IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Environmental Health Criteria 153

Carbaryl

UNEP

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Environmental Health Criteria 153

CARBARYL

First draft prepared by Professor F. Kaloyanova (National Center of Hygiene and Medical Ecology, Sofia, Bulgaria) and Dr P.P. Simeonova (University of Sofia, Bulgaria)

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The **International Programme on Chemical Safety (IPCS)** is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the develop-ment of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria monographs, readers are kindly requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

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A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (Telephone No. 9799111).

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NOTE: The proprietary information contained in this document cannot replace documentation for registration purposes, because the latter has to be closely linked to the source, the manufacturing route, and the purity/impurities of the substance to be registered. The data should be used in accordance with paragraphs 82-84 and recommendations paragraph 90 of the Second FAO Government Consultation (1982).

ENVIRONMENTAL HEALTH CRITERIA FOR CARBARYL

A WHO Task Group on Environmental Health Criteria for Carbaryl met at the World Health Organization, Geneva, from 21 to 25 September 1992. Dr K.W. Jager, of the IPCS, welcomed the participants on behalf of the Director IPCS and the three IPCS cooperating organizations (UNEP/ILO/WHO). The Group reviewed and revised the draft criteria monograph and made an evaluation of the risks for human health and the environment from exposure to carbaryl.

The first draft was prepared by Professor F. Kaloyanova of the National Center of Hygiene and Medical Ecology and Dr P.P. Simeonova, Medical Faculty, University of Sofia, Bulgaria, who also prepared the second draft, incorporating comments received following circulation of the first drafts to the IPCS contact points for Environmental Health Criteria monographs.

Dr K.W. Jager of the IPCS Central Unit was responsible for the scientific content of the document, and Mrs M.O. Head of Oxford, England, for the editing.

The fact that Rhône-Poulenc Agro, Lyon, France, made available to the IPCS and the Task Group its proprietary toxicological information on the product under discussion is gratefully acknowledged. This allowed the Task Group to make its evaluation on a more complete data base.

The efforts of all who helped in the preparation and finalization of this publication are gratefully acknowledged.

1. SUMMARY AND EVALUATION, CONCLUSIONS AND RECOMMENDATIONS

1.1 Summary and evaluation

1.1.1 Identity, properties, and analytical methods

Carbaryl is the common name for the carbamic acid derivative 1-naphthyl *N*-methylcarbamate. The technical grade product is a white crystalline solid, with a low volatility; it is poorly soluble in water, which is stable to light and heat, but easily hydrolysed in alkaline media. The FAO has established a minimum specification of 98% purity, with an impurity limit of 0.05% for β-naphthyl *N*-methylcarbamate.

Carbaryl and its metabolites are analysed using numerous analytical procedures, such as thin-layer chromatography, spectrophotometry, gas chromatography, high pressure liquid chromatography, and chemical ionization mass spectrometry. Detection limits of below one nanogram are achievable and recovery is usually more than 80%.

1.1.2 Production and uses

Carbaryl has been used for about 30 years as a contact and ingestion insecticide with some systemic properties and controls a wide range of pests. The principal production plant is in the USA. Carbaryl is processed by more than 290 formulators into over 1500 different products.

1.1.3 Environmental transport, distribution, and transformation

Under most conditions, carbaryl is not persistent in the environment. In water, the hydrolysis half-life is dependent on the temperature, pH, and the initial concentration, and varies from several minutes to several weeks. The major degradation product is 1-naphthol.

Accumulation of carbaryl, expressed as a bioconcentration factor in the aquatic environment, has been studied in freshwater fish and found to be in the range of 14-75. Carbaryl is adsorbed more readily on soils with a high organic content than on sandy soils. At the usual application rates, under "good agricultural practice", dissipation is rapid, with a half-life of 8 days to 1 month under

normal conditions. Carbaryl may occasionally be carried by rainfall and soil cultivation from the surface into the subsoil (one metre from the surface).

Carbaryl contaminates vegetation, either during spraying, or by migrating through contaminated soil into plants.

The degradation of carbaryl in the environment is determined by the extent of the volatilization, photodecomposition, and chemical and microbial degradation occurring in soil, water, and plants. The rate of decomposition is more rapid under hot climatic conditions.

1.1.4 Environmental levels and human exposure

Food represents the major source of carbaryl intake for the general population.

Residues in total dietary samples are relatively low, ranging from trace amounts to 0.05 mg/kg. In the USA, the daily intake during the first years of carbaryl application was 0.15 mg/day per person (in 7.4% of the composites); this decreased to 0.003 mg/day per person in 1969 (in only 0.8% of the composites). During the period of application, carbaryl may be found, occasionally, in surface water and reservoirs.

