

Jones
Albert
Sevin
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PP #329 F

PESTICIDE BRANCH

Division of Pharmacology, Toxicology Branch

Proposal of a tolerance of 10 ppm of Sevin (1-Naphthyl N-Methyl carbamate) on the meat plus shells of almonds and walnuts, and of 40 ppm (revised upward from 25 ppm because of reservations as to adequacy of this amount to cover residues) on almond hulls.

PESTICIDE PETITION NO. 329

Union Carbide Chemicals Co.
370 Park Avenue
New York, New York
(AF 15-522)

Background (Summary of current tolerances)

1-NAPHTHYL N-METHYLCARBAMATE
(Trade mark name Sevin)

Tolerances

25 p.p.m.

In or on the following raw agricultural commodities:

- Corn fodder
- Corn forage

10 p.p.m.

In or on the following raw agricultural commodities:

- | | | |
|-------------|------------|--------------------------|
| Apples | Egg plants | Peaches |
| Apricots | Grapes | Pears |
| Bananas | Lettuce | Peppers |
| Bons | Nectarines | Plums (fresh prunes) (4) |
| Blueberries | Okra | Strawberries |
| Cherries | | Summer squash |
| Cranberries | | Tomatoes |
| Cucumbers | | |

5 p.p.m.

In or on the following raw agricultural commodities:

Corn (kernels & kernels plus cob, determined after removing husks present when marketed).

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Acute Toxicity

The mean oral LD₅₀ for rats is 0.54 gm/kg; for guinea pigs 0.71 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 1/3 of that produced by a similar dosage of triorthocresyl phosphate. 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. After 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 0.5% Sevin in agar for twenty weeks produced no apparent increase in tumor incidence in groups of 30 C₃H or A/Jax mice.

Five female and 5 male rats were placed on the following levels of Sevin for 90 days. The levels were 0.10, 0.833, 0.011, 0.0035, 0%. There was no effect on mortality, body weight gain, weight of liver or kidneys, micro-pathology of lung, 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 depressed 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

Twenty female and 20 male rats per level were fed 0.04, 0.05, and 0.065% for two years. In addition to these, additional rats were started and killed after 6, 9, 12, and 24 months of feeding at the same levels. There was no effect on the hematocrits of each level at 89, 180, 259, 350, 441, 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 5.04% 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 table in 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 lies between 100 and 400 ppm. Due to the very slight effect at 400 ppm we can reasonably assume 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, ZEN, methyl parathion, parathion, Systox, Trichlorfon, OMPA, Diazinon, Guthion, and Phosinon.

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 excretion 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. Urine samples of 6 samples were examined. Analysis was 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.

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One ml of 0.1 molar sodium perborate and 10 ml of N-Butyl alcohol were added. The color was developed by the addition of 0.2 ml of 1,2,4-trinitrobenzene (0.5% in 95% Ethanol) to each tube and allowing it to stand 30 minutes. The butyl alcohol extracts were centrifuged. Readings (optical density) 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 excrete 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.

Supplementary Toxicity and Metabolic Data

Human Exposure to Sevin

1. Results of 19 months of employee exposure to production, handling, and shipping of Sevin. Average concentration of Sevin ranged from 0.23 to 31 ug (range 0.03-40) of dust/cubic meter of air. Blood cholinesterase and symptomatology: Levels of cholinesterase were mostly within a normal range and only occasionally slightly depressed. There were no clinical or subjective evidence of increased acetylcholine activity.

2. Accidental Ingestion of Sevin

A 19-month old child ingested an unknown amount of Sevin. Gastric lavage was performed within 1/2 hour after ingestion. However, pupillary constriction, salivation, and muscular incoordination occurred. Atropine (0.3 mg) was sufficient to control symptoms and recovery was complete within 12 hours.

3. Metabolism

From Employee Exposure to Air Concentrations

Average urinary 1-naphthol concentrations

Control group

150-400 mcg/100 ml

Test group

41% of 689 urine specimens showed an excess of 1000 mcg of total 1-naphthol/100 ml.

b. From Accidental Ingestion by Child

A urine specimen collected 18 hours after the poisoning of a child previously contained 3140 mcg of 1-naphthol/100 ml of urine.

Discussion and Conclusions

We have included this supplementary data in this report primarily to show that the metabolic fate of Sevin has some similarity in humans and laboratory animals. The formation of 1-naphthol and its excretion in the urine is common to both. While available data do not permit estimation as to what percent of Sevin is metabolized by the human to the naphthol form, the overall data are in support of the safety for the proposed use. (The section titled, Supplementary Toxicity and Metabolic Data, was taken from a preliminary report on the occupational hazards of Sevin insecticide. It is marked confidential because it is a pre-publication copy).

According to food consumption data compiled by the Agriculture Research Service the total of rat-mouse eaten per person per day is 2 gm. This is 0.15% of the total dietary intake daily of 1500 gm. As the request is for 10 ppm of Sevin on meat plus shell on almonds and walnuts, we cannot visualize a hazard when consumed by humans.

According to DF's profiling review almond hulls are a potential stock feed, though we have no information on what part of the total daily diet they might comprise. However, as previously noted, Sevin is permitted at 25 ppm on corn fodder and corn forage and we cannot visualize 40 ppm of Sevin on almond hulls providing quantities of Sevin comparable to that ingested under this current tolerance. However, DF comments should clarify this point.

We feel this use is safe and that the proposed tolerances be granted.

INIT:OGF

E. C. Hagan

ec:DP
DF
MCH

EC:Hagan:bja 4-27-62

Naphthol Excretion in Rats

Group	Urine	Free Naphthol, mg.	Conjugated Naphthol, mg.	Total Naphthol
I	Pre-dose	6.74	6.16	
	24-48 hr.	8.34	18.42	
	72-96 hr.	4.36	5.29	35.4
II	Pre-dose	5.59	7.71	
	24-48 hr.	4.38	11.74	
	72-96 hr.	7.85	8.53	10.5
III	Pre-dose	5.23	5.69	
	24-48 hr.	6.73	10.91	
	72-96 hr.	5.62	6.29	13.7
IV	Pre-dose	5.71	8.74	
	24-48 hr.	7.99	15.07	
	72-96 hr.	3.61	4.00	24.2
V	Pre-dose	1.51	2.57	
	24-48 hr.	7.58	10.58	
	72-96 hr.	2.40	3.66	20.4
VI	Pre-dose	8.42	9.06	
	24-48 hr.	9.09	23.80	
	72-96 hr.	4.07	4.19	45.6

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

Reproduction Studies - None