Environmental Fate and Toxicology of Carbaryl

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1 Introduction

Carbaryl (1-naphthyl-*N*-methyl carbamate; Fig. 1), a carbamate insecticide introduced in 1956 by Union Carbide Corporation, is used worldwide and is a substitute for some organochlorine insecticides (Ribera et al. 2001). Carbaryl is used to

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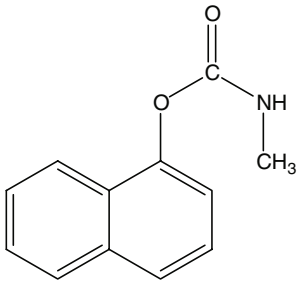

Fig. 1 Chemical structure of carbaryl

control a broad spectrum of insects on more than 120 different crops (Ware 2000). It has also been used to prevent bark beetle infestation in pine trees (Hastings et al. 2001) and as a general garden insecticide (Ware 2000). In 2005, approximately 189,800 lbs of the insecticide was applied in California alone (CDPR 2005). Annual use in the United States has been reported to be 4.5–6.8 million kg (Cox 1993). Several trade names are associated with carbaryl (the most common is Sevin®), and active ingredient (a.i.) use rates range from 0.57 to 4.5 kg/ha (Rajagopal et al. 1984). Carbaryl is available in the forms of a wettable powder, pellets, granules, suspensions, and solutions, and is the second most widely detected insecticide in surface waters in the U.S. (Martin et al. 2003).

2 Chemistry

Carbaryl, similar to most carbamates, inhibits the enzyme acetylcholinesterase (AChE), which is responsible for the degradation of the neurotransmitter acetylcholine in insects. Its inhibition promotes the buildup of AChE at synaptic junctions, resulting in uncontrolled movement, paralysis, convulsions, and possible death (Tomlin 2000). AChE inhibition also causes the toxicity of carbaryl to mammals, although, in contrast to insects, the mammalian effect involves synapses in the peripheral nervous system, including those in glandular structures and at neuromuscular junctions, in addition to those in the central nervous system. Because of the hydrolytic instability of the carbamate-AChE bond, recovery of mammals from acute effects is expected when exposures are low. Other cholinesterases (ChEs) inhibited by carbaryl include the plasma-localized butyryl ChE and the red blood cell-localized AChE. Evidence for inhibition of plasma and/or red blood cell ChEs can be interpreted and used as an indicator of exposure. The physicochemical properties of carbaryl are listed in Table 1; it has a low molecular weight, is moderately soluble in water, and does not readily volatilize (Tomlin 2000).

Table 1 Physicochemical properties of carbaryl

Pure physical state[a]		Colorless or tan crystal
Chemistry Abstracts Service registry number (CAS #)[b]		63-25-2
Molecular weight (g/mol)[a]		201.2
Molecular formula[a]		$C_{12}H_{11}NO_2$
Melting point (°C)[a]		142
Vapor pressure (mPa at 23.5°C)[a]		0.041
Octanol–water partition coefficient (log K_{ow})[a]		2.36
Density (20°C)[a]		1.23
Henry's law constant (atm m^3 g/mol at 25°C)[a]		2.74×10^{-9}
Organic-carbon normalized partition coefficient (K_{oc})[b]		290
λ_{max} (nm)[c]		280
Water solubility (mg/L)	20°C[a]	120
	25°C[d]	104
	40°C[e]	40

Sources: [a]Tomlin (2003); [b]Phillips and Bode (2004); [c]Sheng et al. (2001); [d]Arroyo et al. (2004); [e]Meister (2001).

3 Chemodynamics

3.1 Air

Carbaryl has low volatility because of its low vapor pressure (see Table 1). Additionally, its low Henry's law constant suggests that it will not volatilize from aqueous solutions (Table 1). However, carbaryl may become airborne from sorption to particulates or as a spray drift immediately following application. Drift monitoring from aerial spraying at a rate of 2,250 g a.i./ha on a Vermont apple orchard showed concentrations of 0.70–7.20 μg/plate (a 1-mm-thick Teflon sheet covered the 15-cm-diameter Petri plate), which corresponds to 0.4–4.1 g a.i./ha, as far out as 305 m with 8–12 km/hr winds (Currier et al. 1982). Higher concentrations were observed at 76 m downwind (481 μg/plate) and 12 m upwind (45.9 μg/plate) in the same study. However, it was also noted that all detections decayed to relatively low concentrations within 2 hr after application (<2 ug/m^3; Currier et al. 1982). Airborne carbaryl degrades after reaction with photochemically produced hydroxyl radicals in the atmosphere (Kao 1994), with a reaction rate constant of 3.3×10^{-11} cm^3/sec (Sun et al. 2005).

Low drift concentrations were reported in a California study, with concentrations of up to 1.12 μg/m^3 in the air after ground spraying to control the glassy-winged sharpshooter, *Homalodisca coagulate* (Walters et al. 2003). Although below the adverse health effect concentration (51.7 μg/m^3), the insecticide was present in air up to 47 hr after application (Walters et al. 2003). Shehata et al. (1984) reported atmospheric concentrations of some 0.0035–0.107 μg/m^3 over a Maine forest treated with carbaryl to control the spruce budworm.

In eastern France, atmospheric measurements for carbaryl at remote (non-populated), rural (population, 80,000), and urban (population, 300,000) sites

were, on average, 280, 348, and 577 pg/m^3, with highest detections at 1,800, 696, and 1,420 pg/m^3, respectively (Sanusi et al. 2000). The increased urban and rural concentrations were mainly caused by local agricultural use (Sanusi et al. 2000). Similar concentrations were observed in 1995 at three urban and agricultural sites along the Mississippi River (Foreman et al. 2000). However, the insecticide was detected more frequently in urban versus agricultural sites in Mississippi and Iowa, possibly a reflection of its growing domestic use (Foreman et al. 2000).

3.2 Water

The presence of carbaryl in aquatic systems has important implications for both human and animal health because of exposure via drinking water. Carbaryl is moderately soluble in water, and its solubility predictably increases with temperature and organic solvents (see Table 1). Residues, at low (μg/L) concentrations, have been detected in surface waters adjacent to both agricultural and urban areas of some 42 states (Table 2), although several states have reported a higher frequency of detections in urban versus agricultural areas (Table 2). Carbaryl was one of the four insecticides most commonly detected in urban streams in 2001 (Gilliom et al. 2007). In Florida, Wilson and Foos (2006) reported carbaryl at 0.33–0.95 μg/L in 8 of 457 samples collected from Ten Mile Creek (an important agricultural drainage). Higher concentrations (6.94–1737 μg/L) were detected in several central California locations following carbaryl use to control the glassy-winged sharpshooter (*H. coagulate*; Walters et al. 2003). Conversely, lower concentrations (10–100 ng/L) were reported in the Pinios River of Greece following its seasonal use in the agriculturally important Thessaly region (Fytianos et al. 2006).

Carbaryl has also been found in the groundwater of several states, although at low concentrations; New Jersey reported the highest number of detections across all land-use types (see Table 2). LaFleur (1976) found carbaryl in groundwater within 2 mon of application to Congaree soil (a well-drained riverbed loam), with detection continuing up to 8 mon.

