Jacoby (21)
Registration Division (TS-767)

Registrant: Mobay Chemical Corporation
Kansas City, Missouri

Action Requested: Establishment of a tolerance of 0.2 ppm of bayleton residues in/on grapes "fresh" and in/on melons imported into the United States.

Recommendations:

Toxicology Branch recommends for the establishment of the proposed tolerances for melons.

In view of the fact that Toxicology Branch had previously recommended for the establishment of a tolerance of 2.00 ppm for Bayleton residues on fresh market grapes (PP#1F2171), it will not be possible to grant a tolerance of 0.2 ppm on imported fresh market grapes as requested (Pet 0E2349). Toxicology Branch, therefore, recommends for the establishment of a tolerance of 2.00 ppm for both US grown fresh market grapes and fresh market import grapes to avoid a double standard problem.

Related Actions:

EPA Reg. #3125-318, PP#0G2300, 3125-EUP-RAL, 3125-EUP-RAO, 3125-EUP-149

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Formulation of Bayleton (25% WP):

Active Ingredient

1-(4-chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl) -2-butanone 25%

Inert Ingredient

[redacted] INERT INGREDIENT INFORMATION IS NOT INCLUDED

The inert ingredients of the proposed formulation are all cleared under Section 180.1001(c) or (d) (John Worthington, RCB, April 10, 1980).

Proposed Uses:

For use as a fungicide for the control of various diseases on grapes and melons. Bayleton will be used on grapes at the rate of 5.7-8.6 oz./acre and on melons at the rate of 7 oz./acre.

Toxicology Data:

(See John Doherty memo, February 15, 1978)

A. Bayleton 25% W.P.

Acute oral LD_{50}, rat, 2,828 mg/kg (male), 3,668 mg/kg (female)

Acute dermal LD_{50}, rabbit, > 5,000 mg/kg

Acute inhalation LC_{50}, rat > 20 mg/l

Primary eye irritation; reversible corneal opacity.

Primary skin irriation: not irritating.

B. Bayleton, technical:

1. Acute Studies:

Acute oral, rats, (568 mg/kg (male), 363 mg/kg (female).

Acute I.P. rats, LD_{50} 293 and 321 mg/kg for females and males respectively.

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

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

Primary skin irritation: rabbits negative.

Skin ittitation: rabbits negative.

Skin irritation; human. not ittitant.

Eye irritation; invalid study, dose was not reported.

2. Mutagenicity:

Dominant lethal test, negative for mutagenicity.

Micronucleos test, negative for mutagenicity.

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

3. Subchronic toxicity:

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

Thirteen-week feeding, dogs NOEL > 2400 ppm.

4. Subacute toxicity:

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

Four-hours inhalation, rats, LC_{50} > 453 mg/m^3.

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

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

5. Chronic Toxicity: (submitted with this report)

Two-year feeding (oncogenicity) in rats; not oncogenic, NOEL 50 ppm.

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

Multigeneration reproduction study, rats NOEL 50 ppm.

6. Embryotoxicity and Teratology:

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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 up to a dose level of 113.6 mg/m^3.

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

Toxicology Data Gap:

An adequate metabolism study in an appropriate animal species.

Toxicity Studies Submitted with this Petition:

I. Two-Year Feeding Rats with Bayleton:

This study was conducted by the Institute fur Toxikologie, Wuppertal-Elberfeld, West Germany in July 26, 1978.

Materials and Methods:

Three hundred young Wistar rats with an initial body weight of 85g for males and 78g for females and initial age varied between 32 and 39 days were used in this study. Fifty male and fifty female rats were fed 50, 500 or 5000 ppm of Bayleton per day for 24 months. The material was mixed with pulverized altromin R diet. A control group of 100 male and 100 female rats was used and fed the pulverized diet containing no Bayleton. The mixed diet was prepared once a week. The animals had constant access to feed and tap water. All rats were examined daily for physical appearance, behavioral changes, body weight, food consumption, clinical effects, and toxic and pharmacological responses.

