3-18-82

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

001533

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE:

SUBJECT: Bayleton on Apples and Grapes. (Caswell No. 862 AA; PP No. 1F2474, 1H5292; Acc. No. 070569, 070570).

FROM: George Z. Ghali, Ph.D.
Review Section IV
Toxicology Branch, HED (TS-769)

G. Ghali 3/18/82

TO: Henry Jacoby
Product Manager No. 21
Registration Division (TS-767-C)

and

Environmental Fate Branch, HED (TS-769)

THRU: Christine F. Chaisson, Ph.D.
Review Section IV, Section Head
Toxicology Branch, HED (TS-769)

C.F. Chaisson 3/18/82

Petitioner: Mobay Chemical Corporation
P.O. Box 4913
Kansas City, Mo. 64120

Action Requested:

Establishment of tolerances on apples and grapes at 1.0 ppm.

Establishment of tolerances on grape pomace (wet and dried), apple pomace (wet and dried), and raisin trash at 3.0, 4.0, and 7.0 ppm respectively.

Review of a rat teratology study associated with the above tolerance request.

Evaluation of a revised label as proposed by the registrant.

Conclusion and Recommendations:

1. Bayleton is teratogenic in rats. The risk assessment can not be completed without information on workers exposure. Tox Branch defers to the EFB for workers exposure profile (see Detailed Considerations, next).

178

2. Adequate margins of safety exist for teratogenic and maternal toxicity risks associated with dietary exposure on the basis of a single serving. However, a final recommendation can not be made before the workers exposure analysis is completed by EFB.

3. No recommendations can be made at this time with respect to labeling for the lack of workers exposure information.

Detailed Considerations:

1. The fact that bayleton is a teratogen, implies that any current or future regulatory decision should be based on a complete exposure profile. This includes exposure due to dietary ingestion of the pesticide (dietary exposure) as well as other types of exposures associated with the production and use of this chemical (workers exposure).

   a. Dietary Exposure and Margin of Safety:

   The margin of safety (MOS), defined as the ratio between the NOEL and the exposure, is a useful parameter to assess the risk associated with dietary exposure. The margin of safety can be calculated as follows:

$$MOS = \frac{\text{NOEL (mg/kg)}}{\text{Exposure (mg/kg)}}$$

   For this purpose we will assume arbitrarily that a pregnant womam may consume one pound (450 gm) of apples or grapes (in a single serving) with a residue level of 1.0 ppm (proposed tolerance for apples and grapes). This represents 0.45 mg(0.0075 mg/kg) of the combined residue of bayleton and its major metabolites.

$$MOS\ (\text{terata}) = \frac{50\ \text{mg/kg}}{0.0075\ \text{mg/kg}} = 6666$$

$$MOS\ (\text{Mat. Tox.}) = \frac{10\ \text{mg/kg}}{0.0075\ \text{mg/kg}} = 1333$$

   b. Workers Exposure:

   This parameter is considered an integrated and important component of the overall risk assessment. However, since worker exposure analysis is beyond the jurisdiction of the tox Branch, therefore it's deferred to the Ecological Fate Branch, as per our memo of 3/2/82 to Dr. Dave Severn. Upon the receipt of the EFB report, Tox Branch can then complete the risk analysis and make the necessary recommendations.

2

2. The ADI has been established on the basis of a NOEL of 50 ppm generated from a 2-year feeding study in rat with a 100 fold safety factor. The ADI is calculated to be 0.025 mg/kg/day.

The portion of the ADI utilized by all tox approved tolerances up to this date is 6.19%.

Granting the proposed tolerance for grapes and apples at 1.00 ppm as proposed would constitute 0.03795 and 0.00674 mg in the daily human diet or 2.53 and 0.45% of the ADI respectively.

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.

3

INERT INGREDIENT INFORMATION IS NOT INCLUDED

B. Bayleton, technical:

001533

(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 above information, the compound was questionably positive with a clear-cut no-effect level for teratogenic effect of 50 mg/kg/day.

However, the registrant has just submitted the historical background in addition to another rat teratology study. Review of these data indicated that cleft paletes are treatment - related effects. The NOEL for fetal development/teratology is considered to be at least 50 mg/kg/day, the NOEL for maternal toxicity is considered to be 10 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), Core mininal.

4.

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 and 9/81)

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

Two-year feeding study in dogs, NOEL 100 ppm.

Two-year feeding (oncogenicity) study in mice, not oncogenic, NOEL for systemic toxicity 50 ppm.

Multigeneration reproduction study, rats, NOEL 50 ppm.

Existing Regulatory Actions and RPAR Status:

There are no pending regulatory actions against this chemical, and it is not on the RPAR list.

Review

Teratogenicity Test of MEB 6447 (Bayleton) in Pregnant Rats.

