ALL MATER HEREIN TO BE TREATED AS CONFI TIAL

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1 - SEP 1978

Carbaryl
Caswell # 160
Shaughnessey # 056801

The data presented below have been drawn from the files of Robert Coberly as well as pesticide petitions 902 and 1220. Data drawn from accessions have also been referenced. Pesticide Petition # 7F 1878 indicated that all the required data under the Section 3 guidelines have been sumitted for carbaryl.

Animal Toxicity Data

Acute Oral LD_{50}

Species Tested	LD50 mg/kg
Rat	510 (390 - 670) (95% C.L.)
Rat	540
Guinea pig	280
Rabbit	710

Acute Dermal LD50 (Ref. Accession # 129334)

Species	LD_{50}
Rabbits (M + F)	4000.0 mg/kg

Skin Irritation

Five rabbits were administered with 0.01 milliter of 10% technical Sevin in acetone. No irritation resulted on the shaved bellies of the animals.

Eye irritation

Five rabbits were given 0.05 ml of technical Sevin, applied in excess, as a 10% suspension. Only mild injury resulted in one of the five eyes during the 24 hour observation period.

Subacute Toxicity (dietary)

Five male and five female rats per dose level were fed 0.10; 0.033; 0.011 and 0.0035 percent carbaryl in the diet for ninety days.

There was no observable effect on mortality, body weight gain, liver or kidney weight or appetite. Microscopic examination of lung, liver or kidney revealed no adverse effect.

In a separate stydy lasting ninety-six days five male and five female rats per dose level were fed 0.15 and 0.225 percent carbaryl in the diet.

There was a significant increase in mean kidney weight in females at the 0.15 percent level, and the 0.225 percent level. There was also diffuse cloudy swelling of the tubules. Body weight gains were also surpressed.

In males there was no observable effect at 0.15 percent, but at the 0.225 percent level the mean liver weight was significantly increased.

For both males and females there was no inhibition of the cholinesterase enzyme in brain, liver, erythrocyte or plasma at the end of the ninety-six day study.

Chronic Toxicity

Chronic Feeding (Carpenter, C.P., Weil, C.S., Palm, P.E., Woodside, M. W., Nair, J.H. III, Smyth, H.F., Jr., J. Agr. Food Chem. 9, 30, 1961) (Rat)

No. of Animals. 20 M and 20 F per group.
Feeding Levels. 0. 50, 100, 200, and 400 ppm
Duration. 2 years.
Mortality. No significant differnece between the treated and control animals.

Body Weight. Significant weight depression in male rats only at 400 ppm.
Organ Weight. Kidney and liver/body weight ratios in all treated groups showed no differences from controls.

Clinical Laboratory Tests. Hematological studies reveald no abnormalities. Cholinesterase levels in plasma, red cells and brain showed only a slight transitory depression at a single oral dose of slightly above the LD-50 (560 mg/kg).

Potentiation. These studies indicate no potentiating effect with organic phosphate insecticides.

Metabolism. About one-third of the administered dose appears in the urine as 1-naphthol in the conjugated (glucuronide) from. The fate of the carbamide amine moiety is not known.

Neoplasms. No increase in the incidence of tumors in the treated animals. In a special injection experiment in mice (A/Jax and C3H strains), no tumorigenic effect was noted.

Histopathology. Histological examination of important organs and tissues indicated some liver damage at 400 ppm, but none at the lower levels. In view of the fact that 2-naphthol has been reported to produce cataract in rats, and since 1-naphthol is a metabolite of Sevin, the eyes of the treated rats were carefully examined for cataract. None was found.
No-Effect Level. 200 ppm.

(Carpenter, et al.) (Same reference as above)
Chronic Feeding (Dogs)

No. of Animals. 3 to 4 per group randomly distributed as to sex.
Feeding Levels. 0, 25, 100, and 400 ppm.

Duration. 1 year.

Mortality. All animals survived the experimental period.
Body Weight. All animals made satisfactory gains.
Organ Weight. Kidney and liver/body weight ratios of the treated animals did not differ significantly from the controls.

Clinical Laboratory Tests. Hematological studies, alkaline phosphatase, sulfobromphthalein retention, blood urea nitrogen, and bilirubin determinations did not deviate from control values. Cholinesterase levels and plasma and red cell were followed at appropriate intervals. The values did not differ from controls.

Histopathology. Slight kidney damage at 400 ppm.
No-Effect level. Somewhat less that 400 ppm and at least 200 ppm.

Reproduction/Teratology/Mutagenesis

Reproduction - (PP 518)

A modified procedure of the one appearing in the "Appriaisal of Safety of Chemicals in Food Drug and Cosmetics" was used.