Gross Pathology:

Rats died before the termination of the experiment were dissected grossly examined and neoplasms were fixed in 10% buffered formalin solution. At the termination of the experiment all rats were sacrificed, dissected and grossly examined. The brain, heart, lungs, liver, spleen, kidneys, adrenals, testes and ovaries were removed and weighed.

For the histological examinations, the following tissues were fixed in Bouin's solution for 30 hours and then transferred to 70% alcohol: aorta, eyes, intestine, femur, brain, urinary bladder, heart, testes, pituitary, liver, lung, lymph nodes, parotid glands, seminal vesicle, thyroid and uterus, as well as all macroscopically identified alterations.

Clinical Chemistry Tests:

Tests were performed on 5 male and 5 female rats of each dietary concentration group, at intervals of 1, 3, 6 and 12 months after the start of the experiment, then on 10 male and 10 female rats of each dose group at the end of the 24 month feeding experiment. The clinical chemistry tests included the following: alkalyne phosphatase, glutamate-oxaloacetate tranferase, glutamate-pyruvic transaminase, glutamate dehydrogenase, creatinine urea, blood sugar, cholestrol, bilirubin, total serum protein, and proteinbound iodine.

Enzyme induction was assayed by measuring N-demethylase activity and cytochrom P-450 concentrations in the liver, in 10 male and 10 female rats of each group.

Urinalysis:

Complete urinalysis examination was performed including test of deposit after centrifugation of the urine in 10 male and 10 female rats of each group.

Haematology:

Haematology studies included, erythrocytes, leucocyte, thrombocyte, reticulocyte counts and differential counts, haemoglobin (HCH) and medium cell volume (MCV) and the measurement of thromboplastin time at the end of the feeding experiment.

Results:

1) General Observations:

Physical appearance and behavioral patterns of the rats fed 50 and 500 ppm did not differ from the controls.

The male and female rats of the 5000 ppm group showed violent motor reactions from about week 23 and consumed hardly any food. Following a heavy loss of weight, the rats began to feed again and regained weight. Between week 31 and 37, there was a repetition of this process and numerous rats died and the last of the survivors were killed in a moribund condition in week 39.

2) Food Consumption:

Male and female rats fed dietary concentrations of the test chemical at 50 and 500 ppm, consumed as much as the controls.

3) Body Weight:

Male and female rats of the 50 ppm group gained weight normally as the controls. In the 500 ppm group, slight body weight depressions (< 10%) were noted for the male rat from week 65 and for the female rats from week 5 compared with controls. These difference were statistically significant. The dietary concentration of 5000 ppm caused heavy, statistically significant ($p < 0.01$) depression of male and female body weights.

4) Mortality:

There was no increase in the mortality rate in the 50 and 500 ppm groups as compared to controls. In the 5000 ppm group, significantly more rats ($p < 0.01$) had died (22% of the males and 80% of the females). In week 39, the last of the survivors (5 male rats) were killed in a moribund condition.

5) Blood Tests:

a. Haematology after one month of feeding, showed that the rats at 50 and 500 ppm groups did not display any difference compared to controls. In the 5000 ppm group, the female rats showed statistically significant reduction ($p < 0.05$) of the haemoglobin content, haematocrit percent volume and thrombocytes count.

It is evident that all treated groups at 3 months and up to 24 months, showed significant differences from the controls to several parameters at different times. The values that were particulary outside or on the boundary of the biological range of variation, were the haemoglobin levels in the female rats of the 5000 ppm groups after 6 months, and the erythrocyte count and haemoglobin levels in the female rats of the 500 ppm group at the end of the feeding experiment.

b. Blood sugar and cholesterol levels measured in the rats of the 50 and 500 ppm groups was within normal range. In the 5000 ppm group, the cholesterol level showed statistically significant increase in female rats after one month and in male and female rats after 6 months.

6) Liver Function Tests:

Liver function tests at 1, 12 and 24 months showed that the values measured for the treated groups did not differ from the control group values.

The values measured for N-demethylase activity and cytochrom P-450 concentration in the liver did not differ significantly from the control values.

7) Thyroid Function:

The thyroid function was tested by measuring protein-bound iodine (PBI) and the values measured for the treated groups did not differ significantly from the control groups.