Chemical:

(Bayleton) technical grade 99%, Lot No. Eg 4/75, Pt. 16602/75. (MEB 6447)

Testing Laboratory:

Laboratory of Embryology, Department of Anatomy, St. Marianna University, School of Medicine, Kawasaki, Kanagawa Prefecture, Japan.

Study Identification:

Study No. As 81-3014, Report No. 80257, dated 3/13/81, Acc. No. 070570.

Testing Animal:

Sprague - Dawley rats 9 weeks of age obtained from Charles River-Japan Inc. and acclimated for 2 weeks before mating.

Procedure:

For mating, each female was caged with a male overnight and examined for formation of the vaginal plug in the following morning. The day of finding the vaginal plug was considerd day 0. The test chemical was administered once daily from days 6 to 15 of gestitions at the level, of 0, 10, 25, 50 or 100 mg/kg/day as suspension in 0.5% Cremophor El emulsion by intragastically intubation. One ml of suspension was used per 100g of body weight. Twenty to twenty-one pregnant rats were assigned to each dosage groups except for the 10 mg/kg/day group the number was eventually reduced to 19.

All rats were observed daily for clinical signs, body weight, food consumption. The rats were sacrificed with ether on day 20 of gestation, the abdomen was opened and uterus removed along with ovaries and observed for the numbers of corpora lutea, live fetuses, resorption sites, dead fetuses, sex ratio of fetuses, weights of live fetuses and placentae, deformed fetuses and types of external morphological abnormalities.

One half of the number of live fetuses from each litter were fixed in 90% alcohol and prepared by a modification of the Jensh's technique for skeletal examination. The remaining half of live fetuses were fixed in Bouin's solution and examined with a modified procedure of Wilson.

4

Results:

1. Signs:

Increased motor activity was evident in groups administered 25 mg/kg/day or higher. The degree and duration of these episodes were dose-ralated.

2. Body weight:

During the dosage period, a statistically significant decrease in body weight gain in the 50 and 100 mg/kg groups was observed. However, the weight gains during the entire course of pregnancy did not differ significantly between any treated group and the control group.

3. Food consumption:

No statistical significant differences were observed between control or any treated group.

4. Necropsy:

No treatment-related effects were observed for the numbers of corpora lutea, implants, and live fetuses, sex ratio, placental weights and fetal mortaility.

No external abnormalities were observed in the treated and control groups.

5. Visceral Examination:

Dilation of the renal pelvis was observed in all groups at low frequencies. This did not seem to be a treatment-related effect since it appeared in the control group with the same frequency.

It is most significant that two fetuses from two different litters, in the 100 mg/kg group were found to have cleft palate, (139 fetuses were examined).

6. Skeletal Examination:

The 50 and 100 mg/kg groups showed significantly increased incidence of the presence of fourteenth ribs (lumber ribs), 49 and 92% respectively as against 11% in the control group. This effect is obviously a treatment and dose related effect.

The authors stated that there was a significantly higher degree of skeletal ossification in fetuses from the 100 mg/kg group, as assessed with respect to number of ossified coccygeal vertebrae. This effect is also treatment related.

7

Discussion and Conclusions:

In the current study (Mobay Chemical Corp. Report No. 80257), cleft palates were again observed in two fetuses (139 fetuses examined) from two different litters in the 100 mg/kg group (MDT).

This birth defect was previously observed in two separate studies in In rats (J. Doherty's memo 1978). In one experiment cleft palates were observed in 4 fetuses of the 100 mg/kg group (MDT). The experiment was then repeated using a different dose scale and the cleft palates were again observed in 3 fetuses in the 75 and 100 mg/kg groups (183 fetuses examined).

From the historical backgroung for the spontaneous malformation in rats, it is obvious that cleft palates are seldom seen in rats. Only one fetus out of 24193 examined bewteen 1970 and 1980 was found to have this type of deformity. This deformity occurs spontaneously in rats with a frequency of not more 0.004%.

From the above, it is obvious that this defect is attributable to the administration of the test chemical and can not be viewed as a spontaneous background.

In all three experiments, maternal toxicity was evident at dosage level of 25 mg/kg or above. Maternal toxicity was manifested as increased motor activity and/or depression of maternal weight gain.

Other treatment-related effects are the increase in the incidence of fourteenth ribs (lumber ribs) in the 50 and 100 mg/kg groups, and the higher degree of skeletal ossification in fetuses from the 100 mg/kg group, as assessed with respect to number of ossified coccygeal vertebrae.

In view of the above, we concluded that the test chemcial is teratogenic in rats under the test conditions.

The NOEL for embryonic and fetal development/teratology is considered to be at least 50 mg/kg/day while the NOEL for maternal toxicity is considered to be 10 mg/kg/day.

8.