Two dose levels were administered; 0.01 and 0.0025 grams per kilogram in the diet. There was no difference between treated and control values after statistical analysis. Parameters measured were:

1. mean number of pups per litter
2. indecies (ie., fertility gestations, viability, lactation)
3. body weight at weaning
4. microphathology on random wealings of the F_3 a generation and random selection of 90 day F_3a rats for determination of the presence of terata.

A detailed 3-generation rat reproduction study is contained in pp 1220.

This study in also published (Weil et al Tox. and Appl. Pharm. 26: 21-638, 1973). The maximum doses given to rats were 200 mg/kg/day (4000 ppm) in the diet or 100 mg/kg/day by oral intubation (o.i.). The animals receiving Sevin by dietary inclusion showed normal reproduction and signs of slight toxicity to the adults, such as decreased weight increase and increases in number of days after first mating to birth of litter. The animals dosed by o.i. (100 mg/kg/day) showed adequate reproduction as measured by the four reproduction indexes, several toxic effects on the mating animals however were observed, ranging from increased mortality to decreased weight gain. At a dose of 25 mg/kg/day by o.i no adverse effects were observed. The no effect level for dietary inclusion was 200 mg/kg/day.

The F_3B litter was used for a teratology study. The only adverse effects were observed at the o.i. dose of .100 m/kg/day. The median number of fetuses was reduced from 13 to 11 and the percent of litters with resorption sites was increased from 38.5% to 88.2%. No adverse effect was noted at any other feeding level or o.i. dose. The no effect level for teratogenic effect are thus the same as for the reproduction study.

F_2b males from the reproduction study were used for a dominant lethal mutagenicity study, by mating them to unexposed virgin females. No effects were noted, except for a not dose related increase in percentage of late fetal death in the 4th week mating cycle.

Guinea pig teratology. Pregnant guinea pigs were dosed with 200, 100, 50 and 0 mg/kg/day by o.i or 300, 200, 100 and 0 mg/kg/day by dietary inclusion. The dosage schedule was for one day, two or three days or up to 14 days. At the higher o.i doses the continuing dosing had to be omitted incease of toxicity to the mothers. The dietary doses were given at all dose levels at all of the selected time periods. No skeletal or soft tissue anomalies or increased numbers in resoption sites were noted at any level.

A Bionetic study (June 23, 1973) showed no teratogenic effects in 20 rats each fed 375 mg/kg and 200 mg/kg respectively.

Teratogenic evaluation in Rhesus Monkeys. Eighty monkeys were used. Their esterus cycle was monitored and pregnancy was initiated. (Only one female did not become pregnant.) The monkeys were then divided into 5 groups @ 16 animals; (i) control group (ii) vehicle control (iii) 0.2 mg/kg, (iv) 2 mg/kg and (v) 20 mg/kg. Carbaryl was administered daily from day 20-38 of gestation, in two equal daily doses. The number of live births, abortions and stillbirths as well as gestation length and birth weights were recorded. No significant differences in these parmeters were observed between control and treatment groups. The females underwent clinical observation throughout their pregnancy. No

signs of carbaryl toxicity were detected. Four control and four high dose infants were sacrificed after weaning and they and any other infant dying during the study were autopsied. The cause of infant mortalities (six deaths) was grossly identified at respiratory or G.I. tract infections. Histopathology on the six deaths and 8 sacrificed animals has not been completed. (See Also Addendum)

Neurotoxicity

Five hens were tested to determine the demylelination potential of carbaryl one hen per dose was employed. Doses given were 3.0; 2.0; 1.0; 0.50; and 0.25 grams per kilogram. TOCP was used as a positive control. Hislogical examination of brain, sciatic nerve, and spinal cord revealed no evidence of demyelination.

Oncogenicity

The Mrak Report (Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health December 1959) classified carbaryl as a comound "not positive" for tumor induction on the basis of tests conducted adequately in two or more species, The references to the particular studies in mice and rats are given on page 469 of the report.

Acceptable Daily Intake (ADI) = 0.1 mg/kg body wt. per day

Maximum Permissable Intake = 6.0 mg/day
Theoretical Maximum Residue Conc. = 3.98 mg.
per 1.5 kg/day

Human Toxicity Data

Dermal (Ref. pp. 902)

Human experience does show some irritation by carbaryl to some individuals.

Addendum:

There appears in pp. 902 a summary table of effect and no effect levels for teratogenesis. That table is reproduced here in part.

Teratology

Species	No Effect Intake	Latent Effect
Dog	2.0 mg/kg	3.0 mg/kg
Dog	3.125 mg/kg	6.25 mg/kg

Note that carbaryl is under rebuttable presumption.

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Triggers: Teratogenicity in dogs
Reproduction in non-target species (bees)

This status is as of June 23, 1978. The PD#1 is presently being drafted.

Date: August 16, 1978