3.3 Soil

Sorption to soils, in general, may prevent contamination of both surface waters and groundwater by carbaryl. Soil sorption is rapid, ranging from 0.5 hr (Ahmad et al. 2001a) to 3 hr (Jana and Das 1997), but persistent (from 2 to 16 wk) with a $t_{½}$ of ~8 d for concentrations ranging from 1 to 14 mg/L (Rajagopal et al. 1984). Carbaryl was found to sorb more readily to acidic soils (Rajagopal et al. 1984),

Table 2 Detection of carbaryl in U.S. surface waters and groundwaters[a]

		Carbaryl		
State	Type of land use	Surface water detections (no.)	Groundwater detections (no.)	Concentration range (μg/L)
Alabama	Urban	61	1	0.002–0.422
	Agriculture	19	2	
	Mixed	41	1	
California	Urban	166	–	0.0005–5.20
	Agriculture	251	1	
	Mixed	432	1	
Colorado	Urban	190	–	0.0005–16.5
	Agriculture	27	–	
	Mixed	126	3	
Florida	Urban	39	–	0.003–0.441
	Agriculture	21	–	
	Mixed	39	–	
Georgia	Urban	208	1	0.001–1.90
	Agriculture	20	–	
	Mixed	177	–	
Hawaii	Mixed	8	–	0.007–0.370
	Urban	9	–	
Indiana	Urban	119	–	0.001–0.460
	Agriculture	69	–	
	Mixed	62	–	
New Jersey	Urban	122	5	0.001–1.50
	Agriculture	24	5	0.001–2.41
	Mixed	89	9	
Pennsylvania	Urban	119	–	
	Agriculture	82	1	0.001–5.18
	Mixed	82	9	
Texas	Urban	164	7	
	Agriculture	13	–	0.002–2.0
	Mixed	138	4	
Virginia	Urban	165	2	
	Agriculture	14	–	0.001–33.5
	Mixed	45	3	
Washington	Urban	46	–	
	Agriculture	267	1	0.002–0.267
	Mixed	106	2	
Wisconsin	Urban	27	–	
	Agriculture	8	–	
	Mixed	40	–	

[a] All data from USGS (2007).

and both mineral and organic fractions contributed to its sorption. Mineral interactions are clearly reported in several recent studies. For instance, Sheng et al. (2001) found that potassium-saturated smectite clay (a nonionic, expandable,

hydrophilic clay) is a better sorbent for carbaryl than soil organic matter (SOM); the distribution coefficient (K_d) was five times greater in clay (235) than SOM-rich soil (muck; 54.2). Sheng et al. (2001) estimated that clay saturated with potassium sorbs approximately 35 times more carbaryl than a soil containing 2% SOM.

Interestingly, De Oliveira et al. (2005) found that carbaryl sorption is dependent on surface charge density and is thus site specific. For example, the amount of carbaryl sorbed was reported to be strongly dependent on the presence of specific exchangeable cations and followed the order of Ba ~ Cs ~ Ca > Mg ~ K > Na ~ Li. The polar nature of the carbonyl group was found to directly interact with exchangeable cations such as Mg^{2+} and Na (De Oliveira et al. 2005). Similarly, Jana and Das (1997) demonstrated a positive correlation of carbaryl sorption with surface area, cation-exchange capacity (CEC), and free Al_2O_3 content in Ultisol and Inceptisol soils; sorption isotherms with Indian soils followed reversible S-shaped curves, suggesting multilayer adsorption on the sorbent surface (Jana and Das 1997).

Organic matter is another contributor to carbaryl sequestration in soils. For example, carbaryl movement through soil was found to be a function of SOM content; ~52% carbaryl was leached in 10 rinses from organic-rich soil, whereas only one rinse was required to leach the same amount from a sandy soil (Sharom et al. 1980). The positive contribution of SOM to carbaryl sorption is evident in Table 3; the sorption capacity (K_f) was reported to increase with SOM content in Indian soils (Jana and Das 1997).

A comparison of carbaryl sorption to soils from four countries is presented in Table 4. Although organic carbon influences carbaryl sorption (i.e., K_d), a positive correlation was not observed by Ahmad et al. (2001a). However, in a later study Ahmad et al. (2001b) reported a positive, highly significant, correlation of organic carbon-normalized sorption capacity (K_{oc}) with the aromatic content of SOM. K_d values similar to those presented in Table 4 have been reported (Bondarenko and Gan 2004), indicating the sorption of carbaryl to soils is not very important.

Carbaryl sorption has been predicted to be highly reversible because, in contrast to chemisorption, it is proposed to be nonspecific (Rajagopal et al. 1984). This property, along with reported low K_d values, indicates that soils do not possess the potential to significantly retard carbaryl movement, over time, into either surface

Table 3 The relationship between soil organic matter (SOM) and the sorption capacity (K_f) in four different soils from India

Soil	SOM (%)	K_f (μg/g)/(μg/mL)
Ultisol 1	0.40	0.308
Inceptisol 2	1.10	1.916
Ultisol 2	1.16	2.175
Inceptisol 1	1.70	2.490

Source: Jana and Das (1997)

Table 4 Distribution coefficients (K_d) for carbaryl in several soils

Soil	Organic carbon (g/kg)	K_d	Sand:silt:clay (%)
Pakistan 2[a]	2.79	0.99	22:60:18
Australian 2[a]	3.0	0.19	92:5:3
United Kingdom 2[a]	8.9	1.09	10:67:23
Pakistan 1[a]	13.82	59.67	22:51:27
Australian 1[a]	58	23.02	63:16:21
United Kingdom 1[a]	83.8	8.80	18:39:43
California 1[b]	–	43.4	–
California 2[b]	–	47.7	–

Sources: [a] Ahmad et al. (2001a); [b] California 1 and 2 represent sediment from San Diego Creek and Bonita Creek in California, USA (Bondarenko and Gan 2004).

waters or groundwater; other fate processes (i.e., abiotic or biotic degradation) play an important role in its dissipation.

4 Degradation

4.1 Abiotic

Hydrolysis

Carbaryl is effectively hydrolyzed in water, undergoing a 50% loss at 20°C (pH = 8) in 4 d (Rajagopal et al. 1984). Earlier studies have reported similar degradation times: 6 d in flowing canal water (Osman and Belal 1980), and 1 wk in river water (Eichelberger and Lichtenberg 1971). These investigators and others (Ghauch et al. 2001) have also shown that hydrolysis of the insecticide increases with elevated temperature. Hydrolytic degradation is initiated by hydroxyl radical attack (Fig. 2; Wang and Lemley 2002), producing 1-naphthol as the primary degradation product (Osman and Belal 1980).

Photolysis

Carbaryl has been reported to be photolyzed into 1,2-naphthoquione, 1,4-naphthoquinone, 2-hydroxy-1,4-naphthoquinone, and 7-hydroxy-1,4-naphthoquinone (Fig. 3; Brahmia and Richard 2003); conversion to 1-naphthol via hydroxyl radical attack has also been observed in organic solvents (e.g., acetonitrile and methanol; Fig. 3F). In water, carbaryl produces naphthoxyl radicals, which confirm the cleavage of the carbon–oxygen bonds. However, in oxygen-rich water, solvated electrons could be

