PP 9G0819
FXR-747

b.

UNITED STATES GOVERNMENT

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION

Memorandum

000747

TO : Petitions Control Branch (SC-13)

DATE June 17, 1969

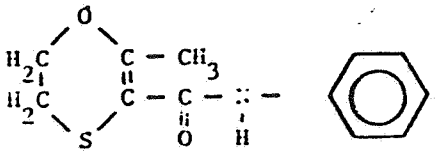
FROM : Dr. J. L. Svirbely J.L.S.
Division of Pharmacology and Toxicology
Petitions Review Branch (SC-970)

SUBJECT: Request for establishment of a temporary tolerance of 0.2 ppm for negligible residues of the fungicide 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide on small grains (wheat, barley and sorghum) and peanuts, on the nuts after shell is removed.

PESTICIDE PETITION No. 9G0 819

Uniroyal Chemical
Bethany, Connecticut
(AF 24-193)

Structural formula:



The petitioner requests establishment of a temporary tolerance of 0.2 ppm for negligible residues of the fungicide 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (Vitavax; D 735; 2,3-dihydro-5-carboxanilido-6-methyl-1,4-oxathiin; DCMO) on wheat grain, barley grain, sorghum grain and peanuts, on the nuts after shell is removed.

The following formulated products, containing technical D 735 (95% pure), are proposed to control seedling diseases on the above crops:

1. Vitavax SP (Vitavax Seed Protectant; Vitavax SP-75WP): a wettable powder formulation containing 75% active ingredient and inert ingredients [redacted] Recommended treatment rates are: 4 oz/100 lbs seed (barley and wheat), 2 to 4 oz/100 lbs seed (sorghum) and 3 to 6 oz/100 lbs seed (peanuts). The formulation can be used as a dry dust, a spray mist or slurry.

2. Vitavax 3L (a liquid formulation containing 34.32% active ingredient and inert ingredients [redacted] This formulation contains 3# active ingredient/gallon and is

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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to be used as a spray mist or slurry for sorghum only at a recommended treatment rate of 4 to 8 oz/100 lbs seed.

A permit has been requested from USDA to ship and use a limited quantity of the formulated products (10,500 lbs Vitavax SP and 100 gallons Vitavax 3L) in commercial agriculture.

Toxicity data, submitted with the petition, included:

1. Acute toxicity studies -- D735 technical; FDRL Labs., 1955.

a. Oral LD_{50} rats = 3.82 ± 0.35 grams/kg

Test material administered as a 10% suspension in 0.5% CMC to rats (equal numbers of males and females of FDRL strain--Wistar derived); 14 day observation period.

b. Dermal LD_{50} rabbits > 8.0 grams/kg

24 hour application of test material as a 50% aqueous slurry to shaved intact skin of albino rabbits; no deaths during 14-day observation period. Primary irritation score at 8 g/kg level was about 1 (average score at 24 and 72 hour readings).

Conclusion: Tech. D735 may be considered to be acutely slightly toxic orally and relatively non-toxic and non-irritating on dermal application.

2. Acute toxicity studies -- D735-75 SP (Vitavax SP); D735-75W

a. Eye irritation study - rabbits. Hazleton Labs., 1968.

Single instillation of 100 mg of test material was made into the conjunctival sac of the left eye of 9 rabbits (both sexes, New Zealand White variety); three eyes were irrigated with tap water at two and four seconds respectively after application and the other three eyes were not irrigated but closed for one second. Untreated right eyes served as controls. Observations for gross signs of eye irritation and systemic toxicity were recorded at Days 1,2,3,4 and 7 following application for all eyes and also on Days 10 and 14 for the nonirrigated eyes.

Results: No evidence of toxic effects from mucous membrane absorption was noted. In the nonirrigated group, the test material produced marked conjunctival irritation, iritis and corneal damage (sodium fluorescein examination) which generally persisted throughout the 14-day observation period. In the irrigated groups, eye irritation (moderate to marked conjunctival redness, chemosis and discharge) was less pronounced as compared to the nonirrigated group; no corneal damage was found on Day 7 (sodium fluorescein examination).

