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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR CARBARYL

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Prepared for

OFFICE OF SOLID WASTE AND
EMERGENCY RESPONSE

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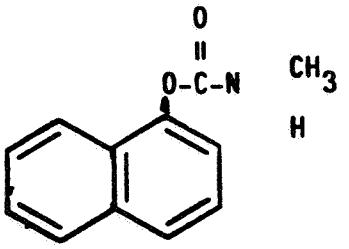
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
DNA	Deoxyribonucleic acid
GI	Gastrointestinal
i.p.	Intraperitoneal
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LD_{Lo}	Lowest lethal dose
MTD	Maximum tolerable dose
ppm	Parts per million
s.c.	Subcutaneous
SCE	Sister-chromatid-exchange
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1 STRUCTURE AND CAS NUMBER

Carbaryl is the common name for 1-naphthyl N-methylcarbamate. It is sold in the United States under the trade name Sevin. The Chemical Abstracts Service (CAS) Registry Number for carbaryl is 63-25-2, and the structure is given below.



Molecular formula: $C_{12}H_{11}NO_2$

Molecular weight: 201.2

There are numerous additional synonyms and trade names for carbaryl (IARC, 1976; NIOSH, 1976), including 1-naphthol N-methylcarbamate; 1-naphthyl methylcarbamate; methylcarbamate 1-naphthalenol; methylcarbamic acid, 1-naphthyl ester; N-methyl-1-naphthyl carbamate; N-methyl-α-naphthyl-urethan; Atoxan; Caprolin; Carpolin; Compound 7744; Dicarbam; Sevidol and Union Carbide 7744.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Carbaryl is a white crystalline solid that is formulated as wettable powders, pellets, granules, dusts, suspensions and emulsifiable concentrate solutions (IARC, 1976). Important physical and chemical properties are summarized below (IARC, 1976; NIOSH, 1976):

Melting point:	142-145°C
Specific gravity:	1.232 at 20°C
Vapor pressure:	0.000041 mm Hg at 25°C 0.00015 mm Hg at 40°C
Henry's Law Constant:	13.1 (unitless) (U.S. EPA, 1981a)

Solubility in water:	40 ppm at 30°C 31 ppm at 8°C in seawater (Karinen et al., 1967)
Solubility in organic solvents:	soluble in acetone, cyclohexanone, and dimethylformamide
Log octanol/water partition coefficient:	2.36 (Kenaga and Goring, 1980; Karickhoff, 1981)

1.3. PRODUCTION DATA

Carbaryl is prepared by the reaction of 1-naphthol and methyl isocyanate, or of 1-naphthol, phosgene and methylamine (Martin and Worthington, 1977).

Carbaryl is manufactured by Union Carbide, Institute, West Virginia (SRI, 1983). The estimated production for 1972 was 53 million pounds/year. Domestic consumption was ~25 million pounds in 1972, including 19 million pounds for agricultural purposes alone (von Rumker et al., 1974).

1.4. USE DATA

Carbaryl is a widely used carbamate insecticide with a broad spectrum of effectiveness on insects. It is used primarily on corn, soy beans, cotton, fruit and nut crops, and vegetable crops (von Rumker et al., 1974), and is approved for home yard and garden use.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

Specific information regarding the fate and transport of carbaryl in the atmosphere was not located in the available literature. Data for photodegradation in water (Section 2.2.) indicate that carbaryl will decompose in air through direct photolysis or UV light accelerated hydrolysis. Carbaryl is likely to enter the atmosphere as a result of spraying and dusting operations, but evaporation from water or soil is not likely to occur to a significant extent (Sections 2.2. and 2.3.). Relatively low soil sorption constants (K_{OC}) in the range of 200-400 and other data discussed in Sections 2.2. and 2.3. suggest that carbaryl may exist in the atmosphere to a limited extent in the particulate sorbed phase.

2.2. WATER

Numerous studies have demonstrated that carbaryl does not persist in natural water when studied in the laboratory (Karinen et al., 1967; Eichelberger and Lichtenberg, 1971; Kanazawa, 1975; Rodriguez and Dorough, 1977; Freitag et al., 1979; Szeto et al., 1979; Sharom et al., 1980; Odeyemi, 1982). When tested at concentrations of <10 ppm at pH 6.5-8, complete disappearance generally occurred within a week at room temperature; at 9°C, Szeto et al. (1979) found 61% loss after 50 days and 80% loss after 42 days in creek and pond water, respectively. Carbaryl is degraded in water by chemical and biological processes, and persistence is significantly increased in the presence of sediments or if pH is lowered. In a field study, Stanley and Trial (1980) determined the rate of disappearance of carbaryl from streams that received drift from spraying of nearby forests. An average disappearance constant of 0.028 $hour^{-1}$ was determined from measurements from nine Maine brooks and rivers (12 sites), and the constant

was not influenced by the size of the stream or the initial concentration of carbaryl in the water (2-16 µg/ℓ). The corresponding half-life is 24.75 hours, a value that is comparable to that reported for natural water in the laboratory. It should be noted, however, that the analytical method used in this study measured both the parent compound and its major chemical degradation product, 1-naphthol in the Maine water (pH ~5.5-7.0).

Carbaryl is degraded in water predominantly by hydrolysis, yielding 1-naphthol, methylamine and CO_2 (Aly and El-Dib, 1971; Wolfe et al., 1978). Kinetic studies have shown that carbaryl is stable to hydrolysis in acidic pH, and that degradation is rapid in basic pH (Aly and El-Dib, 1971; Wauchope and Haque, 1973; Wolfe et al., 1976); hydrolysis half-lives at pH values normally found in the aquatic environment at 27°C were calculated from measured rate constants to be 3.6 years (pH 5), 4.4 months (pH 6), 13 days (pH 7), 1.3 days (pH 8) and 3.2 hours (pH 9) (Wolfe et al., 1976). The hydrolysis of carbaryl is also significantly affected by temperature. Aly and El-Dib (1971) found that the rate of hydrolysis at pH 8.0 (i.e., second order rate constant) increased 2.9 times with a temperature increase from 13-23°C. In experiments conducted with seawater at pH 7.8, the amount of carbaryl (10 ppm) hydrolyzed after 4 days at 3.5, 17, 20 and 28°C was 0% (not detected), 44, 55 and 93%, respectively (Karinen et al., 1967). These data (Karinen et al., 1967) also suggest that salt content (ionic strength) may be an additional important factor affecting the rate of hydrolysis, since hydrolysis at comparable pH and temperature in freshwater is faster (Wolfe et al., 1976) than water with higher salt content.

Limited data are available on the photolysis of carbaryl in water. Wolfe et al. (1976) calculated half-lives of 51 and 64 hours (spring), 46 and 52 hours (summer), 68 and 102 hours (fall) and 103 and 200 hours

(winter) for latitudes of 30°N and 40°N, respectively, for the direct photolysis of carbaryl near the surface (<10 cm) of distilled water. These half-lives were calculated from disappearance quantum yields determined at 20°C and 313 nm, and data further indicated that photolysis is slowed by the presence of oxygen (i.e., under air-saturated reaction conditions) and is pH-dependent in the pH 5-7 range. Experiments conducted under midday summer sunlight (June, latitude 34°N) yielded data that were consistent with the calculated half-lives; the half-life was found to be ~45 hours in distilled water buffered at pH 5.5, and dark controls showed no decomposition. Wolfe et al. (1976) found that 1-naphthol and methyl isocyanate were not products of the direct photolysis of carbaryl at wavelengths >290 nm in either degassed or air-saturated water (pH 5.5), but did not identify the photoproducts. Aly and El-Dib (1972) reported that irradiation of aqueous carbaryl (20 ppm) with 254 nm light for 1 hour resulted in 50, 57 and 78% decomposition at pH 5.0, 7.0 and 8.0, respectively, and that 1-naphthol appeared as a product after 5 minutes of exposure in all cases. Karinen et al. (1967) noted that fluorescent light seemed to have a slight acceleration effect on hydrolysis of carbaryl in seawater at 20°C; hydrolysis averaged ~63% in 4 days in the dark and 72% under fluorescent light.

The oxidation of carbaryl in water under environmental reaction conditions is not expected to be significant when compared with its chemical and photolytic reactivity (Wolfe et al., 1976). The hydrolysis product 1-naphthol should, however, be very readily oxidized. Wauchope and Haque (1973) have reported that 1-naphthol in basic solution (i.e., 1-naphthoxide ion), but not in weakly acidic solutions, photooxidizes to 2-hydroxy-1,4-naphtho- quinone in the presence of room light.

Carbaryl can be degraded by microorganisms in aquatic environments, but the rate of degradation appears to be significant only in waters where hydrolysis is limited (i.e., neutral to acidic pH). Biodegradation of carbaryl has been demonstrated in freshwater samples (Aly and El-Dib, 1972; Szeto et al., 1979; Odeyemi, 1982), in simulated aquatic environments (Liu et al., 1981) and in pure and mixed culture experiments with bacteria isolated from freshwater (Guthrie et al., 1981) and marine water (Sikka et al., 1975). 1-Naphthol, the hydrolysis product of carbaryl, is readily utilized by microorganisms (Karinen et al., 1967; Aly and El-Dib, 1972; Sikka et al., 1975; Bollag et al., 1975), indicating that the hydrolysis step may be the limiting factor for biodegradation in natural waters.

In a study with Nile river water of pH 7.2 (25°C), Aly and El-Dib (1972) found that the concentration of carbaryl decreased progressively with time and that 89% of the added amount (4.75 ppm) disappeared in 6 days. 1-Naphthol appeared as a degradation product (2.2 and 0.8 ppm were detected after 2 and 6 days, respectively), apparently resulting from biological oxidation; these quantities of 1-naphthol did not result from chemical hydrolysis, since a sterile solution showed negligible hydrolysis after 6 days and a half-life of 16 days. The concentration of 1-naphthol reportedly decreased with time, indicating the biodegradation of this compound. Subsequent additions of increasing concentrations of carbaryl disappeared in shorter periods of time with no high buildup of 1-naphthol, thereby indicating microbial acclimatization; at the fourth addition, 17.5 ppm of carbaryl essentially disappeared after 1 day and no 1-naphthol was detected. Respirometric studies with higher levels of compound showed that, following a lag period of one day, oxygen uptake with 40 ppm carbaryl reached 95% of the theoretical amount required to oxidize it completely in 5 days; at 82

ppm carbaryl, an initial low rate of oxidation for 6 days was followed by rapid oxygen uptake, with 74% of the theoretical oxygen was used in 10 days (Aly and El-Dib, 1972).

Studies conducted in a simulated aquatic environment (i.e., in modified cyclone fermentors with a lake sediment/silt loam/activated sludge inoculum) suggest that biodegradation may also contribute significantly to the fate of carbaryl in anaerobic environments or in the presence of sediments with a rich organic nutrient content (Liu et al., 1981). Under anaerobic conditions, the half-life for biodegradation was reported to be 11.6 days when carbaryl was used as the sole carbon source and 6.1 days in the presence of glucose and peptone; the respective half-lives under aerobic conditions were 54 and 7.6 days. These results suggest that while the metabolism process played an insignificant part in carbaryl degradation in an aerobic environment, the biodegradation rate was accelerated somewhat in an anaerobic situation.

Measured soil sorption coefficients (K_{oc}) of 200-400 (Section 2.3.), measured octanol/water partition coefficients (K_{ow}) of 230 (Hansch and Leo, 1979; Kenaga and Goring, 1980; Karickhoff, 1981), and the reasonably low water solubility (see Section 1.2.) suggest that some adsorption of undegraded carbaryl onto bottom mud or sediments will occur; this is confirmed by positive sediment monitoring data (Section 3.1.). Volatilization of 1 ppm carbaryl from natural water in laboratory flasks at 9°C was not observed, a result that is consistent with its Henry's Law Constant value of 13 (U.S. EPA, 1981a).

Szeto et al. (1979) reported that addition of 1 ppm carbaryl to pond water (pH 7.5-7.9) in the presence of bottom sediment resulted in approxi-

mate averages at 40 and 33% recovery of carbaryl from the water and sediment, respectively, after 2 days of incubation at 9°C in laboratory flasks. Initial recovery from the water at day 0 was 90%, and recovery after 7, 14, 21 and 42 days from the water and sediment was approximately 26, 19, 11 and 14%, and 30, 28, 29 and 14% for water and bottom sediments, respectively.

In another study, the carbaryl concentration in seawater (10 ppm, pH 7-8, 8°C) in a laboratory aquarium without mud decreased ~50% in 38 days (Karinen et al., 1967). Most of this decrease was accounted for by the production of 1-naphthol. When 5, 10 or 25 ppm carbaryl was added to similar aquaria that contained estuarine mud, there was a sharp decrease in carbaryl concentration after ~3 days; 1-naphthol production was slight during this period, indicating that absorption by the mud was the major reason for the decline. When mud was present, the concentration of carbaryl plus 1-naphthol decreased to ~10% of the peak (3-day) value within 10 days. The concentrations of 1-naphthol in the aquaria with mud remained at low levels during the course of the 38-day study, indicating a slower rate of decomposition in the mud. In a field study, a 25x25 ft. estuarine mud flat plot was treated with carbaryl (at a rate of 10 lb A.I./acre) mixed with seawater at low tide (Karinen et al., 1967). Analysis showed that carbaryl was detectable in the mud 42 days after application; in 42 days, the concentration of carbaryl decreased from 5.4 to 0.1 ppm in the top 1 inch, from 0.32 to 0.20 ppm at the 2-3 inch level, and was detected at a level of 0.08 ppm at the 4-6 inch level at the termination of the study. 1-Naphthol levels were reportedly low after the first day, which supports the laboratory findings that hydrolysis proceeds slowly in the mud.

2.3. SOIL

Carbaryl does not persist in soil. In an extensive field study, Caro et al. (1974) applied carbaryl granules with corn seed in furrows 1 meter apart

in Coshocton silt loam (average pH 5.2) at a rate of 5 kg/ha, and persistence was measured by sampling in the corn rows at 10 locations on 7 occa- sions throughout the crop season. Regression analysis of the sampling data suggested that ~135 days were required for 95% of the carbaryl to disappear, but this is an overall value for the entire field. The disappearance did not conform to a first order reaction, and data for the individual sample points indicated that the carbaryl remained stable in the soil for 25 to more than 116 days and then degraded rapidly. Although the rate of degrada- tion varied with location, these lag periods indicated that carbaryl degra- dation in the soil was primarily microbiological.

The importance of soil organisms in the degradation of carbaryl was further illustrated by Rodriguez and Dorough (1977), who studied the persis- tence of carbaryl in Maury soil samples (pH not stated) that differed only in previous pesticide treatment. When 10 ppm carbaryl-naphthyl-1-^{14}C was incubated at 27°C in laboratory flasks with soil that had received no recorded pesticide treatment or with soil that had received 4 pounds/acre of carbaryl 6 months prior to collection, ~10 and 72% of the radioactivity, respectively, was lost from the soils after 4 days. Loss of radioactivity continued at a faster, although steady, rate in the previously untreated soil, but little subsequent loss occurred in the previously treated soil; after 120 days, the amount of label lost from the two soils was ~80 and 86%, respectively. Most of the lost radioactivity was attributed to liberation of CO_2 from microbial degradation of the naphthalene ring, and almost all of the terminal residual radioactivity was unextractable from the soil with acetone. Confirmatory studies showed that the most rapid loss of label from the carbaryl-pretreated soil occurred between the first and second day, and that loss of carbaryl was much faster from nonautoclaved soil than from

autoclaved soil, although carbaryl was effectively degraded in the latter. Kazano et al. (1972) found that the persistence of ^{14}C-carbonyl-labeled carbaryl incubated with soil (pH 5-6) at 25°C in the laboratory was influenced by soil type. Production of $^{14}CO_2$ varied from 2.2% (loamy sand) to 37.4% (clay loam) of initial radiocarbon during 32 days of incubation, and the amount of residual ^{14}C in the soil was reportedly roughly proportional to soil organic matter content.

The degradation of carbaryl by isolated soil bacteria and fungi has been reported by numerous investigators, including Boush and Matsumura (1967), Matsumura and Boush (1968), Bollag and Liu (1971a,b), Kazano et al. (1972), Sud et al. (1972), Tu and Miles (1976) and Rodriguez and Dorough (1977). These studies indicate that the bacterial and fungal isolates generally degrade carbaryl in the same manner as observed with soil incubations. Degradation appears to proceed via oxidative modification of the molecule (e.g., N-alkyl and aromatic ring hydroxylation, ring cleavage), leading eventually to hydrolytic cleavage of the ester linkage. A number of metabolites have been identified, including 1-naphthol, 1-naphthyl N-hydroxymethylcarbamate, 4-hydroxy-1-naphthyl methylcarbamate, 5-hydroxy-1-naphthylmethylcarbamate and CO_2, but 1-naphthol (which is also readily degraded by soil microorganisms) is the major metabolite (Sanborn et al., 1977; Mount and Oehme, 1981).

Although microbial transformation apparently plays a major role in the degradation of carbaryl in soil and the rate of degradation may be accelerated in soils recently treated with carbaryl (Rodriguez and Dorough, 1977), it is anticipated that chemical hydrolysis will be the predominant route of degradation in basic soils with a high moisture content (Section 2.2.). Photolysis is expected to be a significant route of degradation for carbaryl at the surface (Section 2.2.).

