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CARBARYL INSECTICIDE

A Preliminary Report on Acute Toxicity and Mutagenic, Carcinogenic, and Teratogenic Effects

Sevin is the registered trademark of Union Carbide Corporation U.S.A., under which various formulations of carbaryl insecticide are marketed. Carbaryl is the common name for the active ingredient, 1 Naphthyl-N-methylcarbamate. This substance is an off-white crystalline solid (mp 142°, V.P. 0.005 mm Hg, 26° C.) which is readily soluable in polar organic solvents, slightly soluable (to 5%) in nonpolar organic solvents and practically insoluable (0.1%) in water. Available commercial forms are Sevin 50W, a wettable powder containing 50 percent carbaryl, Sevin Sprayable which contains 80% water dispersible powder, dusts containing 2-50% carbaryl, granular formulations containing 5-20%, liquid formulations in water and molasses containing 40 or 50%, and sevin 4 oil containing 4 pounds carbaryl per gallon for low volume spray application.

The action of carbaryl, similar to organophosphates is against the cholinesterase enzymes. Unlike organophosphates, the action is competitive and not irreversible. Carbaryl is a contact or stomach poison and not a fumigant or vapor toxicant.

Results of early toxicology studies indicated carbaryl to be relatively safe for broad spectrum use by the general public and in agriculture. However, following field application marked depressions.

were noted in population of certain species of wild animals and fish. Subsequently, teratogenic effects were noted when amounts less than those which caused death were used in long term studies with laboratory animals. In accord with recommendations of the Mrak Report the following review emphasizing acute toxicity, teratogenic, carcinogenic and mutogenic properties of carbaryl is submitted for consideration by the committee.

General Toxicology

Acute toxicity of carbaryl administered by various routes as single doses to various laboratory animals is submitted in the following table.

Acute Effects	Species	Mg/Kg	Source
LD_{50} Oral	Rat	500-800	(1)
	Rat	540	(2)
	Guinea pig	280	(3)
	Rabbit	710	(3)
	Dog	$>$ 759	(3)
	Chicken	2460	(5)
Dermal	Rat	$>$ 4000	(1)
	Rabbit	$>$ 20,000	(6)
LC_{50} Inhalation 4 Hrs.	Guinea pig	$>$ 390 mg/M^3	(4)
5 Hrs.	Dog	$>$ 81.4 mg/M^3	(4)
Eye Irritation	Rabbit	(Slight injury with 10% dust)	(4)

Similar tests were performed with wild mammals, wild birds and fresh water fish. The following table presents acute toxicity values obtained when carbaryl was administered as a single oral dose, as a part of the daily diet, or as a part of the environment (7).

	LD_{50} (mg/kg)	LC_{50} (ppm)
Mammals		
Mule deer	200-400	
Birds		
Young Mallard	>2,179	
Young phesants	>2,000	
Pigeons (Columbian livia)	1,000-3,000	
Sharp tule grouse	780-1700	
Canada geese	1,790	
Mallards**		>5,000
Phesants**		>5,000
Bob white quail**		>5,000
Coturnix**		>5,000
Fish		
Channel cat (24 hrs. at 24c)		19.0
Bluegill (24 hrs. at 24c)		2.5
Rainbow trout (24 hrs. at 13c)		2.0

*Single oral doses fed in capsules.

**Incorporated into the diet of 2 week old birds for 5 days followed with untreated diet for 3 days.

Toxicity of Carbaryl to Molluscs and Arthopids (7) is Indicated in the Following Tabulation.

Molluscs	Exposure Time (HR)	LC_{50} (PPb)
Bay mussel	48	2.3
Pacific oyster	48	2.2
Cochel clam	24	7.3
Anthropods		
Mud shrimp	24	40-130
Ghost shrimp	24	130
	48	30-80
Shore crab	24	270-710
Dungeness crab**	24	630
Red craw fish	48	3000

**Hatching of eggs of Dungeness crab was not prevented by 1 ppm, but the quantity prevented moulting of all prezoeae to zoeae. Survival of zoeae after exposure for 25 days to concentrations 0.1, 0.32, 1, and 10 ppb were 83, 60, 69, 21 and 0 percent respectively.