Conclusion: Eye contact with undiluted test material should be avoided; in case of accidental exposure to eyes, prompt washing with copious quantities of water should be recommended.

b. Inhalation exposure of rats.

(1) 10 male and 10 female rats were exposed for one hour to the aerosol of D735-75W at the nominal concentration of 7.6 mg/liter of air (actual chemical analysis of chamber-laden air was found to be 0.33 mg/liter of air); 4 male and 4 female rats, exposed for one hour to room air, served as controls; all rats were observed during a 14-day period (Hazleton Labs., 1968).

No marked signs of respiratory discomfort were seen during the exposure or observation periods. At necropsy, discolored areas on lungs, liver and kidney were seen more frequently among the rats exposed to the test material than the control rats.

(2) In another study (done at Huntingdon Research Center, England, 1969), 4 male and 4 female rats (CFE strain) were exposed for 6 hours to an atmosphere containing "Vitavax SP 75 WP" dust at a nominal concentration of 5 mg/liter air. The particle size distribution of dust samples were found to be: 80% (1-5 microns), 15% (5-15 microns) and 5% (> 15 microns).

During the exposure, the majority of rats showed some signs of discomfort (eye irritation and nasal discharge) followed by rapid recovery about 1/2 hour after removal from the exposure chamber. During the 14-day observation period, the general behavior and body weight changes of the exposed rats were similar to a similar group of control rats. Gross pathological examination of organs showed no abnormalities.

Conclusion: Based on these two acute rat inhalation studies, Vitavax SP would not be considered as being highly toxic to rats by inhalation exposure.

c. Fish and Wildlife studies (done in accordance with "Procedures for Evaluation of Pesticides & Wildlife," USDI, Fish & Wildlife Service Pesticide Review Staff, December 14, 1964 and Fish & Wildlife Circular #226, August, 1965).

(1) The results of studies to determine the 96-hour LC_{50} values for various species of fish exposed to D735-75 S.T. (Vitavax SP) and to p,p'-DDT (reference standard) have been tabulated as follows:

96-hour LC_{50}

Species	Vitavax SP	p,p'-DDT	
Bluegill sunfish	> 562ppb	0.63ppb (no range calculable)	Hazleton Labs., 1966
Rainbow trout	> 100ppb	> 10ppb	Hazleton Labs., 1967

(2) 5-day old bobwhite quail (10/group) were fed Vitavax SP and p,p'-DDT (positive controls) for 5 days and the basal diet only for an additional 3 days; quail (20/group), fed the basal diet only, served as negative controls. The 8-day LC_{50} values were calculated to be:

8-day LC_{50}

Species	Vitavax SP	p,p'-DDT	
Bobwhite quail	> 5620ppm	790ppm (no range calculable)	Hazleton Labs., 1967

(3) In a 28-day palatability study (done at Huntingdon Research Center, England, 1968), 12 pheasants (10 weeks of age)/group were fed grain (a 2:1 wheat-barley mixture). Group 1 was fed the basal ration only; groups 2 and 3 were fed the grain which had been dressed with Vitavax SP at dietary levels equivalent to normal use level (2 oz/bushel) and twice the normal use level (4 oz/bushel). Higher application rates were not considered feasible owing to the difficulty of getting larger amounts to adhere satisfactorily to the grain. Observations noted during the study:

Mortality: 1/12 (Group 2, Day 24); 3/12 (Group 3, Day 15).

A decreased activity among the birds on the treated diets, especially during the first few days of the test period.

Overall weight gain was less pronounced in Group 3 owing to decreased weight gain during 2nd week.

Food consumption was approximately the same for all groups.

Gross pathological examination of organs showed no significant abnormalities attributable to compound ingestion. Liver lesions of inflammatory nature, noted in 5/12 birds in Group 3 (three that died and two among those sacrificed), were associated with the presence of Histomonas meleagridis; these lesions were consistent with the diagnosis of blackhead disease and there was no evidence to directly relate the disease to the consumption of Vitavax SP.