Some leaching of undegraded carbaryl in soil is likely to occur. Measured soil sorption coefficients (K_{oc}) in the range of 200-400 (Swann et al., 1980; Kenaga and Goring, 1980) and a water solubility of ~40 ppm (see Section 1.2.) suggest that the compound will be moderately mobile. Results of soil sorption and leaching studies indicate that the overriding restraint on movement is organic matter content rather than mineral composition (i.e., clay content) (LaFleur, 1976; Sharom et al., 1980; Aly et al., 1980). When a thin layer of soil was surface-treated with 1-100 µmol carbaryl/kg, mixed, and extracted with water at room temperature (1/1 soil/water ratio) to near equilibrium (2 hours), desorption partition constants (K_b) ranged from 0.12 for Norfolk scl (abbreviation not defined in study) (0.15% organic matter) to 3.7 for Okenee sl (abbreviation not defined; assumed sandy loam) (5.16% organic matter) (LaFleur, 1976). Similar studies with model sand showed that 2% added peat holds carbaryl much more effectively than 20% added kaolin, and that the K_b for sand, kaolin and peat was 0.04, 1.1 and 160, respectively. When one pore volume of water (~6 months rainfall in South Carolina) was added dropwise to the top of a 1 meter soil column that contained 10 µmol carbaryl/kg, carbaryl movement was greatest in Norfolk scl (47% of applied carbaryl in effluent) and least in Okenee sl (0% of applied carbaryl in effluent). In another soil column study, Sharom et al. (1980) found that only 53% of the carbaryl was leached from organic soil (75% organic matter) by 10 rinses of water, whereas 52% of the carbaryl was leached from sand (0.7% organic matter) by the first rinse alone.

In a field study, Caro et al. (1974) determined runoff losses of carbaryl (5.03 kg/ha) that was incorporated into the soil at a depth of 5 cm simultaneously with seed corn. Of the 4 kg of carbaryl applied to the

field, only 5.77 g (0.14%) was lost during the growing season in runoff water and sediments. Over 90% of this loss occurred in a single rainfall 19 days after application, and most of the carbaryl (4.34 g) was lost in the runoff water. Felley (1971) noted that losses of carbaryl in runoff are apparently minor, even when it is applied on the surface and not incorporated into the soil, but these data indicate that a high volume rainfall occurring shortly after carbaryl administration can generate low-level transport.

The low vapor pressure of carbaryl suggests that unadsorbed compound will not significantly volatilize from soil. LaFleur (1976) reported the results of a desorption study indicating that mean carbaryl loss by volatilization during application to soil was <3%. In this study, thin layers of various soils were surface-treated with 1-100 µmol carbaryl/kg in 0.001 M or 0.01 M ethanol solution, the treated soil was tumbled to obtain homogenous distribution and the solvent was permitted to evaporate at least 24 hours. When 10 µmol carbaryl/kg in 0.01 M ethanol was added dropwise to the surface of a 1 meter soil column, mean carbaryl loss during application was ~1% (LaFleur, 1976). Although not specifically stated, the reported molar concentrations reflect the concentration of aqueous ethanol and not the concentration of carbaryl in the ethanol. Additionally, the volumes of application were not reported.

3. EXPOSURE

3.1. WATER

The mean levels of carbaryl that have been detected in water samples collected at 111 stations in STORET are 4.7 µg/ℓ in unfiltered water (195 samples, range 0-335 µg/ℓ), 4.8 µg/ℓ in filtered water (67 samples, range 0.04-62 µg/ℓ), 38.9 µg/kg in wet sediment (10 samples, range 0.1-231 µg/kg) and 87.3 µg/kg in dry sediment (27 samples, range 0.1-770 µg/kg). The preponderance of samples was taken from rural stream/river and lake water.

3.2. FOOD

In a 1963-1969 survey of residues in United States foods (Duggan et al., 1971), the percentage of samples of large fruit and grains/cereals with carbaryl residues was 4.1 and 1.4, respectively. Most of the detected residues were between 0.03 and 2.0 ppm.

3.3. INHALATION

Monitoring data on levels of carbaryl in ambient air were not located in the available literature. The mean air concentration of carbaryl in the air inhaled by 38 urban applicators (application of carbaryl incidental to their employment or leisure activities) who made a total of 50 individual applications was determined to be 0.02 µg/ℓ, with a maximum recorded level of 0.28 µg/ℓ (Gold et al., 1982); the maximum total respiratory exposure was 0.70 µg/kg bw/hour.

3.4. DERMAL

The relative contribution of dermal exposure to total ambient exposure could not be determined from the available literature. The dermal exposure of carbaryl applicators was measured by Gold et al. (1982). The mean rates of exposure were 3.85 and 0.26 µg cm^{-2} hr^{-1}, respectively, for the

outside of the clothing and the skin beneath the clothing. The rate of exposure to the hands of applicators was 2.36 and 24.96 $\mu g\ cm^{-2}\ hr^{-1}$, respectively, for applicators with and without gloves. The maximum dermal exposure recorded in this study was 2.86 $mg\ kg^{-1}\ hr^{-1}$.

4. PHARMACOKINETICS

An abundance of information exists in the literature concerning the absorption, distribution, metabolism and excretion of carbaryl following administration to humans and experimental animals by various exposure routes and under many conditions. Several excellent reviews are available, including IARC (1976), Mount and Oehme (1981) and NIOSH (1976); these reviews were used in conjunction with selected primary papers in the preparation of Chapter 4.

4.1. ABSORPTION

Rapid absorption of carbaryl by both humans and experimental animals following oral, dermal and inhalation exposure has been well documented. Carbaryl absorption by humans occurs following oral ingestion (Farago, 1969; Lopez, 1970), during inhalation exposure (Best and Murray, 1962) or percutaneously during direct contact with the skin (Feldmann and Maibach, 1974; Maibach et al., 1971). Hwang and Schanker (1974) instilled ^{14}C-labeled carbaryl into the lungs and intestines of rats and found that the compound was rapidly absorbed by both the lungs and intestines through the process of simple diffusion; absorption in the lungs was 2.5 times faster than in the intestines. Following oral administration of ^{14}C-labeled carbaryl to rats, Casper et al. (1973) observed rapid and near complete (82%) gastric absorption of the compound within 1 hour after dosing. Absorption of carbaryl from the GI tract of animals was also reported by other investigators (Houston et al., 1975; Pekas, 1974; Cambon et al., 1981; Mount et al., 1981).

4.2. DISTRIBUTION

A 2-compartment open pharmacokinetic model has been described in experimental animals for carbaryl distribution between a well-perfused central compartment and a more slowly-perfused peripheral or tissue compartment

(Houston et al., 1974, 1975; Pipy et al., 1980). Strother and Wheeler (1980) also described a biphasic model for both pregnant and nonpregnant rats. Fernandez et al. (1982) applied open 2- and 3-compartment models to the kinetics of carbaryl and its metabolites, respectively, in rats. Carbamate metabolites of carbaryl have been reported to undergo enterohepatic circulation in rats, lengthening the time of residence in the body (Marshall and Dorough, 1979; Houston et al., 1974).

Declume and Benard (1977) administered [methyl-^{14}C]-labeled carbaryl orally to pregnant rats, and Strother and Wheeler (1980) administered [ring-^{14}C]- or [carbonyl-^{14}C]-labeled carbaryl by i.p. injection to pregnant rats. Radioactivity crossed the placenta within 1 hour after dosing and was rapidly distributed in the developing fetus. Declume and Benard (1977) detected radiolabeled compound in the eye, liver and brain of the fetus, while Strother and Wheeler (1980) reported radioactivity in the fetal brain, heart and lungs.

Bukin and Filatov (1965) administered a single oral dose of 400 mg carbaryl/kg bw to rabbits, and analyzed the resulting distribution of parent compound by paper chromatography. Carbaryl was rapidly distributed in tissues and excretory fluids within 30 minutes after dosing, as follows (in decreasing order of concentration): bile, urine, kidney fat, heart, liver, spleen, testes, kidneys, lumbar muscles, femoral muscles, cerebellum, medulla oblongata, brain (assumed to mean cerebrum) and lungs. Following a single oral dose of 100, 200 or 300 mg carbaryl/kg bw to rabbits, Bukin and Filatov (1965) did not detect any parent compound in the tissues or organs at 24-80 hours after dosing. Mount et al. (1981) found significant residues of carbaryl in the liver, heart and brain of male rats 24-48 hours after administering single oral doses of 450, 800 or 1200 mg carbaryl/kg bw.

Following a single oral dose of ^{14}C-labeled carbaryl (label location not specified) at a level of 0.9 mg/kg, ^{14}C was detected in the testes, prostate gland and seminal vesicles of male mice (Thomas et al., 1974). Thomas (1981), in his introductory remarks for the 10th Target Organ Symposium (The Testes), reported that carbaryl has been found in the testes of rats, mice and dogs administered the pesticide.

Following percutaneous administration of carbaryl to steers and cows, carbaryl residues were found in the liver, kidneys, muscles and omental and perirenal fat of steers 3 days after treatment but not 7 days after treatment, and in the milk of cows up to 69 hours after application (Hurwood, 1967). Distribution of carbaryl residues to the tissues was rapid but only temporary in both studies. In most cases, elimination of carbaryl residues from adult body tissues was completed within a few days after treatment.

4.3. METABOLISM

Extensive reviews on the metabolism of carbaryl in mammals are available, including Ryan (1971), Kuhr and Dorough (1976) and Menzie (1969). The metabolism of carbaryl has been investigated in rats (Knaak et al., 1965; Krishna and Casida, 1966; Houston et al., 1975; Sullivan et al., 1972; Pipy et al., 1981; Strother, 1970; Ryan, 1971; Pekas, 1979; Mehendale and Dorough, 1971; Benson and Dorough, 1979; Lin and Dorough, 1974), mice and gerbils (Benson and Dorough, 1979), guinea pigs (Knaak et al., 1965, 1968; Knaak and Sullivan, 1967; Rickard and Dorough, 1979; Ryan, 1971; Benson and Dorough, 1979), rabbits (Ryan, 1971), dogs (Knaak et al., 1965, 1968; Knaak and Sullivan, 1967; Ryan, 1971), monkeys, pigs, sheep (Knaak et al., 1965, 1968; Knaak and Sullivan, 1967), dairy cattle (Whitehurst et al., 1963; Dorough, 1967) and humans (Knaak et al., 1965, 1968; Knaak and Sullivan, 1967; Ryan, 1971; Strother, 1970; Chin et al., 1974). These studies have

identified some of the hydrolytic and oxidative metabolites of carbaryl, as well as several conjugated metabolites of carbaryl. The liver appears to be the primary site of carbaryl metabolism, regardless of species or route of exposure.

Mount and Oehme (1981) described four metabolic pathways for carbaryl, all of which generally yield metabolites of lesser toxicity than the parent compound. These metabolic schemes include the methylol route, by which the methyl group on the nitrogen (carbamic acid) is converted to $-CH_2OH$; formation of 1-naphthol by hydrolysis; hydroxylation of the naphthyl ring (at position 3, 4, 5, 6 or 7), possibly via epoxide intermediates, to yield hydroxylated carbaryl metabolites that are subsequently conjugated and then excreted; and glucuronidation of the carboxy group.

Following single oral doses of [naphthyl-^{14}C]- or [methyl-^{14}C]-labeled carbaryl to rats, guinea pigs, monkeys, swine, sheep, dogs and humans, or [carbonyl-^{14}C]-labeled carbaryl to rats, several 1-naphthyl and 4-(methylcarbamyloxy) 1-naphthyl glucuronide and sulfate conjugates were detected in the urine and/or feces of treated animals (Knaak et al., 1965, 1968; Knaak and Sullivan, 1967). The occurrence of these metabolites in each species is shown in Table 4-1. Knaak et al. (1968) reported that the major difference in carbaryl metabolism between humans and animals is that carbaryl is hydrolyzed to 1-naphthol to a greater extent by humans than by other mammals tested. 1-Naphthol is conjugated and excreted as 1-naphthyl sulfate or glucuronide. Sulfate or glucuronide conjugates of 1-naphthol were excreted by all species tested except dogs; monkeys and swine excreted little of these metabolites. All species except dogs also hydroxylated carbaryl, excreting the hydroxylated metabolites as a glucuronide or sulfate conjugate [4-(methylcarbamoyloxy)-1-naphthyl glucuronide or sulfate]. Dogs

TABLE 4-1

Carbaryl Metabolites Detected in Rats, Guinea Pigs, Monkeys, Swine, Sheep, Dogs and Humans[a]

Metabolites	Labeled Forms of Carbaryl[b]			Unlabeled Carbaryl[f]
	Naphthyl-^{14}C[c]	Methyl-^{14}C[d]	Carbonyl-^{14}C[e]	
Unidentified neutrals	rats, guinea pigs, monkeys, swine, sheep, dogs	rats, guinea pigs, monkeys, swine, sheep, dogs	rats	rats, humans (following both oral and inhalation exposures)
1-Naphthyl methylcarbamate N-glucuronide	guinea pigs	guinea pigs	ND	rats
1-Naphthyl methylimidocarbonate-o-glucuronide	rats, guinea pigs, monkeys, swine, sheep, dogs	rats, guinea pigs, monkeys, swine, sheep, dogs	rats	rats, humans (following oral exposure)
4-(Methylcarbamoyloxy)-1-naphthyl glucuronide	rats, guinea pigs, monkeys, swine, sheep	rats, guinea pigs, monkeys, swine, sheep	rats	rats, humans (following oral exposure)
1-Naphthyl glucuronide	rats, guinea pigs, swine, sheep	ND	ND	rats, humans (following both oral and inhalation exposures)
4-(Methylcarbamoyloxy)-1-naphthyl sulfate	rats, guinea pigs, monkeys, sheep	rats, guinea pigs, monkeys, sheep	rats	rats
1-Naphthyl sulfate	rats, guinea pigs, monkeys, sheep	ND	ND	rats, humans (following both oral and inhalation exposures)

TABLE 4-1 (cont.)

Metabolites	Labeled Forms of Carbaryl[b]			
	Naphthyl-^{14}C[c]	Methyl-^{14}C[d]	Carbonyl-^{14}C[e]	Unlabeled Carbaryl[f]
Unidentified Metabolite A	rats, guinea pigs, dogs	rats, guinea pigs, monkeys, dogs	rats	rats, humans (following oral exposure)
Unidentified Metabolite B	guinea pigs, dogs	guinea pigs, dogs	ND	ND
Unidentified Metabolite C	ND	sheep	ND	ND
Unidentified Metabolite D	sheep	sheep	ND	ND

[a]Source: NIOSH (1976); Knaak et al. (1965, 1968); Knaak and Sullivan (1967)

[b]Analysis by radiometric techniques; rats and guinea pigs treated intraperitoneally; monkeys, swine, sheep and dogs treated orally.

[c]Animals tested include rats, guinea pigs, monkeys, swine, sheep and dogs.

[d]Animals tested include rats, guinea pigs, monkeys, swine, sheep and dogs.

[e]Rats were the only species tested.

[f]Analysis by fluorometric techniques; rats treated orally; humans treated orally or by inhalation.

ND = Not detected

appeared to conjugate carbaryl (enol form) directly, forming 1-naphthyl methylimidocarbonate O-glucuronide. All other species tested also excreted this metabolite (Knaak et al., 1965, 1968; Knaak and Sullivan, 1967).

Other identified metabolites of carbaryl include 5,6-dihydro-5,6-dihydroxycarbaryl in rats and guinea pigs (Sullivan et al., 1972) and dairy cows (Dorough, 1967), thioether conjugates in rats (Ryan, 1971), glucuronide or sulfate conjugates of 5,6-dihydroxycarbaryl or N-hydroxymethylcarbaryl in rats (Chen and Dorough, 1979), and mercapturic acids, S-(4-hydroxy-1-naphthyl)cysteine and S-(5-hydroxy-1-naphthyl)cysteine (Bend et al., 1971).

Of the identified metabolites of carbaryl, 5-hydroxycarbaryl and 1-naphthol may be more toxic than the parent compound under certain circumstances (Carpenter and Weil, 1970; Bollag et al., 1975).

4.4. EXCRETION

The major route of excretion for carbaryl and its metabolites following oral administration for most mammalian species is the urine; however, the dog excretes ~50% of the administered dose in the feces (Knaak et al., 1965, 1968; Knaak and Sullivan, 1967). For rats and dogs administered single oral doses of [naphthyl-^{14}C]-labeled carbaryl, 10 and ~50%, respectively, of the administered radioactivity was detected in the feces. Following single oral administration of [methyl-^{14}C]-labeled carbaryl, 68 and 23% of the radioactivity was detected in the urine of rats and dogs, respectively. When rats were given ^{14}C-carbaryl labeled at various positions, excretion was nearly complete by 3 days. 95% of the naphthyl-label was eliminated in the urine and feces; 99% of the carbonyl-label was eliminated in the urine, feces and respiratory CO_2; and ~91% of the methyl-label was eliminated in the urine, feces, CO_2 and carcasses. Guinea pigs receiving i.p. injections of either [naphthyl-^{14}C]- or [methyl-^{14}C]-labeled carbaryl

excreted 85% of the administered doses in the urine within 24 hours. Rats given i.p. injections of [naphthyl-^{14}C]-, [methyl-^{14}C]- and [carbonyl-^{14}C]-labeled carbaryl excreted 73, 47 and 48%, respectively, of the administered doses in the urine within 24 hours.

Shah and Guthrie (1977) reported that rabbits rapidly absorbed a dermal dose of ^{14}C-carbaryl (label location not reported), and eliminated the highest concentrations of carbaryl metabolites within 24 hours in the urine and feces. Hurwood (1967) reported that dairy cows sprayed with carbaryl (percutaneous absorption) excreted the intact compound in the milk in decreasing concentrations from 5-77 hours postdosing.

Two human volunteers who ingested a single dose of 2 mg carbaryl/kg bw were reported to have 25% of the administered dose as carbaryl metabolites (measured by fluorometric techniques) in the urine within 4 days after ingestion (Knaak et al., 1968).

5. EFFECTS

5.1. CARCINOGENICITY

At present, only equivocal evidence of carbaryl's carcinogenicity in laboratory animals has been reported. The IARC (1976) found the data to be insufficient for an evaluation of the carcinogenicity of carbaryl.

A contaminant of carbaryl, 2-naphthyl methylcarbamate, can be produced if contaminated 1-naphthol (a carbaryl precursor) is used in manufacture. The 2-naphthyl isomer has been reported to be carcinogenic (Argauer and Warthen, 1975). Four domestic carbaryl samples were analyzed and contained no detectable 2-naphthol methylcarbamate, but four samples of foreign carbaryl contained 0.52-5.60% of the contaminant.