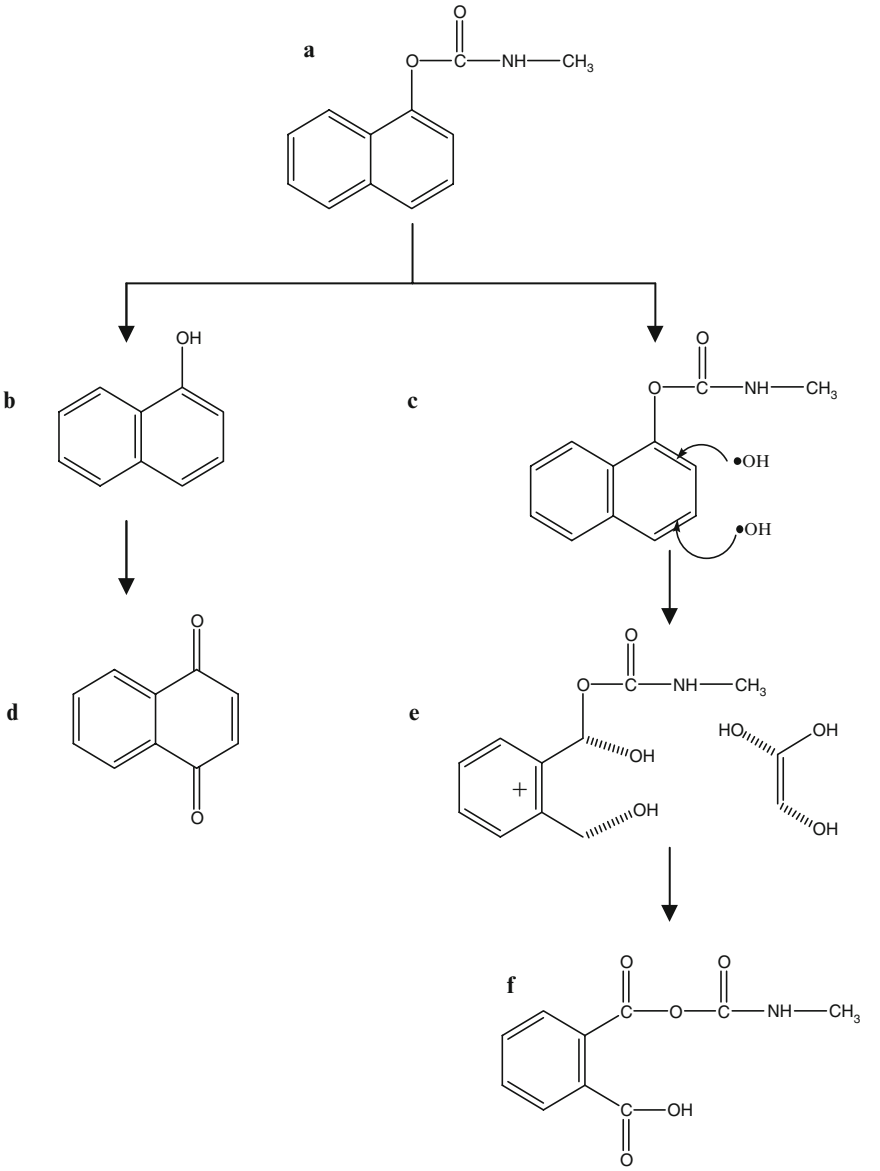

Fig. 2 The degradation pathways (Wang and Lemley 2002) of carbaryl (**a**) by hydroxyl radical attack (**c, e**) showing the degradation products: 1-naphthol (**b**), 1,4-naphthoquinone (**d**), and phthalic acid-O-yl N-methylcarbamate (**f**)

transformed into superoxide anions that can recombine with radical cations or with 1-naphthoxyl radicals. Both reactions are expected to produce naphthoquinones after reduction (Brahmia and Richard 2003).

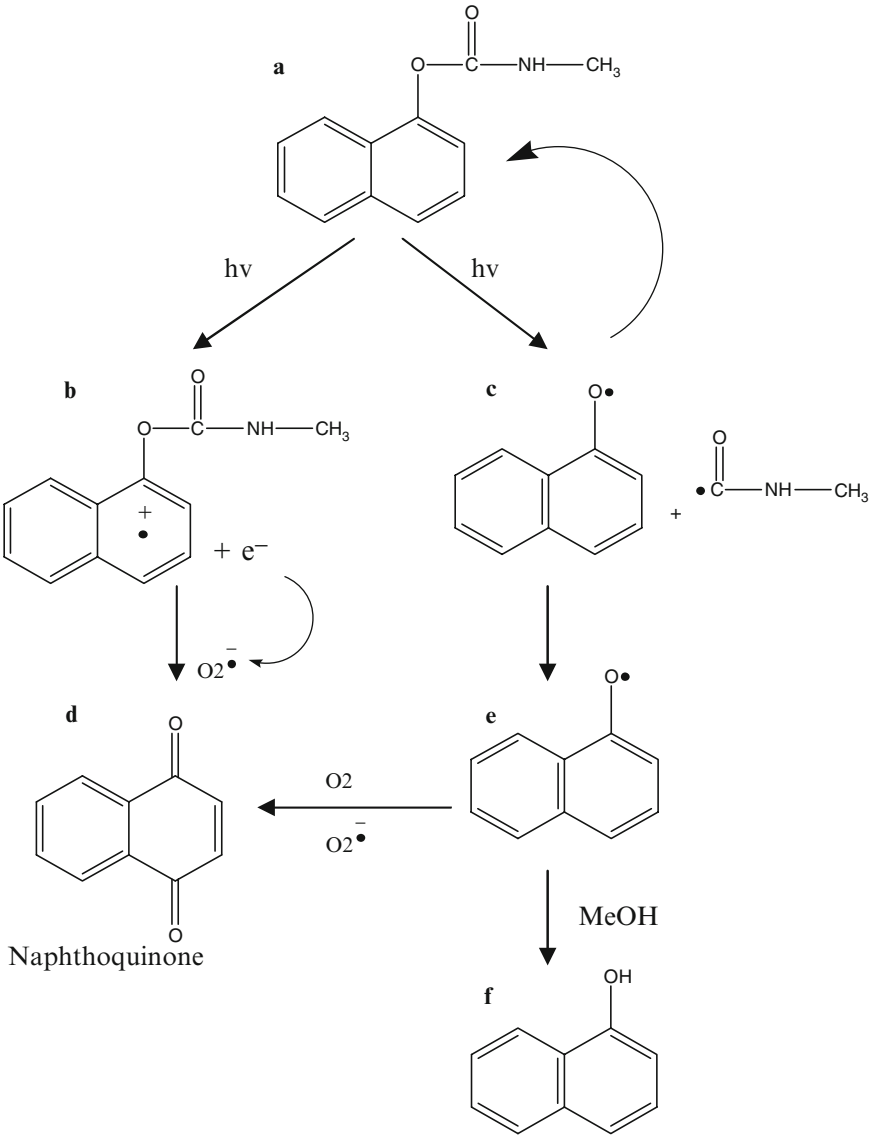

Fig. 3 Proposed (Brahmia and Richard 2003) photolytic degradation pathway for carbaryl (**a**). The parent compound is distributed into radicals (**b, c**) via photolytic processes. 1-Naphthoxyl (**c**) may then react with oxygen to yield naphthoquionone (**d**) or 1-naphthol (**f**)

Indirect photolysis of carbaryl has been reported by Miller and Chin (2002). They found that photo-enhanced degradation was both seasonally and spatially dependent. Nitrate and dissolved organic matter (DOM) were primary constituents responsible for the formation and reaction of hydroxyl radicals with carbaryl (Miller and Chin 2002).