8) Urinalysis:

The results of the urinalysis on 5 male and 5 female rats per group after 1, 3, 6 and 12 months on the experiment diet and 10 male and 10 female rats per group at the end of the experiment did not reveal any differences between the treated rats and the controls.

9) Some degree of pneumonitis was present in all groups.

Conclusions:

1) The compound does not seem to have any carcinogenic potential under the test conditions and at the dosage levels tested.

2) The NOEL can be established at 50 ppm.

Core-Classification:

Core-Minimum

II. Two-Year Feeding Study in Dogs

This study was conducted from August 1975 to August 1977 on the technical grade of Bayleton, Batch#16004/75 (88.9%) and Batch#16002/75 (92.7%).

Materials and Methods:

Thirty-two Beagle dogs 17-25 week old, and weighed 5.9-7.9 kg were used in this study. Four males and four females were randomly allocated to each of the four groups and housed singly.

The animals were fed pulverized dry feed (Altromin H Chow) containing 100, 330 or 1000 then 2300 ppm. The third group was fed diet containing 1000 ppm for 54 weeks then on 7000 ppm from week 55 to week 104. A control group was fed on diet free of the test chemical. The dogs were provided with tap water. Food and water consumptions were measured. The animals were checked daily for physical appearance and behavioral pattern.

Reflex test, ophthalmoscopy, haematology, clinical chemistry and urinalysis were done at 13, 27, 40, 53, 66, 79, 92 and 104 weeks.

At the end of the feeding study, all dogs were anethetized with Evipan-Na, sacrificed by exsanguination, dissected and grossly examined.

General Checks:

All dogs were examined daily for physical appearance and behavioral patterns. Food and water consumptions were recorded. Body weight gain was measured at 7 day intervals during the first 52 weeks and thereafter at 14 days intervals. The reflex test included pupillary reflex, patellar reflex, flex or reflex and extensor thrust. Body temperature was also checked in the same time.

Ophthalmoscopy:

In the ophthalmoscopic examinations, the conjunctivae and the outer parts of the eye (selera, cornea) were inspected. The transparent media (lens, vitreous humor) and the ocular fundus were examined with the ophthalmoscope.

Haematology:

The haematology tests included, erythrocytes, haematocrits, haemoglobin, thrombocyte, reticulocyte count, differential blood count, medium cell haemoglobin, sedimentation rate and thromboplastin time.

Clinical Chemistry:

The clinical chemistry tests included, blood, sugar, plasma urea, creatinine, bilirubin, cholestrol, sodium, potassium, calcium, total protein, glutamate-oxaloacetate transferase, glutamate-pyravate transaminase, and alkaline phosphatase.

In addition, the N-demethylase activity and cytochrome P-450 were assayed in liver tissues at necropsy.

Urinalysis:

Urinalysis tests included protein, sugar, blood and pH using Combi-Uristix reagents (Ames), in addition to the volume and specific gravity. The positive urines were then examined microscopically and quantitatively graded.

Necropsy:

At the end of the feeding period, all dogs were anethsetized with Evipan-Na, sacrificed, dissected and grossly examined. Brain, heart, liver, spleen, kidneys, pituitary, thyroid, adrenals, testes, ovaries, prostate gland and pancreas were grossly examined and weighed.

The following tissues were fixed in Bouin's solution and in 10% Formal-calcium solution, respectively for histopathological examination: heart, lung, liver, spleen, kidneys, adrenals, pituitary, thyroid, testes, epididymides, prostate gland, uterus, ovaries, Glandula parotis, pancreas, thymus, oesophagus, stomach, duodenum, jejunum, ileum, colen, mesenteric lymph nodes, gall bladder, urinary bladder, eyes, fasciculs optici, nervous ischiadicus, aorta, skeletal muscle (M. quadriceps femoris), bones (sternum and femur) and bone marrow (femur).

The brain was fixed in 4% Formol-calcium solution. In addition, two bone marrow smears were prepared per each dog.

Results:

a. Mortality

All dogs survived the two-year treatment.

b. Clinical observation:

There were no differences in physical appearance and behavioral patterns between the treated and control dogs.

