

OCCUPATIONAL EXPOSURES DURING 1976 THROUGH 1978
IN CALIFORNIA ASSOCIATED WITH EXPOSURE TO CARBARYL
AND A REVIEW OF THE TOXICOLOGY OF THIS PESTICIDE

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SUMMARY

Carbaryl, an N-methyl carbamate which inhibits cholinesterase, has caused few acute human poisonings in California although it has wide usage as a pesticide in large quantities in agriculture, homes, and gardens. In California, in 1976 through 1978, there were 27 incidents reported by physicians in which employees were occupationally exposed to carbaryl. Information for this report was gathered from Doctors' First Reports of Work Injury, other medical reports, and follow-up investigations. Of these 27 incidents, 16 resulted in systemic illness, 14 in skin irritation, and 5 in eye irritation. The systemic illnesses were typical for N-methyl carbamate poisoning of mild to moderate severity. In one study in dogs this chemical appeared to be teratogenic; tests in other animals were negative. High doses orally can result in detection of nitroso-carbaryl, a carcinogen in the digestive tract. It is doubtful if the potential for teratogenicity or carcinogenicity, which can be shown to occur under laboratory conditions, indicates a potential hazard to the users of products containing carbaryl or to the consumers of products which might contain currently legal residue levels of this chemical.

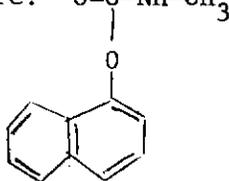
INTRODUCTION

Carbaryl is an N-methyl carbamate insecticide which is effective against many pests, and is used on a wide variety of crops, poultry, domestic animals, and household and garden pests. The recorded California usage was 853,434 pounds in 1976; 1,783,475 in 1977; and 928,196 in 1978. These figures do not include a large home and garden usage. The toxic action of this compound is due to its ability to inhibit cholinesterase, resulting in excess acetylcholine at the nerve endings of the parasympathetic and motor nerves. Excessive inhalation or dermal exposure can result in headaches, abdominal cramps, pinpoint pupils, pain in the chest, vomiting, diarrhea, sweating, and salivation. These effects can be relieved by atropine; however, respiratory paralysis resulting from the very high doses cannot be relieved by atropine. Unlike the same symptoms caused by organophosphate compounds, 2-PAM is of no value and is considered to be contraindicated in carbaryl poisoning, based on experimental dog studies. However, carbaryl has a low toxicity for man, and serious poisonings rarely occur.

Experimental studies in dogs have shown that high doses of carbaryl may be teratogenic, but the lack of similar action in other species of animals raises doubt as to the significance of this effect to man. It has been shown that feeding high levels of nitrite and carbaryl to rats can result in the formation of nitrosocarbaryl, a proven teratogen and carcinogen. However, the possibility that a sufficiently high level of nitrite will be present in the stomach simultaneously with an adequate amount of carbaryl at the right pH is considered a remote possibility, and does not present a significant hazard to man when exposed as an applicator or from eating food containing a residue of this pesticide.

TECHNICAL INFORMATION

Chemical name : 1-Naphthyl N-methylcarbamate.
Common names : Carbaryl, Sevin.
Trade names : Hexavin, Karbaspray, Ravyon, Septene, Sevin, Tricarnam.
Chemical structure: $\text{O}=\text{C}-\text{NH}-\text{CH}_3$



Chemical Properties: Technical (94%) chemical: White crystals, M.P. 142°C.
Solubility in water at 30°C 40 ppm. Soluble in polar solvents.

Chief Impurity: Alpha-naphthol 0.4%.

Molecular Weight: 201.2.

Chemical Reactivity: Stable to alkaline and acid hydrolysis. Stable to ultraviolet light. Noncorrosive.

Action: A cholinesterase inhibitor.

<u>Acute Toxicity:</u>	<u>Oral LD</u> 50
Rat	850mg/kg
Mouse	110mg/kg
Cat	250mg/kg
Dog	500-800mg/kg
Monkey	1,000mg/kg
Rabbit	Dermal 4000

Antidote: Atropine sulfate. Do not use 2-PAM or cholinesterase-inhibiting drugs; they are contraindicated.

Applications: For control of insect pests on a wide range of crops, forest lands, range land, lawns, ornamentals, poultry, and pets.

Formulations: Baits, dusts, wettable powders, oil, and aqueous dispersions and granules.