Indications of toxicity have been observed in wild populations of mammals, birds following application of 2 lb carbaryl per acre. Biomass and number of arthropods were reduced by more than 95 percent in an area treated with carbaryl (8). Number of arthropds in treated area remained below that in the untreated area for 5 weeks but total biomass returned to normal after 7 weeks. Cotton rat

reproduction was delayed with a subsequent reduction in population following this application. This observation was corroborated by laboratory studies which are discussed in the section of this report on teratogenic, carcinogenic and mutogenic effects.

Sufficient data is not available to access the acute toxic effects of carbaryl on man. However, present information suggests that humans absorb carbaryl and excrete conjugated forms of alpha-naphthal following exposure. In laboratory trials humans ingested carbaryl in daily oral doses of 0.06 and 0.12 mg/kg for six weeks without serious effects or appreciable cholinesterase depressions (9). In the group receiving 0.12 mg/kg the ratio of amino acids to creatinine in urine was higher than the control group indicating decrease in reabsorption of amino acids by the proximal convoluted tubule. In another study two humans volunteers ingested a single 2 mg/kg oral dose without effect; from this trial only 28 percent of the ingested dose was recovered in urine (10). Mild depression (15%) in acetyl cholinesterase activities of blood of inhabitants were observed after interiors of mud huts had been sprayed with 2 gm/m^3 of carbaryl (11). Seven days after this application alpha-naphthol in urine was elevated by a mean value of 20 ug/ml. In an isolated instance one individual was acutely poisoned after oral injection of a single 250 mg dose of carbaryl. This exposure did not threaten life but the subject was temporarily incapacitated (12).

Absorption of carbaryl and human responses to exposure were determined during the first 19 months of production in a chemical plant (13). Factors used to determine effects of exposure were measurements of blood cholinesterases, physical examinations, measurement of alpha-naphthol in uring for absorption, amounts of airborne carbaryl for potential exposure.

The following tables summarize results from air sampling and urine analysis.

Location	Air Samples (mg/m^3)		
	No Sample	Range	Mean
Amination house	49	0.03-0.73	0.23
Air separation house	2	29.00-34.00	31.00
Stacker and shippers	6	0.05-1.52	0.64
Bagger	18	0.02-1.60	0.75

Work Assignment	Alpha Napthol (ug/100 ml) Range	Mean	Carbaryl* Absorbed/24Hrs.(mg)
Resin operator	700-2700	1520	114
Bag house cleaner	2600-4000	3060	229
Shipping bagger	1000-3700	2460	149
Sevin production operator	1700-3800	2700	202

*Values assume 1500 ml urine per day and an average excretion of 28% of absorbed carbaryl.

During peak production periods mean cholinesterase value of workers under heaviest exposure conditions were 30 percent less than

mean values of controls. Several of the men who had the apparent highest exposures to carbaryl also had elevated values for serum bilirubin and lower blood urea nitrogen estimations some of which were of questionable significance. Both of these factors returned to normal as soon as the men were removed from exposure conditions (14).

The number of cases of acute human poisoning from the use of carbaryl is meager. Existing records show that no bonified cases have been reported since 1969. Some allegations have been reported but follow-up with attending physicians shows that the cause of illness may have been natural illness rather than exposure to carbaryl (14).

The low toxicity values of carbaryl and lack of acute poisonings of humans following its application have allowed a broad spectrum of uses in agriculture and by the home owner in the yard, house, on pets, and on humans. Little information is available concerning the total amounts of household pesticides used in the United States. In Salt Lake County, Utah, an area of 764 sq. miles and a population of 440,000, 200,811 lbs. of pesticide were applied between July 1967 and July, 1968. Domestic application accounted for one half of the pesticide used, and the inorganic pesticide arsenic for about 80 percent of the domestic use. In contrast, based on 475,362 household in the state of Arizona with a population of 1,204,000, 9,600,000 lbs of insecticides were used.

