AUGUST 25 1961

PP 302 DF

PESTICIDE PROGRAM

[redacted]

Division of Pharmacology, Toxicology Branch

Petition proposing tolerances for Sevin on various foreign and other commodities.

Pesticide Petition No. 302

Union Carbide Chemicals Co.
Heller Institute of
Industrial Research
New York 17, New York
(AF 15-5[illegible])

Request is for tolerances for residues of Sevin (1-Naphthyl N-Meth[illegible] as follows:

A 100 ppm in or on the green forage of alfalfa, bean, clovers, [illegible] grasses, sorghums, soy beans, and sugar beet tops. A 100 ppm in or on the cured hay of alfalfa, bean, clovers, cowpea, grasses, peanut, soy beans, and rice straw. Ten (10) ppm in or on sorghum grain. Five (5) ppm in or on potatoes (not plus hull), rice, soy beans, and sorghum.

Acute Toxicity

The mean oral LD50 for rats is 0.54 gm/kg; for guinea pigs 0.28 gm/kg; and for rabbits 0.71 gm/kg.

Although Sevin has a potential for producing weakness and paralysis of the leg muscles, its effect is only about 1/8 of that produced by a similar dosage of tetraethoxypyrophosphate. However, dosage levels of 1 gm/kg Sevin did not produce this effect. Skin absorption studies in rabbits show that though Sevin is absorbed, it is difficult to give a lethal dose in this manner.

In rats a substantial portion of oral Sevin appears in the urine as alpha naphthol (some free and some conjugated); 10-45% was excreted within 48 hours.

Atropine sulfate was found to control the poisoning effects very well.

Dogs receiving an oral dose of 0.375 gm/kg of Sevin showed slight erythrocyte cholinesterase inhibition (67% of the predosed mean three hours after dosing of 33% inhibition).

With guinea pigs an oral dose of 300 mg/kg Sevin produced a marked effect on erythrocyte, plasma and brain cholinesterase.

One dog per level received 5, 10, 15 mg/kg of Sevin iv. [illegible] 24 hours there was 82% inhibition of plasma cholinesterase of the dog receiving 10 mg/kg and 86% inhibition of the plasma cholinesterase of the dog receiving 15 mg/kg. There was no significant effect on the erythrocyte cholinesterase.

Subacute Toxicity

Subcutaneous injections of 0.2 ml of 0.05% Sevin in agar for twenty weeks produced no apparent increase in tumor incidance in groups of 30 C3H or A/Jax mice.

Five female and 5 male rats were placed on the following levels of Sevin for 5 days. The levels were 0.10, 0.033, 0.011, 0.0035, 0%. There was no effect on mortality, body weight gain, weight of liver or kidneys, microscopic pathology of the liver, kidneys or appetite.

In addition 5 female and 5 male rats per group were fed 0.15 and 0.225% Sevin for 96 days. The body weight gain of the females at 0.225% was decreased and the mean liver weight of the males was significantly increased. The mean kidney weight of the females at both levels increased significantly. There was a diffuse cloudy swelling of the kidney tubules. There was no inhibition of the cholinesterase of the brain, liver, erythrocyte or plasma at the end of the 96 day feeding study.

Chronic Toxicity

20 female and 20 male rats per level were fed 0.04, 0.02, 0.01, and 0.005% Sevin for two years. In addition to these, additional rats were started and killed after 6, 9, 12, and 24 months of feeding at these levels. There was no effect on the hemocrits of each level at 89, 180, 269, 358, 543, and 729 days of age. After 1 year there was cloudy swelling of the convoluted and loop tubules, primarily in the proximal tubules, in the rats on 0.04% Sevin. At the end of 2 years, there was cloudy swelling of the central hepatic cords of the rats on 0.04% Sevin. In addition the male rats on this same level had decreased body weight gain. Examination of the eyes of the rats receiving Sevin for one year and 54 days showed no cataracts. The "no effect" level in rats was 200 ppm. There was no indication of any carcinogenic effect of Sevin.

Groups of 3 or 4 dogs were fed capsules containing 7.2, 1.8, 0.45 and 0 milligrams of Sevin per kilogram body weight 5 days per week for one year. These dosages approximated 400, 100, 25 and 0 ppm in the dry diet. The experimenters concluded that there were no gross changes nor permanent degenerative changes in the tissues of any of the dogs which could be charged to treatment. There is mention, however, that sections of the kidneys of dogs which had received the equivalent of 400 ppm in the diet showed cloudy swelling of the convoluted and loop tubules. They state that similar lesions although to a lesser degree were present in control dogs. From the examination of the [illegible]ble on changes in individual dogs Dr. Nelson concluded that there is slight kidney damage, the exact degree of which cannot be determined with the few dogs on this experiment. No blood changes were observed at any dosage level.