Manufacturer: Union Carbide Corporation.

OCCUPATIONAL EXPOSURE INCIDENTS THAT OCCURRED DURING 1976

In 1976, there were 14 occupational exposure incidents involving carbaryl that were reported by physicians to the California Department of Food and Agriculture. Of these, 7 were suspected systemic illnesses, 6 were skin exposure incidents, and 1 involved eye exposure.

Suspected Systemic Illnesses

A worker was loading airplanes with Fundal and Sevin. Later he experienced stomach cramps, excessive salivation, and shortness of breath. The doctor diagnosed the illness as acute gastroenteritis and found that the worker's cholinesterase level was within normal limits. These symptoms were typical for carbaryl poisoning. Blood samples are usually not collected soon enough or analyzed soon enough after N-methyl carbamate exposure to detect the transient cholinesterase depression which occurs.

While spraying tomatoes with Sevimol 4, Lannate, and a wettable sulfur, a farm worker removed his protective coveralls due to the heat, and later experienced nausea, vomiting, weakness, and shaking of the knees. The physician diagnosed the malady as gastritis from excess pesticide exposure. It is possible Lannate was a factor in causing this illness. There was no lost work time resulting from the illness.

After being exposed to Sevin, a tree surgeon reported that he was nauseated and dizzy, and having difficulty walking. No mention was made of how the pesticide was being used, what protective clothing was worn, if any, and how he was exposed. He was treated and told by the physician to stay in bed for 1 day.

A farm worker was cultivating a field when an aerial applicator began dusting the field with carbaryl. Before the worker could get off the field, he was engulfed by drift. He later became weak and was taken to a hospital emergency room. The employer was found to have been negligent in not warning the worker that the field was going to be sprayed, and the aerial applicator was negligent in spraying a field occupied by a person.

A gardener was pouring Sevin concentrate into a can and accidentally poured some of the chemical on his hand. About 3 hours later, he felt nauseated and dizzy. The period of disability, as reported by the physician, was 2 days.

A nursery salesman, while demonstrating the effectiveness of Sevin to a customer, mixed some of the pesticide in a coffee cup and sprinkled it on springtails. Later, without having washed or rinsed it, he drank some coffee out of the same cup. Subsequently, he became ill and experienced extreme headaches. The doctor diagnosed the illness as an accidental anticholinesterase poisoning. Two days after exposure to the Sevin, the man returned to work.

Following the application of Sevin to trees, an applicator said he was having chest pains as a result of exposure to the pesticide. The patient was attended to by a physician.

Skin Exposure Incidents

An exterminator, wearing the required protective equipment, was spraying both diazinon 4E and Sevin 50W in a warehouse and other commercial buildings. One day later, a rash appeared on his legs, hands, and arms. The employer stated that the worker has had minor skin problems for a number of years. He was treated by a physician. It is possible that the diazinon or the solvent it was dissolved in was a factor in this illness.

After a tomato crop was sprayed with Sevin and Difolatan, a farm worker, pulling a harvesting bin with a tractor, developed a skin rash. None of his fellow workers became ill. The worker was back on the job the next day. This effect was probably due only to Difolatan, a known sensitizer, and not Sevin.

A farm worker, while spraying with Sevin, developed a rash on the arm and under the chin. There was no reported lost time as a result of the illness.

A hospital kitchen was sprayed with a mixture of Sevin 50W, Dursban, and Malathion 8 by a pest control worker. Within a couple of hours, a dietary aid developed swollen and itchy cheeks and eyes. The illness was diagnosed as a chemical hypersensitivity reaction. The exposed person returned to work 2 days later. It is possible one of the other pesticides was a causative factor.

A farm worker was applying Sevin to tomato plants and later developed a rash. The doctor diagnosed the malady as contact dermatitis. There was no loss of work time.

While spraying roses with a 5% dust formulation of Sevin, a gardener's face was accidentally exposed to the chemical. Several small, itchy, red bumps appeared several days later. No reported disability resulted from the incident.

Eye Exposures

While exterminating a bee hive, a man being stung by bees accidentally sprayed Sevin into his left eye, resulting in chemical conjunctivitis. He was wearing the required equipment. The reported period of disability was 6 days.