4.2 Biotic

Microbial

The microbial degradation of carbaryl has been reported in several studies. For instance, ring ^{14}C-labeled carbaryl degraded at a constant rate in 120 d, leaving behind 15% –20% of the parent compound in soil as monitored by the release of $^{14}CO_2$ (Rodriguez and Dorough 1977). Shorter degradation times have been observed by Menon and Gopal (2003) in that carbaryl was found to dissipate to below detection levels within 45 d (DT_{50} = 14.93). However, this relatively rapid degradation was attributed to high temperatures and precipitation. Still shorter DT_{50}s have been reported, ranging from 0.15 d (Wolfe et al. 1978) to several days (Tomlin 2003). Under aerobic soil conditions, reported DT_{50}s were 7–14 d in sandy loam and 14–28 d in clay loam (Tomlin 2003). Bondarenko and Gan (2004) observed aerobic DT_{50} values of 1.8 and 4.9 d in soils containing organic matter at 1.8% (sand:silt:clay = 76:15:9) and 1.25% (sand:silt:clay = 46:32:22), respectively. Pseudo-first-order kinetics have been applied to describe the microbial degradation of carbaryl in moist soils (Venkateswarlu et al. 1980). However, inhibition of its degradation can occur when ammonium is added to the enrichment cultures (Rajagopal et al. 1983), possibly indicating that carbaryl may serve as a source of essential nitrogen for microbes.

Degradation has been observed to be more rapid in flooded (anaerobic) soils than aerobic soils; the DT_{50} was reported to be 13–14 d in flooded soils and 23–28 d in aerobic soils (Venkateswarlu et al. 1980). Rajagopal et al. (1983) observed a DT_{50} of 10–15 d in both submerged laterite and sodic soils, and that degradation was faster in soils previously treated with carbaryl. However, recently Bondarenko and Gan (2004) reported that under anaerobic conditions carbaryl was slowly degraded, with DT_{50} values from 125 to 746 d, depending on soil conditions, sorption capacity, and aging of the soil with the insecticide.

Mechanisms of degradation have also been reported. Karinen et al. (1967) showed carbaryl ring degradation through 1-naphthol, its primary degradate, to CO_2. Thus, ring hydroxylation is the first step in microbial degradation. Such findings are supported by Rajagopal et al. (1983), who noted that hydrolysis was the major pathway of degradation in flooded (anaerobic) soils (see Fig. 4). The primary product, 1-naphthol, has a DT_{50} of approximately 12–14 d (Menon and Gopal 2003), and can be further transformed to phenolic radicals, which polymerize to organic matter in soils (Rajagopal et al. 1984). Complete degradation from carbaryl to maleylpyruvate is reported for an isolated *Micrococcus* species (Fig. 4) by Doddamani and Ninnekar (2001).

Other microbial strains capable of degrading carbaryl have also been identified, including bacteria of the genera *Achromobacter, Pseudomonas (e.g., P. cepacia), Arthrobacter*, and *Xanthomonas* (Venkateswarlu et al. 1980; Rajagopal et al. 1984). Degradation by the fungus *Penicillium implicatum* has also been demonstrated (Menon and Gopal 2003). However, carbaryl has been found to inhibit the growth of some strains of rhizobia (Rajagopal et al. 1984).

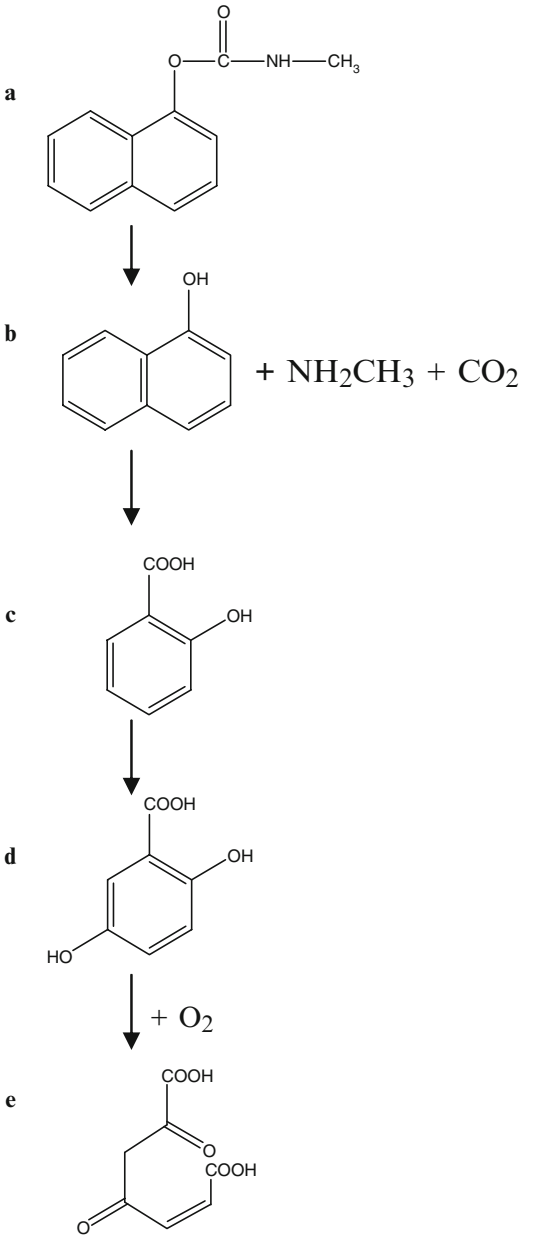

Fig. 4 Proposed degradation pathway of carbaryl by Micrococus sp. (Doddamani and Ninnekar 2001). Carbaryl (**a**) is reduced to 1-naphthol and methylamine (**b**), which is then degraded to salicylic (**c**) and gentrisic (**d**) acid. The acids are then oxidized to maleylpyruvate (**e**)

Higher-Order Organisms

The metabolism of carbaryl has been extensively studied in mammals. In general, it does not accumulate in mammalian tissue and is rapidly metabolized to less-toxic substances, particularly 1-naphthol, which are eliminated in urine and feces (Tomlin 2000). The main pathways include oxidation, via hydroxylation and epoxidation, and hydrolysis (Carpenter et al. 1961; Dorough and Casida 1964). For instance, hydrolysis of carbaryl by earthworms forms 1-naphthol (Stenersen 1992). A hydrolytic mechanism has been proposed by Sogorb et al. (2002) in which carbaryl reacts with tyrosine residues on rabbit serum albumin to yield 1-naphthol and carbamylated albumin. Water molecules then attack the carbamylated complex, releasing carbamic acid and free enzymes, the latter of which are involved in a new catalytic cycle; carbamic acid probably decomposes to CO_2 and methylamine (Sogorb et al. 2002). Metabolites detected in urine of human workers exposed to carbaryl were both 1-naphthyl-glucoronide and 1-naphthylsulfate (Sogorb et al. 2004). Carbaryl metabolism in human liver microsomes and by cytochrome P450 isoforms was investigated by Tang et al. (2002). They found three major metabolites: 5-hydroxycarbaryl, 4-hydroxycarbaryl, and carbaryl methylol (Fig. 5). Interestingly, these are the same as those formed by plants (Tomlin 2003).