Occasional vomiting observed immediately after feeding and sporadic diarrhoea seen in some dogs of all groups including the control. From the start of the second treatment year, one dog of group III (D826) was seen to vomit mucus and/or food mash after almost every feeding. In weeks 52 and 66, one dog of group I (D816) had epileptiform attacks associated with laboratory tests.

Female dogs of all groups had a good state of nutrition. The female dogs D 836 and D 808 group II temporarily appeared a little lean in the second treatment year. The male dogs, on the other hand, had a less good to moderate state of nutrition except those in group I.

A particular effect seen once or repeatedly in various dogs, mainly in the second treatment year, was the presence of blood in feces. This effect was seen in all groups including control.

c. Food consumption:

Male dogs, except for two (D 839/control; D 825/group I), always completely consumed their food ration. Food intake by the female dogs was much more often incomplete; only D 840/control group, D 803/group II and D 844/group II completely consumed their food rations.
Very incomplete food intake by the Female dogs in group III was treatment related.

Water consumption was about equal in all groups.

d. Body weights:

Both males and females of all treated groups and the control group gained weight normally during the first year. In the second year the control and groups I (50 ppm and II (500 ppm) made a slight weight gain while group III didnot make any gain.

e. Body temperature and pulse rates:

The rectal temperatures in some dogs (D 840/control; D 811, D 825, D 814/group I; D 836, D 810, D 803/ group II; D 755/group III) showed a light transient increase after 13 treatment weeks without any evident cause.

f. Neurological findings:

Testing of the reflexes did not reveal any variations from normal.

2. Ophthalmoscopic findings:

There were symptoms of sporadic conjunctivitis in some dogs and responded to brief treatment with Leukomycin or Scheroson F ophthalmicum. In dog D 781/II the cure was not attainable despite repeated treatment. However, this effect was not treatment-related.

3. Results of Laboratory Tests:

a. Haematology:

The values obtained for haematocit, haemoglobin, medium cell haemoglobin, erythrocyte count, reticulocyte count and thrombocyte count are all within the physiological range and provided no indication of any alterations attributable to dietary administration of the test chemical.
The differential blood counts revealed that all values were within the normal physiological values.
The sedimentation rate was also within the physiological range in all dogs.

b. Clinical Chemistry:

The tests of plasma and Serum showed that the values for glucose, urea, creatinine, bilirubin, cholestrol, total protein, GOT, GPT and the electrolyte concentrations did not differ appreciably between treated dogs and controls.

Alkaline phosphatase activity was slightly higher in group III than in control at the start of the feeding treatment and significantly ($p<0.05$) increased in the second year.

No significant difference in the liver-specific GPT has been observed between treatments and control groups.

c. Microsomal enzyme activity:

The activity of N. demethylase was significantly ($p<0.05$) increased in both female and male dogs of group III. Activity of Cytochrom P-450 showed only a minimal increase at the dietary level of 2,000 ppm.

4. Gross Pathology (Necropsy)

During the course of the feeding study, blood was sometimes seen in the feces in D 811 and 822/100 ppm, D 844, D 807 and D 845/330 ppm, and 834/1,000 resp. 2,000 ppm. However, as lesion or u/ceration were seen in any part of the intestinal region at necropsy. Other treatment related effects were not seen.

5. Organ weight

No appreciable differences in weight were evident between the control group and the three treated groups for the majority of organs. The liver weight in group III was signigicamtly heavier ($p<0.05$) than in other treated groups and the control groups. The average spleen weight in group III was lower than in the other treated groups and control groups. However, the difference was not significant either for the absolute or relative weight.

6. Histopathological Examination:

No treatment related effects have been seen.

Discussion and Conclusion:

1. It can be concluded from all the results of the chronic toxicity study on dogs that Bayleton dietary concentration of up to and including 100 ppm were tolerated by the dogs for two years without causing toxic effects.

2. The NOEL can be established at 100 ppm.

Core Classification:

Core-minimum.