OCCUPATIONAL EXPOSURE INCIDENTS THAT OCCURRED DURING 1977

In 1977, there were 13 occupational exposure incidents involving carbaryl reported by physicians to the California Department of Food and Agriculture. Of these, 5 were suspected systemic illnesses, 4 were skin exposure incidents, and 4 were eye exposure incidents.

Suspected Systemic Illnesses

A nursery/greenhouse worker accidentally tipped a bag from a shelf in a pesticide locker room where she was working. The package broke and she inhaled the fumes, causing chest tightness. She was taken to a hospital where she was examined, treated, and released. Her estimated period of disability was 2 days.

A helicopter sprayed Sevin and Plictran 50 where a laborer was working. The employee became ill. He washed up and was rushed to a doctor. He appeared slightly dizzy and nauseated. A small dose of atropine was administered. The diagnosis was exposure to pesticides. No days of work were missed.

A worker was spraying trees along a street when a clamp came loose and the hose went out of control while under 500 p.s.i. of pressure. This amount of pressure forced the pesticide mixture under his mask and shield. He inhaled fumes and got some in his mouth. He was taken to a hospital where he was treated. The pesticides involved were Malathion 5E and Sevin 50 WP. His period of disability from work was 2 days. All recommended protective equipment was worn, and the employee had been instructed in pesticide safety. The employee stated there is no warning when the clamps are going to come loose. When the accident occurred, only 1 clamp was being used instead of 2. This has since been changed.

Another tree sprayer was sprayed when the hose broke and sprayed liquid Sevin mixture onto his face. He also inhaled dust while mixing the powder. The worker complained of headache, nausea, and vomiting, but had no complaints at the time of examination. The period of disability from work was 2 days.

A structural pest control operator was exposed to Sevin and Dursban during his work. Later that night, he started feeling sick, and itching occurred in his eyes, pubic area, hair, and ears. The diagnosis was inconclusive as to whether the cause was an allergy to one of the chemicals or scabies. Kwell lotion was used for treatment, and Benadryl tablets were also given to the patient. No days of work were missed.

Skin Exposure Incidents

A greenhouse worker was exposed to Sevin while he was bringing a spray rig back to the laboratory to be filled with pesticide. The spray nozzle fell off the rig and, while a student by-stander reached for the nozzle, he inadvertently twisted the on-and-off valve, spraying the remaining residue into the worker's face. The insecticide exposure was received to the face, head, and mouth area. Mild cephalalgia was the only finding. Copious washing with water, a shower, and observation supplemented treatment for the patient. No days of work were missed.

While spraying with an 80% Sevin solution, a ground applicator got some of the pesticide on his skin. He developed contact dermatitis of the arms and abdomen and was treated by a physician. There were no days of work missed.

Two mixer/loaders for ground applications were working with Sevin 50W when some of the powder collected on their collars and caused a reaction. The area on the neck and throat of both men became red and infected and there was some excoriation and desquamation. All the required and appropriate safety equipment was worn. No work days were missed.

Eye Exposure Incidents

An exterminator was applying Sevin Granular 5% with a grass seed spreader when the dust of the chemical pellets got in his eye. Due to chemicals, he developed conjunctivitis of the right eye and secondary bacterial infection. Cortisporin ointment was used for treatment. No work days were missed.

While working in his office, a salesman heard a hissing sound. When he stood up to investigate it, he was hit in the face and eyes with insecticide escaping from a hole in an old, rusted, pressurized can that had been stored on the shelf in his office. He immediately washed his face and eyes with water, and then went to see a doctor. He had severe burning of the eyes for several minutes and a red irritation in his eyes for 2 days. Lavage and Pontocaine drops were used in treatment. One day of work was missed. Ortho Rose and Floral Spray (containing carbaryl) was the pesticide involved.

A ground applicator was spraying Sevin Sprayable 80 and got some in his eyes. His eyes were irrigated and Neosporin was dispensed for treating the eyes. There were no estimated days of disability.

A mixer/loader for aerial applications was loading an airplane when the pesticide loading hose broke. The pesticide Sevimol (carbaryl) sprayed into his eyes producing eye pain. He was diagnosed as having eye irritation. No days of work were missed.

OCCUPATIONAL EXPOSURE INCIDENTS THAT OCCURRED DURING 1978

Suspected Systemic Illnesses

While loading Sevimol into a ground rig, the liquid spilled on the exhaust pipe of the pump. The worker inhaled fumes and later experienced dizziness, nausea, and a headache. He was examined by a physician and released. He did not lose any work time.