(4) No adverse effects were noted following the administration of Vitavax SP (gelatin capsule) at a dose of 2000 mg/kg in 3 male partridges (gray species) and in 3 female partridges (red species); study done at National Institute of Agronomy, France, 1968.

Conclusion: The acute toxicity studies indicate that Vitavax SP is less toxic than p,p'-DDT to bluegill sunfish, rainbow trout and bobwhite quail; the results from the palatability study with pheasants and the administration of 2000 mg/kg to partridges indicate that no toxic response to birds in the wild state would be anticipated.

3. Repeated dermal application of D 735-75W (Vitavax SP) on rabbits: Hazleton Labs., 1968. 11/20/68

Test material (spread on premoistened gauze) was applied 5 days a week for a total of 15 applications to the closely clipped intact and/or abraded abdominal skin of 10 male and 10 female albino rabbits (New Zealand White variety) at dosage levels of 1.5 and 3.0 g/kg. The test area was covered with a binder and a collar was attached around the neck of each rabbit to preclude ingestion of the test material. The binder and collar were removed after a 6-hour contact period and the abdominal skin was washed with water. A control group (5 rabbits of each sex) which received no compound (gauze moistened with water) was subjected to the same experimental conditions as the test groups.

No effect attributable to compound related effects, following repeated dermal applications, was noted with respect to the following criteria:

a. Daily observations on mortality and toxic effects and signs of dermal irritation. Purple coloration imparted by test material tended to obscure observations for erythema.

b. Weekly body weights.

c. Clinical laboratory studies, done initially and prior to the 15th application, included: hematology (RBC, Ht, WBC and differential counts) and urine analysis (appearance, pH, total solids, sugar, ketones, protein, bilirubin, occult blood and microscopic examination of the sediment). These studies were done on each animal of the control group and 1/2 of the animals of the test groups.

d. Necropsy on all rabbits (sacrificed on 3rd day after last application); microscopic examination of liver, kidney and skin (all control rabbits and 1/2 rabbits of the test groups).

Conclusion: Repeated dermal application of Vitavax SP at dosage rates of 1.5 and 3.0 g/kg did not induce marked toxic effects in rabbits.

4. Rat and dog feeding studies with tech. D735.

a. 90-day rat feeding study FDRL, 1966

10 male and 10 female weanling rats (FDRL strain-Wistar derived)/group were fed tech. D-735 at dietary levels equivalent to 200, 600, 2000, 6000, and 20,000 ppm; a control group (15 rats of each sex) received the basal diet only; the diets were available on an ad libitum basis.

Criteria used for evaluation of compound-effects were:

(1) Daily observations for behavior, appearance and mortality.

(2) Weekly body weight and food intake records efficiency of food utilization determined after 12th week.

(3) Clinical laboratory determinations, done on 5 rats of each sex of the 0, 2000, and 6000 ppm groups, included: hematology (Hb, Ht, WBC and differential counts); clinical chemistry (blood urea nitrogen, glucose and serum alkaline phosphatase); urine analysis (pH, sp.g., albumin, glucose, occult blood, bile, and microscopic examination of the centrifuged sediment).

(4) Gross pathological examination of all rats at necrospy; absolute and relative organ weights of liver, kidneys, adrenals, pituitary, thyroid and gonads. Microscopic examination of representative organs and tissues of 10 rats of each sex from the control group and 5 rats of each sex in the 6000 and 20,000 ppm groups; microscopic examination limited to liver, kidneys and bone marrow of 5 rats of each sex in 200, 600 and 2000 ppm groups.

Results: No deaths in any group. Decrease in weight gain, food intake and food utilization, noted at levels exceeding 600 ppm, was related to dosage. Increase in blood urea nitrogen and a decrease in Hb for females of 20,000 ppm group. Gross pathologic examination did not indicate any specific dose-related effect. Relative weights of liver, kidneys, thyroids and gonads tended to be significantly increased at levels exceeding 600 ppm; in male rats, the relative weight of the adrenals was significantly increased at the 6000 and 20,000 ppm levels, and that of the pituitary, at the 20,000 ppm level. Microscopic examination showed marked inflammatory and degenerative changes in the kidneys at levels of 600 ppm or higher.

