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Memorandum

TO : Dr. Herbert Blumenthal,
Petitions Review Branch, DTE

DATE: 9-19-66

FROM : K. H. Jacobson,
Lab. Investigations Branch, DTE

SUBJECT: BALAN, benefin, a pre-emergent pesticide

File: PP# 7G0528

PESTICIDE PETITION 7G0528 and 7F0514, Elanco Products Company, Div. of Eli Lilly and Company, Indianapolis, Indiana

This is an evaluation of toxicity data submitted by Elanco on BALAN (benefin) (N-butyl-N-ethyl-a,a,a-trifluoro-2,6-dinitro-p-toluidine). Petitioner submits data to show that 1250 ppm in rats' diet and 500 ppm in dogs' diet are no-effect levels.

Acute toxicity data:

Technical benefin at doses of 2 g/kg (orally) in M and F rabbits, M and F mongrel dogs, and hens, 5 g/kg in mice (sex unspecified), and 10 g/kg in M and F rats and in weanling rats failed to cause death. The LD50 in newborn rats (less than 24 hours old) was 0.79 g/kg. There were no signs of intoxication observed in dogs or hens; there were no morphological changes in 2 dogs examined.

Subacute toxicity in rats:

Rats were fed benefin for 3 months at 0, 1250, 5000, 10,000 and 20,000 ppm; there were 10 M and 10 F rats at each dose level. Deaths among males occurred only at the control (4/10) and highest (1/10) levels. Deaths among females occurred at 0 (1/10), 1250 (1/10), 2500 (2/10), and at 5000 (2/10).

There was retarded growth in the two highest groups. There was a dose-related "depression of red cell components". This red cell depression was not of consequence in rats on the 1250 ppm level. Organ to body weight ratio data were: amongst males, kidney and liver ratios higher in animals on 2500 ppm and higher, thyroid and adrenal weights higher in animals on 10,000 and 20,000; amongst females, liver weights were elevated at 2500 ppm and higher, kidney and thyroid weights were elevated at 10,000 and 20,000 (the body weights were decreased at these two highest feeding levels). Mean total body weight gains were decreased approximately as dose increased, and feeding efficiency was decreased as dose increased; this was not significant in males, nor in females except at 10,000 and 20,000 ppm. The authors found no significant morphological changes except inclusion bodies in liver cell cytoplasm of 1 male at 10,000 and 1 female at 20,000. I noted a significant increase

over controls in hyaline globules in renal convoluted tubules, especially at 1250 ppm but to a lesser extent at each higher dose; Dr. Kent Davis suggested that this was of no significance, especially under the circumstance of failing to find more significant renal changes as the dose went up over 10-fold.

I can agree with the petitioner's finding that 1250 ppm was without effect on rats fed benefin for 3 months; higher doses were effect levels, though on closer study there could be some question whether 2500 were an effect level.

Subacute toxicity in dogs:

Mongrel dogs were given benefin by capsule daily at doses equivalent to feeding levels of 0, 500, 2000, and 8000 ppm daily; there were 3 M and 3 F at each dose level.

At 500 ppm, 1 M vomited several times in the first 3 weeks and in 1 F blood and mucus were seen in the morning stool once in the 7th week. Dogs on 2000 and 8000 reduced their consumption of food; half the dogs on 2000 ppm lost enough weight so that their daily dose needed adjustment. There was rapid weight loss in all dogs on 8000 ppm, and treatment was terminated during the second or third month in 4. Particles of reportedly unchanged benefin were observed in the feces of all treated dogs.

There were no significant hematological changes at 500 ppm. Hemoglobin, hematocrit and RBC were decreased at the two high levels. One dog at 8000 had a significant change in alkaline phosphatase and SGPT, BSP retention was elevated, and the bone marrow myeloid: erythroid cell ratio was high. BSP retention was slightly elevated in another dog at 8000 ppm. Other observations made, with no significant change, were: other blood counts including platelet count, sedimentation rate, prothrombin time, BUN, blood sugar, and urinary sugar and protein.

Post-mortem, 1 dog at 8000 ppm had inhibition of spermatogenesis; 3 other dogs were emaciated. Mean organ to body weight ratios (except gonads) were elevated in the 8000 ppm group. While the increase in liver to body ratios from control to 500 ppm groups was not statistically significant at the 5% level, there appeared to be

a regression of liver to body weight ratios with dose from controls to 500, 2000 and 8000 ppm. After suitable cogitation and consultation, I have concluded that no significance should be placed on this increased liver weight amongst mongrel dogs fed 500 ppm.

Analyses of dog fat for benefin showed chemically significant amounts in all but control animals; there was no evidence of adverse effects from this deposition.

It is concluded that 3 months' feeding of mongrel dogs at 500 ppm was without effect, but similar feeding at 2000 and 8000 ppm caused marked effect.

Summary:

It is concluded from submitted toxicological data that BALAN (benefin) caused no effect on 3 months' feeding in rats at 1250 ppm and in dogs at 500 ppm. Thus, the toxicological data support the petitioner's requests for negligible tolerance on peanuts.

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