III. Mutagenicity Test in Bacterial Systems:

1. Rec-Assay:

a) Materials and Methods:

Bayleton (technical 97%) was tested using (H-17, Rec^+) and (H-45, Rec^-) strains of Bacillus subtilis with and without metabolic activation. Both tester strains were streaked on B-II agar plate media. Test chemical was dissolved in DMSO and 0.02 ml of each solution was placed on a 10mm diameter filter paper disk. The disk was placed in the plate in a way to cover the starting point of streak. The plates were incubated at 37°c for 24 hours and the inhibition zone was measured. Negative and positive controls were included.

b) Results:

Bayleton did not show any mutagenic activity under the test conditions.

2. Reverse Mutation Assay

a. Materials and Methods

Bayleton (technical) was tested using strains TA 98 and TA 100 of Salmonella typhimurium with and without metabolic activation (Aroclar induced rat liver). The bacterial tester strain was exposed to the test chemical on petri plates, and the plates were incubated at 37°C for 2 days. The number of revertants was counted. Positive and negative controls were included.

b. Results

Again, Bayleton did not cause any increase in the number of revertant colonies beyond the control level.

Discussion and Conclusion:

Only one concentration of S-9 was used in both tests. Two replicates only were done for each treatment. The chemical did not show mutagenic effects in both tests under the experimental conditions.

IV. Multigeneration Reproduction Study on Rats

Materials and Methods:

The study was conducted by Institute Fur Toxikologie, W. Germany on technical Bayleton (batch 16002/75). All histopathological studies were done by Consultox Laboratories, Ltd., London. The study was performed on SPF rats (Wistar W.74 strain), 32 to 39 days old with a body weight of 45-55g. The rats were housed singly and received Altromin R powdered diet and tap water ad libitum.

The rats were divided into four groups, and were fed altromin R powdered diet containing Bayleton at 0, 50, 300 or 1800 ppm. Each test group consisted of 10 male and 20 female rats. The rats were treated with the test chemical thoughout the study period, including mating, gestation and lactation. The test diets were prepared freshly every week by mixing the test compound with powdered rat feed.

The adult rats were weighed weekly. The body weights of the pups were measured immediately after delivery, 5 days after birth, and weekly intervals thereafter.

The rats selected for the study were housed singly until they were sexually mature (approx. 100 days old), then they were mated. During the mating period, two females were housed together with one male for 10 or 20 days. The male rats were rotated so that each female was mated with three different males for a period longer than one estrous cycle. After the mating, the rats were again housed singly.

Immediately after birth, the pups were grossly examined for malformations. Further examinations for malformations were made also during the lactation period.

Necropsy:

The rats which died during the study were necropsized to establish the cause of death.

The 4-week-old pups of the F_{3b} generation were ansthetized with ether, sacrificed by exsanguination and then dissected. The following tissues were fixed in formalin for histopathological examination: eyes; brain, thyroid, thymus, heart, lung, liver, spleen, pancreas, mesenteric lymph nodes, stomach, small intestine, kidneys, adrenals, ovaries, testes, uterus and epididymis.

Results:

1. F_0 Generation (parents)

   a. Behavioral patterns, mortality and body weights to weaned male and female rats:

      During the study period, the rats of the 50 and 1800 ppm groups did not differ in physical appearance and behavioral patterns from the controls.

      Of the F_0 generation, one female of the 300 ppm group died after the 2nd mating.

      There were no significant differences in body weights between treated groups and the controls except for 1800 ppm group where a significant body weight depression was observed in the females ($p<0.01$).

   b. First and second mating of F_0 generations:

      a. Fertility:

         After a pretrentment lasting 70 days, the rats were mated in a ratio of 2:1. After delivering and nursing offspring to weaning followed by a period of recovery, the females were mated for the second time. Fertility was slightly lower for the 1800 ppm group.

      b. Litter size:

         The average litter sizes at birth ($p0.05$) and before and after reduction ($P0.01$) to 10 pups per litter was significantly reduced for the 1800 ppm group (F_{1a}). Some reduction in size was also observed for F_{1b} before reduction. The litter size in the 1800 ppm group was significantly smaller than the control (p 0.05).

c. Lactation rates:

The location performance of dams in the 1800 ppm group was significantly affected where fewer pups were mourished after both matings (p 0.05).

d. Body weights of pups at birth on the average body weights of the young of F_{1a} and F_{16} were not significantly different from those of the control (p 0.05) at birth. The young of 50 and 300 ppm groups made weight gains comperable with those of the control (p 0.05), but in the 1800 ppm group did not gain as much weight. This difference was statistically significant (p 0.05).