Of this amount house and garden use was 6.7 percent, and only 3 percent of that was carbamates (7). In the opinion of Union Carbide Corporation a breakdown of carbaryl sales in the U.S.A. more accurately reflect actual uses than other estimates. The following table of end-use and formulation based on and estimated 19,950,000 lbs. carbaryl sold during 1971 was compiled by salesmen, Regional Sales Managers and Management of Union Carbide Corporation (15).

Percent of Market by End Use		Percent of Market by Formulation	
General Agriculture		UCC Consumer Products	
Forage	31 %	Sevin 80 Sprayable (10.6-43)	40 %
Cotton	22	Sevimol 4 (1016-68)	15
Other raw crops	5	Sevin 50 Wettable (1016-41)	12.5
Vegetables	15	Sevin 4 Oil (1016-70)	1
Fruit	8		
Forest	6		
Poultry	2.5		
SUBTOTAL	90.5 %	SUBTOTAL	68.5 %

Home & Garden		Customer End Products	
Turf	5 %	Sevin 50 Dust Base (1016-60)	25 %
Fruit & Veg.		Manufacturing Concentrates	2.5
WP	2	(10160TG, - TU, - TL)	
Dust	1	Customer Liquid Suspensions	3.5
EC & Solns.	1	Customer Emulsion Concentrates	0.5
Pets	0.5	(from 1016-TE)	
SUBTOTAL	9.5%	SUBTOTAL	31.5%

Of the total 1971 sales an anticipated 1,875,000 lbs will be sold for home use. Dust, wettable powder, and liquid formulations containing 5-10 percent carbaryl are available for this market.

Teratogenic, Carcinogenic and Mutagenic Effects

Effects from exposures to quantities of carbaryl less than those required for acute response have been reported from long term studies in experimental animals. These effects include mutagenesis, increase incidence of tumor formation, and increases in impairment of reproduction and occurrence of deformaties and stillborn among offspring.

Abnormal meosis has been reported in anther of barley sprayed with 500 ppm carbaryl. Abnormal mitosis was observed in barley roots exposed to 0.25 and 0.5 percent saturated solutions of carbaryl, and chromosome aberrations resulted when saturated solutions were used (16).

Treatment with carbarly arrested mitosis in Allium cepa root tips (17).

Application of sublethal amounts of carbaryl to individual house flies caused a reduction in egg productions but did not affect hatchability of the eggs. With 1 ug per fly 50.3 percent reduction was obtained, with 0.6 ug reduetion was 24.1 percent (18).

Application of 0.5 mg per acre carbaryl caused 42 percent reduction in productivity of red back voles and disfunction of the uterus (19).

As was mentioned earlier 50 percent reduction in a population of cotton rats was observed following application of 2 lb per acre carbaryl. In laboratory studies number of litters born and number of females giving birth were reduced more than 50 percent following oral doses of 1.1 mg per day for 10 days (7).

Carbaryl was administered to rats for 12 months at 7, 14, and 70 mg per kg. This caused changes in liver and kidney, lengthened estrous cycle, affected ovarian structure, affected structure and function of pituitary, thyroid and adrenal glands, and reduced survival time under complete starvation. Carbaryl caused focal histological changes is testes and reduced sperm mobility in a time dose manner (20-22).

Carbaryl was administered to rats perorally at 50, 100, and 300 mg per kg per day for three months. Estrous period was disturbed, fertility was reduced and mobility of sperm was reduced. Number of pups in each litter was reduced one half of the control. Various stages of development of embryoes were observed at 9 - 10th day. As dosage continued females became sterile (23).