Conclusion: Based on the microscopic changes noted in the kidney at levels of 600 ppm or higher, a no-effect level of 200 ppm can be estimated for tech. D-735 in this 90-day rat feeding study.

b. 2-year rat feeding study Hazleton Labs., 1969

30 male and 30 female weanling rats (Charles River Caesarean-derived strain)/group were fed tech. D735 at dietary levels of 100 ppm (Group 2), 200 ppm (Group 3) and 600 ppm (Group 4); 60 rats of each sex comprised the control group (Group 1) and received the basal diet only; the diets were available on an ad libitum basis. Criteria used for evaluation of compound-effects were:

(1) Daily observations for mortality.

(2) Records of appearance, general behavior, individual body weights and food consumption, maintained weekly for first 6 months, twice monthly for 7-12 months and monthly for the remaining 12 months.

(3) Clinical laboratory studies, done on 5 rats of each sex/group:

Hematology (RBC, Ht, Hb, WBC and differential counts), done at 3, 6, 12, 18 months and at termination.

Clinical chemistry (sodium, potassium and chloride determinations in blood and urine, done at 3, 6, 12 and 18 months). Fasting blood sugar, blood urea nitrogen, SGPT, prothrombin time and methemoglobin were also done at 6 and 12 months and at termination.

Urine analyses (appearance, pH, sp.g., sugar, acetone, protein, bilirubin, occult blood and microscopic examination of the sediment), done at 6 and 12 months and at termination.

Body temperature measurements were taken from 10 control rats of each sex and 5 rats of each sex from each test group at months 0, 1, 3, 6, 12 and 24.

(4) Necropsy on rats that died or those sacrificed (10 rats of each sex from the control group and 5 rats of each sex of each test group at 6 and 12 months; all surviving rats at termination except male rats in Group 4 and Group 2 which were sacrificed during weeks 89 and 102 respectively).

(5) Weights of heart, liver, spleen, kidneys and testes were recorded prior to and those for thyroids and adrenals after fixation. Organ/body weight ratios were calculated.

(6) Microscopic examination of representative organs and tissues from the control and 600 ppm level rats; selected tissues from all other groups.

Results: Gain in weight was significantly lower in male rats of 600 ppm group than the other groups during the first year; fluctuations in body weight was less pronounced among the females than males during the 2nd year.

Food consumption during the 2-year study was generally less for the 600 ppm group than the other groups.

Mortality at 18 months was higher in the males of the 600 ppm group than in the other groups; mortality for all groups was high during the last quarter as a result of a spontaneous lung disease.

No significant compound-related differences between the control and test groups were indicated from the clinical chemistry studies.

Mean body temperatures taken periodically were comparable among the rats of the test and control groups.

Aside from incidence of lung disease, gross pathological examination of organs showed no consistent changes attributable to ingestion of D735.

Absolute and relative thyroid weights were higher for all test groups than the controls at the 6 month sacrifice period and also for the 600 ppm female rats at the 12 month period. Weights of kidneys, heart and spleen, determined at 12 months for the 600 ppm females, and the kidney weights for the 600 ppm male group, at termination, were significantly lower than the control values.

Microscopic examination of organs and tissues at 6 and 12 months and at termination did not show any compound-induced alterations.

Conclusion: Based on the mortality and decreased weight gain among the male rats at the 600 ppm level, a no-effect level of 200 ppm can be estimated for D735 from this 2-year rat feeding study.

c. 2-year dog feeding study Hazleton Labs., 1969 245/09

4 male and 4 female young adult beagles/group were fed D735 at dietary levels of 100 ppm (Group 2), 200 ppm (Group 3) and 600 ppm (Group 4). A control group (Group 1, consisting of 6 beagles of each sex) were fed the basal diet only. The diets were available on an ad libitum basis. Criteria used for evaluation of effects were:

(1) Daily observations on appearance, behavior, appetite and signs of compound effect.