2. F_{1b} generation:

a. Body weights and mortality of weaned male and females rats:

Rats fed on 1800 ppm had significantly lower body weight (p 0.01). Of the F_{1b} generation, 3 male and 1 female died of massive bronchopneumonia.

b. First and second mating of F_{1b} generation:

a. Fertility:

Pregnancy rate was significantly reduced in the F_{1a} and F_{1b} in the 1800 ppm group (p0.05).

b. Litter size:

The average numbers of pups delivered per litter after both matings in the 50 and 300 ppm groups were not attected, while the average size of the first litter in the 1800 ppm group was smaller than the control.

c. Lactation rates:

The lactation performance in the 50 and 300 ppm groups were not significantly affected (p0.05), this parameter could not be assessed for the 1800 ppm group because only one single litter was delivered in this group after both matings.

d. Body weights of pups (F_{2a} and F_{2b} generations) at bith and during 4 week lactation period.

The average body weights of the pups at birth in the 50 and 300 ppm groups were not significantly affected. Although the average pup body weight in the single litter delivered in the 1800 ppm group was less than all other groups, the difference could not be tested statistically because of the number of pups was too small.

The growth of the young of the 50 ppm group was almost identical with those of the control during the lactation period for the F_{2a} generation.

After the second mating, only the pups of the 50 ppm group gained weight similar to control ($p > 0.05$) while the pups of the 300 ppm group were less than the controls during the lactation period ($p > 0.05$).

e. Malformations:

The inspection of the pups immediately after birth and during the lactation period did not reveal any signs of malformations.

3. F_{2b} generation:

A. Body weights and mortality of weaned male and female rats:

There were no dose-related or statistically significant difference ($p>0.05$) between rats of the 50 and 300 ppm groups and the control of the F_{2b} generation.

B. First and second matings of the F_{2b} generation:

a. Fertility:

Fertility was not affected in the 50 and 300 ppm groups compared to controls ($p > 0.05$).

b. Litter size:

After both matings the number of pups in the 50 and 300 ppm groups were about as many as the control. The number of survivors in the 50 and 300 ppm groups at 5 days were as large as the control.

c. Lactation rate:

The number of pups in the 50 and 300 ppm groups nourished up to 4 weeks were as large as the control group.

d. Body weight of pups (F_{3a} and F_{3b}) at birth and during lactation period:

No significant effect on growth of the young in the 50 ppm group. However, the young of 300 ppm group mostly had significantly lower body weights than controls ($p. 0.05$).

e. Inspection for malformations:

None of the young of the F_{3a} and F_{3b} generations showed any signs of malformations whether at birth or during the lactation period.

4. Necropsies of young of F_{3b} generation:

One male and one female 4-week old pup from each of 10 mothers in each dose group were anesthetized with ether, sacrificed and grossly examined. No alterations attributable to administration of the test compound were seen.

5. Histopathological examination:

The histopathological examination did not provide any indications of treatment related morphological alterations in the 4-week old pups of the F_{3b} generation.

Conclusions:

The NEL can be established at 50 ppm.

CORE-Classification:

Core-Minimum.

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File last updated 3/24/81

not recorded 3/24/81

ACCEPTABLE DAILY INTAKE DATA

RAT.Older NOEL mg/kg	NOEL ppm	s.f.	ADI mg/kg/day	MPI mg/day(60kg)
2.500	50.00	100	0.0250	1.5000

Unpublished,Tox Approved PP# 0G2300,1G2432

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(6)	0.100	0.03	0.00005
Wheat(170)	0.100	10.36	0.01554

MPI	THRC	% ADI
1.5000 mg/day(60kg)	0.0479 mg/day(1.5kg)	3.19

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Current Action PP# 0E2393,1E2459,0F2349

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cucumbers,not pickl(47)	0.100	0.34	0.00051
Tomatoes(163)	0.200	2.67	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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Proposed / 2 year feeding / rat

Terata. NOEL = 50 mg/kg / 100 = .025 mg/kg = ADI