Sevin administered orally to both male and female rats daily at 5 and 15 mg per kg over one year period significantly changed enzymatic activity of testis and ovaries, prolonged estrous cycle, altered functional state of spermatozoa and reduced fertility of female. Sevin at 2 mg per kg per day did not significantly affect functions of sex glands. F_1 and F_2 generations were more significantly affected than the parents. Relatively high percentage of deaths among progeny indicated decreased resistance to Sevin. Some young rats in the F_3 generations from rats receiving 5 and 15 mg Sevin per kg had tail curvatures caused by damaged vertebrae (24).

During a 22 month observation period rats were treated twice weekly perorally with water suspension containing 5 percent of the LD_{50} amount of carbaryl or once subacutaneously with a similar amount in paraffin pellets. Of the starting number receiving oral doses, 6 percent had tumors and 20 percent survived the oral treatment. In the subcutaneous group 4.1 percent had tumors and 20.8 percent survived. Control group showed 96 percent survival and 2 percent with tumors. Types of tumors observed included fibrosarcoma under skin of right femor of 2 rats, one rat with polymorphocelular sarcoma which penetrated the stomach wall but did not involve other organs of the peritoneum. Another rat had many nodes with the appearance of bone in the lungs, diaphragm and peritoneum; a primary tumro on the right femur appeared to be an osteosarcoma with multiple metatheses. Sevin (97.65% 1-naphthyl-N-methylcarbamate) was obtained from Skyolovosky chemical factory (25).

Teratogenic effects have been observed in guinea pigs, dogs, mice and chickens. Changes in axial skelton of guinea pig fetuses, particularly in the cervical vertebrae, were observed after pregnant females received orally single or 10 daily doses of 350 mg per kg of carbaryl (26).

Immediately after mating and during gestation groups of female beagle dogs were fed diets containing 50, 25, 12.5, 6.25, 3.185, and 0 mg per kg carbaryl. Teratism was observed in pups from dams fed all but the lowest level. At highest dose level were an unexplained number of bitches with dystocia due to atonic uterine musculature. Included in terata were abnormal thoracic fissures with varying degrees of intestinal agenesis and displacement, of brachygnathia, elucid pups, failure of skeletal formation and superfluous phlanges. Several pups exhibited multiple defects that were difficult to categorize (27). Woodward Research Corporation fed groups of female beagle dogs dietary levels of 12.5, 5.0 and 2.0 mg/kg carbaryl per day during pregnancy. More stillborn pups were produced in treated groups than in the control group. Abnormalities in pups included cleft palate, umbilical hernia, fat masses in the heart, extravasation of blood in myocardium, and unilateral microphthalmia (28).

Teratogenic effects have been observed in selected inbred strains of mice, when carbaryl was incorporated into the diet at 66.7 and 200 ppm. In 2 litters at 200 ppm level, a total of 7 instances of skeletal malalignment, nonfusion, incomplete ossification, and one case of cleft palate and gross facial malformation were noted,

as opposed to no malformations in the lower group and two cases of cleft palate in controls. Carbaryl plus piperonyl butoxide did not show an overall increase in abormalities, but resulted in significantly more cystic kidney at doses above 10 mg/kg carbaryl + 100 ul/kg piperonyl butoxide. Carbaryl in dimethylsulfoxide injected into mice induced significantly greater incidence of hydrocephaly and skeletal abnormalitie than dimethylsulfoxide alone (29).

Pregnant female mice were fed diets containing equivalence of 0, 10, and 30 mg/kg carbaryl during entire gutation period. Caesarean section were performed on one half the female at the 18th day, the other half were allowed to rear their pups for 96 hours. No differences were noted in mean fetal weight, length of gestation or pup mortality at the different levels of carbaryl fed. However, two litter of the group reviewing 30 mg/kg/day had 6 percent malformed offspring compared with 2.09 percent for normal animals. No teratogenic effect were claimed (30).

Chicken and duck eggs were injected with carbaryl at 10 and 1000 ug/egg near the middle of embryogenesis. Congenital foot deformatives were observed in both species, some of which were permanent. These consisted of medial or plantar flexion of phalanges at the interphalangeal or metacarpophalanged joints, with medial rotation or the tarsus. A few cases of retarded bone growth at the interfrontal and frontopancital sutures with encephalocele or hydrocephalus were noted (31).