Factors inhibiting enzymatic hydrolysis have also been noted. For instance, Sogorb et al. (2004) suggest that long-chain fatty acids are better inhibitors of carbaryl hydrolysis than shorter ones. Several organic compounds can inhibit its hydrolysis as well. For example, the organophosphorus insecticide chlorpyrifos inhibits carbaryl

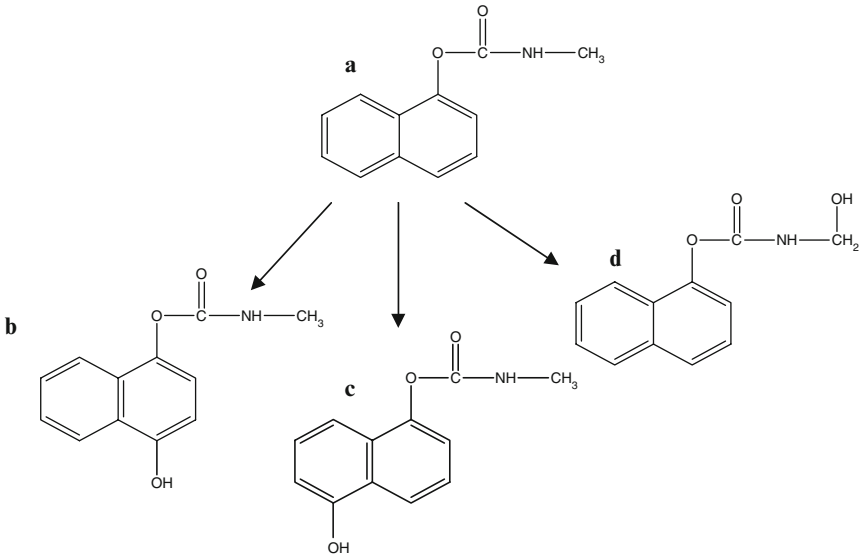

Fig. 5 The cytochrome P450-dependent metabolism (Tang et al. 2002) of carbaryl (**a**) to 4-hydroxycarbaryl (**b**), 5-hydroxycarbaryl (**c**), and carbaryl methylol (**d**)

hydrolysis (Tang et al. 2002); the activated form of ethyl parathion, paraoxon, inhibits hydrolysis by 44% (Sogorb et al. 2004).

Carbaryl has been observed to react with certain nitrogen-containing compounds, such as sodium nitrite, to form nitrosocarbaryl, which has been found to cause skin cancer when painted on mice (Deutsch-Wenzel et al. 1985), and cancer of the stomach in rats (Lijinsky and Schmahl 1978; Lijinsky and Taylor 1976). Nitrosocarbaryl belongs to the *N*-nitrosoamines class of chemicals, of which some 70% to date have been found to be carcinogenic (Cox 1993).

5 Toxicity

5.1 Insects and Aquatic Organisms

Carbaryl is highly effective for controlling insect pests. For example, it is used to control several mammalian ectoparasites, including the cattle tick *Boophilus microplus*. The tick is endemic to Mexico, having been eradicated from the U.S. in 1961 (Li et al. 2005). Several strains of *B. microplus* are highly susceptible to carbaryl; LC_{50}s range from 0.0025% to 0.0031% (Li et al. 2005). Carbaryl is also highly toxic to the honeybee, with a topical LD_{50} of 1 μg (Tomlin 2003).

Although carbamate pesticides do not persist in the environment, there may still be short-term cumulative effects on the reproduction of aquatic organisms. For instance, Tripathi and Singh (2004) found that doses of 2, 5, and 8 mg/L altered biochemical function in the nervous, hepatopancreatic, and ovotesticular tissues of the snail *Lymnaea acuminate*. Specifically, glycogen, pyruvate, total protein, and nucleic acid levels were reduced after 96 hr exposure, whereas lactate and free amino acid levels were increased (Tripathi and Singh 2004). Carbaryl can also affect embryo development. For example, Tripathi and Singh (2004) reported that the number of eggs produced by the freshwater snail *Lymnaea acuminate* was reduced by 49% at 2 mg/L; no eggs were laid at 5 or 8 mg/L. The rate of neonatal survival was also significantly reduced by 53% after exposure of hatchlings for 28 d to 2 mg/L. In a similar study, Todd and Van Leeuwan (2002) found that the average mortality of zebrafish eggs (*Danio rerio*) was reduced (~20%) after low-level exposures (<0.05 mg/L). Although the insecticide did not directly kill embryos, it had a significant effect on embryo size.

When zebrafish were exposed to 0.017 mg/L carbaryl, they developed more slowly and hatched later compared to the controls; delayed hatching exposes the embryos to predation. The toxicity of carbaryl to several aquatic species is summarized in Table 5. Note that carbaryl is toxic to the water flea, shrimp, and freshwater snail at parts per billion (ppb) levels and to fish at parts per million (ppm) levels. The results suggest that this insecticide should not be used in or near water bodies, particularly during the rainy season.

Table 5 The aquatic animal toxicology of carbaryl

Aquatic organism	Test	Concentration (mg/L unless noted)
Juvenile trout[a]	96-hr LC_{50}	4.27–6.18
Toad larvae[a]	96-hr LC_{50}	17.68–34.77
Juvenile trout[a]	IC_{50}	19 μg/L
Toad larvae[a]	IC_{50}	7.580
Rainbow trout[b]	96-hr LC_{50}	1.3
Sheepshead minnow[b]	96-hr LC_{50}	2.2
Bluegill sunfish[b]	96-hr LC_{50}	10
Mysid shrimp[b]	96-hr LC_{50}	5.7 μg/L
Eastern oyster[b]	48-hr LC_{50}	2.7
Shrimp larvae[c]	96-hr LC_{50}	30 μg/L
Common carp[d]	96-hr LC_{50}	7.85
Freshwater snail[e]	24-hr LC_{50}	20.05
Freshwater snail[e]	96-hr LC_{50}	14.19
Water flea (*Bosmina longirostris*)[f]	24-hr LC_{50}	8.6 μg/L
Water flea (*Bosmina fatalis*)[f]	24-hr LC_{50}	4.1 μg/L
Water flea predator (*Leptodora kindtii*)[f]	24-hr LC_{50}	3.6 μg/L

Sources: [a]Ferrari et al. (2004); [b]Tomlin (2003); [c]Reyes et al. (2002); [d]De Mel and Pathiratne (2005); [e]Tripathi and Singh (2001); [f]Sakamoto et al. (2005).

5.2 Animals

Acute oral LD_{50}s as well as the irritation and sensitization properties for carbaryl are presented in Table 6. The lower LD_{50}s in rats reported for intraperitoneal (IP) versus oral exposure suggest that either hepatic (or possibly gastrointestinal) metabolism and excretion mediate the response to carbaryl, or that absorption from the IP route is faster than by the oral route, resulting in temporally higher blood and tissue concentrations.

The most detailed accounts of rodent responses to low, orally gavaged doses of carbaryl come from a series of studies with Sprague–Dawley rats reported by a single laboratory in the 1990s. Definitive acute effects, including pinpoint pupils, ataxic gait, tremors, a reduction in motor activity counts, and body weight gain decrements were noted at doses as low as 10 mg/kg; doses up to 125 mg/kg produced salivation and/or wet muzzle, overall gait incapacity, and an mpaired visual placing response (Brooks et al. 1995; Robinson and Broxup 1997). In addition, there were increases in hindlimb splay (males; at high doses), arousal and number of rears, positional passivity, auricular startle responses, and males lying on their ventral surface. Finally, there were decreases in locomotor activity, extensor thrust, tail- and toe-pinch responses, urination and defecation in males, vocalization upon cage removal in females, forelimb and hindlimb grip strength, and body temperature. These effects largely abated by day 7 and 14. Beyrouty (1992) reported similar effects in orally gavaged Sprague–Dawley rats, although generally not at doses lower than 40 mg/kg.