Innes et al. (1969) conducted a carcinogenicity bioassay on many compounds, including carbaryl, for the National Cancer Institute in two strains of first filial generation mice, designated B6C3 and B6AK. Groups of 18 male and 18 female neonates of both strains received 0 or 4.64 mg carbaryl/kg by gavage on days 7-28 of age and thereafter in the diet at a level of 0 or 14 ppm for 18 months. No significant increase in tumor incidence was found among treated groups in any tissues examined histopathologically. Similar groups of mice given an s.c. injection of 100 mg carbaryl/kg dissolved in dimethylsulfoxide on day 28 of age and observed until age 78 weeks had tumor incidences that were not significantly different from the dimethylsulfoxide-injected mice (Innes et al., 1969).

Carpenter et al. (1961) reported that the lung tumor incidence was not increased as compared to nontreated controls in groups of 30 male A/Jax or C3H mice given weekly s.c. injections of 10 mg carbaryl for 5 months.

Carpenter et al. (1961) also reported the absence of increased tumor incidence in CF-N rats fed carbaryl for 2 years. Groups of 20 male and 20

female rats were given diets containing 0, 50, 100, 200 or 400 ppm carbaryl; survivors were killed after 732-736 days of treatment. In addition, gross and histopathological evaluations were performed on auxiliary (concurrently maintained) groups of control and exposed rats at 6, 9, 12 and 24 months of exposure. Survival was unaffected by treatment and no specific tumor type or tumor sites were associated with treatment. The numbers of tumor-bearing rats among the 40 rats/group were 9, 11, 7, 6 and 11 for dietary exposures of 0, 50, 100, 200 and 400 ppm, respectively.

Triolo et al. (1982) observed no significant increase in lung tumor induction in two separate experiments wherein female A/J mice were fed 1000 ppm carbaryl for 20 weeks. Of 16 treated mice in the first experiment, 5 developed lung tumors, compared with 1 lung tumor-bearing animal of 11 untreated control mice. Of a second group of 31 treated mice, 3 had lung tumors compared with 7 lung tumor-bearing animals of 31 untreated control mice. Differences between treated and control groups were not statistically significant.

The carcinogenicity of carbaryl after dietary and s.c. administration has been reported in a Russian study. Andrianova and Alekseev (1970) administered by gavage 30 mg carbaryl/kg to 60 mongrel male rats twice weekly for up to 22 months. A group of 48 untreated male mongrel rats served as controls. Of the 12 surviving treated rats, 3 had fibrosarcomas and 1 had an osteosarcoma. Of the 46 surviving untreated rats, only 1 had a fibrosarcoma. Elevated tumor incidence was reported to be statistically significant ($p<0.01$). Subcutaneous implantation of a paraffin pellet containing 20 mg carbaryl/kg killed 38 of 48 mongrel rats after 22 months. The 10 survivors had implantation site sarcomas. Of the 48 untreated controls 46 survived 22 months, and 1 animal had a fibrosarcoma. The results of this

study are difficult to interpret due to the high mortality in treated groups, lack of information on control groups and the possible contamination of the test compound (NIOSH, 1976).

Shimkin et al. (1969) gave 16 male A/He mice 12 i.p. injections of 0.5 mg carbaryl in tricaprylin over a 4-week period. Lung tumors were observed in 6 of 15 survivors 20 weeks after treatment. Controls consisted of 28 tricaprylin injected rats and 31 untreated rats. Lung tumors developed in 7 and 2 animals, respectively, in these groups. The percentage of lung tumor-bearing animals in the treated group was not significantly increased over controls ($p>0.05$). This bioassay was developed as a short-term test to indicate the possible carcinogenic potential of a compound. The usual criteria for a positive response is both an increase in the number of animals with lung tumors and an increase in the number of lung tumors per tumor-bearing animals.

Carbaryl can be nitrosated in the presence of nitrite in mildly acid milieu, such as the human stomach (IARC, 1976), in vitro in dilute aqueous solution at pH 1-3.5 (Eisenbrand et al., 1975; Elespuru and Lijinsky, 1973) or in rat gastric juice in vitro (Beraud et al., 1979). N-Nitrosocarbaryl induced lung tumors in all surviving (14/16) rats given a single s.c. injection of 1000 mg/kg and observed for 450 days. No tumors were observed in controls (Eisenbrand et al., 1975).

No significant incidence of malignant tumors was observed in female Sprague-Dawley rats given 300 mg carbaryl by gavage over a 10-day period or 90 mg carbaryl and 120 mg sodium nitrite by gavage over a 3-day period and observed until death (Lijinsky and Taylor, 1977).

5.2. MUTAGENICITY

Carbaryl has been evaluated for its potential mutagenicity in several short-term tests using bacteria, fungi, Drosophila, mammalian cells in culture, and whole-mammal assays. The biological endpoints for determination of the potential mutagenicity of carbaryl were: gene mutation, structural/numerical chromosome aberrations, DNA repair synthesis, mitotic recombination, and sister chromatid exchange. The available studies on carbaryl are outlined in Table 5-1. A detailed evaluation of the mutagenicity data on carbaryl can be found in U.S. EPA (1981b).

The ability of carbaryl to cause gene mutations in bacteria has been extensively studied (see Table 5-1). The majority of the test results were reported as negative. It should be emphasized that the negative results are not wholly unequivocal. Appropriate concurrent controls and adequate concentration ranges were sometimes not used, an exogenous metabolic activation system was not always included, and in some cases the available data are not sufficient to determine whether an adequate test was conducted. There were some reported occurrences of weak responses (Egert and Greim 1976, Jaszczuk et al. 1979). Because these responses were weak at high doses, the possibility of an impurity or impurities with mutagenic activity should be considered.

Carbaryl has also been reported as weakly mutagenic in eukaryote assays, namely a Drosophila sex-linked recessive lethal test (Brzeskij and Vaskov 1971) and a forward mutation assay using Chinese hamster V79 cells (Ahmed et al., 1977a). These studies have deficiencies and are considered merely suggestive evidence of weak mutagenicity. Wojciechowski et al. (1982) reported carbaryl as negative in a Chinese hamster V79 gene mutation test.

TABLE 5-1

Summary of Mutagenicity Test Results for Carbaryl

Assay	Indicator Organism	Application	Concentration or dose	Exogenous Activation System	Response[a]	Comments	Reference
A. Gene mutation tests: Bacteria							
Reverse mutation	S. typhimurium TA1535 TA1537 TA1538 TA98 TA100	plate incorporation	10-1500 µg/plate	±S9	- - - - -		De Lorenzo et al., 1978
Reverse mutation	S. typhimurium TA1535 TA1536 TA1537 TA1538	plate incorporation	60-1000 µg/plate	±S9	- - - -		Marshall et al., 1976
Reverse mutation	S. typhimurium TA1535 TA1537 TA100 TA98	plate incorporation	0-2000 µg/plate	±S9	- - - -		McCann et al., 1975
Reverse mutation	S. typhimurium TA1535 TA1536 TA1537 TA1538	plate incorporation	0.02 µg/plate		- - - -		Shirasu et al., 1976
Reverse mutation	S. typhimurium TA98 TA100 TA1535 TA1537 TA1538	spot test	50 nmol		- - - - -		Blevins et al., 1977
Reverse mutation	S. typhimurium TA98 TA100 TA1535 TA1537 TA1538	plate incorporation	0.00115-11.5 µg/plate		- - - - -		Blevins et al., 1977

TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or dose	Exogenous Activation System	Response[a]	Comments	Reference
Reverse mutation	S. typhimurium G46, TA1535, TA1000, C3076, TA1537, D3052, TA1538, TA98	gradient plates		±S9	=, =, =, =, =, =, =, =		Probst et al., 1981
Reverse mutation	S. typhimurium TA1538	liquid suspension	100 µM	± mouse microsomes plus cofactors	+wk[b]	Weak response after activation. A dose-response was not determined and positive findings were not confirmed on a repeat test.	Egert and Greim, 1976
Reverse mutation	S. typhimurium TA1535, TA1536, TA1537, TA1538	plate incorporation	500-1000 µg/plate	±S9	=, =, =, =		Marshall et al., 1976
Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537	NR	0.25-1000 µg/plate		+wk[b], +wk[b], +wk[b], +wk[b]	Although a weak increase in the number of revertants was reported, there was no indication whether this increase was 2-fold or greater.	Jaszczuk et al., 1979
Reverse mutation	E. coli WP2	spot test	10% in buffer saline		-		Ashwood-Smith et al., 1972
Reverse mutation	E. coli WP2, WP2 uvrA	plate incorporation	100 nmol/mL	±S9	=, =		Probst et al., 1981
Reverse mutation	E. coli B/r WP2	spot test	0-10 mg/plate		-		Uchiyama et al., 1975
Reverse mutation	E. coli WP2, WP2 uvrA	spot test	0.02 mg/plate		-, -		Shirasu et al., 1976

TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or dose	Exogenous Activation System	Response[a]	Comments	Reference
Reverse mutation	E. coli WP2	spot test	NR		-		Nagy et al., 1975
	WP2 uvrA				-		
Reverse mutation	E. coli WP2 WP2 uvrA	gradient plates		±S9	+		Probst et al., 1981
Reverse mutation	E. coli K12, gal⁻ nad⁻, arg⁻, MTR⁻	liquid suspension	NR	± mouse microsomes plus cofactors	+		Egert and Greim, 1976
Reverse mutation	E. coli K12, lac⁻ leu⁻, cys⁻	spot test	NR		-		Fiscor and Nil Lo Piccolo, 1972
Reverse mutation	Bacillus subtilis 1681-		NR	0.07%	-		DeGiovanni-Donnelly et al., 1968
Reverse mutation	Serratia marcescens	spot test	NR		-		Fahrig, 1974
Forward mutation	E. coli	liquid incubation test, spot test	NR		-		Fahrig, 1974
Forward mutation	Haemophilus influenza (novobiocin resistance)	liquid suspension	0.1 mM for 1-9 min.		-		Elespuru et al., 1974

TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or dose	Exogenous Activation System	Response[a]	Comments	Reference
A. Gene mutation tests: Insects and mammalian cells in culture							
Recessive sex-linked lethal and sublethal mutations	D. melanogaster	Fed	1% suspension in a diluted sugar syrup for 24 hours		+wk[b]	Although authors conclude carbaryl is a weak mutagen to D. melanogaster, inducing a low rate of recessive sex-linked lethal and sublethal mutations, their evidence is considered only suggestive because of an inadequate sample size.	Brzeskij and Vaskov, 1972
Forward mutation (ouabain resistance)	Chinese hamster lung V79 cells	cell culture	0.01 mM for 2 days		+wk[b]	No dose-response relationship demonstrated	Ahmed et al., 1977a
Forward mutation (ouabain resistance)	Chinese hamster lung V79 cells	cell culture	0.01-0.1 mM for 3 days	± irradiated Syrian hamster cells	=		Wojciechowski et al., 1982
B. Cytogenetic tests: Lower eukaryotes							
Nondisjuction	Aspergillus nidulans	plate test	0.1 mg/mL		-		Morpurgo et al., 1979
B. Cytogenetic tests: Plants							
Root tip mitosis: Allium cepa		root treatment	25 ppm and 50 ppm for 24 hours		+	Dose-related C-mitotic effects (multipolar anaphases, mitotic arrest, chromosome lagging, tetraploidy).	Amer et al., 1965
Root tip mitosis: Allium cepa		root treatment	25, 50, and 100 ppm for 4 hours		+	Dose-related C-mitotic effects (chromosome lagging, tetraploidy, chromosome stickiness, bridges, mitotic arrest).	Amer et al., 1971
Root tip mitosis: Vicia faba and Gossypium barbadense		seed treatment	100 ppm for 6, 12, 24, and 48 hours		+		

Assay	Indicator Organism	Application	Concentration or dose	Exogenous Activation System	Response[a]	Comments	Reference
Pollen mother cell meiosis: Vicia faba		2-week-old plants sprayed weekly for one month	saturated solution		+	Abnormal meiosis (anaphase bridges, chromosome lagging, stickiness)	Amer and Farah, 1968
Meiotic effects in corn		seed treatment and injection into anthers of plants	0.12% and 0.25% aqueous solution for 48 hours (seeds) and 6 hours (anthers)		+	Abnormal meiosis (bridges, stickiness)	Brankovan, 1972
Mitosis: Hordeum vulgare		seed treatment	500, 1000, 1500 ppm for 6, 12, and 24 hours		+	C-mitotic effects (chromosome lagging, fragments, bridges)	Wuu and Grant, 1966
Meiosis: Hordeum vulgare		seed and plant treatment	1000 ppm for 12 hours (seeds) and 500 ppm (plants)		+	Abnormal meiosis (e.g., chromosome stickiness, bridges, univalents, polyploidy, fragments, micronuclei)	Wuu and Grant, 1967
B. Cytogenetic tests: Mammalian cells in culture							
Polyploidy	Chinese hamster V79 cells		5×10^{-6} to 10^{-4} M		+	Dose-related increase at $\geq 5\times10^{-6}$ M	Sabharwal and Lockard, 1979
Polyploidy	Chinese hamster fibroblast cells		0.0075-0.03 mg/mL		+	Increase at 0.0075 mg/mL	Ishidate and Odashima, 1977
Aneuploidy/ polyploidy	Chinese hamster V79 cells		0, 50, and 100 for 1-3 days	±S9	+	Increase in frequency of cells with elevated chromosome numbers (>22) at 100 µM. This effect was decreased by addition of glutathione or S9. Multiple chromatid exchanges observed.	Onfelt and Klasterska, 1983
Human embryonic fibroblasts			20, 40, and 80 µg/mL for 24 hours		+	29.2% of cells aneuploid (primarily hypodiploidy) at 80 µg/mL; chromosome fragments also found.	Kazarnovskaya and Vasilos, 1977

TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or dose	Exogenous Activation System	Response[a]	Comments	Reference
Human embryonic fibroblasts			20, 40, and 80 µg/mL for 6, 24, and 48 hours, technical product reported as containing 84% active ingredient		+	Dose-related C-mitotic effects	Vasilos et al., 1972
Human embryonic fibroblasts			0.001, 0.01, 100, and 1000 mg/mL		+	Dose-related C-mitotic effects	Shpirt, 1975
B. Cytogenetic tests: Whole mammals							
Mitotic studies in epithelium from small intestine crypts and cornea of rats			85% commercial preparation, acute: 400 mg/kg (one-half LD_{50}), 80 mg/kg, 40 mg/kg, and 20 mg/kg		+	C-mitotic effects and chromosome fragmentation	Vasilos et al., 1975a
Mitotic studies in splenic follicles, corneal epithelium, and epithelium of glandulae intestinales of rats			85% commercial preparation, subacute: 5 and 20 mg/kg (28 administrations) orally; chronic: 0.05 to 8 mg/kg/day for 6 months orally		+	C-mitotic effects and chromosome fragmentation	Vasilos et al., 1975b
Micronucleus test in mice			10^{-8} M i.p. or daily for one week via intubation		-		Degraeve et al., 1976
Micronucleus test in mice	Swiss male	fed in distilled water	two doses of 146 mg/kg separated by a 24-hour interval		-		Rani et al., 1980

TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or dose	Exogenous Activation System	Response[a]	Comments	Reference
Dominant lethal	male rats	diet	200 mg/kg/day on 7 successive days		-		Weil et al., 1973
Dominant lethal	male rats	oral	100 mg/kg on 7 successive days		-		Weil et al., 1973
Dominant lethal	mice	oral	50 and 100 mg/kg/day on 5 successive days		-		Epstein et al., 1972
Host-mediated reverse mutation	S. typhimurium G46	i.p. injection of S. typhimurium into male Swiss mice 24 hours after last oral treatment	438 mg/kg/day orally on 3 successive days		-		Rani et al., 1980
C. Other studies indicative of DNA-damaging activity							
Sister chromatid exchange	Chinese hamster lung V79 cells		10^{-5} to 10^{-4} M		+	Dose-related increase at $\geq 10^{-5}$ M	Sabharwal and Lockard, 1979
Unscheduled DNA synthesis	SV-40 transformed human fibroblasts (VA-4)	cell culture	1-1000 µM for 8 hours	±S9	+	Dose-related increase at ≥1 µM; S9 did not increase UDS activity	Ahmed et al., 1977b
Unscheduled DNA synthesis	primary rat hepatocytes (Fischer 344)	cell culture	100 nmol/mL for 5 hours		-		Probst et al., 1981
DNA synthesis	rat thymocytes (Wistar)	cell culture	1-100 µg/mL		+	22% inhibition on DNA synthesis at 10 µg/mL	Rocchi et al., 1980
DNA synthesis	human lymphocytes	cell culture	50 µg/mL		+	62% inhibition on DNA synthesis at 50 µg/mL	Rocchi et al., 1980
Unscheduled DNA synthesis	human lymphocytes	cell culture	50 µg/mL		-		Rocchi et al., 1980

TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or dose	Exogenous Activation System	Response[a]	Comments	Reference
DNA strand breaks as determined by sedimentation profiles	human skin fibroblasts	cell culture	100 μM for 1 hour		-		Regan et al., 1976
Mitotic gene conversion	S. cerevisiae D4	cell culture	1000 ppm (4.97mM) dissolved in DMSO for 16 hours		-		Siebert and Eisenbrand, 1974
Mitotic gene conversion	S. cerevisiae	liquid incubation test	NR		-		Fahrig, 1974
Recombination	Bacillus subtilis Marburg 17a Marburg 45T	NR	0-10 mg/plate		- -		Uchiyama et al., 1975

[a]Responses: +, positive; -, negative; =, negative with and without S9 activation system; ±, positive with and negative without S9 activation system; ∓, negative with and positive without S9 activation system

[b]wk = weak or borderline mutagenic response

NR = Not reported; i.p. = intraperitoneal

Other tests indicative of DNA-damaging activity have primarily been negative. These included tests for DNA strand breakage and mitotic recombination (Uchiyama et al., 1975; Fahrig, 1974; Regan et al., 1976; Siebert and Eisenbrand, 1974). Inconsistent results have been reported for DNA repair tests (Ahmed et al., 1977b; Probst et al., 1981; Rocchi et al., 1980). Sister chromatid exchange formation in V79 cells was reported as positive (Sabharwal and Lockard, 1979).