The "no effect" dosage level for the one year dog study [redacted] between 100 and 400 ppm. Due to the very slight effect at 400 ppm we can [redacted] that 200 ppm Sevin fed for one year would be a "no effect" level in dogs.

Acute Potentiation

Because this carbamate had definite cholinesterase inhibiting activity, potentiation studies were required. Using 5 female rats per level, there was no acute oral potentiation with the following organic insecticides: Malathion, EPN, Methyl Parathion, parathion, Systox, Trithion, OMPA, Diazinon, Guthion and Phosdrin.

Metabolism

Work was done by Mellon Institute of Industrial Research. In these studies a recovery experiment was conducted using 6 groups of 3 rats each. Each rat was given an oral dose of 15 mg of Sevin. Urinary naphthol was followed for 4 days after dosing. Control urine was collected 48 hours prior to dosing. The 24, 48, 72, and 96 hour urine collection were pooled. Three sets of 6 samples were examined. Analysis were made on 0.1 ml portions of urine diluted to 1 ml. Hydrolysis of conjugates was effected by heating each sample with 0.1 ml of 10 normal hydrochloric acid at 100 degrees centigrade for 1 hour. Neutralization was effected by addition of 0.5 ml of 2 molar sodium carbonate. One ml of 0.1 molar sodium perborate and 10 ml of N-Butanol were added. The color was developed by the addition of 0.2 ml of N, 2, 6-Trichloroquinoneimine (0.5% in 95% Ethanol) to each tube and allowing it to stand 30 minutes. The butyl alcohol extracts were centrifuged. Readings (colorimetric) were made at 620 millimicrons against a water blank.

The following table shows the pattern of free and conjugated naphthol excreted after a 15 mg dose of Sevin. The excess in the 24 to 48 hour concentration over the average plus the 72 to 96 hour excretion has been calculated in terms of the initial dose. The investigators state that 10 to 45% of the dose is excreted within 48 hours, and that naphthol concentration falls rapidly to an approximate control level. Naphthol is excreted chiefly in the conjugated form, probably as the glucuronide. Investigators state further that less than 50% of the Sevin naphthol concentration shows up in the urine which is substantiated by work of others involving the administration of alpha naphthol, directly, to experimental animals.

Naphthol Excretion Rate

Group	Urine	Free Naphthol, mgm.	Conjugated Naphthol, mgm.	Percentage of Dose as Total Naphthol
I	Predose	6.74	6.16	
	24-48 hr.	8.34	18.42	35.4
	72-96 hr.	4.36	5.29	
II	Predose	5.59	7.71	
	24-48 hr.	4.38	11.79	10.0
	72-96 hr.	7.85	8.53	
III	Predose	5.23	5.69	
	24-48 hr.	6.73	10.91	13.7
	72-96 hr.	5.62	6.29	
IV	Predose	5.71	8.74	
	24-48 hr.	7.93	15.07	24.2
	72-96 hr.	3.61	4.00	
V	Predose	1.51	2.57	
	24-48 hr.	7.58	10.58	20.4
	72-96 hr.	2.40	3.66	
VI	Predose	8.42	9.06	
	24-48 hr.	9.09	23.00	45.6
	72-96 hr.	4.07	4.19	

The fate of the hydrolyzed carbamate amine moiety is not known.

Reproduction Studies - None

Division of Food comments regarding milk and meat residues

Division of Food, referring to their review of Pesticide Petition No. 243, restate the conclusion that there is an absence of residues of Sevin of 1-Naphthol, and of the conjugates of 1-Naphthol in milk. While method sensitivity is not too sharp in some instances (0.1 ppm of naphthol as conjugate) the highest level of Sevin fed, 450 ppm, where milk (and meat) was subjected to chemical analysis is from 3 to 4½ times (level of residue on green forage may approach 150 ppm) that requested as a tolerance. Division of Food feels that we should expect none in the milk of dairy cattle fed a diet containing 100 ppm.

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With regard to meat Division of Food stuffs: "The use in animal feeding of a daily diet consisting entirely of the subject Sevin treated forage, grain and field crops, or of their by-products will not result in residues in meats."

Conclusions:

The proposed tolerances for Sevin are safe, Sevin, 1-Naphthol, and conjugates of 1-Naphthol are absent from milk and meat intended for human consumption.

E. G. Hagen

INIT: OGH

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