Table 6 The acute toxicity and primary irritation properties of technical grade carbaryl

Animal	Test	US EPA toxicity category	Amount (mg/kg unless noted)
Rat (male)[1–5]	Oral LD_{50}	II	233–840
Rat (Female) [1–5]	Oral LD_{50}	II	246–610
Mouse[4]	Oral LD_{50}	II	108–650
Rabbit[1]	Oral LD_{50}	III	710
Guinea pig[1,4]	Oral LD_{50}	II	280
Dog[4]	Oral LD_{50}	II	250–795
Cat[4]	Oral LD_{50}	II	125–250
Swine[4]	Oral LD_{50}	III	1,500–2,000
Deer[4]	Oral LD_{50}	II	200–400
Monkey[4]	Oral LD_{50}	III	>1,000
Rat[4]	Dermal LD_{50}	III	>2,000 to >5,000
Rabbit[2,6]	Dermal LD_{50}	III	>2,000
Rat[7]	4-hr Inhalation LC_{50}	III	0.873 mg/L
Rat[8]	4-hr Inhalation LC_{50}	III	2.50 mg/L
Rat (female)[9]	Oral LD_{50}	II	437.5
Mouse (female)[9]	Oral LD_{50}	III	515
Guinea pig[10,11]	Dermal sensitization	Negative	–
Rabbit	Dermal irritation	IV	–
Rabbit	Eye irritation	IV	–
Rat (male adult)[12]	Intraperitoneal LD_{50}	–	64
Rat (male weanling at 23 d)[12]	Intraperitoneal LD_{50}	–	48

Sources: [1]Mellon Inst. (1957); [2]Union Carbide (1983a–d); [3]Union Carbide (1985); [4]Cranmer (1986); [5]Larson (1987b); [6]Larson (1987a); [17]Holbert (1989); [8]Dudek (1985); [9]Rybakova (1966); [10]Larson (1987c); [11]US EPA (2002); [12]Brodeur and DuBois (1963).

An attempt to determine the time of peak brain ChE inhibition after oral gavage (at 10 mg/kg) showed that enzyme activity was suppressed by 46% of control levels within 0.5 hr in males and by 54% in females (Brooks and Broxup 1995). The degree of inhibition declined steadily after 1 hr, although inhibition was still evident at the high dose of 125 mg/kg at 24 hr. Except for one 10 mg/kg male exhibiting muzzle/urogenital staining at 0.5 hr, behavioral and/or clinical signs, including tremors and autonomic changes, were seen only at 50 and 125 mg/kg. The time to peak effect was also determined to be in the 0.5–1 hr range, generally lessening after that time.

Desi et al. (1974) noted a biphasic response during 50 d dietary exposure of Wistar rats to carbaryl at 10 or 20 mg/kg/d. During the first 15 d, performance times in T-mazes actually improved (i.e., the learning times decreased), whereas after that point performance then worsened (i.e., learning times increased). The authors ascribed the initial improvements to "enhanced irritability" of the central nervous system (CNS). Their conviction that the CNS was the main site of action was strengthened by the observation that "the animals were able to move quickly even during the second period" (i.e., the period of decreased maze function). This observation was further supported by the evidence that electroencephalograms and brain cholinesterase activities were altered by carbaryl.

Conversely, Austin (2002) was unable to elicit behavioral or morphological signs in Sprague–Dawley rats during 4 wk of daily (6–7 hr/d) dermal treatment with up to 100 mg/kg/d carbaryl, although that dose resulted in a body weight gain decrement during the day 5 to day 12 period. Weekly postdose measurements of erythrocyte ChE activities revealed significant suppression on days 5 and 12 at 50 and 100 mg/kg/d; however, by 26 d no such effects were evident. Brain ChE activities measured on day 26 revealed up to 15% inhibition at 50 mg/kg/d and 24% inhibition at 100 mg/kg/d. However, it was not clear if these effects were acute or if they occurred after several daily doses.

Dogs dietarily exposed to doses as high as 35 mg/kg/d carbaryl for 1 yr did not exhibit clinical signs (Hamada 1987). Nonetheless, ChE activities were suppressed at all time points, often by significant margins. For brain ChE, which was measured only at the 52-wk study termination point, the level of inhibition reached 36% at the high dose, although a significant 20% level of inhibition was noted in females even at the low dose of 3.7 mg/kg/d. Erythrocyte ChE inhibition up to 56% was noted at the high dose (week 5), with nonstatistically significant inhibition of up to 14% (week 13) noted at the low dose. Plasma cholinesterase inhibition reached 66% (week 5) at the high dose, with significant inhibition of up to 23% (week 13) noted at the low dose.

Carbaryl administered to mice through the diet over a 2-yr period induced significantly elevated hemangiosarcomas and hemangiomas in males at the mid and high doses of 145 and 1,249 mg/kg/d (Hamada 1993a). Females experienced a significant increase in tumors at the high dose only; a nonstatistically significant increase was noted in males at the low dose of 14 mg/kg/d. In addition, significant elevations of hepatocellular carcinomas and adenomas were detected in high-dose females, as were kidney tubular adenomas and carcinomas in high-dose males. Other observations included unscheduled deaths (females at the high dose), clinical signs (at both mid and high doses), ChE suppression (at both mid and high doses, with a suggestion of a low-dose effect), and body weight effects (at the high dose). Nononcogenic histopathology was noted in the bladder (intracytoplasmic droplets/pigment; at mid and high doses), eye (cataracts; at the high dose), and spleen (abnormal pigmentation; at the high dose). Although there is some question about the biological significance of the effects at the high dose, which may have exceeded the maximum tolerated dose, the presence of hemangiosarcomas and hemangiomas at the mid and low doses demonstrated the carbaryl carcinogenic potential.

Dietary exposure of rats at doses up to 485 mg/kg/d for 2 yr led to hyperplastic and neoplastic lesions in the urinary bladder of both sexes, particularly at the high dose (Hamada 1993b). These effects included hyperplasia, transitional cell papillomas, transitional cell carcinomas, squamous metaplasia, high mitotic index, and atypia.

Carbaryl tested positive in one of five gene mutation studies (Lawlor 1989; Grover et al. 1989; Young 1989; Ahmed et al. 1977a; Onfelt and Klasterska 1984), four of six chromosomal aberration studies (Weil 1972; Murli 1989; Ishidate and Odashima 1977; Marshall 1996; Grover et al. 1989; Soderpalm-Berndes and Onfelt 1988), and two of four DNA damage studies (Ahmed et al. 1977b; Cifone 1989;

Onfelt and Klasterska 1984; Sagelsdorff 1994). The insecticide should thus be viewed as potentially genotoxic. Because virtually all the positive studies were performed *in vitro*, they were considered less relevant than the *in vivo* studies on whole organisms. One study in V79 Chinese hamster fibroblasts showed that, as is carbaryl, 1-naphthol was toxic and induced c-mitosis, an aberrant form of mitosis that may reflect effects on mitotic spindle formation (Soderpalm-Berndes and Onfelt 1988).

Nitrosocarbaryl, the potentially carcinogenic derivative, was formed more readily from carbaryl in the very acidic guinea pig stomach versus the less acidic rat stomach (Rickard and Dorough 1984). In addition, Eisenbrand et al. (1975) demonstrated that nitrosocarbaryl could be produced from carbaryl and nitrite under acidic *in vitro* conditions. Nitrosocarbaryl has been reported to cause single-strand breaks in cultured human fibroblasts (Regan et al. 1976).

