Dr. Schmidt

September 2, 1971

Request for establishment of residues of Frucote® (2-aminobutane) in or on citrus at 50 ppm, in the kidney of cattle at 3 ppm, and in the fat, XXX liver, meat and milk of cattle at 0.75 ppm.

TO: Drew Baker, Petitions Control Branch

Review of toxicity data:

Pesticide Petition No. 1F1157

Elanco Products Division
Eli Lilly Co.
Indianapolis, Indiana 46206

Frucote® (2-aminobutane) is to be used as a fungicide for post-harvest control of diseases of oranges, lemons, grapefruit, tangerines and tangelos.

A temporary tolerance for Frucote was granted for apples, lemons and oranges at 20 ppm November 1965. The toxicity data for this request was submitted in Pesticide Petition No. 6G0456 and was reviewed by GEWhitmore (see memo September 28, 1965, February 15, 1968 and November 21, 1968).

A request for a tolerance of residues of Frucote® at 35 ppm, on whole unwashed oranges, was made in PP# 7F0520 (see memo GEWhitmore January 12, 1966). Summary of pertinant toxicity data from previous evaluations:

| Acute Toxicity | $LD_{50}$ g/kg |
|---|---|
| Adult Rats - oral | 1.5 - 4.6 |
| Weanling Rats - oral | 1.2 - 1.6 |
| hen | 0.25 |

| Subacute Toxicity | | |
|---|---|---|
| 90 day feeding Rat | N.E. level | 2500 ppm |
| 90 day feeding Dog | N.E. level | 5000 ppm |

Chronic Toxicity

| | | |
|---|---|---|
| 2 year feeding Rat | N.E. level | 2500 ppm |
| 2 year feeding Dog | N.E. level | 5000 ppm |

Reproductive Study

| | | |
|---|---|---|
| 3-generation rat reproduction | N.E. level | 5000 ppm |

Teratology Study

N.E. level in rabbits at 75 mg/kg and 100 mg/kg

New data submitted with present petition:

Cow feeding studies have demonstrated that there are residues of Frucote® in milk from the ingestion of this compound. Consequently, the Division of Toxicological Evaluation (memo of conference March 25, 1968) recommended that a second mammalian reproduction study would be necessary to support more than negligible residues in milk. The petitioner states that "to satisfy the species request, Dr. Blumenthal and Dr. Fitzhugh agreed to accept a two generation rabbit reproduction study". This reviewer can find no memorandum in the files of PP# 6G0456 or 7F0520 pertaining to this statement. Following is the evaluation of such a study:

Reproduction Study (2 generation-rabbit)

The original design for the study was sent to Dr. O.G. Fitzhugh, October 2, 1968. It was intended to be set up thusly:

| Level of Frucote | No. of Females | No. of Males |
|---|---|---|
| 0 | 10 | 5 |
| 2500 ppm | 8 | 5 |
| 5000 ppm | 8 | 5 |

Feeding was to be continuous from 4 weeks before breeding until after the first litters were weaned. However, the high dietary level was not accepted and 2 female rabbits died from anorexia and weight loss. Therefore, these high level animals were shifted to the 2500 ppm level on the 44th test day. The final set up was the; control group, 10 females, 5 males and; 2500 ppm group, 14 females, 10 males. Breeding was made on the 53rd and 54th test days by artificial insemination with specimens from 2 control and 2 treated males.

The compound fed was 2-aminobutane-phosphate since this is now the commercial product. The rat reproduction study submitted earlier was made with 2-aminobutane acetate.

Offspring from the $F_1$ generation were fed the control and 2500 ppm diets from weaning and were bred at 180 days. Does were artificially inseminated as above and brother-sister matings were avoided.

Parental parameters - one male and female control rabbit died, one male and one female from the 2500 ppm diet and 3 females from the group that recieved 5000 ppm for 44 days died. The following table shows the reproductive performance and the fetal weight at weaning.

| | Fertility Index% | Gestation Index % | Live Birth Index % | Lactation Index % | Weight at Weaning | Growth* Index at Weaning |
|---|---|---|---|---|---|---|
| Control $F_1$ | 80 | 100 | 61 | 80 | 303.2 | .25 |
| 2500 $F_1$ | 79 | 82 | 100 | 100 | 330.4 | .29 |
| Control $F_2$ | 100 | 87.5 | 71 | 66 | 370.0 | .27 |
| 2500 $F_2$ | 100 | 91.6 | 87 | 84 | 289.5 | .29 |

* $\frac{\text{Weight at 7 days}}{\text{Weight at weaning}}$

From these data on Frucote (2-aminobutane) there is no indication of any adverse influence on fertility, duration of gestation, the delivery of live progeny or growth rate until weaning.

Milk samples from these does were tested for Frucote residue and it was found that the control animals' milk contained 0.69 ppm; at the 2500 ppm feed level the milk contained 53.2 ppm and at the 5000 ppm feed level the milk contained 40.2 ppm. This indicates that offspring of these animals were consuming Frucote residue from the milk at levels up to 53.2 ppm. According to the growth index (weight of litter at 7 days/weight of litter at weaning) there was no significant difference between the controls and the treated. N.E. level was 2500 ppm.

Milk transfer study Rats

Fifteen pregnant rats were placed in individual wire mesh gages and allowed to deliver. Twenty four hours after delivery, the litters were reduced to 10 newborn each. After 5 days three groups were formed and allowed to consume, ad libitum, one of the following Frucote diets:

Group I - 0

Group II - 500 ppm

Group III - 2500 ppm

After the females had been stimulated for milk let-down, 1-2 ml of milk were collected from each dam and frozen. These samples were then tested, by thin layer chromatography (TLC) and gas-liquid chromatography; for the presence of sec-butylamine.

The data in the table below are average's of the actual recoveries of Frucote in the milk of all rats.

| Control | | 500 ppm ration | | 2500 ppm ration | |
|---|---|---|---|---|---|
| 7 day | 9 day | 7 day | 9 day | 7 day | 9 day |
| .42 ppm | 0.48 ppm | 2.5 ppm | 2.4 ppm | 25 ppm | 15 ppm |

A possible explanation for the Frucote level found in the control animals is its conversion from butyric acid which is synthesized by the animal. This would indicate that the offspring received up to 25 ppm with no delitarious effect on growth rate. N.E. level is 2500 ppm.

Calculated amount of Frucote in daily dietary from requested tolerances:

Total Citrus

4% = 0.060 kg x 50 mg/kg = 3.00 mg/day

Milk

100% - 1.50 kg x 0.75 mg/kg = 1.13 mg/day

Meat, fat, liver

12% = 0.18 kg x 0.75 mg/kg = 0.15 mg/day

Kidney

0.1% = 0.0015 Kg x 3 mg/kg = 0.005 mg/day

4.285 mg/day

From the various studies we find the no-effect level is 2500 ppm based upon the chronic feeding study in rats. Using 100-fold margin of safety, 25 ppm (1.25 mg/kg) of Frucote in the daily dietary could be supported. For a 60 kg man this would equal 75.0 mg/day. Since the maximum that would be added from the proposed uses is 4.3 mg/day, there is a sufficient margin of safety (9-fold in addition to the 100-fold factor).

Recommendations

We recommend that the proposed tolerances aressafe and that they be granted to the petitioner on the basis of the data presented with this and previous petitions.

Robert Schmidt, DVM
Toxicology Branch, PTD

cc: OGFitzhugh
JGCummings
PRD/EPA
Atlanta Branch (Lewis)
Perrine Branch
Division Reading File
Branch Reading File
PP# 1F1157
RS

RS:dtb:initCHW