(2) Weekly records of body weights, food and compound consumption.

(3) Clinical laboratory studies, done at months 0, 1, 3, 6, 12, 18 and 24.

Hematology (RBC, Ht, Hb, WBC and differential counts)

Biochemical determinations: Fasting blood sugar, prothrombin time, blood urea nitrogen, SGPT, serum alkaline phosphatase and bromsulphalein liver function tests. Methemoglobin determinations were done on all dogs at months 0, 3, 6, 12 and 24. Additional biochemical tests done on 4 males of each sex in Group 1 and all dogs in the test groups were: phenolsulfonphthalein kidney function tests (PSP), done at months 0, 3, 6, 12 and 24; serum Na, K, and chloride, done at months 0, 3, 6, 12, 18 and 24; urinary Na, K and chloride, done at months 0, 3, 6 and 12.

Urine analyses: Appearance, sp.g., pH, sugar, acetone, protein, bilirubin, occult blood, and microscopic examination of the sediment.

(4) Rectal body temperature were done on all dogs at months 0, 1, 3, 6, 12 and 24.

(5) Metabolism studies: 24-hour urine and feces samples, collected from two and/or three male dogs (600 ppm level) during the 78th and 81st week respectively, from 4 mal control dogs during the 83rd week and from one dog of each sex (0, 100 and 600 ppm levels) during the 103rd week, were frozen and shipped to the petitioner for residue analysis of D735 and possible metabolites.

(6) Gross pathological examination of organs and tissues (one dog of each sex at end of 1st year and the survivors at the completion of the 2-year study). Terminal absolute and relative organ weights were recorded for brain, pituitary, thyroid, heart, liver, spleen, kidneys, adrenals and testes; frozen samples of fat, muscle, kidneys and liver (0, 100 and 600 ppm levels) were submitted to the petitioner for residue analysis of D735 and possible metabolites.

(7) Microscopic examination of representative organs of tissues from dogs (control and 600 ppm group) and selected organs (pituitary, thyroid, liver, kidneys, adrenals and gonads) from 100 and 200 ppm groups.

Results: Minor fluctuations in food consumption and body weight in all groups; transient clonic seizures observed in one female dog (600 ppm level) during 86th week.

Mortality: One female dog (200 ppm level) found dead during 51st week--sharp decline in weight noted prior to death and encapsulated abscess in right diaphragmatic lobe of lung was found at necropsy.

Data from clinical laboratory studies and gross pathological examination of organs showed no consistent changes attributable to compound ingestion. Terminal absolute and relative organ weights showed no apparent compound-related trends

Microscopic examination of organs and tissues fed D735 for 2-years at levels of 100, 200 and 600 ppm did not show any histopathological alterations.

Analysis of fat, muscle and kidneys of dogs, fed D735 for two years at levels of 100 and 600 ppm, showed either trace or no total residues (< 1 ppm, sensitivity of colorimetric procedure used) at either feeding level; the liver had 1 and 5 ppm total residues at the 100 and 600 ppm levels respectively; the urine and feces showed 10 and 26 ppm total residues respectively at the 600 ppm level (urine and feces from the 100 ppm level were not analyzed). Total residues consisted of D735 and its sulfoxide metabolite (5,6-dihydro-3-carboxanilido-2-methyl-1,4-oxathiin-4-oxide; F 831). In the urine examined, considerable quantities of a water soluble anilide-complex were detected in addition to D735 and FS31.

Conclusion: A no-effect level of 600 ppm can be estimated for D735 from this two year dog feeding study since no histopathological alterations were observed and residues of D735 and its sulfoxide metabolite were not found to be stored in the fat and tissues at this level.