The general population can be exposed to carbaryl during pest control operations in both the home and recreation areas.

Workers can be exposed to carbaryl during its manufacture, formulation, packing, transportation, storage, and during and after application. Concentrations in the working-air environment during production varied from < 1 mg/m^3 to 30 mg/m^3. Significant dermal exposure may occur in industrial and agricultural workers if protective measures are inadequate.

1.1.5 Kinetics and metabolism

Carbaryl is rapidly absorbed in the lungs and digestive tract. In human volunteers, dermal absorption of 45% of an applied dose in acetone occurred in 8 h. However, *in vitro* dermal penetration data and toxicity data indicate that dermal absorption usually occurs at a much lower rate.

The principal metabolic pathways of carbaryl are ring hydroxylation and hydrolysis. As a result, numerous metabolites are formed and subjected to conjugation with the formation of water-soluble sulfates, glucuronides, and mercapturates, excreted in the urine. Hydrolysis results in the formation of 1-naphthol, carbon dioxide, and methylamine. Hydroxylation produces 4-hydroxycarbaryl, 5-hydroxycarbaryl, *N*-hydroxymethylcarbaryl, 5-6-dihydro-5-6-dihydroxycarbaryl, and 1,4-naphthalendiol. The principal metabolite in humans is 1-naphthol.

Under normal exposure conditions, the accumulation of carbaryl in animals is unlikely. Carbaryl is excreted primarily via the urine, since the product of its hydrolysis, 1-naphthol, is mainly detoxified to water-soluble conjugates. Enterohepatic cycling of carbaryl metabolites is also considerable, especially after oral administration.

The hydrolysis product, *N*-naphthol carbamic acid, is spontaneously decomposed to methylamine and carbon dioxide. The methylamine moiety is later demethylated to carbon dioxide and formate, the latter being excreted mainly in the urine.

Carbaryl metabolites are also present in a small percentage of the absorbed doses in saliva and milk.

1.1.6 Effects on organisms in the environment

LC_{50} values for crustacea vary from 5 to 9 μg/litre (water fleas, mysid shrimps), 8 to 25 μg/litre (scud), and 500 to 2500 μg/litre (crayfish). Aquatic insects have a similar range of sensitivity. Plecoptera and Ephemeroptera (stoneflies and mayflies) are the most sensitive groups. Molluscs are less susceptible with EC_{50}s in the range of a few mg/litre. For fish, most LC_{50} values are between 1 and 30 mg/litre. Salmonids are the most sensitive group.

The acute toxicity for birds is low. The LD_{50} for waterfowl and game birds is > 1000 mg/kg. The most susceptible bird tested is the red-winged blackbird (LD_{50}= 56 mg/kg). There was no evidence of field effects on birds in forest areas sprayed with 1.1 kg carbaryl/ha.

Carbaryl is very toxic for honey-bees and earthworms. The oral LD_{50} for the former is 0.18 μg/bee (about 1-2 mg/kg).

There are indications that carbaryl may temporarily influence the species composition of both terrestrial and aquatic ecosystems. For

instance, one study showed that effects on certain terrestrial invertebrate communities may persist for at least 10 months following a single application.

1.1.7 Effects on experimental animals and in vitro test systems

The acute toxicity, expressed as the LD_{50}, varies considerably according to species, formulation, and vehicle. Estimates of the oral LD_{50} for the rat range from 200 to 850 mg/kg. Cats are more sensitive with an LD_{50} of 150 mg/kg. Pigs and monkeys are less sensitive with an LD_{50} of > 1000 mg/kg.

The maximum achievable aerosol concentration of carbaryl of 792 mg a.i./m^3 during a 4-h exposure resulted in the mortality of one out of five female rats. Carbaryl aerosols, at concentrations of 20 mg/m^3, decreased cholinesterase activity (ChEA) in cats during single 4-h exposures, but this concentration did not have any observable effects in rats.

Carbaryl is a mild eye irritant and has little or no sensitizing potential. During long-term studies, the NOEL was 10 mg/kg body weight (200 mg/kg diet) for rats, and 1.8 mg/kg body weight (100 mg/kg diet) for dogs. The long-term inhalation NOEL for cats is 0.16 mg/m^3. Carbaryl has a low cumulative potential.

1.1.7.1 Reproduction

Carbaryl has been shown to affect mammalian reproduction and perinatal development adversely in a number of species. Effects on reproduction include impairment of fertility, decreased litter size, and reduced postnatal viability. Developmental toxicity is seen as increased *in utero* death, reduced fetal weight, and the occurrence of malformation. With the exception of a small number of studies, all adverse reproductive and developmental effects were noted only at doses that caused overt maternal toxicity, and, in a number of cases, the maternal animal was more sensitive to carbaryl than the conceptus. The maternal toxic effects included lethality, decreased growth, and dystocia. Data indicate that the reproductive and developmental processes of mammals are not especially sensitive to carbaryl compared with the susceptibility of the adult organism.