Negative results have been reported for carbaryl in whole-mammal tests which detect clastogens (chromosome-breaking agents). These included dominant lethal assays in rats (Weil et al., 1973) and mice (Epstein et al., 1972), and micronucleus assays in mice (Degraeve et al., 1976; Rani et al., 1980). The micronucleus assay is also thought to detect agents that affect the spindle apparatus. However, several other cytogenetic studies in meiotic and mitotic cells of plants, mitotic mammalian cells in culture, and mitotic cells in whole mammals strongly suggest that carbaryl affects the spindle apparatus and causes chromosome nondisjunction. Chromosome nondisjunction leads to aneuploidy (loss and gain of whole chromosomes) or polyploidy (increase of chromosome number in multiples of the basic number), which are considered to be significant mutagenic effects. Although much of the evidence for aneuploidy induction is indirect [i.e., observations on cell division where treatment caused mitotic arrest, chromosome lagging, etc.; generally referred to as -mitotic effects (i.e., colchicine-like action)], there were some studies on aneuploidy induction. For example, the recent study of Onfelt and Klasterska (1983) showed an increase in aneuploid and polyploid cells after treatment of Chinese hamster V79 cells with carbaryl. Although the fungi test for chromosome nondisjunction was reported as negative (Morpurgo et al., 1979), colchicine, a well-known spindle

inhibitor, appears to be ineffective at inducing aneuploidy/polyploidy in lower eukaryotes [see Bond and Chandley (1983) for review].

It should be pointed out that there were deficiencies in many of these cytogenetic studies; e.g., the purity of the carbaryl was sometimes not given, the toxicity of the concentrations tested was not described, and the frequency of each specific aberration was not reported. Nevertheless, the consistency of the positive results obtained by different investigators using different test systems strongly suggests that carbaryl has the potential to cause aneuploidy/polyploidy. In addition, carbaryl is a carbamate pesticide, and other carbamates, such as methyl benzimidazole carbamate, have been reported to cause chromosome nondisjunction [see Bond and Chandley (1983) for review].

If a mutagen reached the germinal tissue, it would have the potential to cause mutations that may contribute to the burden of genetic disease. Germinal numerical chromosome aberrations would contribute to human morbidity and mortality by spontaneous abortions and various genetic disorders (e.g., Down's syndrome, Turner's syndrome, etc.) [see Hook (1983) for review]. Although there are no studies for meiotic nondisjunction in mammals, other studies provide suggestive evidence that carbaryl (or an active form or forms of the chemical) may reach mammalian germ tissue. For example, Wyrobek et al. (1980) reported elevation of sperm abnormalities in carbaryl-exposed workers. Krylova and Denisova (1973) also reported pathological changes in spermatozoa of a small rodent called the Mongolian tree creeper, which inhabited an area sprayed with carbaryl. In laboratory studies, adverse effects on spermatozoa were seen in carbaryl-treated rats and mice (Kitagawa et al. 1977, Degraeve et al. 1976, Shtenberg and Rybakova 1968). In contrast, some investigators have reported no significant gonadal effects attributable to carbaryl (Dikshith et al. 1976, Weil et al. 1972).

In summary, while the majority of studies concerning the mutagenicity of carbaryl contain differences, the body of evidence nevertheless indicates that carbaryl is not very active at causing gene mutations or structural chromosome aberrations. The available studies, however, do strongly suggest that carbaryl may induce numerical chromosome aberrations (aneuploidy/polyploidy) as its mutagenic endpoint. All of the mammalian studies were on mitotic cells. It should be noted that with respect to somatic-numerical cell risk, aneuploidy induction has been proposed as a possible chromosomal mechanism in carcinogenesis and tumor promotion (Tsutsui et al. 1983, Onfelt and Klasterska 1983). Although no testing of meiotic mammalian nondisjunction has been performed, other studies have suggested that carbaryl may reach the germ tissue in mammals, and thus may carry a first-generation risk (e.g., embryonic, fetal, and infant death, and genetic disorders).

5.3. TERATOGENICITY

Oral administration of carbaryl was teratogenic to rabbits, guinea pigs, beagle dogs and miniature swine, but not to mice, rats, hamsters or monkeys (Murray et al., 1979; Robens, 1969; Weil et al., 1973; Smalley et al., 1968; Earl et al., 1973; Benson et al., 1967; Coulston, 1971; Dougherty and Coulston, 1975). These teratogenicity tests are summarized in Table 5-2.

Equivocal determinations were obtained for fetotoxicity with mice and for teratogenicity with rabbits and guinea pigs. It is possible to explain these varying results by examining inadequacies in experimental design (small number of animals tested, only a single dose level tested), different methods of administration (gavage and dietary), the presence or absence of maternal toxicity, or some combination of these. Oral administration of carbaryl by gavage at a dose of 150 mg/kg/day to mice produced significant maternal toxicity, but no embryotoxicity or teratogenic effects, while

TABLE 5-2

Teratogenicity Testing of Carbaryl

Route	Species/ Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days	Observation Day*	Maternal Response	Fetal Response	Reference
oral, gavage	mice/CF-1	41 control; 23 low dose; 37 high dose	cottonseed oil	0, 100 or 150 mg/kg/day	6-15 of gestation	18	100 mg/kg/day: 1 of 23 treated died 150 mg/kg/day: significant maternal toxicity (salivation, ataxia and lethargy); statistically significant ($P<0.05$) number of maternal deaths (10 of 37)	No significant incidence of fetal malformations	Murray et al., 1979
oral, diet	mice/CF-1	35 control; 44 treated	diet	0 or 5660 ppm (equivalent doses of 0 or 1166 mg/kg/day)	6-15 of gestation	18	No significant adverse effects	Significantly decreased mean fetal body weight and length; delayed ossification of skull-bones and of sternebrae	Murray et al., 1979
oral, diet	mice	20/dose level	diet	0, 10 or 30 mg/kg	6 through end of gestation	normal parturition	No difference between treated and control dams in mortality, behavior, physical condition, resorptions or fetal deaths	No difference in fetal mortality or body weight between treated and control fetuses. At the 30 mg/kg level, an incidence of 9 "minor" fetal abnormalities in 2 litters, as compared with 2 such abnormalities in controls, was not considered to be treatment-related by the authors	Benson et al., 1967

TABLE 5-2 (cont.)

Route	Species/ Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days	Observation Day*	Maternal Response	Fetal Response	Reference
oral, gavage	rabbits/ New Zealand white	28 control; 20 low dose; 14 high dose	cottonseed oil	0, 150 or 200 mg/kg/day	6-18 of gestation	29	Significant maternal toxicity at 200 mg/kg/day level; mild maternal toxicity at 150 mg/kg/day level	150 mg/kg/day: single incidence of omphalocele; statistically significant decrease in fetal body weight ($P<0.05$) 200 mg/kg/day: significantly increased incidence of omphalocele ($P<0.05$); statistically significant decrease in delayed ossification of the fifth sternebra ($P<0.05$)	Murray et al., 1979
oral	rabbits/ New Zealand white	21 control; 9 low dose; 4 mid dose; 4 high dose	gelatin capsules	0, 50, 100 or 200 mg/kg	5-15 of gestation	28	No treatment-related maternal toxicity	No treatment-related embryotoxicity or induction of terata at any dose tested	Robens, 1969
oral, gavage	hamsters/ Golden Syrian	10 control; 8 treated/ dose level	0.5 g sodium carboxymethyl cellulose, 0.4 g Tween 60, 0.9 g sodium chloride, 2.0 g benzyl alcohol and water	0 or 125 mg/day	6-8 of gestation	14 or 15	Maternal toxicity, manifested in diarrhea, salivation and incoordination	No treatment-related effect on fetal mortality or body weight; no increase in incidence of bone anomalies	Robens, 1969
oral, gavage	hamsters/ Golden Syrian	10 control; 6 treated/ dose level	0.5 g sodium carboxymethyl cellulose, 0.4 g Tween 60, 0.9 g sodium chloride, 2.0 g benzyl alcohol and water	0 or 250 mg/day	7 or 8 of gestation	14 or 15	Maternal toxicity, manifested in diarrhea, salivation and incoordination; lethal to 2 of 6 dams	Increased fetal mortality; no effect on fetal body weight; no increase in incidence of bone anomalies	Robens, 1969

TABLE 5-2 (cont.)

Route	Species/ Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days	Observation Day*	Maternal Response	Fetal Response	Reference
oral	guinea pigs/ Coulson	31 control; 26 multiple doses; 40 single doses	gelatin capsules	0 or 300 mg/kg	multiple doses on days 11-20 or single doses on day 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 of gestation	50	Multiple doses on days 11-20 were lethal to 10 of 26 dams treated. Single doses were lethal to 5 of 40 dams treated.	Multiple doses: increased fetal mortality; decreased litter size; incidence of 11 terata as compared to 2 for controls. Terata in treated animals were bone defects occurring most frequently in the cervical vertebrae. Single doses: average litter size and percent fetal mortality were similar to control values; incidence of 9 terata, all occurring when dams were exposed on day 12, 13, 14, 15 or 16; treatment on day 13 resulted in 2 fetuses with no kidneys or genital organs, one of which also had fused thoracic vertebrae and ribs; other terata in treated animals were bone defects occurring most frequently in the cervical vertebrae.	Robens, 1969
oral, peroral intubation	guinea pigs	controls and treated: 5/ dose level except 10/ dose level on days 10-24 of gestation	corn oil	0, 50, 100 or 200 mg/ kg	10 and 11; 12; 13; 14; 12-14; 15; 16; 15 and 16; 17-19; 20-24; 10-24 of gestation	34 or 35	Decreased mean body weights	No treatment-related embryotoxic or teratogenic effects at any dose level tested	Weil et al., 1973

TABLE 5-2 (cont.)

Route	Species/ Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days	Observation Day*	Maternal Response	Fetal Response	Reference
oral, diet	guinea pigs	controls and treated: 5/ dose level except 10/ dose level on days 10-24 of gestation	diet	0, 100, 200 or 300 mg/kg	10 and 11; 12; 13; 14; 12-14; 15; 16; 15 and 16; 17-19; 20-24; 10-24 of gestation	34 or 35	No treatment-related maternal effects at any dose level tested	No treatment-related embryotoxic or teratogenic effects at any dose level tested	Weil et al., 1973
oral, peroral intubation	rats	NR	corn oil	0, 3, 7, 25 or 100 mg/kg	various intervals throughout gestation or until weaning of the pups	18 or 19	100 mg/kg: significantly increased percent mortality ($P<0.001$)	100 mg/kg: significantly decreased median number of total and viable fetuses ($P<0.05$); significantly increased percentage of litters with resorption sites ($P<0.05$); no treatment-related teratogenic effects at any dose level tested	Weil et al., 1973
oral, diet	rats	NR	diet	0, 7, 25, 100 or 200 mg/kg	various intervals throughout gestation or until weaning of the pups	18 or 19	No treatment-related maternal effects at any dose level tested	No treatment-related embryotoxic or teratogenic effects at any dose level tested	Weil et al., 1973

TABLE 5-2 (cont.)

Route	Species/ Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days	Observation Day*	Maternal Response	Fetal Response	Reference
oral, diet	beagle dogs	16, 10, 10, 18, 9 or 8, respectively, at the given dose levels	diet	0, 3.125, 6.25, 12.5, 25 or 50 mg carbaryl/kg body weight	throughout gestation (average gestation period = 62 days)	normal parturition, except 6 on day 55	Increased number of difficult births (dystocia) among treated animals - placental separation from uterus and atonic uterine musculature was observed in these animals; significantly decreased reproductive capacity at 50 mg/kg level	At increasing dose levels, decreased body weight gain and increased mortality in nursing pups when compared to controls, probably due to an effect of carbaryl on lactation; decreased percent of pups born alive at all dose levels tested. Teratogenic effects: 0 pups (0%) at 0 and 3.25 mg/kg; 3 pups (9%) at 6.25 mg/kg; 14 pups (18%) at 12.5 mg/kg; 3 pups (13%) at 25 mg/kg; 1 pup (14%) at 50 mg/kg; teratogenic effects were defined to include abdominal-thoracic fissures with varying degrees of intestinal agenesis and displacement, varying degrees of brachygnathia, acaudate pups, failure of skeletal formation and superfluous phalanges	Smalley et al.,1968; Earl et al., 1973

TABLE 5-2 (cont.)

Route	Species/ Strain	No. Dams at Start	Vehicle	Daily Dose or Exposure	Treatment Days	Observation Day*	Maternal Response	Fetal Response	Reference
oral, diet	miniature swine	6, 5, 7 or 7, respectively, at the given dose levels	diet	0, 4, 8 or 16 mg/kg/day	20 days before mating and throughout gestation or from 7 days after mating to the end of gestation	normal parturition	8 mg/kg/day: 3 sows had irregular estral periods; 1 sow had pyometra; decreased percent of pregnancies 16 mg/kg/day: decreased percent of pregnancies	8 mg/kg/day: 22% resorptions (control percent not determined); in 1 litter, 2 fetuses with crooked tails, 1 runt, and ananous fetus with anomalotrophic effects. 16 mg/kg/day: 8% resorptions (control percent not determined); increased percent stillborn (13.0% as compared to 6.1% for controls); 1 abnormal fetus with ecaudate nanosomus and phocomelia of all limbs.	Earl et al., 1973

*Day 0 of gestation was designated as the day of mating (Murray et al., 1979) or the day after mating (Robens, 1979) for rabbits, as the observation of a vaginal plug in CF-1 mice (Murray et al., 1979), or as the day after mating for hamsters and guinea pigs (Robens, 1969). Day 1 of gestation was designated as the day of mating for beagle dogs (Smalley et al., 1968) and miniature swine (Earl et al., 1973), or as the observation of a vaginal plug for guinea pigs and rats (Weil et al., 1973). The remaining studies were only available as abstracts or summaries in NIOSH (1976), and the designation of day 0 or 1 of gestation was not reported.

NR = Not reported

dietary administration of carbaryl to mice at a much larger dose produced mild fetotoxicity in the absence of maternal toxicity, (Murray et al., 1979) and at a smaller dose produced equivocal evidence of fetotoxicity (Benson et al., 1967). Significant maternal toxicity, embryotoxicity and terata (omphalocele) were observed when rabbits were given gavage doses of 200 mg carbaryl/kg/day (Murray et al., 1979), while neither maternal toxicity, embryotoxicity, nor teratogenic effects were observed at the same dose given orally as gelatin capsules (Robens, 1969). The small number of animals (4 or 9/dose level) used by Robens (1969), however, may not have been sufficient. A significantly increased incidence of teratogenic effects was observed in the fetuses of guinea pigs when the dams were given a single dose level of carbaryl that induced significant maternal lethality (Robens, 1969). Weil et al. (1973) did not find similar results in guinea pigs after testing carbaryl under various dose levels, two methods of administration and many different exposure periods during organogenesis.

Earl et al. (1973) administered carbaryl to miniature swine at a level of 0, 4, 8 or 16 mg/kg/day in the diet for 20 days before mating and throughout gestation, or from 7 days after mating to the end of gestation. One malformed fetus was observed at the 8 mg/kg/day level, and another at the 16 mg/kg/day level. In a follow-up experiment, Earl et al. (1973) administered carbaryl to miniature swine in dietary concentrations of 0, 16 or 32 mg/kg/day for 20 days before mating and throughout gestation, or from 7 days after mating to the end of gestation. Neither maternal toxicity nor teratogenic effects were observed at the two dose levels. The carbaryl used in this follow-up experiment, however, had been stored for 12-15 months (between the two experiments). Therefore, Earl et al. (1973) speculated that the carbaryl may have partially decomposed, resulting in a loss of teratogenic potential.

5.4. OTHER REPRODUCTIVE EFFECTS

Several studies of the effects of carbaryl administration on the reproduction of experimental animals were encountered.

Collins et al. (1971) administered carbaryl to groups of 20 pairs of weanling Osborne-Mendel rats (mated at 100 days of age) in dietary levels of 0, 2000, 5000 or 10,000 ppm through three generations. For each dietary level, the parental rats (F_0) were mated to produce two F_1 generations, the second of which (F_{1b}) produced two F_2 generations, and the F_{2b} rats produced the two F_3 generations. Only the 10,000 ppm level caused decreased female fertility, with F_2 rats failing to produce an F_{3b} generation. Mortality of pups was increased at the 5000 and 10,000 ppm levels. Dose-related decreases in litter size and mean weanling body weights were significantly different from control values.

The results in Mongolian gerbils treated similarly (Collins et al., 1971) were as follows. F_3 generation gerbils receiving carbaryl in the diet at a level of 10,000 ppm produced one litter, but not a second litter. At lower dose levels, reduced fertility, reduced litter size and reduced pup viability were observed in F_2 and F_3 rats, but not in a dose-related manner. The number of pups surviving to weaning was significantly reduced from control values at $\geq$4000 ppm in all generations and at 2000 ppm in F_2 and F_3 gerbils.

In another 3-generation reproduction study (Weil et al., 1973), 4-month-old F_0 rats were mated to produce the F_{1a} generation, and at 3-month intervals thereafter they were remated to produce the F_{1b} and F_{1c} generations. F_{1a} rats (4 months old) were mated to produce F_{2a} rats, which were mated at 4 months of age to produce F_{3a} rats, at 6 months of age to produce F_{3b} rats and at 7.3 months of age to produce the F_{3c} generation.

The F_0 parents were given the first dose of carbaryl at 5 weeks of age. The pesticide was administered daily either in the diet at 0, 7, 25, 100 or 200 mg/kg bw (a 100 mg/kg plus corn oil group was also included, probably to observe effects of the oil on absorption; however, the reason for this group was not discussed by the authors) or by gavage in corn oil at 0, 3, 7, 25 or 100 mg/kg. Rats receiving 100 mg/kg/day by gavage had daily signs of cholinesterase inhibition throughout the 3 generations, significantly increased mortality of male and female parents of each generation, decreased number of pups born alive (F_2 and F_3 pups), prolonged periods between first mating and birth of a litter (F_{1b}), decreased number of mated females to produce litters (F_{1b}), reduced median number of total viable fetuses and an increased percentage of litters with resorption sites. Lower doses by gavage were without effect. Dietary administration resulted in no increased mortality at any dose in any generation. The F_{2a} generation receiving dietary administration of 100 or 200 mg carbaryl/kg/day had prolonged periods between first mating and birth of a litter (Weil et al., 1973).