Two reproductive toxicity studies by Pant et al. (1995, 1996) used Wistar rats exposed to carbaryl by daily gavage at 50 mg/kg/d for 90 d (5 d/wk). Impacts noted on testicular enzymes, sperm counts, sperm motility, sperm morphology, and testicular morphology supported the conclusions of two earlier studies by Rybakova (1966) and Shtenberg and Rybakova (1968), as well as the suggestive epidemiological results summarized in the following section. Narotsky and Kavlock 1995) observed fetal resorption in 2 of 13 pregnant rats and a 6% weight decrement in pups exposed *in utero* to carbaryl by gavage at 104 mg/kg/d, a dose that also caused overt toxicity in the dams. A study in gerbils demonstrated impairments in several reproductive indices at and above a dietary dose of about 160 mg/kg/d (Collins et al. 1971). However, Tyl et al. (2001) did not observe effects on reproductive indices in rats subjected to dietary carbaryl, although there was some suggestion that pup survival through 14 d was reduced at the mid and high doses of 21–36 mg/kg/d and 92–136 mg/kg/d, respectively. No attempt to ascertain sperm morphology was undertaken in the Tyl el al. (2001) study.

Aside from developmental delays, possibly mediated by suppressed maternal weight gains, the studies of Repetto-Larsay (1998) and Tyl et al. (1999) provided minimal evidence for carbaryl-induced developmental toxicity in rats and rabbits, although omphalocele was present at gavage doses 150 and 200 mg/kg/d in an older rabbit study (Murray et al. 1979). However, Smalley et al. (1968) demonstrated severe maternal and fetal effects in beagle dogs following dietary exposure to carbaryl during gestation, including (1) increased dystocia at all dose levels (3.125–50 mg/kg/d); (2) three mothers sustaining total fetal deaths (one each at 6.25, 25, and 50 mg/kg/d); (3) decreased pup weight gains in the combined treatment groups; (4) decreased conception rate at the high dose; (5) no pups born alive at the high dose; (6) decreased percentage of pups weaned (effect possibly present at levels as low as 6.25 mg/kg/d), and (7) increased litters with pups bearing abnormalities (6.25 mg/kg/d and above). Observed abnormalities included abdominal-thoracic fissures with varying degrees of intestinal agenesis and displacement, varying degrees of brachygnathia, ecaudate pups (i.e., without a tail), failure of skeletal formation, failure of liver development, and superfluous phalanges.

5.3 Humans

Baron (1991) reviewed several studies involving systemic carbaryl exposures in humans. No effects were observed in one acute oral study with males at doses as high as 2 mg/kg. In another study, a scientist investigating possible antihelmintic properties of carbaryl ingested approximately 2.8 mg/kg. Epigastric pain followed by profuse sweating began after 20 min, followed by lassitude and vomiting. Recovery was evident after 1 hr (although 3 mg antidotal atropine had been ingested by then) and completed by 2 hr. Similarly, a researcher who intentionally ingested carbaryl at 5.45 mg/kg on an empty stomach experienced vision changes, nausea, and lightheadedness within 80–90 min post dose. Despite two doses of atropine, profuse sweating, hyperperistalsis, and weakness were present by 97 min, with maximal symptomology at 2 hr; complete reversal of symptoms occurred by 4 hr.

Dickoff et al. (1987) reported responses in a patient found comatose 3 hr after ingestion of approximately 500 mg/kg carbaryl. The following overt symptoms were noted within 1–2 d: salivation, miosis, eyelid twitching/fasciculation/abnormal movements, flaccid tone, pulmonary edema, diarrhea, incontinence, low systolic blood pressure and body temperature, elevated heart rate, intubation for control of breathing and bronchial secretion, lack of responsiveness to voice or pain, lack of spontaneous limb movement, ankle clonus (but no plantar response), diarrhea, abdominal cramping, and dark brown heme-negative urine. Within 3–6 d, the following were apparent: prickling foot/leg/hand pain and other diffuse pain, leg paralysis, absent tendon reflexes, occasional rapid involuntary flexion of knees and hips, hand weakness, inability to sit alone, sensory loss in extremities, pseudoathetotic arm movements, proximal right leg movements, no voluntary motor units or only single unit recruitment patterns in distal leg muscles, no abductor digiti quinti response decrement after repetitive ulnar nerve stimulation, and symmetrically diffuse electroretinogram. After 3 wk, responses included impaired finger strength, inability to stand, plantar responses were flexor, persistent tenderness to distal palpation, marked impairment to pin and vibration below the knees, and absent position sense in toes and impaired in ankles (normal in fingers); after 5 wk responses consisted of bilateral foot drop, no volitional motor units below knees, pin sensation absent in lower legs, toe position/vibration absent, diminished compound muscle action potential amplitudes in tested nerves, slight slowing of leg conduction velocities, low amplitude evoked sensory nerve responses, increased insertional activity in electromyogram, muscle fibrillations and positive waves, and periods of diffuse/symmetric slowing with electroencephalograms. By 9 mon the patient experienced a return to normal strength except for bilateral ankle/toe weakness; jerk responses were elicited in triceps only. There was a persistent loss of toe vibration/proprioception, pin and touch responses were reduced to midcalf, and electroencephalograms exhibited normal characteristics. The authors suspected that carbaryl induced a delayed polyneuropathy similar to the delayed syndrome known to occur with organophosphate exposures.

Branch and Jacqz (1986) described the extensive toxic sequelae in a 75-yr-old man exposed accidentally, but over a prolonged period, to a 10% carbaryl dust formulation that occurred during and after six monthly treatments of his house to

combat fleas; of particular concern was the evidence for permanent neurological damage. Tomography undertaken several years later revealed progressive dilation of the cerebral ventricles "associated with a reduction in cerebral function and intellectual capacity." Interestingly, the patient's wife and son experienced some initial symptoms, although they resolved without the appearance of longer-term disabilities. Continuing treatment of the patient with cimetidine to ameliorate gastric symptoms was a possible confounding factor.

Wyrobek et al. (1981) conducted an epidemiological investigation of testicular function among carbaryl-exposed factory workers. This study failed to establish a clear connection between exposure and seminal defects, although the data suggested an increase in oligospermia (defined as a sperm count $<20 \times 10^6$/mL) and teratospermia (defined as exhibiting >60% abnormal sperm forms). A more recent study of factory workers from China demonstrated significantly higher levels of sperm chromosomal aberrations and DNA damage in an occupationally exposed population (Xia et al. 2005). Meeker et al. (2004a,b) noted an association between 1-naphthol levels in the urine and a series of sperm toxicity parameters, including decreased sperm concentrations, decreased sperm motility, and increased DNA single-strand breaks resulting in high tail % (a measure of the proportion of DNA in the electrophoretic tail) in comet assays. However, it was not known if the 1-naphthol originated as a metabolite of carbaryl or naphthalene or had another source. The possible reproductive effects of carbaryl were considered in an epidemiological study of pregnancy outcomes following exposure to males from farm families in Ontario, Canada (Savitz et al. 1997). In conjunction with carbaryl exposure the adjusted odds ratio for miscarriage increased, suggesting that exposure of reproductive-aged males could result in clinically manifested reproductive impacts.

Several potential carbaryl exposure scenarios were considered in the U.S. Environmental Protection Agency's recent interim health hazard assessment (US EPA 2004). In addition, the USDA Pesticide Data Program documented the presence of both carbaryl and 1-naphthol in many raw agricultural commodities destined for sale within the United States (http://www.ams.usda.gov/pdp), and these are highlighted in the US EPA recent dietary risk assessment on carbaryl (US EPA 2003), as well as in the California Department of Pesticide Regulation (CDPR) upcoming dietary risk assessment, which assesses dietary exposure and the possibility of toxic responses to California residents. From 1992 to 2005, the California Pesticide Illness Surveillance Program documented 32 illness incidents with a reasonable possibility of association with carbaryl exposure alone, as well as 57 others with a reasonable possibility of association with carbaryl in combination with other pesticides (http://www.cdpr.ca.gov/docs/whs/pisp.htm).