1.1.7.2 Mutagenicity

Carbaryl has been evaluated for its potential mutagenicity in a number of *in vitro* and *in vivo* tests, in bacterial, yeast, plant, insect, and mammalian systems, testing a variety of end-points.

The available evidence indicates that carbaryl does not have any DNA-damaging properties. There have been no reports of confirmed induction of mitotic recombination, gene conversion, and UDS in prokaryotes (*H. influenzae, B. subtilis*) and eukaryotes (*S. cerevisiae, A. nidulans*, cultured human lymphocytes, and rat hepatocytes) *in vitro*.

Negative results were obtained in tests for gene mutations in a large number of bacterial assays, with the exception of two cases. In several studies of gene mutations in mammalian cells *in vitro*, carbaryl produced only one equivocal positive result in a cell culture study. However, the study had several shortcomings and the result has not been confirmed in any other comparable studies.

Chromosomal damage with high dosages of carbaryl has been reported *in vitro* in human, rat, and hamster cells, and in plants. No such effects have been observed in mammalian tests *in vivo*, even at doses as high as 1000 mg/kg.

Carbaryl has been shown to induce disturbances in the spindle fibre mechanism in plant and mammalian cells *in vitro*. The relevance of plant assays for extrapolation to humans is unclear.

It can be concluded that the available data-base does not support the presumption that carbaryl poses a risk of inducing genetic changes in either the somatic or the germinal tissue of humans.

The nitrosated product of carbaryl, *N*-nitrosocarbaryl, is capable of inducing mitotic recombination and gene conversion in prokaryotes (*H. influenzae, B. subtilis*) and eukaryotes (*S. cerevisiae*) *in vitro*, and gives positive results in *E. coli* spot tests.

Furthermore, experimental results indicate that *N*-nitrosocarbaryl binds to DNA, causing alkali-sensitive bonds and single-strand breakage.

Nitrosocarbaryl has not been established as a clastogen *in vivo* (bone marrow and germ cells), even at high toxic doses.

1.1.7.3 Carcinogenicity

Carbaryl has been studied for its carcinogenic potential in numerous studies on rats and mice. The results of most of these studies were negative, but the studies were old and did not meet contemporary standards. However, new studies on mice and rats, which meet modern standards, are in progress.[a]

The latest IARC evaluation (IARC, 1987) concluded that there were no data on cancer in humans and that the evidence of carcinogenicity in experimental animals was inadequate. Carbaryl could not be classified as to its carcinogenicity for humans (Group 3).

N-nitrosocarbaryl has been shown to induce tumours locally in rats (either sarcoma at the site of injection or forestomach squamous cell carcinoma, when given by the oral route). Given the human chemistry of carbaryl, the risk of *N*-nitrosocarbaryl carcinogenicity in humans from carbaryl exposure can be judged as negligible.

1.1.7.4 Effects on different organs and systems

(a) Nervous system

The effects of carbaryl on the nervous system are primarily related to cholinesterase inhibition and are usually transitory. The effects on the central nervous system were studied in rats and monkeys. Oral doses of 10-20 mg carbaryl/kg for 50 days were reported to disrupt learning and performance in rats.

In a small study on pigs, carbaryl (150 mg/kg body weight in the diet for 72-82 days) was reported to produce a number of neuromuscular effects. Reversible leg weakness was noticed in chickens given high doses of carbaryl. No evidence of demyelination was observed in the brain, sciatic nerve, or in spinal cord sections examined microscopically. Similar effects were not observed in long-term rodent studies.

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[a]These studies have not yet been reviewed by the IPCS. The company performing these studies has indicated that there is a significant increase in tumours at the highest dose in both species.

(*b*) *Immune system*

Carbaryl, when administered *in vivo*, at doses causing overt clinical signs, has been reported to produce a variety of effects on the immune system. Many of the effects described were detected at doses close to the LD_{50}. Most studies on rabbits and mice at doses permitting survival have not produced significant effects on the immune system. Shortcomings of several of these studies were a lack of consistency and, sometimes, overt contradiction between results, which prevents the description of a defined immunotoxic mechanism.

(*c*) *Blood*

Carbaryl has been reported to affect coagulation, but there are conflicts about the direction of the effect. In glucose-6-phosphate dehydrogenase-deficient sheep erythrocytes, carbaryl produced a dose-dependent increase in methaemoglobin (Met-Hb) formation. Human serum albumin reacted *in vitro* with the ester group of carbaryl. Carbaryl binds free blood amino acids.