5. Three generation (2 litters/generation) rat reproduction study. Hazleton Labs., 1968.

D735 was fed to rats (Charles River Caesarean-derived strain; usually 10 males and 20 females/group) through three parental (P) and three filial (F) generations at dietary levels of 0, 100, 200 and 600 ppm. Individual body weights, food consumption and observations of the general behavior of the rats were recorded at weeks 0, 4 and 9 (P_1), weeks 0, 6 and 12 (P_2) and weeks 0, 8 and 12 (P_3). Records were kept of the number of conceptions, number and size of litters, number of stillbirths and deaths, and weight of pups at 24 hours, at 15 days and weaning (21 days). All pups were observed for gross signs of abnormality. At weaning, representative pups from each litter were sacrificed for gross pathological examination. At termination of the study, 10 F_{3B} weanlings of each sex from the test and control groups were sacrificed for gross pathological examination; representative organs and tissues were preserved in 10% neutral buffered formalin.

A summary of the various indices, average litter size and weight of the pups at weaning are tabulated as follows:

Summary of Reproduction Data --- D735

(Charles River Caesarean-derived strain rats)

Generation	Dosage ppm	Mating	Litter	F.I.	G.I.	LBI	L.I.	Av. litter size at weaning M	F	Av. wt.(g.) at weaning M	F
P1	0	1	A	96.7	100	100	97.8	5	5	57	54
		2	B	100	96.7	97.9	99.1	6	7	54	53
	100	1	A	95.0	100	99.5	96.6	5	6	57	54
		2	B	95.0	94.7	99.1	99.3	6	7	55	52
	200	1	A	95.0	100	97.8	96.1	6	6	55	53
		2	B	100	100	99.6	97.4	6	6	57	53
	600	1	A	90.0	100	99.5	97.8	5	7	53	52
		2	B	94.7	100	99.6	93.8	6	7	51	49
P2	0	1	A	100	100	100	99.6	6	6	56	54
		2	B	100	100	99.6	96.2	6	7	52	49
	100	1	A	95.0	100	99.5	97.4	6	5	58	55
		2	B	90.0	100	99.6	95.8	6	7	52	49
	200	1	A	100	100	100	99.3	6	6	55	52
		2	B	95.0	100	98.4	98.0	7	6	53	50
	600	1	A	90.0	100	99.5	99.4	5	6	51	49
		2	B	100	95.0	99.6	98.0	7	6	48	46
P3	0	1	A	93.3	100	100	95.2	6	5	54	52
		2	B	96.7	100	98.1	72.3	6	7	54	50
	100	1	A	95.0	100	100	94.7	5	6	52	50
		2	B	95.0	100	100	81.6	6	7	49	45
	200	1	A	95.0	100	96.6	96.6	6	6	54	52
		2	B	94.7	100	100	81.3	6	7	53	51
	600	1	A	100	100	100	96.1	6	6	49	47
		2	B	100	100	98.9	85.6	7	7	48	44

F.I.--Fertility index: percentage of matings resulting in pregnancies.
G.I.--Gestation index: percentage of pregnancies resulting in birth of live litters.
LBI --Live birth index: percentage of pups born alive
L.I.--Lactation index: percentage of pups that survived the 21-day lactation period.

Results: Statistical analysis of the various indices did not indicate adverse effects on the reproductive performance of the parental rats. A moderate growth depression in the weight of pups was noted at the 600 ppm level (statistical analysis was limited to the F_{1A}, F_{1B} and F_{2A} litters).. No malformations were noted among the pups of the test and control groups; no consistent, compound-related gross changes were noted in the organs and tissues from representative F_{3B} weanling rats at terminal sacrifice.

Conclusion: Based on the moderated growth depression noted among the pups at the 600 ppm level, a no-effect level of 200 ppm can be estimated for D735 from this 3-generation rat reproduction study.

Specific Comments

Using the rat as the more sensitive species to evaluate the various criteria employed to assess the toxic effects of tech. D735 during the 2-year rat and dog feeding studies and the 3-generation (2 litters/generation) rat reproduction study, a no-effect level of 200 ppm (10 mg/kg) can be estimated. On utilizing the 100-fold safety factor, residues of D735, reasonably safe for man, are calculated to be 2 ppm (0.1 mg/kg).