A worker had been spraying an orchard with Sevin and Omite for about 30 hours over a 3-day period. Illness symptoms of nausea, dizziness, and a tightness in his chest developed on the fourth day.

A spray rig driver mixed his own loads, and did not wear a respirator while mixing, loading, or applying. He became dizzy and nauseated. He was treated by a physician and released.

A mechanic sprayed a shop area with Sevin and diesel oil to control yellow jackets. He became ill and was taken to a physician for treatment. He did not lose any days of work.

Skin Injuries

A spray rig driver broke out in a rash after about 6 weeks of applying carbaryl. He had noticed the same problem after similar use patterns in previous years. The injury was treated by a physician with prednisone. He has not done any further spray work since the injury.

A worker was applying Sevin Bait 5% when he developed a rash on his hands, legs, and neck. His injury was treated by a physician.

A worker was flagging for an aerial application of Sevin bait when she broke out in a rash. Her injury was treated by a physician with hydrocortisone cream. She lost 8 days of work.

A gardener was assisting a structural pest control operator in locating a hornet's nest. As the gardener walked on the other side of a fence (out of the applicator's view) he was sprayed by Sevin. He developed a rash on his wrists, neck, and abdomen. He was examined by a physician and released. No work time was lost.

DISCUSSION AND REVIEW OF THE LITERATURE ON THE TOXICITY OF CARBARYL

Human Illnesses in California

Identified occupational human illnesses in California due to overexposure to carbaryl do not often occur. They tend to be mild, recover rapidly and chronic effects have not been identified.

Absorption and Excretion

Feldman and Maibach (1974) found that 73% of the radioactive carbaryl applied to the forearms of men was absorbed, based on the recovery of radioactivity in the urine. However, there was a low urine recovery of

radioactivity when the radioactive carbaryl was injected intravenously. Since this is a factor in calculating the dermal absorption, there is doubt as to the accuracy of this measurement. Nye and Dorough (1976) measured the absorption of carbaryl injected endotracheally into the lungs of rats as an aerosol. All the inhaled dose was absorbed, and 90% was recovered in the urine in 24 hours. Casper et al (1973) found that [¹⁴C] carbaryl administered intragastrically in anesthetized rats was rapidly absorbed and appeared unchanged in the portal blood. In similar experiments in Hwang and Schanker (1974) using rats, and Shah and Guthrie (1975) using mice, showed there was complete and rapid absorption from the stomach and intestinal tract.

Metabolism

Knaak et al (1965) (1967) (1968) administered radio-labelled carbaryl orally to dogs, rats, guinea pigs, monkeys, sheep, and man. The pattern of metabolites for man differed from that of the animals, which may be an important factor when applying the finding of embryotoxic effects from high doses in an animal--the dog, for example--to man.

Toxicity

The toxicity of carbaryl to several species of animals was determined by Carpenter et al (1961). Atropine protected dogs from lethal doses, but 2-PAM was found to be of no value. In rats, the plasma cholinesterase reached its lowest value in 4 hours while the erythrocytes and brain reached their lowest levels in 30 minutes. All levels returned to normal in 24 hours. A study on the neuro-muscular degenerative potential was made in chickens. A single dose was given subcutaneously dissolved in lard at 3.0, 2.0, 1.0, 0.5, and 0.25 grams/ Kg. Transient weakness developed at the 2.0 gram/Kg dose, and was ascribed to cholinesterase inhibition. Marchi staining technique showed no pathology in the brain or peripheral nerves.

Serrone et al (1966) found that monkeys were more tolerant to carbaryl than rats and dogs, being able to tolerate a 1.0 gm/Kg oral dose. In a 6-month study, they showed no cholinesterase inhibition below 600 mg/Kg. Brain and plasma cholinesterase levels were decreased within 15 minutes after an oral dose in rats. Electron microscopic studies demonstrated vacuolation of the epithelium of the proximal tubules, but no disturbance of renal function was observed.

Shtenberg and Rybakova (1968) fed rats 7, 14, and 70 mg/Kg/day orally for 12 months and found a progressive decrease in blood cholinesterase. The 70 mg/Kg dose caused a stimulation of the adenohipophysis, with a disturbance of the rhythm of the estrous cycle, increase in the corpora lutea, and atretic follicles in the ovary, decreased spermatic motility, disturbed spermatogenesis, and impaired thyroid function. The possibility of a direct effect could not be excluded.