Hatchability of chick eggs injected with 0, 1, 2 and 4 mg/egg varied inversely with the doses between 0 and 70%. When combinations of phosdrin and malathion, phosdrin and sevin, or malathion and sevin were injected into eggs prior to incubation, some of the chicks developed dwarfision of legs and wings, irregular breaks, and edema of brain and other parts of the body. Sevin alone caused edema in different parts of the body (32).

Effects of carbaryl in eggs, previously described were caused by feeding chickens diets containing 0, 75, 150, 300, and 600 ppm sevin for 3 weeks. Hatchability of eggs decreased as level of pesticide in diet increased. Amount of pesticide in egg and number of deformalities in hatched chickens increased with level of sevin in diet (33).

Conflicting results and difference in conclusions which cannot be resolved are found in reports which describes effects observed when experimental animals were treated with subtoxic amounts of carbaryl for prolonged periods. In trials with chickens amounts of carbaryl in diets which caused teratogenic effects or reduced hatchability were in excess of what would be present without diliberate adulteration. Critics of these trials fail to consider the significance of possible additional exposure to chickens following treatment of litter and roost with carbaryl or dusting the brids for lice and mite control.

Lack of agreement in results of rat studies presented by Russian and American investigators may be due to difference in susceptability of different strains of rats to carbaryl or to differences in impurities present in the preparations of insecticides. Reduced rates of reproduction, impared formation of sperm, effects on pituitary and adrenal glands and sterilization of female rats were stressed in Russian reports, but purity and source of carbaryl was not discussed. Relatively minor effects on reproduction were reported by American workers to have occured with highest levels of carbaryl, but these observations were not considered to be significant by statistical analysis. Positive controls were not included in either study. It cannot be assumed that the American work refutes the results obtained by the Russians.

Different results from trials with dogs were reported by two separate groups of American workers. In one study 3.1 mg per kg was reported as the no effect level in highly inbred beagle dogs. Only slight effects were reported from the highest level used in beagle dogs in a second by the other group. No attempts were made during the second study to test susceptability of the dogs with known teratogenic agents.

Hazards to Human from Use of Carbaryl

Present evidence indicates little or no danger of acute poisoning from carbaryl as a food contaminate. Over 90 percent of carbaryl applied to food crops dissipates within 3-10 days. When used within recommended guidelines residues on food and forage crops have not

exceeded established tolerance value. Results from market basket surveys indicate levels of carbaryl on dietary components are less than recommended tolerances for acceptable intake (0.02 mg per kg per day).

In spite of the difference in results reported by different investigators birth defects associated with oral injestion of carbaryl have been reported. The possibility of similar occurrances in humans from exposure to carbaryl cannot be ignored. Although no means is known for accurately projecting results from animal experimentation to humans, some appreciation of the hazards of carbaryl might be gained by comparing amounts of carbaryl associated with human exposure with no-effect level projected from experimental animals to man. In dogs the no-effect level was 3.1 mg/kg. (120 ppm) A comparable dose for a 70 kg human would be 210 mg. (intubated dose) Vanderkar (12) reported as a mean 19.8 ug per ml of alpha-naphthol in urine of villagers 7 days after application of carbaryl to huts. If 24 hour urine volume were assumed to be 1500 ml alpha-naphthol would represent about 70 percent of the no-effect level. Of interest is a mean depression of 15 percent observed in cholinesterase values in blood taken concurrently with the urine samples. In an industrial study (13) depression of blood cholinesterases as great or 30 percent were observed among plant workers with calculated daily excretion of alpha-naphthol equivalent to daily absorption of 149-229 mg carbaryl. (71-109 percent of the no-effect level).

Sufficient data are not available to assess hazards of carbaryl among different segments of the population. Based on end-use figures and proposed uses from labels the reviewer's opinion is that the greatest potential risk might be associated with home use.

Sevin absorbed very readily through human skin. About 70% absorption.

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