

February 16, 1959

Division of Pharmacology

Evaluation of the Pharmacological data submitted in support of a pesticide petition for Sevin (N-Methyl-1-naphthylcarbamate)

Pesticide Petition No. 193

Union Carbide Corp. (AF15-522)

The petitioner requests a tolerance of 10 ppm Sevin on apples, peaches and beans, and submits the following data from the Mellon Institute of Industrial Research in support of this request.

Acute Toxicity

The mean oral LD50 for rats is 0.54 gm/kg; for guinea pigs 0.23 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 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 24 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 or 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 0.05% Sevin in agar for twenty weeks produced no apparent increase in tumor incidence in groups of 30 C3H or A/Jax mice.

5 female and 5 male rats were placed on the following levels of Sevin for 90 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, micropathology of lung, liver, kidneys or appetite.

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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

20 female and 20 male rats per level were fed 0.04, 0.02, 0.01, 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 a 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 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 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.

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#### 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, Santon, Trithion, OHP, Diazinon, Guthion and Phosdrin. In addition there was no potentiation between Sevin and the following: Chlordane, Crag Fly Repellent, Crag Fungicide Mylone, Crag Glyodin, Crag Herbicide 1, Crag Herbicide DCU, DDT, Dieldrin, Ferimate, Lethane 384, Lindane, Lime Sulfur, Thionite and Toxaphene.

#### Conclusion

The requested tolerance of 10 ppm Sevin on apples, peaches, and beans is safe. Since the "no effect" dosage levels in rats and dogs are approximately 260 ppm, this tolerance in all foods would allow a margin of safety of 20. However, based on the per capita food consumption estimate of the Department of Agriculture the use of Sevin on all fruits and vegetables (they make up approximately 26% of the total frozen food as sold in the grocery store) would allow for a margin of safety of approximately 77. However, this increases considerably when allowance is made for the discarding of citrus rinds and other portions of fruits and vegetables. The proposed tolerance of 10 ppm on apples, peaches and beans will result in a margin of safety greater than 100.

*WLF*  
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1-14-69