In contrast to these findings, Dikshith et al (1976) dosed male rats orally with 200 mg/Kg for 3 days a week for 90 days, and there were no overt signs of toxicity. No marked biochemical changes were found in liver, testes,

and kidney. The blood and brain showed a decrease of cholinesterase of 34 percent and 12 percent respectively but there were no symptoms of toxicity.

Jordan et al (1975) studied the effect of the daily intraperitoneal ingestion of 20 mg/Kg in male mice. At 10 and 20 days, the animals were killed and histological studies made of the testes, intestine, liver, brain, kidneys, hypophysis, and spleen. No changes were found in the testes where spermatogenesis was normal. There were no histopathological changes in any of the organs. Karyological studies showed an increase in the volume of cell nuclei in the neurosecretory neurocytes of the hypothalamus, the significance of which was not discussed.

Nir et al (1966) were concerned whether high doses of carbaryl-fed chickens as an acaricide would have an adverse effect on their health or accumulate in their tissues. Twenty-seven White Leghorn hens were divided into 3 groups: "A" received 180 mg/Kg/day, "B" received 54 mg/Kg/day, and "C" was a control group. They were fed the diet for 60 days. Birds in group "A" showed no changes in behavior or in egg production, and no hematological or histopathology. Birds in group "B" stopped laying at 3 days, became restless, had diarrhea, and showed a marked decrease in food intake. Histopathological changes were fatty degeneration of the liver, interstitial myocarditis, and degeneration of the ovary and the spleen. All the hens died in 5 weeks. No residues were found in the muscles of birds in group "A" but carbaryl and naphthol was found in the muscles and fat of birds in group "B". One week after the cessation of administration, there was no naphthol in the tissues or feces of any bird, indicating the rapid excretion of the carbaryl.

Toxicology in Man

The toxicological effects of carbaryl in man were studied on human volunteers by Wills et al (1968). Single oral doses of 0.5, 1.0, or 2.0 mg/Kg produced no objective signs of intoxication. One group of 5 men was given .06 mg/Kg daily for 6 weeks, and a second group received .13 mg/Kg/day for 6 weeks, with a control group receiving a placebo for the same length of time. No subjective or objective evidence of deleterious action was found. No significant changes were found in hematology, blood chemistry, or urine examination. There was a slight decrease in the plasma ChE in one individual on a single day.

Best and Murray (1962) studied the blood cholinesterase and 1-naphthol levels in the urine of workers exposed to air concentrations of carbaryl dust levels from 0.23-31.0 mg/cu.m. During an 8 month test period, a total of 283 whole blood samples were tested for cholinesterase activity expressed as moles of acetylcholine hydrolyzed. The lowest activity in 25 controls was 2.1 moles while 32/138 samples from workers were between 2.1 and 1.65 moles. None of the workers had symptoms of cholinesterase inhibition. The 1-naphthol level in the urine varied between 600-1,800 micrograms/100 ml, and was correlated with the level of exposure. Apparently, the rapid metabolism and excretion of carbaryl prevents a significant decrease in cholinesterase and clinical symptoms in spite of heavy exposure.

Comer et al (1975) studied the exposure of workers in formulating plants bagging 4-5% carbaryl dust, and spraymen operating tractor-drawn power air-blast equipment applying .04-0.6% carbaryl to orchards. Dermal contamination was measured by pads attached to the clothing. The amount inhaled was measured by analyzing the pads of respirators worn by the workmen. The formulating plant workers had a dermal exposure of 59 mg/hr and 1.1 mg/hr by inhalation. Field spraymen had an average dermal exposure of 59 mg/hr and .09 mg/hr by inhalation. No cholinesterase studies were done, but 1-naphthol levels in urine varied from 0.2-65.0 ppm, with a mean of 8.9 ppm. Calculated as mg/hr gives a figure of 5.6 mg/hr as carbaryl which, compared to the 75 mg/hr dermal exposure, would indicate a low dermal absorption; much lower than the 73 percent reported by Feldman (1974).

