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SPB

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Reg. No. 148-RTL, Referral Date - 11/7/69, Fungicide

Mr. Henry S. Bussey, Head
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With reference to Dr. R. E. Pittman's letter of January 2, 1970, we have reviewed the data submitted in section C of the petition for a tolerance on 1,4-dithia-anthraquinone-2,3-dicarbonitrile (Dithianon).

These data will be taken into consideration during future review of labels for use of this fungicide.

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cc:
BF-219
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TOX FILE

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DATA SUMMARY

DITHIANON

Acute Oral Toxicity (Quail)	:	LD_{50} (males) = 280 mg/kg LD_{50} (females) = 430 mg/kg
Acute Intraperitoneal Toxicity (Mouse)	:	LD_{50} = 49 mg/kg
Primary Skin Irritation (Rabbit)	:	No effect
Eye Irritation (Rabbit)	:	Washed: conjunctival irritation Unwashed: conjunctival ulceration, swelling of iris, corneal opacity.
Chronic Rat Feeding-2 years (completion of 18 month study)	:	Conclusions unchanged.
Chronic Dog Feeding-2years (completion of 12 month study)	:	1000 ppm: distinct evidence of liver damage, rise in SAP and SGPT, increased liver weight, histological changes. 400 ppm: increased liver weight. 40 ppm: no effect
Reproductive Function (Rat)	:	20 ppm: possible increase in pup mortality but not in all generations. 200 ppm: weight gain suppression in adults, some deaths during parturition, increase pup mortality in some generations 500 ppm: Same as above plus reduced pup weight at birth and weaning.

Teratogenic Study (Rat)	:	210 mg/kg; all females died before termination of pregnancy. 25 mg/kg; Increased incidence of early and late abortions 70 mg/kg; weight gain suppression in adults. Increased abortions, number of living fetuses at lower limit of normal, increased number of fetal runts, average fetal weight lower than normal, 21/94 of fetuses with unossified sternabrae--considered to be delayed development due to adult toxicity.
Acute Inhalation Toxicity (Rat) -DELAN, 75% Dust-	:	At 1 mg/liter for 6 hr; no deaths, lethargy and dyspnea during exposure, rapid recovery.

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COMMENTS

Dithianon has moderate to low acute oral toxicity. It has little to no irritating effect on the skin but is very irritating to the eye. Inhalation at 1 mg/liter of air for 6 hours cause nothing more than transient labored breathing and lethargy. Chronic feeding at high levels (1000 ppm) may cause liver damage. Reproduction appears to be influenced at relatively low levels. There was some indication of increased pup mortality at 20 ppm. Although 70 mg/kg given to mothers caused the occurrence of unossified sternabrae in offspring, this probably cannot be classified as a teratogenic effect and the effect was not seen at lower doses.

Little comment can be made concerning the safety of this compound until the use pattern is clarified.

DITHIANON - TECHNICAL [redacted]

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Acute Oral Toxicity (Quail)

Ten adult Coturnix quails of each sex were tested at each of 4 or 5 different dose levels. Dithianon was dispersed in water with Tween 80 and given by oral intubation. Birds were observed for 21 days. The LD_{50} for males was 280 mg/kg; for females 430 mg/kg.

Acute Intraperitoneal Toxicity (Mouse)

Ten male and 10 female mice were injected intraperitoneally with a 0.2% aqueous suspension of dithianon in 0.5% CMC at each of 5 different doses (32, 40, 50, 56 and 64 mg/kg). The LD_{50} at one day was 60 mg/kg, at 7 days, 49 mg/kg. Staggering was noted in 3-5 minutes. Slight paralysis of the hind feet persisted up to 24 hours. Most of the animals lost weight during the first 4 days. Most deaths occurred during the first week. Capsular fibrosis of the liver was noted in most mice that did not die during the 2 week period.

Primary Skin Irritation (Rabbit)

Portions of 0.5 g of dithianon were moistened with distilled water and applied to a patch 4 cm^2 in area on each of 3 rabbits with intact skin and 3 rabbits with abraded skin. Rabbits weighed an average of 2.25 kg. Exposure was for 24 hr. No signs of irritation developed during the 7 day observation period.