As reviewed by NIOSH (1976), a 3-generation reproduction study from the Russian literature (Shtenberg and Ozhovan, 1971) reported that very low doses of carbaryl, 2 and 5 mg/kg, administered by gastric intubation to "second (F_2) through fifth (F_5) generation" rats for 6 months (matings were performed after 4 months of treatment) resulted in reproductive effects. Treated male rats of the F_2, F_3 and F_4 generations had significantly reduced sperm motility, spermatogenesis and sperm survival when compared with controls. Treated females of the F_3 and F_4 generations had estrus cycle changes (shortened estrus, prolonged interestrus) which were apparent after 3 months of treatment with 5 mg/kg and at 6 months with

2 mg/kg doses. Dose-related reductions of litter size occurred in all generations as did decreased pup survival. Histological examination of testes and ovaries from treated rats revealed dystrophic spermatogenic epithelia and sclerotic ovarian follicles.

Administration of 50 mg carbaryl/kg by gavage to pregnant Sprague-Dawley rats on day 18 of gestation caused inhibition of acetylcholinesterase activity in blood, brain and liver of both the dams and the fetuses within 30 minutes of treatment (Cambon et al., 1978, 1980). The effects persisted in the dams for up to 12 hours in blood, 5 hours in brain and 24 hours in liver. In fetuses, the inhibition of the enzyme persisted for 12 hours in blood, 12 hours in brain and 5 hours in liver. When carbaryl at doses of 6.25, 12.5, 25 or 50 mg/kg was administered, inhibition of acetylcholinesterase in the blood of dams and fetuses was seen at the lowest dose. Maternal brain tissue enzyme was also inhibited at 6.25 mg/kg, but effects on fetal brain acetylcholinesterase activity did not occur at doses <50 mg/kg. Doses of 1-5 mg/kg administered from day 11 or 19 of gestation until term were without effect (Declume et al., 1979).

Mature female rhesus monkeys treated with carbaryl at 2 or 20 mg/kg/day by gavage throughout gestation had increased, although not directly dose-related, incidences of abortions as compared with vehicle-treated controls (Coulston, 1971). The number of monkeys/group was too small to allow any conclusions to be drawn.

A follow-up study, in which 15-16 monkeys/group were treated orally with carbaryl at 0, 0.2, 2.0 or 20 mg/kg/day (in capsules) from day 20-38 of gestation, did not show an association between carbaryl treatment and an increased incidence of abortion or stillbirth among rhesus monkeys (Dougherty and Coulston, 1975).

Oral doses of carbaryl at 100 or 300 mg/kg for 3 months caused decreased frequency or absence of estrus, proestrus and diestrus in rats (Vashakidze, 1965). Treated females had prolonged pregnancies, reduced litter sizes and deformed wombs. Treated males were infertile.

Treatment of male rats with 0, 7, 14 or 70 mg carbaryl/kg orally for 12 months (Shtenberg and Rybakova, 1968) resulted in a dose-dependent decrease in sperm motility, edema of testicular tissue, spermatogenic epithelia destruction and reduced numbers of spermatozoa. Treated female rats had estrus cycle changes at the 14 and 70 mg/kg doses.

Carbaryl in oral doses of 8.5, 17 or 34 mg/kg daily for 5 days in male Swiss-Webster mice caused no changes in testes or prostate weights and failed to inhibit the uptake of ^{3}H-testosterone by the mouse prostate (Thomas, 1974; Thomas et al., 1974). When ^{14}C-carbaryl was administered, only small amounts of radioactivity were detected in prostate, seminal vesicles, testes, seminal plasma and epididymal fat.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Carpenter et al. (1961) reported the absence of permanent degenerative changes in rats and dogs upon chronic and subchronic oral carbaryl administration. Groups of 5 male and 5 female CF-N rats were given 0, 1500 or 2250 ppm carbaryl diets for 96 days. Upon gross and histopathological examination, the only effects noted among low-dose animals were increased kidney weights in the females. Among high-dose animals, minor diffuse cloudy swelling of the kidney tubules occurred, and females had increased kidney and body weights, while males had an increased liver/body weight ratio. Food consumption was not affected (Carpenter et al., 1961).

Groups of 20 male and 20 female CF-N rats were given 0, 50, 100, 200 or 400 ppm carbaryl in the diet for 2 years. Additional animals were killed at intervals during the experiment as described in Section 5.1. Histological and hematological evaluations revealed no increased tumor incidence, no treatment-related effect on hematocrit values and no lesions in any tissues other than slight changes in the kidney and liver of high dose rats. A significantly increased incidence ($p<0.002$) of cloudy swelling of the hepatic cords was observed in randomly selected animals from the high dose group only at the end of the experiment. Specific incidences were not enumer- ated. Cloudy swelling of the kidney was observed in high dose animals; the incidence was statistically significantly elevated at the end of 1 year of treatment but not at the end of 2 years of treatment (Carpenter et al., 1961).

Groups of 2 male and 2 female Basenji cocker dogs were given gelatin capsules containing 0, 0.45, 1.8 and 7.2 mg carbaryl/kg 5 days/week for 1 year. No significant treatment-related effects on blood cholinesterase levels or other hematological parameters were observed. Histopathological evaluation revealed a diffuse cloudy swelling in the kidneys of dogs only at the high dosage level. This effect was judged to be transient, as it was observed in controls, but to a lesser extent (Carpenter et al., 1961).

Shtenberg and Rybakova (1968) orally administered 0, 7, 14 or 70 mg carbaryl/kg to groups of 24 male and 24 female rats (strain not specified) for up to 12 months. Growth inhibition and decreased blood cholinesterase activity were observed in the two high dose groups, but not in the low dose group. Increased gonadotrophic hormone production in the hypophysis, increased adrenal gland activity and decreased thyroid activity in treated groups were also observed. Reproductive effects were also observed as discussed in Section 5.4.

Dikshith et al. (1976) conducted a subchronic study in which groups of 7 male albino rats received 0 or 200 mg carbaryl/kg by gavage 3 days/week for 90 days. Biochemical evaluation showed significant increases in testicular succinic dehydrogenase and adenosine triphosphatase and hepatic glucose-6-phosphatase activities compared with controls. In addition, significant decreases in hepatic acid phosphatase and blood cholinesterase activities were attributable to carbaryl treatment. No gross or microscopic abnormalities were observed in the blood, liver, kidneys, testes, sperm or brains of treated rats. No adverse effects on survival or fertility were observed. (The biochemical effects reported here are based upon data and statistical significance levels provided in a table in the referenced publication. The authors, however, conclude that carbaryl produces no biochemical changes in rats, although the quantitative data reported are in contrast with their conclusions).

Wakakura et al. (1978) observed ultrastructural and metabolic anomalies in the livers of male Wistar rats given 50 doses of carbaryl (3 mg/dose) by gavage over a period of 1 year. Of the rats treated, four received restricted daily diets, 3 hours of feeding followed by 21 hours of fasting. Carbaryl treatment was given to three of the rats and they were placed on a random feeding schedule. A control group of 13 rats received physiological saline by gavage. All groups were observed for 60 days after treatment, during which a random feeding schedule was followed. Determinations of blood glucose and immunoreactive insulin levels were made before and after treatment. Carbaryl treated rats had elevated blood glucose levels and slight reductions in serum immunoreactive insulin. Upon histopathological evaluation, morphological changes in the livers of treated rats were observed (i.e., virtual absence of hepatic glycogen granules and swollen granular endoplasmic reticulum).

5.6. OTHER RELEVANT INFORMATION

Many data are available regarding the acute toxicity of carbaryl in a variety of species. The lethal doses (or concentrations) are listed in Table 5-3 (NIOSH, 1983).

Several investigators have examined the effects of short-term occupational exposure to carbaryl. The hydrolysis product of carbaryl, 1-naphthol, has been identified in the urine of production plant workers (Best and Murray, 1962) and formulating plant workers (Durham and Wolfe, 1962). Whorton et al. (1979) evaluated the exposure of carbaryl production workers and reported the absence of correlation between carbaryl exposure and reduction of sperm count.

Leavitt et al. (1982) and Gold et al. (1982) evaluated groups of pesticide applicators involved in spraying carbaryl. Results indicated that the predominant exposure route is dermal, with the forearms and hands having the highest exposure. Acetylcholinesterase levels of exposed applicators were not significantly different from normal. No alterations in blood acetylcholinesterase activity was observed in humans given 0.06 or 0.12 mg carbaryl/kg daily for 6 weeks (Wills et al., 1967). A decrease in the urinary amino acid:creatinine nitrogen ratio, however, was observed at the higher dose level (Wills et al., 1968).

The effects of carbaryl administration (usually by i.p. injection) on certain parameters of behavior in the rat have been reported by several investigators. Operant behavior in obtaining food or water and in avoiding shock can be affected by doses as low as 5-20 mg/kg (Anger and Wilson, 1980), and activity on the running wheel can be impaired with a dose of <1 mg/kg (Singh, 1973).

TABLE 5-3

Acute Lethal Toxicity of Carbaryl*

Species	Route	LD_{50} (or LC_{50})
Rat	oral	250 mg/kg
Rat	dermal	400 mg/kg
Rat	inhalation	721 mg/m³
Rat	intraperitoneal	48 mg/kg
Rat	intravenous	41.9 mg/kg
Mouse	oral	438 mg/kg
Mouse	intraperitoneal	25 mg/kg
Rabbit	oral	710 mg/kg
Rabbit	dermal	2000 mg/kg
Guinea pig	oral	280 mg/kg
Cat	oral	150 mg/kg

*Source: NIOSH, 1983

Subacute or acute oral carbaryl administration has been reported to inhibit brain cholinesterase in rats (Desi et al., 1974), and to reduce body temperature and plasma cholinesterase activity in mice (Ahdaya et al., 1976). Carbaryl administration has been reported to alter the immune response of rabbits (Street and Sharma, 1975) and mice (Wiltrout et al., 1978).

6. AQUATIC TOXICITY

The data on carbaryl toxicity in aquatic organisms are quite extensive (U.S. EPA, 1983; Mount and Oehme, 1981). Because of the limited nature of this profile, those studies dealing with fish and aquatic organisms that are not native to the United States (Bailey et al., 1970) will not be reviewed.

6.1. ACUTE

The acute toxicity of carbaryl has been tested in many species of freshwater fish (Table 6-1). The most sensitive species tested were the lake trout, Salvelinus namaycush, yellow perch, Perca flavescens, and the Coho salmon, Oncorhynchus kisutch, having 96-hour LC_{50} values of 0.690, 0.745 and 0.764 mg carbaryl/ℓ, respectively (Macek and McAllister, 1970; Johnson and Finley, 1980). The most resistant species tested, having respective 96-hour LC_{50} values of 15.80, 20.0 and 31.80 mg carbaryl/ℓ were the channel catfish, Ictalurus punctatus, the bullhead, Ictalurus melas, and the mosquito fish, Gambusia affinis. Woodward and Mauck (1980) demonstrated the dependence of carbaryl toxicity to cutthroat trout, Salmo clarkii, on the pH of water. The 96-hour LC_{50} values determined in pH 6.5, 7.5 and 8.5 water were 6.00, 3.95 and 0.97 mg carbaryl/ℓ, respectively, in this trout species. Post and Schroeder (1971) demonstrated that small and immature fish were more sensitive than larger, more mature fish of the same species.

The acute toxicity of carbaryl to marine species of fish has been investigated less extensively (Table 6-2). The 96-hour LC_{50} value for striped bass, Morone saxatilis, was 1.0 mg carbaryl/ℓ (Korn and Earnest, 1974). Stewart et al. (1967) reported 24-hour static median lethal concentrations of 3.9, 4.1 and 6.7 for the shiner perch, Cymatogaster oggregata, English sole, Parophrys vetulus, and the three spined stickleback, Gasterosteus aculeatus, respectively.

TABLE 6-1

Acute Lethal Effects of Carbaryl to Freshwater Fish in a 96-Hour Bioassay[a]
(LC_{50})

Species	Mean Concentration (mg/ℓ)	Method	Reference
Rainbow trout, Salmo gairdneri	4.34	static	Macek and McAllister, 1970
Rainbow trout, S. gairdneri	1.470	static	Post and Schroeder, 1971
Cutthroat trout, Salmo clarkii	0.970[b]	static	Woodward and Mauck, 1980
Cutthroat trout, Salmo clarkii	1.500[c]	static	Post and Schroeder, 1971
Brown trout, Salmo trutta	1.95	static	Macek and McAllister, 1970
Brook trout, Salvelinus fontinalis	1.070[c]	static	Post and Schroeder, 1971
Lake trout, Salvelinus namaycush	0.690	static	Johnson and Finley, 1980
Coho salmon, Oncorhynchus kisutch	0.764	static	Macek and McAllister, 1970
Coho salmon, O. kisutch	1.300	static	Post and Schroeder, 1971
Chinook salmon, Oncorhynchus tshawytscha	2.40	flow-through	Johnson and Finley, 1980
Atlantic salmon, Salmo solar	4.50	static	Johnson and Finley, 1980
Bluegill sunfish, Lepomis macrochirus	6.76	static	Macek and McAllister, 1970
Green sunfish, Lepomis cyanellus	11.2	static	Johnson and Finley, 1980
Redear sunfish, Lepomis microlophus	11.20	static	Macek and McAllister, 1970

TABLE 6-1 (cont.)

Species	Mean Concentration (mg/ℓ)	Method	Reference
Black crappie, Pomoxis nigromaculatus	2.60	static	Johnson and Finley, 1980
Largemouth bass, Micropterus salmoides	6.4	static	Macek and McAllister, 1970
Goldfish, Carassius auratus	13.20	static	Macek and McAllister, 1970
Carp, Cyprinus carpio	5.28	static	Macek and McAllister, 1970
Carp, C. carpio	1.7	static	Chin and Sudderruddin, 1979
Fathead minnow, Pimephales promelas	14.60	static	Macek and McAllister, 1970
Mosquito fish, Gambusia affinis	31.80	static	Chaiyarach et al., 1975
Channel catfish, Ictalurus punctatus	15.80	static	Macek and McAllister, 1970
Channel catfish, I. punctatus	1.30	static	Brown et al., 1979
Black bullhead, Ictalurus melas	20.00	static	Macek and McAllister, 1970
Yellow perch, Perca flavescens	5.10	static	Johnson and Finley, 1980
Yellow perch, P. flavescens	0.745	static	Macek and McAllister, 1970

[a]Values for low body weight group of trout.

[b]Carbaryl was most toxic to trout in pH 8.5, soft water, as reported here.

[c]Toxicity data from tests of <96-hours duration have not been reported here, although they may exist in the original reference for a specific species.

TABLE 6-2

Acute Lethal Effects of Carbaryl to Marine Fish in a Static Bioassay
(LC_{50})

Species	Duration (hours)	Mean Concentration (mg/ℓ)	Reference
Shiner perch, Cymatogaster aggregata	24	3.9	Stewart et al., 1967
English sole, Parophrys retulus	24	4.1	Stewart et al., 1967
Stickleback, Gasterosteus aculeatus	24	6.7	Stewart et al., 1967
Striped bass, Morone saxatilis	96	1.0	Korn and Earnest, 1974

The acute lethal effects of carbaryl have been studied in many aquatic invertebrates including crustaceans, insects and mollusks (Table 6-3). In general, the mollusks, both freshwater and marine species, tended to be the most resistant to carbaryl, with LC_{50} values between 2.2 and 125.0 mg/ℓ. The lethal concentrations (24-, 48- or 96-hour values) among crustaceans range from 0.00026 mg/ℓ for the 24-hour LC_{50} in Daphnia magna (Rawash et al., 1975) to a 96-hour LC_{50} of 2.43 mg/ℓ in the crayfish, Procarnbarus simulans (Chaiyarach et al., 1975).

6.2. CHRONIC

The effects of 0.1 mg/ℓ carbaryl exposure for a period of 5 months was studied in the estuarine spot, Leiostomus xanthurus (Lowe, 1967). Although mortality was high in both control and experimental groups (65%), no carbaryl-related mortality could be determined. Histopathological examination showed no exposure-induced tissue changes. Parasitic lesions of the brain detected in treated fish may have been due to a treatment-related, lower resistance to infestation by the parasite (Lowe, 1967). Carbaryl was shown to inhibit brain acetylcholinesterase activity (68% of normal) in spot treated for 13 days with 1.0 mg/ℓ, but only slight inhibition was noted after 2.5 and 5 months exposure at 0.1 mg/ℓ.

The effects of carbaryl exposure to embryos of the killifish, Fundulus heteroclitus, and medaka, Oryzias latipes, have been examined (Weis and Weis, 1974; Solomon and Weis, 1979). Circulatory anomalies and cardiac malformations were associated with carbaryl exposure in embryos of both fish. In the killifish, treatment at 10 mg/ℓ caused a reduction in successful axis formation (at 2 days), reduced pigment formation and feeble or nondiscernible heartbeat (at 3 days) and arrested development at stage 22 or 24 (Weis and Weis, 1974). Exposure to 10 mg carbaryl/ℓ for 3 days caused the

TABLE 6-3

Acute Lethal Effects of Carbaryl to Aquatic Invertebrates

Species	Duration[a] (hours)	Mean Concentration (mg/ℓ)	Method	Effect	Reference
Mud shrimp, Upogebia pugettensis	48	0.04	static	LC_{50}	Stewart et al., 1967
Grass shrimp, Palaemonetes kadiakensis	96	0.12	static	LC_{50}	Chaiyarach et al., 1975
Ghost shrimp, Callianassa californiensis	48	0.03	static	LC_{50}	Stewart et al., 1967
Crayfish, Procambarus simulans	96	2.43	static	LC_{50}	Chaiyarach et al., 1975
Blue crab, Callinectes sapidus	48	0.550	flowthrough	EC_{50}[a]	Butler, 1963
Shore crab, Hemigrapsus oregonensis	24	0.27	static	LC_{50}	Stewart et al., 1967
Dungeness crab, Cancer magister	24	0.60	static	LC_{50}	Stewart et al., 1967
Amphipod, Gammarus pulex	48	0.029	static	LC_{50}	Bluzat and Seuge, 1979
Prawn, Penaeus aztecus	48	0.0025	flowthrough	EC_{50}[a]	Butler, 1963
Amphipod, Gammarus pseudolimnaeus	96	0.007[b]	static	LC_{50}	Woodward and Mauck, 1980
Water flea, Daphnia magna	24	0.00026	static	LC_{50}	Rawash et al., 1975
Water flea, Daphnia pulex	48	0.0064	static	LC_{50}	Johnson and Finley, 1980
Stone fly, Pteronarcella badia	96	0.011[c]	static	LC_{50}	Woodward and Mauck, 1980
Mosquito larvae, Culex pipiens	24	0.075	static	LC_{50}	Rawash et al., 1975
Bay mussel, Mytilus edulis	48	2.3	static	LC_{50}	Stewart et al., 1967
Pacific oyster, Crassostrea gigas	48	2.2	static	LC_{50}	Stewart et al., 1967
Mactrid clam, Rangia cuneata	96	125.0	static	LC_{50}	Chaiyarach et al., 1975
Cockle clam, Clinocardium nuttallii	24	7.3	static	LC_{50}	Stewart et al., 1967
Freshwater clam, Limnaea stagnalis	48	21.0	static	LC_{50}	Bluzat and Seuge, 1979
Freshwater oligochaete, Lumbriculus variegatus	96	8.2	static	LC_{50}	Bailey and Liu, 1980

[a]Effect was loss of equilibrium or mortality.