Jegier (1964) found that during the spraying of orchards with carbaryl, air concentrations at the tractor driver's breathing zone had a mean value of 0.6 mg/cu meter. Dermal exposure was measured by analyzing gauze patches attached to the clothing. The inhalation and dermal exposure was .29 and 25.3 mg/man/hr respectively, and the total of 225.6 mg/man/hr is .025% of the toxic dose. No toxic symptoms were noted in any of the workers.

Reproductive and Teratogenic Effects

A 3-generation study of technical carbaryl added to the diet of rats was made by Weil et al (1972), which showed that 10 mg/Kg per day did not produce an effect on fertility, gestation, viability of pups, or lactation. A rat study for possible teratogenic effects was done by feeding levels up to 500 mg/Kg/day in the diet without an increase in teratogenic anomalies, and with no effect on fertility or gestation. A reproduction study comparing dose levels up to 200 mg/Kg/day in feed with up to 100 mg/Kg given as a single oral dose by intubation. The oral dose of 100 mg/kg given by intubation caused mortality, signs of cholinesterase inhibition, and reduced fertility. None of these effects were seen in groups dosed in the diet. The difference was due to the sudden peak absorption into the blood stream unlike the lower levels resulting from the gradual absorption from the diet, the way poisoning would occur in man. Other studies were reviewed and those using per-os intubation and species of animals with a metabolic pattern unlike man were considered to be of no value.

Collins et al (1971) also did a 3-generation study in rats, using dietary levels of 0, 2,000, 4,000, 6,000, and 10,000 ppm. Fertility was decreased only at the 10,000 ppm level, with a decrease in litter size, number of live born progeny, number of survivors to day 4, and number weaned. A comparative study in gerbils using the same dose levels showed that the changes occurred at lower dose levels but were not clearly dose related.

Robens (1969) gave guinea pigs multiple doses of carbaryl of 300 mg/Kg by intubation on days 11-20, and produced a mortality of 40% in the dams, fetal mortality of 17.5%, and 11 terata. Single doses caused a 12.5% mortality in the dams, 65% fetal mortality and 9 terata. The same experiment was repeated using 100 and 200 mg/Kg doses in the rabbit without mortality to the dams, fetal mortality, or terata. When hamsters were given single doses of 125 mg/Kg on days 6, 7, and 8, there was no mortality

in the dams, and 10% fetal mortality. At the 250 mg/Kg dose level, there was a 30% fetal mortality. All the hamsters had cholinergic signs, but there were no bone defects in 4 fetuses chosen at random.

Weil et al (1973) compared the effect of carbaryl on rat and guinea pig reproduction and teratogenesis, dosing the animals by diet and intubation. The intubed animals showed cholinergic symptoms, but none of the diet groups did, indicating the importance of the route of administration. There was no evidence of mutagenesis or teratology in the rat experiments, or teratology in guinea pigs at the maximum tolerated dose levels.

Smalley (1968) fed groups of 6 beagles carbaryl in their diet during pregnancy at levels of 0, 3.125, 6.25, 12.5, 25, and 50 mg/Kg/day. Half the dogs in each group had dystocia due to uterine atony, and the dams were either sacrificed or the pups were removed by hysterectomy. There were no cases of dystocia in the controls, and the cause was attributed to carbaryl toxicity. Terata were found in 9-18 percent of the pups in the 4 higher doses, but the incidence was not dose related. The results could have been due to acute carbaryl toxicity rather than true teratogenesis.

Earl et al (1973) fed dogs the same dosage levels as those used by Smalley (1968), namely, 6.25, 12.5, 15, and 50 mg/Kg/day, during pregnancy. 14.7 percent of the total number of pups had various abnormalities but, since the results were not tabulated, it is uncertain if the effects were dose-related. His Table 3 was actually taken from Smalley's paper.

Reproduction in mice was studied by DeNorscia and Lodge (1973) who fed dose levels of 250, 500, 1,000, and 2,000 ppm in the feed. Offspring of this trial were then used for a second generation study. The percent of females becoming pregnant, the average litter size, and the average number of live-born were not significantly different in the first and second generation study. No mention was made of toxicity or teratogenesis.

Ghadiri and Greenwood (1966) injected 1, 2, and 4 mg/egg of carbaryl into the yolk sac of fertile chicken eggs, which caused a few chicks to have edema in different parts of the body, but no terata. However, if a mixture of Sevin and malathion, or Sevin and phosdrin, was injected at the same dose levels, striking abnormalities developed in the wings, legs, beak, and brain.