6 Mammalian Toxicokinetics and Metabolism

Struble (1994) studied the disposition of radiolabeled carbaryl in Sprague–Dawley rats following administration by oral gavage and reported that it was excreted primarily via urine during the first 24 hr, although substantial residues appeared in

feces and exhaled air as CO_2 (detectable when the label resided on the carbonyl or *N*-methyl carbon, but not when on the naphthalene ring). Metabolites were conjugated with sulfate or glucuronic acid. For animals receiving 1 mg/kg, about half the dose was detected in the urine during the first 6 hr, 80% –90% by 24 hr, and only slightly more by 168 hr. For animals receiving 50 mg/kg, urinary excretion was somewhat slower: 12% –20% by 6 hr, 64% –69% by 24 hr, and 78% –81% by 168 hr. Fecal excretion was also significant: by 168 hr, some 6% –13% of the dose appeared in the feces.

Krolski et al. (2003) examined the kinetics of [naphthyl-1-^{14}C]-carbaryl in blood and other tissues after oral (1.08 or 8.45 mg/kg), dermal (17.25 or 102.95 mg/kg) and intravenous (i.v.; 0.80 or 9.20 mg/kg) exposure. Peak levels of radioactivity were detected in blood at 15 and 30 min for both the low and high dose oral treatments, respectively; at 4 and 12 hr for dermal application; and were already maximal by the first time point (5 min) after i.v. injection. By 24 hr after oral dosing, radioactivity levels had decreased to 0.81% –2.4% of their peaks in blood fractions (both doses), 0.60% –2.4% in brain (both doses), 0.67% in liver (high dose only), and 0.32% in fat (high dose only). With dermal dosing, radioactivity levels had decreased to 15.9% –25.8% of their peaks in blood fractions (both doses), 27.1% –30.6% in brain (both doses), 24.4% in liver (high dose only), and 15.6% in fat (high dose only) by 24 hr. Finally, with an i.v. dose, by 24 hr radioactivity levels had decreased to 4.6% –10.5% in blood fractions (both doses), 1.1% –1.3% in brain (both doses), 5.7% in liver (high dose only), and 0.72% in fat (high dose only).

The pharmacokinetic disposition of carbaryl in mice (Totis 1997; Valles 1999), guinea pigs (Knaak et al. 1965), and sheep (Knaak et al. 1968) appeared generally similar to those in the rat, although there were significant technical problems with the guinea pig and sheep studies, as they employed few animals and left large fractions of the administered dose unanalyzed. A possible exception to the rat model was the dog, where approximately equal fractions of an oral carbaryl dose were excreted after 24 hr in urine and feces (Knaak and Sullivan 1967). However, these data, reported by the same investigators, suffered from similar problems. Speculation about the tendency toward tumor formation at high doses in a more recent mouse study (see above) centered on a shift in the urinary metabolite pattern at the comparatively high dose of 8,000 ppm (~1600 mg/kg/d), where there were increases in metabolites derived from epoxide intermediates (Valles 1999).

Three major metabolic pathways, presumably hepatic, were identified in the rat (Struble 1994): (1) arene oxide-mediated hydroxylation and subsequent conjugation; (2) hydrolytic decarbamylation, to form 1-naphthol, and subsequent conjugation; and (3) oxidation of the *N*-methyl group. Three urinary metabolites found in rat urine [1-naphthyl glucuronide, 1-naphthyl sulfate, and 4-(methyl-carbamyloxy)-1-naphthyl glucuronide] were not found in dog urine (Knaak and Sullivan 1967). In addition, few hydrolytic products were found in the urine of a singly dosed monkey (Knaak et al. 1968). The toxicological significance of these species differences is not clear. Humans appear to have the ability to decarbamylate carbaryl, as factory workers were found to excrete 1-naphthyl glucuronide and 1-naphthyl sulfate. This finding led to speculation that humans are similar to rats in their pharmacokinetic handling of the insecticide

(Knaak et al. 1965). However, a later study showed that intentionally dosed humans excreted only 25% –30% of carbaryl in urine after 24 hr, indicating that the fate of very significant fractions of the dose was unknown (Knaak et al. 1968).

Several studies estimating the degree to which carbaryl is absorbed through the skin has been previously reviewed by DPR (2006). Feldman and Maibach (1974) reported that 73.9% was absorbed by humans within 120 hr following an initial 24-hr dermal application of ^{14}C-carbaryl at 4 μg/cm^2 (vehicle: acetone). Because other routes of disposition and excretion were not monitored, a 13.5-fold correction factor was imposed on the urinary value, based on the observation that only 7.4% of an i.v. dose appeared in the urine in 24 hr. However, the position of the ^{14}C label was not reported. If, for example, the carbonyl or *N*-methyl carbon (as opposed to the naphthalene ring) was labeled, much of it would have been excreted as CO_2, resulting in an underestimate of urinary excretion and consequent overestimate of absorption. Shah and Guthrie (1983) determined carbaryl absorption at the same dermal dose of 4 μg/cm^2 (vehicle: acetone) applied to rat skin for up to 120 hr. Radiolabel in all tissues and excreta was measured, obviating the need for correction factors. Thus, they reported 72.1%, 75.1%, and 95.7% absorption at 12, 24, and 120 hr, respectively. Cheng (1995) also exposed rats to the insecticide by the dermal route for up to 24 hr, but at 35.6, 403, and 3,450 μg/cm^2. However, instead of acetone, aqueous carboxymethylcellulose was used as the vehicle. The author reported that absorption was inversely related to dose, with 24-hr values of 34%, 25%, and 4% with ascending dose. Ultimately, it appears that dose has a greater influence than vehicle choice in determining dermal carbaryl absorption (DPR 2006).

7 Summary

Carbaryl is an agricultural and garden insecticide that controls a broad spectrum of insects. Although moderately water soluble, it neither vaporizes nor volatilizes readily. However, upon spray application the insecticide is susceptible to drift. It is unstable under alkaline conditions, thus easily hydrolyzed. Carbaryl has been detected in water at ppb concentrations but degradation is relatively rapid, with 1-naphthol identified as the major degradation product. Indirect and direct photolysis of carbaryl produces different naphthoquinones as well as some hydroxyl substituted naphthoquinones.

Sorption of the insecticide to soil is kinetically rapid. However, although both the mineral and organic fractions contribute, because of its moderate water solubility it is only minimally sorbed. Also, sorption to soil minerals strongly depends on the presence of specific exchangeable cations and increases with organic matter aromaticity and age. Soil microbes (bacteria and fungi) are capable of degrading carbaryl; the process is more rapid in anoxic than aerobic systems and with increased temperature and moisture.

Carbaryl presents a significant problem to pregnant dogs and their offspring, but some have questioned the applicability of these data to humans. In addition, for

toxicokinetic and/or physiological reasons, it has been argued that dogs are more sensitive than humans to carbaryl-induced reproductive or developmental toxicity. However, these arguments are based on either older pharmacokinetic studies or on speculation about possible reproductive differences between dogs on the one hand and rats and humans on the other. In view of the wider evidence from both human epidemiological and laboratory animal studies, the question of the possible developmental and reproductive toxicity of carbaryl should be considered open and requiring further study.

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