[b]Data for pH 7.5 water

[c]Data for pH 6.5 water

development of a defective "tube heart" in up to 15% of the exposed killifish embryos. In the medaka, carbaryl at 5 mg/ℓ or greater caused heart abnormalities in 96% or more of the developing embryos. Once again, many anomalies were classified as undifferentiated tubular-type hearts. Circular abnormalities, edema and clotting were also prevalent in treated medaka eggs (Solomon and Weis, 1979). Developmental arrest was reported in embryos treated with 30.0 mg carbaryl/ℓ.

When embryos of the South African clawed toad, Xenopus laevis, were treated with 1 mg carbaryl/ℓ, slight edema and ventral curvature were reported (Elliott-Feeley and Armstrong, 1981). The LC_{50} for embryos for 24 hours postgastrulation was 4.7 mg/ℓ. In the embryos surviving at 10 mg/ℓ, severe abnormalities were reported. Tadpoles (larvae) were treated at 0.1, 1.0 or 10.0 mg/ℓ for 24 hours and showed dose-related changes in swimming behavior. Ninety-six, 92 and 94% of the tadpoles treated at 0.1, 1.0 and 10.0 mg carbaryl/ℓ, respectively, for 24 hours survived and had developed normally at 2 weeks after exposure (Elliott-Feeley and Armstrong, 1981).

6.3. PLANT EFFECTS

The growth and assimilation of radiolabeled sodium carbonate in the freshwater green alga, Scenedesmus quadricaudata, was determined after treatment with 0.1 or 1.0 mg carbaryl/ℓ (Stadnyk et al., 1971). Oddly, carbaryl treatment was associated with a dose-related increase in cell growth and uptake of ^{14}C, with 44 and 57% increases in the 0.1 and 1.0 treated groups, respectively, when compared with controls. Bringmann and Kuhn (1977) reported that the toxicity threshold, the concentration where cell multiplication inhibition became evident, for carbaryl in S. quadri-

cauda was 1.4 mg/ℓ. O'Kelley and Deason (1976) reported similar findings in toxicity tests with 36 species of algae belonging to the genera Chlorella, Scenedesmus, Nitzschia, Golinkiniopsis, Monoraphidium, Actinastrum, Koliella and Carteria. At 0.01 and 0.1 mg carbaryl/ℓ, algal growth was similar to controls. At 1.0 mg/ℓ, 18 of 36 culture species showed slightly inhibited growth. Treatment at 10.0 and 25.0 mg carbaryl/ℓ caused some algal species to be severely inhibited (<50% of control growth), while other species showed stimulated growth in comparison with controls (O'Kelley and Deason, 1976).

The effects of carbaryl on the growth of four marine algal species was tested by Walsh and Alexander (1980). The 4- and 12-day EC_{50} values for growth inhibition were determined photometrically for chlorophyll content in Chlorococcum sp., Chlorella sp., Skeletonema costatum and Nitzschia angularum. The values were 2.1 and 2.7 mg/ℓ, 1.0 and 1.2 mg/ℓ, 1.7 and 1.8 mg/ℓ, and 1.5 and 1.6 mg/ℓ, respectively, for the four species at 4 and 12 days (Walsh and Alexander, 1980).

6.4. RESIDUE

Pertinent data regarding carbaryl residues in the aquatic environment could not be located in the available literature.

6.5. OTHER RELEVANT INFORMATION

The uptake, metabolism and biliary excretion of carbaryl was studied in rainbow trout, Salmo gairdneri (Statham et al., 1975). Carbaryl at 0.25 mg/ℓ was absorbed from the water and metabolized, with ~30% of the absorbed dose appearing in the bile within 24 hours. The biliary metabolites identified were, in decreasing prevalance, unchanged carbaryl, 1-naphthol glucuronide, 5,6-dihydrodihydroxycarbaryl and an unidentified polar metabolite (Statham et al., 1975). A bile:water concentration ratio

of radiolabeled carbaryl was 947 after 24 hours of exposure at 0.25 mg/ℓ (Statham et al., 1976). In channel catfish, Ictalurus punctatus, carbaryl was absorbed from the water and from a treated diet. The accumulation of carbaryl or metabolite residues was 11 ng/g tissue after 56 days of exposure to 0.25 mg carbaryl/ℓ water (Korn, 1973). Accumulation from dietary carbaryl, 2.8 mg/kg/week, was 11 and 9 ng/g tissue at 3 and 56 days, respectively (Korn, 1973). Fish accumulated 1% or less of the available pesticide. Tissue residues were eliminated rapidly in dietary treated fish, while elimination was slower in those exposed to carbaryl in the water. The author (Korn, 1973) suggested that carbaryl in the water is hydrolyzed to α-naphthol, which has a greater retention in fish tissues than the parent compound.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The ACGIH (1982) recommends a TLV of 5 mg/m³ for an 8-hour TWA and a 15-minute STEL of 10 mg/m³.

NIOSH (1983) recommends a concentration limit of 5 mg/m³ for a 10-hour TWA, and OSHA (1981) has established a standard for occupational carbaryl exposure of 5 mg/m³ for an 8-hour TWA.

Tolerances for carbaryl residues have been established for a variety of raw agricultural commodities. A tolerance of 0.1 ppm has been established for the meat, fat and meat by-products of cattle, goats, horses, sheep and swine. A tolerance of 1 ppm has been established for the liver and kidney of these animals.

According to the Federal Register (FR), tolerances for carbaryl residues on vegetable raw agricultural commodities intended for human consumption range from 0 ppm for barley, oat and rye grain to 12 ppm for berries, spinach and collard and mustard greens. Carbaryl tolerances for residues on raw agricultural commodities intended for livestock consumption are set at 100 ppm for hay, straw, forage and fodder of grains and other vegetables (40 CFR 180.169).

An ADI value for humans of 0.01 mg/kg has been reported by WHO (1974).

7.2. AQUATIC

Guidelines and standards specifically for the protection of aquatic organisms from the toxic effects of carbaryl could not be located in the available literature. Assuming the maximum application rate of 4.6 kg/hectare, a body of water 1 meter in depth would have a concentration of 0.34 mg carbaryl/ℓ (Korn, 1973). Providing a body of water were sprayed directly at this application rate, toxic effects could be significant.

8. RISK ASSESSMENT

The well designed and well reported chronic studies of Innes et al. (1969), Carpenter et al. (1961) and Triolo et al. (1982) have failed to demonstrate the carcinogenicity of carbaryl. An elevated number of animals with lung adenomas has been reported to occur upon i.p. administration to strain A mice, but an increased number of tumors/tumor-bearing animal must also be observed to be regarded as a positive response in this bioassay. Andrianova and Alekseev (1970) reported an increased incidence of tumors in rats given carbaryl by gavage for up to 22 months; however, the use of a compound of questionable purity (foreign carbaryl is thought to contain 2-naphthyl methylcarbamate), excessive mortality among treated animals and the lack of experimental details (no Russian translation) detract from the usefulness of this study.

Carpenter et al. (1961) reported the absence of increased tumor incidence in rats fed 50-400 ppm of carbaryl in the diet for 2 years, and in rats given weekly s.c. injections of 10 mg carbaryl for 5 months. Cloudy swelling of the hepatic cords and a transient increased incidence of cloudy swelling of the renal tubules was observed in rats fed 400 ppm, but not 200 ppm.

Russian investigators have reported adverse reproductive effects at a dosage as low as 2 mg/kg (Shtenberg and Ozhavan, 1971; Shtenberg and Rybakova, 1968), but the test compound was of unknown purity. No adverse reproductive effects were reported in the 3-generation study of Weil et al. (1973) wherein 25 mg carbaryl/kg/day of known composition was administered by gavage to rats. Carbaryl was teratogenic in some species when administered at relatively high dosages, and there is some evidence of teratogenicity in beagle dogs and miniature swine at lower dosages (Section 5.3.).

Earl et al. (1973) reported a single incidence of terata in fetuses of swine at each of the 8 and 16 mg carbaryl/kg/day levels. In a follow-up experiment, however, Earl et al. (1973) did not observe any teratogenic effects at dose levels of 16 or 32 mg carbaryl/kg/day. It is not possible to draw definitive conclusions from this study for use in risk assessment because of the small numbers of animals tested and because the lack of teratogenic effects observed in the follow-up experiment may or may not have been due to decomposition of the carbaryl, which had been stored for 12-15 months before use. The teratogenicity study with beagle dogs (Smalley et al., 1968; Earl et al., 1973) is also not appropriate for human risk assessment, as dogs may not be a suitable experimental model for humans, because of marked differences between dogs and other mammals (including humans) in the metabolism of carbaryl (see Section 4.3.) (NIOSH, 1976). Also, the U.S. EPA, in an evaluation of the teratogenicity of carbaryl published in the Federal Register (1980), concluded that the teratogenicity study with beagle dogs was not adequate in terms of numbers of animals and observation of the dams during treatment. Studies with swine were mentioned but not discussed. The Agency concluded that carbaryl "would not constitute a potential human teratogenic or reproductive hazard under proper environmental usage."

The data of Carpenter et al. (1961) will be used to derive an ADI because a compound of known purity was administered to a sufficient number of animals (20 of each sex) via an environmentally relevant route (diet) for a significant portion of the rat's lifespan (2 years). The highest reported dosage that produced no adverse effects was 9.6 mg/kg/day (based on observed food intake) in female rats weighing ~0.3 kg. An ADI of 0.096 mg/kg/day is obtained by dividing 9.6 mg/kg/day by an uncertainty factor of 100 (10 to extrapolate from animals to humans and 10 to protect the most sensitive individuals). This ADI is equivalent to 6.72 mg/day for a 70 kg man.

9. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1982. TLVs, Threshold Limit Values for Chemical Substances in Work Air, adopted by ACGIH for 1982. Cincinnati, OH.

Ahdaya, S.M., P.V. Shah and F.E. Guthrie. 1976. Thermoregulation in mice treated with parathion, carbaryl or DDT. Toxicol. Appl. Pharmacol. 35(3): 575-580.

Ahmed, F.E., N.J. Lewis and R.W. Hart. 1977a. Pesticide induced ouabain resistant mutants in Chinese hamster V79 cells. Chem.-Biol. Interact. 19(3): 369-374.

Ahmed, F.E., R.W. Hart and N.J. Lewis. 1977b. Pesticide induced DNA damage and its repair in cultured human cells. Mutat. Res. 42(2): 161-173.

Aly, O.M. and M.A. El-Dib. 1971. Persistence of some carbamate insecticides in the aquatic environment. I. Hydrolysis of sevin, baygon, pyrolan and dimetilan in waters. Water Res. 5(12): 1191-1205.

Aly, O.M. and M.A. El-Dib. 1972. Persistence of some carbamate insecticides in the aquatic environment. Advan. Chem. Ser. 111: 210-243.

Aly, M.I., N. Bakry, F. Kishk and A.H. El-Sebae. 1980. Carbaryl adsorption on calcium-bentonite and soils. Soil Sci. Soc. Am. J. 44(6): 1213-1215.

Amer, S. 1965. Cytological effects of pesticides. I. Mitotic effects of N-methyl-1-naphthyl carbamate (Sevin). Cytologia. 30: 175-181.

Amer, S.M., and O.R. Farah. 1968. Cytological effects of pesticides. III. Meiotic effects of N-methyl-1-naphthyl carbamate (Sevin). Cytologia. 33: 337-344.

Amer, S.M., M.A. Hammouda, and O.R. Farah. 1971. Cytological and morphological effects of the insecticide N-methyl-1-naphthyl-carbamate (Sevin). Flora (Jena). 160: 433-439.

Andrianova, M.M. and I.V. Alekseev. 1970. On the carcinogenic properties of the pesticides sevin, maneb, ciram and cineb. Vap. Pitan. 29: 71. (Cited in IARC, 1976)

Anger, W.K. and S.M. Wilson. 1980. Effects of carbaryl on variable interval response rates in rats. Neurobehav. Toxicol. 2(1): 21-24.

Argauer, R.J. and J.D. Warthen, Jr. 1975. Separation of 1- and 2-naphthols and determination of trace amounts of 2-naphthyl methylcarbamate in carbaryl formulations by high pressure liquid chromatography with confirmation by spectrofluorometry. Anal. Chem. 47: 2472. (Cited in NIOSH, 1976)

Ashwood-Smith, M.J., J. Trevino, and R. Ring. 1972. Mutagenicity of Dichlorvos. Nature. 240: 418-420.

Bailey, H.C. and D.H.W. Liu. 1980. Lumbriculus variegatus, a benthic oligochaete, as a bioassay organism. ASTM STP 707. p. 205-215.

Bailey, R.M., J.E. Fitch, E.S. Herald, et al. 1970. A List of Common and Scientific Names of Fishes from the United States and Canada. Am. Fish. Soc. Spec. Pub. No. 6, Washington, DC.

Bend, J.R., G.M. Holder, E. Protos and A.J. Ryan. 1971. Water-soluble metabolites of carbaryl (1-naphthyl N-methylcarbamate) in mouse-liver preparations and in the rat. Austr. J. Biol. Sci. 24: 535-546. (Cited in IARC, 1976)

Benson, B.W., W.J. Scott and R.P. Belliles. 1967. Sevin -- Safety evaluation by teratological study in the mouse. Unpublished report submitted to Union Carbide Corp. 19 p. (Cited in NIOSH, 1976)

Benson, W.H. and H.W. Dorough. 1979. Comparative carbamate ester hydrolysis in four mammalian species. Toxicol. Appl. Pharmacol. 48(1): A139.

Beraud, M., B. Pipy, R. Derache and D. Gaillard. 1979. Formation of the carcinogen, N-nitrosocarbaryl, by interactions between an insecticide of the carbamate, carbaryl series and sodium nitrate in rat gastric juice. Food Cosmet. Toxicol. 17(6): 579-583. (French with English Abstract)

Best, E.M., Jr. and B.L. Murray. 1962. Observations on workers exposed to Sevin insecticide - A preliminary report. J. Occup. Med. 4: 507-517. (Cited in NIOSH, 1976; Leavitt et al., 1982)

Blevins, R.D., M. Lee and J.D. Regan. 1977. Mutagenicity screening of five methyl carbamate insecticides and their nitroso derivatives using mutants of Salmonella typhimurium LT2. Mutat. Res. 56(1): 1-6.

Bluzat, R. and J. Seuge. 1979. Effects of 3 insecticides (lindane, fénthion and carbaryl): Acute toxicity on 4 species of limnic invertebrates; chronic toxicity in the pulmonate mollusk Lymnaea. Environ. Pollut. 18(1): 51-70.

Bollag, J-M. and S-Y. Liu. 1971a. Degradation of sevin by soil microorganisms. Soil Biol. Biochem. 3(4): 337-345.

Bollag, J-M. and S-Y. Liu. 1971b. Metabolism of carbaryl by a soil fungus. J. Agric. Food Chem. 19(3): 487-490.

Bollag, J-M., E.J. Czaplicki and R.D. Minard. 1975. Bacterial metabolism of 1-naphthol. J. Agric. Food Chem. 23: 85. (Cited in Mount and Oehme, 1981)

Bond, D.J. and A.C. Chandley. 1983. Aneuploidy. Oxford Univ. Press, Oxford, England.

Boush, G.M. and F. Matsumura. 1967. Insecticidal degradation by Pseudomonas meolphthora, the bacterial symbiote of the apple maggot. J. Econ. Entomol. 60: 918-920.

Brankovan, O. 1972. The meiotic effect of Sevin 50 after treatment of corn in the embryonic and generative phases of development. Arhiv za Poljopriv-redne Nauke. 25:(90) 128-138.

Bringmann, V.G. and R. Kuhn. 1977. Grenzwerte der Schadwirkung wasser-gefahrdender Stoffe gegen Bakterien (Pseudomonas putida) und Grunalgen (Scenedesmus quadricauda) im Zellvermehrungshemmtest. Z. f. Wasser und Abwasser-Forschung. 10: Jahrgang. Nr. 3/4/77, 87-98.

Brown, K.M., D.C. Anderson, S.G. Jones, L.E. Deuel and J.D. Price. 1979. The relative toxicity of four pesticides in tap water and water from flooded rice paddies. Int. J. Environ. Stud. 14(1): 49-54.

Brzeskij, V.V. and V.I. Vaskov. 1972. Mutation studies and fertility calculation with Drosophila melanogaster under the effects of carbaryl. Agnew. Parasitol. 13: 23-28.

Bukin, A.L. and G.V. Filatov. 1965. Sevin toxicity for mammals and birds. Veterinariia. 42: 93-95. (Rus.) (Cited in NIOSH, 1976)

Butler, D.A. 1963. A Review of Fish and Wildlife Service Investigations During 1961 and 1962. Circ. 167, Fish Wildl. Serv., Washington, DC. 25 p. (Cited in U.S. EPA, 1983)

Cambon, C., C. Declume and R. Derache. 1978. Inhibition of acetylcholines-terase from fetal and maternal tissues after oral intake of carbaryl (1-naphthyl-N-methyl-carbamate) by pregnant rats. Biochem. Pharmacol. 27(22): 2647-2648.