Dougherty et al (1971) studied the effect of daily oral doses of 2 and 20 mg/Kg of carbaryl on monkeys (*Macacca mulata*). Both dose levels caused an increase in the number of abortions, but an examination of the aborted fetuses and live infants showed no gross evidence of teratogenesis.

Ghadiri et al (1967) fed laying hens 75, 150, 300, and 600 ppm of carbaryl and malathion and a mixture of the two pesticides in the feed, and determined the hatchability and teratogenic effects in the chicks. They reported that the "percentage of deformities increased as the concentration of the pesticide in the diet increased" but did not state whether it was due to either pesticide alone or the mixture of the two. It is very difficult to evaluate the significance of this study.

Mutagenesis

Carbaryl was shown not to be mutagenic in the Ames test by Marshall (1976), McCann and Ames (1975), Ashwood-Smith (1972), and Siebert and Eisenbrand (1974). Weill (1973), using the rat, and Epstein et al (1972), using the mouse in the dominant lethal test showed that carbaryl was not mutagenic.

Amer (1965) exposed the roots of *Allium cepa* to a saturated solution of Sevin (85% sprayable powder), and noted disturbances in mitosis in the root tip. When placed in pure water, mitosis returned to normal. Amer and Farah (1968) sprayed plants (*Vicia faba*) with a saturated aqueous solution of Sevin weekly, and studied pollen meiosis and sterility. There were abnormalities in meiosis but the pollen was not sterile. It is difficult to see the significance of these results to mutagenesis in man.

Carcinogenesis

Innes (1969) studied the carcinogenicity of a number of pesticides by giving 7-day-old mice the maximum tolerated dose by stomach tube daily for 18 months, at which time they were sacrificed and examined grossly and histologically for tumors. The number found was compared to a controlled group. Carbaryl did not cause a significant increase in tumors. Shimkin (1969) injected A/He mice intraperitoneally with 6 mg of carbaryl dissolved in tricaprillin 3 times a week for 4 weeks, and examined them at 20 weeks for lung tumors. The treated mice averaged 0.7 lung tumors per mouse compared to 0.3 in the control group. Forty percent of the treated mice had tumors, compared to 25 percent in the controls. There was no statistical evaluation of this data for significance.

Carpenter et al (1961) did a 2-year feeding study in rats with doses of .005, .01, and .04% in the diet, and found no increase in the number of tumors over the controls.

The Problem of Nitrosocarbaryl

It has been shown that, in vivo, carbaryl reacts with nitrous acid at a low pH to form a N-nitrosocarbaryl, as shown by Egert and Greim (1976), Siebert and Eisenbrand (1974), and Elespuru et al (1974). Nitrosocarbaryl has been shown to be a mutagen and carcinogen by Eisenbrand et al (1974, 1976) and Lijinski and Elespuru (1976). In vivo, studies with secondary amines which are easily nitrosated have shown that when secondary amines and nitrite are given together by gavage to rats and mice, they develop cancer. When the nitrite and amines were fed separately, no tumors developed as quoted in Mirvish (1975)). The failure of animals to develop tumors when fed carbaryl would indicate that nitrosocarbaryl was not formed. This would not be due to a lack of nitrite since it has been shown by Spiegelhalter (1976) and Tannenbaum (1974) that the diet contains nitrate which is secreted in the saliva where bacteria reduce it to nitrite. However, the amount reaching the stomach at one time is small, and the concentration in the gastric contents is kept low by rapid absorption into the blood stream. Since the nitrosation reaction requires a high concentration of nitrite and amine, there is little chance for the reaction to occur under natural

circumstances. There are also inhibitors of the reaction, notably ascorbic acid and Vitamin E, in the diet. There are many naturally occurring amines in the diet which react more rapidly with nitrite than does carbaryl.

Significance of Adverse Effects on Test Animals

It is doubtful that the amounts of carbaryl that users inhale or absorb through the skin or that consumers ingest with treated commodities are adequate to produce any adverse effects in man.

Some have expressed concern about interpreting the data suggesting possible teratogenicity from the dog studies. These studies are now being repeated.

CONCLUSIONS

Carbaryl is a widely used low-toxicity n-methyl carbamate pesticide which when properly used has a low hazard for acute human poisoning and no well-documented potential for chronic effects.

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