Eye Irritation (Rabbit)

One tenth g of dithianon was instilled into the left eye of each of nine rabbits. In 3 it was left unwashed in 3 it was washed out after 2 seconds

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and in 3 it was washed out after 4 seconds with 20 ml of warm water. Washed eyes were examined for one week and only when washing was after 4 seconds exposure was there any evidence of conjunctival irritation. Signs of irritation disappeared from this group after 48 hours. When eyes were left unwashed conjunctival ulceration, swelling of the iris and opacity of the whole cornea were noted. By the end of 2 weeks most of these symptoms had greatly subsided or disappeared. However, there was still some opacity of the cornea.

Chronic Rat Feeding (2 year)

This study was the completion of the 18-month study previously reported and summarized. Observations and conclusions remain essentially unchanged. Tumor incidence was no greater in treated than controls. A total of 70 animals was used in each treatment group.

Chronic Dog Feeding (2 year)

This is an extension of the 12 month study previously reported and summarized. There were no deaths, or eye changes during the study. At 1000 ppm there was a temporary reduction in food intake, a decrease in hemoglobin, hematocrit and red cell count but no progession to a clinical degree of anemia. There was an elevation of SAP within 4 weeks and SGPT after 38 weeks and an increase in serum protein, including B-globulin within 4 weeks. Weights of liver, kidneys, thryoids, pituitary and pancreas were increased at this dose. Liver histology also revealed hepatocyte enlargement and the presence of macrophages containing a brown material (Lipofuscin?, indicating increased "wear" on the hepatocytes).

In some animals there was an increased fibroblastic reaction and an inflammatory cell infiltration. At 400 ppm a significant increase in liver weight was noted and pituitary, thyroid, kidney and pancreas weights were slightly but not significantly higher than controls. Urinalyses were normal in all groups.

Reporductive Function (Rat)

Parent animals (F_0 generation) were about 40 days old when test diets were begun. Diets contained 0, 20, 200 or 500 ppm dithianon. Animals received these diets for about 100 days before mating. First mating litters (F1A) were raised only through weaning. Second mating litters (F1B) were subsequently used to produce F2A and F2B generations and F2B litters were used to produce F3A and F3B generations. The period between weaning and mating of any given litter was about 80 days.

Some of the parent animals on 200 and 500 ppm diets showed an inferior general condition with some weight gain suppresion. Four females died during parturition in the upper 2 treatment groups. At birth the only consistent adverse findings were reduced litter and pup weights at 500 ppm. Increased pup mortality was noted in all treatment groups but not in all generations. Mean pup weight at weaning was consistently depressed in the 500 ppm group but was seen only at the matings of the F2B generation in the other groups. There was no evidence of increased incidence of foetal malformations in any group. There were increases in liver and kidney and possibly adrenal (male) weights of adults in the 500 ppm group.

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Teratogenic Study (Rat)

From 16 to 20 females were placed in each of 4 different groups. The animals received 0, 25, 70 or 210 mg dithianon/kg on the 7th through 17th day of pregnancy. Material was administered orally. Surviving rats were killed on the 21st day of pregnancy.

Symptoms seen to be dose related were ruffed fur, possivity and diarrhea. Rats receiving 70 mg/kg gained less weight than controls, whereas rats in the 210 mg/kg group progressively lost weight. All animals in this latter group died before the 18th day of pregnancy.

Both early and late abortions were higher than controls, even at 25 mg/kg. The number of living fetuses in this latter group was within the control range although at 70 mg/kg this number was at the lower limit of normal. The number of fetal runts was slightly high and the average fetal weight and length were somewhat lower than normal in the 70 mg/kg group. In this latter group 21 out of 94 fetuses had unossified sternabrae. This was much higher than for controls but was not considered a teratogenic effect, rather it was considered to be retardation of development related to adult toxicity.

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DELAN- Spritzpulver 75% Dust

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Acute Inhalation Toxicity (Rat)

Eight rats were exposed to the dust of Delan Spritzpulver 75% at a concentration of 1 mg/liter for 6 hours. They were observed for 14 days. During exposure animals became lethargic and developed dyspnea. Respiration and general behavior rapidly returned to normal after termination of exposure. A transient weight loss was noted during the first day after exposure. 98% of the particles ranged from 1-15 μ.

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