Cambon, C., C. Declume and R. Derache. 1980. Fetal and maternal rat brain acetylcholinesterase: Isoenzymes changes following insecticidal carbamate derivative poisoning. Arch. Toxicol. 45(4): 257-262.

Cambon, C., Y. Fernandez. M. Falzon and S. Mitjavila. 1981. Variations of the digestive absorption kinetics of carbaryl with the nature of the vehicle. Toxicology. 22(1): 45-51.

Caro, J.H., H.P. Freeman and B.C. Turner. 1974. Persistence in soil and losses in runoff of soil-incorporated carbaryl in a small watershed. J. Agric. Food Chem. 22(5): 860-863.

Carpenter, C.P. and C.S. Weil. 1970. Cited as a personal communication. J. Agric. Food Chem. 18: 1015. (Cited in Mount and Oehme, 1981)

Carpenter, C.P., C.W. Weil, P.E. Palm, et al. 1961. Mammalian toxicity of 1-naphthyl-N-methylcarbamate (Sevin insecticide). J. Agric. Food Chem. 9: 30-39.

Casper, H.H., J.C. Pekas and W.E. Dinusson. 1973. Gastric absorption of a pesticide (1-naphthyl-N-methylcarbamate) in the fasted rat. Pestic. Biochem. Physiol. 2: 391-396. (Cited in NIOSH, 1976)

Chaiyarach, S., V. Ratananun and R.C. Harrel. 1975. Acute toxicity of the insecticides toxaphene and carbaryl and the herbicides propanil and molinate to four species of aquatic organisms. Bull. Environ. Contam. Toxicol. 14(3): 281-284.

Chen, K.C. and H.W. Dorough. 1979. Glutathione and mercapturic acid conjugates in the metabolism of naphthalene and 1-naphthyl-N-methylcarbamate (carbaryl). Fed. Proc. 38: 585. (Cited in Mount and Oehme, 1981)

Chin, Y.N. and K.I. Sudderuddin. 1979. Effect of methamidophos on the growth rate and esterase activity of the common carp Cyprinus carpio L. Environ. Pollut. 18(3): 213-220.

Chin, B.H., J.M. Eldridge and L.J. Sullivan. 1974. Metabolism of carbaryl by selected human tissues using an organ-maintenance technique. Clin. Toxicol. 7(1): 37-56.

Collins, T.F.X., W.H. Hansen and H.V. Keeler. 1971. The effect of carbaryl (Sevin) on reproduction of the rat and the gerbil. Toxicol. Appl. Pharmacol. 19: 202-216.

Coulston, F. 1971. The effect of carbaryl on reproduction in the rhesus monkey. Albany Med. College, Inst. Exp. Pathol. Toxicol., Albany, NY. 18 p. (Cited in NIOSH, 1976)

Declume, C. and P. Benard. 1977. Autoradiographic study of the distribution of an anticholinesterase agent, 1-naphthyl-N-methyl-^{14}C-carbamate in the pregnant rat. Toxicol. Appl. Pharmacol. 39(3): 451-460. (Fre.)

Declume, C., C. Cambon and R. Derache. 1979. The effects on newborn rats of repeated carbaryl administration during gestation. Toxicol. Lett. 3(4): 191-196. (Abstract)

DeGiovanni-Donnelly, R., S.M. Kolbye, and P.D. Greeves. 1968. The effects of IPC, CIPC, Sevin, and Zectran on Bacillus subtilis. Experientia. 24: 80-81.

Degraeve, N., M. Moutschen-Dahmen, N. Houbrechts, and A. Colizzi. 1976. The hazards of an insecticide carbaryl used alone and in association with nitrites. Bulletin dela Societe Royale des Sciences de Liege. 45: 46-57.

DeLorenzo, F., N. Staiano, L. Silengo and R. Cortese. 1978. Mutagenicity of diallate, sulfallate and triallate and relationship between structure and mutagenic effects of carbamates used widely in agriculture. Cancer Res. 38(1): 13-15.

Desi, I., L. Gonczi, G. Simon, I. Farkas and Z. Kneffel. 1974. Neurotoxicologic studies of two carbamate pesticides in subacute animal experiments. Toxicol. Appl. Pharmacol. 27(3): 465-476.

Dikshith, T.S.S., P.K. Gupta, J.S. Gaur, K.K. Datta and A.K. Mathur. 1976. Ninety day toxicity of carbaryl in male rats. Environ. Res. 12: 161-170.

Dorough, H.W. 1967. Carbaryl-C^{14} metabolism in a lactating cow. J. Agric. Food Chem. 15: 261. (Cited in Mount and Oehme, 1981)

Dougherty, W.J. and F. Coulston. 1975. Teratogenic evaluation of carbaryl in the rhesus monkey (Macaca mulatta). Unpublished report submitted to Union Carbide Corp., June 6. (Cited in NIOSH, 1976)

Duggan, R.E., G.Q. Lipscomb, E.L. Cox, R.E. Heatwole and R.C. Kling. 1971. Pesticide residue levels in food in the U.S. from July 1, 1963 to June 30, 1969. Pestic. Monit. J. 5: 73. (Cited in Mount and Oehme, 1981.)

Durham, W.F. and H.R. Wolfe. 1962. Measurement of the exposure of workers to pesticides. Bull. WHO. 26: 75. (Cited in Leavitt et al., 1982)

Earl, F.L., E. Miller and E.J. Van Loon. 1973. Reproductive, teratogenic and neonatal effects of some pesticides and related compounds in beagle dogs and miniature swine. Pestic. Environ.: Continuing Controversy, Paper Inter-Am., Conf. Toxicol. Occup. Med. p. 253-266.

Egert, G., and H. Greim. 1976. Formation of mutagenic N-nitroso compounds from the pesticides prometryne, dodine, and carbaryl in the presence of nitrite at pH 1. Mutat. Res. 37: 179-186.

Eichelberger, J.W. and J.J. Lichtenberg. 1971. Persistence of pesticides in river water. Environ. Sci. Technol. 5(6): 541-544.

Eisenbrand G., O. Ungerer and R. Preussmann. 1975. Reaction of nitrite with pesticides. II. Formation, chemical properties and carcinogenic activity of the N-nitroso derivative of N-methyl-1-naphthyl carbamate (carbaryl). Food Cosmet. Toxicol. 13(3): 365-367.

Elespuru, R.K. and W. Lijinsky. 1973. Formation of carcinogenic nitroso compounds from nitrite and some types of agricultural chemicals. Food Cosmet. Toxicol. 41(5): 807-817.

Elespuru, R., W. Lijinsky and J.K. Setlow. 1974. Nitrosocarbaryl, as a mutagen of environmental significance. Nature. 247: 385-387.

Elliott-Feeley, E. and J.B. Armstrong. 1981. Effects of fenitrothion and carbaryl on Xenopus laevis development. Toxicology. 22(4): 319-335.

Epstein, S.S., E. Arnold, J. Andrea, W. Bass and Y. Bishop. 1972. Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23: 288-325.

Fahrig, R. 1974. Comparative mutagenicity studies with pesticides. IARC Sci. Publ. 10: 161-181.

Farago, A. 1969. Fatal suicidal case of Sevin (1-naphthyl-N-methylcarbamate) poisoning. Arch. Toxicol. (Berl.) 24: 309-315. (Ger.) (Cited in NIOSH, 1976)

Federal Register. 1980. Determination not to initiate a rebuttable presumption against registration (RPAR) of pesticide products containing carbaryl; availability of decision document. Vol. 45, No. 241, p. 81869-81876.

Feldmann, R.J. and H.I. Maibach. 1974. Percutaneous penetration of some pesticides and herbicides in man. Toxicol. Appl. Pharmacol. 28(1): 126-132.

Felley, D.R. 1971. Diss. Abstr. B 31: 6040. (Cited in Caro et al., 1974)

Fernandez, Y., M. Falzon, C. Cambon-Gros and S. Mitjavila. 1982. Carbaryl tricompartmental toxicokinetics and anticholinesterase activity. Toxicol. Lett. 13(3-4): 253-258.

Fiscor, G., and G.M. Nil Lo Piccolo. 1972. Survey of pesticides for mutagenicity by the bacterial plate assay method. EMS News. 6: 6-8.

Freitag, D., H. Geyer, W. Klein, A.G. Kraus, E. Lahaniatis and F. Korte. 1979. An approach for comparative screening of the environmental behavior of chemical. Ecotox. Environ. Safety. 3: 144-151.

Gold, R.E., J.R. Leavitt, T. Holcslaw and D. Tupy. 1982. Exposure of urban applicators to carbaryl. Arch. Environ. Contam. Toxicol. 11(1): 63-67.

Guthrie, R.K., V.A. Anugwelem and E.M. Davis. 1981. Responses of bacteria to the presence of carbaryl in water. II. Pure culture vs. mixed culture response. Water Res. Bull. 17: 1005-1007.

Hansch, C. and A.J. Leo. 1979. Substituent Constants for Correlation Analysis in Chemistry and Biology. John Wiley and Sons, New York.

Hook, E.B. 1983. Perspective in mutation epidemiology: Contribution of chromosome abnormalities to human morbidity and mortality and some comments upon surveillance of chromosome mutation rates. Mutat. Res. 114: 389-423.

Houston, J.B., D.G. Upshall and J.W. Bridges. 1974. Pharmacokinetics and metabolism of two carbamate insecticides, carbaryl and landrin, in the rat. Xenobiotica. 5(10): 637-648.

Houston, J.B., D.G. Upshall and J.W. Bridges. 1975. Studies using carbamate esters as model compounds to investigate the role of lipophilicity in the gastrointestinal absorption of foreign compounds. J. Pharmacol. Exp. Ther. 195(1): 67-72.

Hurwood, I.S. 1967. Studies on pesticide residues. 2. Carbaryl residues in the body tissues and milk of cattle following dermal application. Queens J. Agric. Anim. Sci. 24: 69-74. (Cited in NIOSH, 1976)

Hwang, S.W. and L.S. Schanker. 1974. Absorption of carbaryl from the lung and small intestine of the rat. Environ. Res. 7(2): 206-211.

IARC (International Agency for Research on Cancer). 1976. Carbaryl. In: Some Carbamates, Thiocarbamates and Carbazides. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, Vol. 12. IARC, WHO, Lyon, France. p. 37-54.

Innes, J.R.M., B.M. Ulland, M.G. Valerio, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. J. Natl. Cancer Inst. 42: 1101-1114.

Ishidate, M., Jr., and S. Odashima. 1977. Chromosome tests with 134 compounds on Chinese hamster cells in vitro - A screening for chemical carcinogens. Mutat. Res. 48: 337-354.

Jaszczuk, E., T. Syrowatka and J. Cybulski. 1979. Mutagenic activity of propoxur, carbaryl and their nitroso derivatives: Induction of reversion in Salmonella typhimurium. Rocz. Pansw. Zakl. Hig. 30(1): 81-88. (Pol.)

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. U.S. Dept. Interior, Fish Wildl. Serv., Resource Pub. 137, Washington, DC. 98 p.

Kanazawa, J. 1975. Uptake and excretion of organophosphorus and carbamate insecticides by freshwater fish, motsugo, Pseudorasbora parva. Bull. Environ. Contam. Toxicol. 14: 346-352.

Karickhoff, S.W. 1981. Semi-empirical estimation of sorption of hydrophobic pollutants on natural sediments and soils. Chemosphere. 10: 833-846.

Karinen, J.F., J.G. Lamberton, N.E. Stewart and L.C. Terriere. 1967. Persistence of carbaryl in the marine estuarine environment. Chemical and biological stability in aquarium systems. J. Agric. Food Chem. 15(1): 148-156.

Kazano, H., P.C. Kearney and D.D. Kaufman. 1972. Metabolism of methylcarbamate insecticides in soils. J. Agric. Food Chem. 20(5): 975-979.

Kazarnovskaya, M.L., and A.F. Vasilos. 1977. The effect of Sevin on the chromosomal appartus of cells in vitro. Zdravaookhranenie. 20(4): 14-16.

Kenaga, E.E. and C.A.I. Goring. 1980. Relationship between water solubility, soil sorption, octanol-water partitioning and concentration of chemicals in biota. In: Aquatic Toxicology, Proc. 3rd Ann. Symp. Aquatic Toxicol., ASTM, Philadelphia, PA. p. 79-115.

Kitagawa, K., M. Wakakura, and S. Ishikawa. 1977. Light microscopic study of endocrine organs of rats treated by carbamate pesticide. J. Tox. Sci. 2: 53-60.

Knaak, J.B. and L.J. Sullivan. 1967. Metabolism of carbaryl in the dog. J. Agric. Food Chem. 15: 1125. (Cited in NIOSH, 1976; Mount and Oehme, 1981)

Knaak, J.B., M.J. Tallant, W.J. Bartley and L.F. Sullivan. 1965. The metabolism of carbaryl in the rat, guinea pig and man. J. Agric. Food Chem. 13: 537. (Cited in NIOSH, 1976; Mount and Oehme, 1981)

Knaak, J.B., M.J. Tallant, S.J. Kozbelt and L.J. Sullivan. 1968. The metabolism of carbaryl in man, monkey, pig and sheep. J. Agric. Food Chem. 16(3): 465-470.

Korn, S. 1973. Uptake and persistence of carbaryl in channel catfish. Trans. Am. Fish. Soc. 102(1): 137-139.

Korn, S. and R. Earnest. 1974. Acute toxicity of twenty insecticides to striped bass, Morone saxatilis. Calif. Fish Game. 60(3): 128-131.

Krishna, J.G. and J.E. Casida. 1966. Fate in rats of the radiocarbon from ten variously labeled methyl- and dimethylcarbamate-^{14}C insecticide chemicals and their hydrolysis products. J. Agric. Food Chem. 14: 98. (Cited in Mount and Oehme, 1981)

Krylova, T.V., and A.V. Denisova. 1973. Action of Sevin on the Mongolian tree creeper. Biol. Nauki. 16(10): 25-30.

Kuhr, R.J. and H.W. Dorough. 1976. Carbamated Insecticides: Chemistry, Biochemistry and Toxicology. CRC Press, Cleveland, OH. p. 103-124, 146, 258-286. (Cited in Mount and Oehme, 1981)

LaFleur, K.S. 1976. Carbaryl desorption and movement in soil columns. Soil Sci. 121: 212-216.

Leavitt, J.R., R.E. Gold, T. Holcslaw and D. Tupy. 1982. Exposure of professional pesticide applicators to carbaryl. Arch. Environ. Contam. Toxicol. 11(1): 57-62.

Lijinsky, W. and H.W. Taylor. 1977. Transplacental chronic toxicity test of carbaryl with nitrite in rats. Food Cosmet. Toxicol. 15(3): 229-232.

Lin, T. and H.W. Dorough. 1974. Influence of insecticide exposure on the in vivo and in vitro metabolic activity of rats. Arch. Environ. Contam. Toxicol. 2(4): 364-377.

Liu, D., K. Thomson and W.M.J. Strachan. 1981. Biodegradation of carbaryl in simulated aquatic environment. Bull. Environ. Contam. Toxicol. 27(3): 412-417.

Lopez, C. 1970. Therapy with corticosteroid compounds in acute poisoning with carbaryl and organophosphate pesticides. Int. Arch. Arbeitsmed. 26: 50-62. (Cited in NIOSH, 1976)

Lowe, J.I. 1967. Effects of prolonged exposure to Sevin on an estuarine fish, Leiostomus xanthurus La cepede. Bull. Environ. Contam. Toxicol. 2(3): 147-155.

Macek, K.J. and W.A. McAllister. 1970. Insecticide susceptibility of some common fish family representatives. Trans. Am. Fish. Soc. 99(1): 20-27.

Maibach, H.I., R.J. Feldmann, T.H. Milby and W.F. Serat. 1971. Regional variations in percutaneous penetration in man. Pestic. Arch. Environ. Health. 23: 208-211. (Cited in NIOSH, 1976)

Marshall, T.C. and H.W. Dorough. 1979. Biliary excretion of carbamate insecticides in the rat. Pestic. Biochem. Physiol. 11: 56. (Cited in Mount and Oehme, 1981)

Marshall, T.C., H.W. Dorough and H.E. Swim. 1976. Screening of pesticides for mutagenic potential using Salmonella typhimurium mutants. J. Agric. Food Chem. 24(3): 560-563.

Martin, H. and C.R. Worthington, Ed. 1977. Pesticide Manual, British Crop Protection Council, 5th ed. 593 p.

Matsumura, F. and G.M. Boush. 1968. Degradation of insecticides by a soil fungus, Trichoderma viride. J. Econ. Entomol. 61(3): 610-612.

McCann, J., E. Choi, E. Yamaski, and B.N. Ames. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. 72(12): 5135-5139.

Mehendale, H.M. and H.W. Dorough. 1971. Glucuronidation mechanisms in the rat and their significance in the metabolism of insecticides. Pestic. Biochem. Physiol. 1(3-4): 307-318.

Menzie, C.M. 1969. Metabolism of Pesticides. U.S. Dept. Interior, Bur. Sport Fish., Wildl. Spec. Sci. Rep., Wildl. No. 127. (Cited in Mount and Oehme, 1981)

Morpurgo, G., D. Bellincampi, G. Gualandi, L. Baldinelli and C.O. Serlupi. 1979. Analysis of mitotic nondisjunction with Aspergillus nidulans. Environ. Health Perspect. 31: 81-95.

Mount, M.E. and F.W. Oehme. 1981. Carbaryl: A literature review. Residue Rev. 80: 1-64.

Mount, M.E., A.D. Dayton and F.W. Oehme. 1981. Carbaryl residues in tissues and cholinesterase activities in brain and blood of rats receiving carbaryl. Toxicol. Appl. Pharmacol. 58(2): 282-296.