Division of Pesticides' petition data review of May 5, 1969 concludes that the metabolism of Vitavax in plants has been adequately delineated; Vitavax is degraded in soils, animals and plants by oxidation to its sulfoxide metabolite (5,6-dihydro-3-carboxanilido-2-methyl-1,4-oxathiin-4-oxide; F 831) and no further oxidation to the corresponding sulfone (F 461) or hydrolysis of either component has been noted. Vitavax and its sulfoxide metabolite are absorbed by roots and seeds and translocated in plants. Plant residues consist primarily of the sulfoxide metabolite with lesser amounts of the parent compound; as the plants approach maturity, the extractable residues (mainly F 831) are converted to anilide-lignin complexes.

Radiotracer studies with barley, cotton and wheat seeds, treated with ^{14}C-Vitavax (tagged in the benzene and/or the heterocyclic ring) at rates equivalent to field treatment and grown to maturity under greenhouse and field conditions, showed residues in the harvested seeds to be less than 0.05 ppm (sensitivity of the method).

Adequate analytical methods (which determine total residues of the parent compound, the sulfoxide metabolite and any free aniline which may be present) are available for enforcement purposes. Residues in or on the grains (barley, sorghum and wheat) or kernels of peanuts would not exceed the proposed tolerance of 0.2 ppm even if two applications had been made on the seeds. Residues in the refined peanut oil or peanut oil meal would not exceed the tolerance proposed on the kernel; the processing of the oil involves a caustic treatment which would hydrolyze Vitavax so that no residues of Vitavax, per se, would be expected in the refined peanut oil or peanut oil meal.

Tolerances were not requested by the petitioner on barley, sorghum and wheat forage or peanut hay which are feed items for cattle--residues on these items would not exceed the proposed tolerance of 0.2 ppm for the grains. Although no livestock feeding studies with Vitavax were submitted with the petition, DOP has concluded that, based on the 2-year dog feeding study which indicated that residues of Vitavax and its sulfoxide metabolite do not store in the fat or tissues of dogs from prolonged feeding of D735 at very high levels, there is no reasonable expectancy of residues in meat, milk, poultry tissues and eggs (Category 3 of Section 120.6) from the ingestion of any of the treated crops under consideration up to the proposed tolerance level.

DOP has directed attention that, in the wettable powder and liquid formulations, inert ingredients such as [redacted] were cleared for use under 120.1001 whereas [redacted] were not cleared for use under 120.1001.

Division of Pharmacology and Toxicology concurs with DOP's list of adjuvants not cleared for use under 120.1001 with the exception of [redacted] for which 90-day rat and dog feeding studies were submitted [redacted] The use of a non-certified color additive and adjuvants which have not been cleared under 120.1001 precludes the use of seeds treated with either formulation as feed items for humans and livestock. However, due to the expected evaporation of solvents as well as degradation of adjuvants by bacteria in the soil, there would be little likelihood that significant toxic residues would be translocated in the growing plant or in the grain at harvest from such treated seeds to constitute health hazard.

CONCLUSION:

The toxicity data for D735 submitted in the 2-year rat and dog feeding studies as well as a 3-generation (2 litters/generation)/rat reproduction study, support the safety of the proposed temporary tolerance of 0.2 ppm for negligible residues of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide and its metabolite 5,6-dihydro-3-carboxanilido-2-methyl-1,4-oxathiin-4-oxide (calculated as 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide) on small grains (barley, sorghum and wheat) and peanuts, after shell is removed. DOP has concluded that there is no reasonable expectancy of residues in meat, milk, poultry tissues and eggs (Category 3 of Section 120.6) from the ingestion of residues up to the 0.2 ppm proposed tolerance level. Due to the expected lack of migration of adjuvants, there is little likelihood that significant toxic residues would be translocated in the growing plant or in the grains at harvest, from seeds treated with the proposed formulations of D735, to constitute health hazard.

INIT:HBlumenthal
cc: SC-970, SC-330, SC-300, VM-100
PP # 9G0819, FAP #s 544 & 1386

JLSvirbely:mmt 6/17/69

6/25/69 6/26/69