Murray, F.J., R.E. Staples and B.A. Schwetz. 1979. Teratogenic potential of carbaryl given to rabbits and mice by gavage or by dietary inclusion. Toxicol. Appl. Pharmacol. 51(1): 81-89.

Nagy, Z., I. Mile and F. Antoni. 1975. The mutagenic effect of pesticides on Escherichia coli WP2 try$^-$. Acta Microbiol. Acad. Sci. Hung. 22: 309-314.

NIOSH (National Institute for Occupational Safety and Health). 1976. Criteria for a Recommended Standard...Occupational Exposure to Carbaryl. U.S. DHEW Pub. 77-107-192.

NIOSH (National Institute for Occupational Safety and Health). 1983. RTECS (Registry of Toxic Effects of Chemical Substances). February, 1983.

Odeyemi, O. 1982. Relative stability of carbaryl in tropical ecosystems. Environ. Pollut., Ser. A. 29(3): 207-213.

O'Kelley, J.C. and T.R. Deason. 1976. Degradation of pesticides by algae. ORD, U.S. EPA. EPA 600/3-76-022. 41 p.

Onfelt, A., and I. Klasterska. 1983. Spindle disturbances in mammalian cells. II. Induction of viable aneuploid/polyploid cells and multiple chromatid exchanges after treatment of V79 Chinese hamster cells with carbaryl. Mutat. Res. 119: 319-330.

OSHA (Occupational Safety and Health Administration). 1981. General Industry Standards. OSHA Safety and Health Standards reprinted from 29 CFR 1910. U.S. Dept. Labor. p. 631-637.

Pekas, J.C. 1974. Absorption of pesticidal carbamates from perfused intestinal loops in conscious swine. Food Cosmet. Toxicol. 12(3): 377-379.

Pekas, J.C. 1979. Further metabolism of naphthyl N-methylcarbamate (carbaryl) by the intestine. Pestic. Biochem. Physiol. 11(1): 166-175.

Pipy, B., D. Gaillard, M. Beraud and R. Derache. 1980. Phagocytic activity of the rat reticuloendothial system and the pharmacokinetics of an anti-cholinesterasic insecticide: Carbaryl. Xenobiotica. 10(10): 785-793.

Pipy, B., D. Gaillard and R. Derache. 1981. Phagocytic activity of the réticulo-endothelial system in the rat and rates of in vivo excretion of metabolites of carbaryl and in vitro microsomal metabolism. Biochem. Pharmacol. 30(6): 669-672.

Post, G. and T.R. Schroeder. 1971. Toxicity of four insecticides to four salmonid species. Bull. Environ. Contam. Toxicol. 6(2): 144-156.

Probst, G.S., R.E. McMahon, L.E. Hill, C.Z. Thompson, J.K. Epp and S.B. Neal. 1981. Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: A comparison with bacterial mutagenicity using 218 compounds. Environ. Mutagen. 3(1): 11-32.

Rani, M.V.U., O.S. Reddi and P.P. Reddy. 1980. Mutagenicity studies involving aldrin, endosulfan, dimethoate, phosphamidon, carbaryl and ceresan. Bull. Environ. Contam. Toxicol. 25(2): 277-282.

Rawash, I.A., I.A. Gaaboub, F.M. El-Gayar and A.Y. Al-Shazli. 1975. Standard curves for nuvacron, malathion, Sevin, DDT and Kelthane tested against the mosquito Culex pipiens L. and the microcrustacean Daphnia magna straus. Toxicology. 4(2): 133-144.

Regan, J.D., R.B. Setlow, A.A. Francis and W. Lijinsky. 1976. Nitroso-carbaryl: Its effect on human DNA. Mutat. Res. 38: 293-302.

Rickard, R.W. and H.W. Dorough. 1979. Formation and fate of nitrosamides in animals. Toxicol. Appl. Pharmacol. 48(1): A138.

Robens, J.F. 1969. Teratologic studies of carbaryl, diazinon, norea, disulfiram and thiram in small laboratory animals. Toxicol. Appl. Pharmacol. 15(1): 152-163.

Rocchi, P., P. Perocco, W. Alberghini, A. Fini and G. Prodi. 1980. Effect of pesticides on scheduled and unscheduled DNA synthesis of rat thymocytes and human lymphocytes. Arch. Toxicol. 45(2): 101-108.

Rodriguez, L.D. and H.W. Dorough. 1977. Degradation of carbaryl by soil microorganisms. Arch. Environ. Contam. Toxicol. 6(1): 47-56.

Ryan, A.J. 1971. The metabolism of pesticidal carbamates. CRC Crit. Rev. Toxicol. 1(1): 33-54.

Sabharwal, P.S. and J.M. Lockard. 1979. Induction of sister chromatid exchange and polyploidy by carbaryl in V79 cells. In Vitro. 15(3): 172-173.

Sanborn, J.R., R.M. Francis and R.L. Metcalf. 1977. The degradation of selected pesticides in soil: A review of published literature. U.S. EPA, Cincinnati, OH. EPA 600/9-77022. 616 p.

Shah, P.V. and F.E. Guthrie. 1977. Dermal absorption, distribution and the fate of six pesticides in the rabbit. In: Pesticides Management and Insecticide Resistance, D.L. Watson and A.W.A. Brown, Ed. Academic Press, NY. p. 547-554. (Cited in Mount and Oehme, 1981)

Sharom, M.S., J.R. Miles, C.R. Harris and F.L. McEwen. 1980. Persistence of 12 insecticides in water. Water Res. 14(8): 1089-1093.

Shimkin, M.B., R. Wieder, M. McDonough, et al. 1969. Lung tumor response in strain A mice as a quantitative bioassay of carcinogenic activity of some carbamates and aziridines. Cancer Res. 29: 2184. (Cited in IARC, 1976)

Shirasu, Y., M. Moriya, K. Kato, A. Furuhashi and T. Kada. 1976. Mutagenicity screening of pesticides in the microbial system. Mutat. Res. 40: 19-30.

Shpirt, M.B. 1975. Toxicological evaluation of dichlorodipheny-trichloroethane (DDT), hexachlorocyclohexane (HCCH), tetramethyl-thiuramdisulfide (TMTD), Sevin, and Zineb when acting on a human cell structure. Gig. Tr. Prof. Zabol. 17:(3) 32-34.

Shtenberg, A.I. and M.V. Ozhovan. 1971. The effect of low Sevin doses on the reproductive function of animals in a number of generations. Vopr. Pitan. 30: 42. (Cited in NIOSH, 1976)

Shtenberg, A.I. and M.N. Rybakova. 1968. Effect of carbaryl on the neuroendocrine system of rats. Food Cosmet. Toxicol. 6: 461-467. (Cited in NIOSH, 1976)

Siebert, D. and G. Eisenbrand. 1974. Induction of mitotic gene conversion in Saccharomyces cerevisiae by N-nitrosated pesticides. Mutat. Res. 22: 121-126. (Cited in NIOSH, 1976)

Sikka, H.C., S. Miyazaki and R.S. Lynch. 1975. Degradation of carbaryl and 1-naphthol by marine microorganisms. Bull. Environ. Contam. Toxicol. 13(6): 666-672.

Singh, J.M. 1973. Decreased performance behavior with carbaryl, an indication of clinical toxicity. Clin. Toxicol. 6(1): 97-108.

Smalley, H.E., J.M. Curtis and F.L. Earl. 1968. Teratogenic action of carbaryl in beagle dogs. Toxicol. Appl. Pharmacol. 13(3): 392-403.

Solomon, H.M. and J.S. Weis. 1979. Abnormal circulatory development in medaka caused by the insecticides carbaryl, malathion and parathion. Teratology. 19(1): 51-62.

SRI (Stanford Research Institute). 1983. Directory of Chemical Producers, U.S.A. SRI, Menlo Park, CA.

Stadnyk, L., R.S. Campbell and B.T. Johnson. 1971. Pesticide effect on growth and ^{14}C assimilation in a freshwater alga. Bull. Environ. Contam. Toxicol. 6(1): 1-8.

Stanley, J.G. and J.G. Trial. 1980. Disappearance constants of carbaryl from streams contaminated by forest spraying. Bull. Environ. Contam. Toxicol. 25(5): 771-776.

Statham, C.N., S.K. Pepple and J.J. Lech. 1975. Biliary excretion products of 1-naphthyl-N-methylcarbamate-1-^{14}C (carbaryl) in rainbow trout (Salmo gairdneri). Drug Metab. Dispos. 3(5): 400-406.

Statham, C.N., M.J. Melancon, Jr. and J.J. Lech. 1976. Bioconcentration of xenobiotics in trout bile: A proposed monitoring aid for some waterborne chemicals. Science. 193(4254): 680-681.

Stewart, N.E., R.E. Millemann and W.P. Breese. 1967. Acute toxicity of the insecticide, Sevin, and its hydrolytic product, 1-naphthol, to some marine organisms. Trans. Am. Fish. Soc. 96(1): 25-30.

Street, J.C. and R.P. Sharma. 1975. Alteration of induced cellular and humoral immune responses by pesticides and chemicals of environmental concern. Quantitative studies of immunosuppression by DDT, Aroclor 1254, carbaryl, carbofuran and methylparathion. Toxicol. Appl. Pharmacol. 32(3): 587-602.

Strother, A. 1970. Comparative metabolism of selected N-methylcarbamates by human and rat liver fractions. Biochem. Pharmacol. 19(8): 2525-2529.

Strother, A. and L. Wheeler. 1980. Excretion and disposition of (14C) carbaryl in pregnant, nonpregnant and fetal tissues of the rat after acute administration. Xenobiotica. 10(2): 113-124.

Sud, R.K., A.K. Sud and K.G. Gupta. 1972. Degradation of Sevin (1-naphthyl-N-methyl carbonate) by Achromobacter sp. Ch. Mikrobiol. 87: 353-358.

Sullivan, L.J., J.M. Eldridge, J.B. Knaak and M.J. Tallant. 1972. 5,6-Dihydro-5,6-dihydroxycarbaryl glucuronide as a significant metabolite of carbaryl in the rat. J. Agric. Food Chem. 20(5): 980-985.

Swann, R.L., D.A. Laskowski, P.J. McCall, K. Vander Kuy and H.J. Dishburger. 1980. A rapid method for first approximation of environmental parameters utilizing reverse phase high performance liquid chromatography (RP-HPLC). Unpublished paper.

Szeto, S.Y., H.R. MacCarthy, P.C. Oloffs and R.F. Shepherd. 1979. The fate of acephate and carbaryl in water. J. Environ. Sci. Health. B14: 635-654.

Thomas, J.A. 1974. Actions of pesticides and other drugs on the male reproductive system. NTIS PB 237381/9GA. 41 p.

Thomas, J.A. 1981. Introductory remarks on the testes. Environ. Health Perspect. 38(0): 3-4.

Thomas, J.A., C.S. Dieringer and L. Schein. 1974. Effects of carbaryl on mouse organs of reproduction. Toxicol. Appl. Pharmacol. 28: 142-144.

Triolo, A.J., W.R. Lang, J.M. Coon, D. Lindstrom and D.L. Herr. 1982. Effect of the insecticides toxaphene and carbaryl on induction of lung tumors by benzo(a)pyrene in the mouse. Toxicol. Environ. Health. 9(4): 637-649.

Tsutsui, T., H. Maizumi, J.A. McLachlan and J.C. Barrett. 1983. Aneuploidy induction and cell transformation by diethylstilbestrol: A possible chromosomal mechanism in carcinogenesis. Cancer Res. 43: 3814-3821.

Tu, C.M. and J.R.W. Miles. 1976. Interactions between insecticides and soil microbes. Residue Rev. 64: 17-65.

Uchiyama, M., M. Takeda, T. Suzuki and K. Yoshikawa. 1975. Mutagenicity of nitroso derivatives of N-methylcarbamate insecticides in microbiological method. Bull. Environ. Contam. Toxicol. 14: 389-394.

U.S. EPA. 1981a. Treatability Manual. I. Treatability data. U.S. EPA, Washington, DC. EPA 600/2-82001A.

U.S. EPA. 1981b. Preliminary report on the mutagenicity of carbaryl. Reproduction Effects Assessment Group, Washington, DC. EPA 600/6-81-001.

U.S. EPA. 1983. AQUIRE: Aquatic Information Retrieval Database. Online: March 18.

Vashakidze, V.I. 1965. Some questions on the harmful influence of Sevin on the sexual function of experimental animals. Soobshch. Akad. Nauk. Gruz. SSR. 38: 471. (Cited in NIOSH, 1976)

Vasilos, A., V.D. Dmetrienko, and I.G. Shroyt. 1972. Colchicine-like action of Sevin on human embryonic fibroblasts in vitro. Bull Eskp. Biol. Med. 73: 91-93.

Vasilos, A.F., V.D. Dmitrienko, and I.G. Shroit. 1975a. Disruption of the mitotic system following acute Sevin poisoning. Izv. Akad. Nauk Mold. SSR Ser. Biol. i.Khim. Nauk. 3: 64-67.

Vasilos, A.F., V.D. Dmitrienko, and I.G. Shroit. 1975b. Changes in mitosis in chronic poisoning of rats with Sevin. Izv. Akad. Nauk Mold. SSR Ser. Biol. i.Khim. Nauk. 4: 45-47.

von Rumker, R., E.W. Lawless and A.F. Meiners. 1974. Production, distribution, use and environmental impact potential of selected pesticides. Prepared by Midwest Research Institute, RVR Consultants, Kansas City, MO for Council on Environmental Quality, Washington, DC. Contract No. RQC-311. NTIS PB 74 238-795.

Wakakura, M., S. Ishikawa and S. Uga. 1978. Ultrastructural hepatic changes by carbamate pesticide (Sevin) in rats. Environ. Res. 16(1-3): 191-204.

Walsh, G.E. and S. Alexander. 1980. A marine algal bioassay method: Results with pesticides and industrial wastes. Water Air Soil Pollut. 13(1): 45-55.

Wauchope, R.D. and R. Haque. 1973. Effects of pH, light and temperature on carbaryl in aqueous media. Bull. Environ. Contam. Toxicol. 9(5): 257-260.

Weil, C.S., M.D. Woodside, C.P. Carpenter, and H.F. Smyth, Jr. 1972. Current status of tests of carbaryl for reproductive and teratogenic effect. Toxicol. Appl. Pharmacol. 21: 390-404.

Weil, C.S., M.D. Woodside, J.B. Bernard, N.I. Condra, J.M. King and C.P. Carpenter. 1973. Comparative effect of carbaryl on rat reproduction and guinea pig teratology when fed either in the diet or by stomach intubation. Toxicol. Appl. Pharmacol. 26(4): 621-638.

Weis, P. and J.S. Weis. 1974. Cardiac malformations and other effects due to insecticides in embryos of the killifish, Fundulus heteroclitus. Teratology. 10(3): 263-267.

Whitehurst, W.E., E.T. Bishop, F.E. Critchfield, et al. 1963. The metabolism of Sevin in dairy cows. J. Agric. Food Chem. 11: 167. (Cited in Mount and Oehme, 1981)

WHO (World Health Organization). 1974. 1973 Evaluation of some pesticide residues in food. WHO Pestic. Res. Serv., No. 3. p. 141-176. (Cited in IARC, 1976)

Whorton, M.D., T.H. Milby and H.A. Stubbs. 1979. Testicular function among carbasyl-exposed employees. J. Tox. Environ. Health. 5: 929-941.

Wills, J.H., E. Jameson, A. Stein, et al. 1967. Effects of oral doses of carbaryl on man. Toxicol. Appl. Pharmacol. 10: 390. (Cited in Desi et al., 1974)

Wills, J.H., E. Jameson and F. Coulston. 1968. Effects of oral doses of carbaryl on man. Clin. Toxicol. 1: 265. (Cited in IARC, 1976)

Wiltrout, R.W., C.D. Ercegovich and W.S. Ceglowski. 1978. Humoral immunity in mice following oral administration of selected pesticides. Bull. Environ. Contam. Toxicol. 20(3): 423-431.

Wójciechowski, J.P., P. Kaur and P.S. Sabharwal. 1982. Induction of ouabain resistance in V-79 cells by four carbamate pesticides. Environ. Res. 29(1): 48-53.

Wolfe, N.L., R.G. Zepp, G.L. Baughman, R.C. Fincher and J.A. Gordon. 1976. Chemical and photochemical transformation of selected pesticides in aquatic systems. U.S. EPA, Athens, GA. EPA 600/3-76-067. 153 p.

Wolfe, N.L., R.G. Zepp and D.F. Paris. 1978. Use of structure-reactivity relationships to estimate hydrolytic persistence of carbamate pesticides. Water Res. 12(8): 561-563.

Woodward, D.F. and W.L. Mauck. 1980. Toxicity of five forest insecticides to cutthroat trout and two species of aquatic invertebrates. Bull. Environ. Contam. Toxicol. 25(6): 846-854.

Wuu, K.D. and W.F. Grant. 1966. Morphological and somat chromosomal abberations induced by pesticides in barley (Hordeum vulgare). Can. J. Genet. Cytol. 8: 481-501.

Wuu, K.D. and W.F. Grant. 1967. Chromosomal abberations induced by pesticides in meiotic cells of barley. Cytologia. 32: 31-41.

APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. TLVs: Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1982. Documentation of the Threshold Limit Values for Chemical Substances in Work Air. Cincinnati, OH. 94 p.

Bruin, P., G.J. Bergen and J.J. Desta, Ed. 1980. Handling Chemicals Safely, 2nd ed. Dutch Assoc. Safety Experts, Dutch Chemical Industry Assoc., and Dutch Safety Institute, The Netherlands. 1013 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, Vol. 2A, 3rd rev. ed. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, Vol. 2B, 3rd rev. ed. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, Vol. 2C, 3rd rev. ed. John Wiley and Sons, NY. p. 3817-5112.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

Muir, G.D., Ed. 1977. Hazards in the Chemical Laboratory, 2nd ed. The London Chemical Society, London. 473 p.

NTP (National Toxicology Program). 1982. Carcinogenesis Testing Program. Chemicals on Standard Protocol. Management Status, December 31.

Proctor, N.H. and J.P. Hughes. 1978. Chemical Hazards of the Workplace. J.B. Lippincott Co., Philadelphia, PA. 533 p.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.