(*d*) *Liver*

Disturbances have been reported in the carbohydrate metabolism and protein synthesis and detoxification function of the liver in mammals. Carbaryl is a weak inducer of hepatic microsomal drug-metabolizing activity. Phenobarbital sleeping time is shortened. The hepatic levels of cytochrome P-450 and b_5 are increased. Changes in liver metabolism may account in part for the three-fold increase of the carbaryl LD_{50} in carbaryl-pretreated rats.

(*e*) *Gonadotropic function*

Carbaryl has been reported to increase the gonadotropic function of the hypophysis of rats.

1.1.7.5 Primary mechanism of toxicity

Carbaryl is an inhibitor of cholinesterase activity. This effect is dose-related and quickly reversible. There was no aging of the carbamylated cholinesterase. All identified metabolites of carbaryl

are appreciably less active cholinesterase inhibitors than carbaryl itself.

1.1.8 Effects on humans

Carbaryl is easily absorbed through inhalation and via the oral route and less readily by the dermal route. Since the inhibition of cholinesterase (ChE) is the principal mechanism of carbaryl action, the clinical picture of intoxication is dominated by ChE inhibition symptoms, such as: increased bronchial secretion, excessive sweating, salivation, and lacrimation; pinpoint pupils, bronchoconstriction, abdominal cramps (vomiting and diarrhoea); bradycardia; fasciculation of fine muscles (in severe cases, diaphragm and respiratory muscles also involved); tachycardia; headache, dizziness, anxiety, mental confusion, convulsions, and coma; and depression of the respiratory centre. Signs of intoxication develop quickly after absorption and disappear rapidly after exposure ends.

In controlled studies on human volunteers, single doses of less than 2 mg/kg were well tolerated. A single dose of 250 mg (2.8 mg/kg) produced moderate ChE inhibition symptoms (epigastric pain and sweating) within 20 min. Complete recovery occurred within 2 h of treatment with atropine sulfate.

In cases of occupational overexposure to carbaryl, mild symptoms are observed long before a dangerous dose is absorbed, which is why severe cases of occupational intoxication with carbaryl are rare. During agricultural application, dermal exposure may play an important role. No local irritative effect is usually observed, however, the appearance of a skin rash after accidental splashing with carbaryl formulations has been described.

There are conflicting data about the effects of carbaryl on sperm count and changes in sperm morphology in plant workers. No adverse effects on reproduction have been reported.

The most sensitive biological indicator of carbaryl exposure is the appearance of 1-naphthol in the urine and a decrease in ChE activity in the blood. Levels of 1- naphthol in the urine can be used as a biological indicator, if there is no 1-naphthol in the working environment. During occupational exposure, 40% of the urine samples contained more than 10 mg total 1-naphthol/litre. In one case of acute intoxication, 31 mg/litre was found in the urine. The

hazard level is >10 mg/litre and the symptomatic level 30 mg 1-naphthol/litre urine (*Data sheet on carbaryl*, WHO, 1973, VBC/DS/75.3).

Measurement of the ChE activity can be a very sensitive test for monitoring, provided that measurement is carried out soon after exposure.

1.2 Conclusions

The hazards of carbaryl for human beings are judged to be low, because of its low vapour pressure, rapid degradation, rapid spontaneous recovery of inhibited cholinesterase, and the fact that symptoms usually appear well before a dangerous dose has accumulated in the body. Good carcinogenicity studies, which meet modern standards, are not yet available.

1.2.1 General population exposure

Residue levels of carbaryl in food and drinking-water, which remain after its normal use in agriculture, are far below the acceptable daily intake (ADI) (0.01 mg/kg body weight per day) and are not likely to produce health hazards in the general population.

1.2.2 Subpopulations at high risk

Use of carbaryl for public health purposes in the home or in recreation areas may create overexposure, if the rules for its application are neglected.

1.2.3 Occupational exposure

By enforcing reasonable work practices, including safety precautions, personnel protection, and proper supervision, occupational exposure during the manufacture, formulation, and application of carbaryl will not create hazards. Undiluted concentrations must be handled with great care, because improper work practices may cause skin contamination. Air concentrations in the workplace should not exceed 5 mg/m^3.

1.2.4 Environmental effects

Carbaryl is toxic for honey-bees and earthworms. It should not be applied to crops during flowering.

With normal use, carbaryl should not cause environmental concern. Carbaryl is adsorbed on soil to a great extent and does not readily leach into ground water. It is rapidly degraded in the environment and therefore is not persistent. Use of carbaryl should not result in harmful short-term effects on the ecosystem.

1.3 Recommendations

- The handling and application of carbaryl should be accomplished with the care given to all pesticides. Instructions for proper usage, provided on the package containing the chemical, should be carefully followed.

- The manufacture, formulation, use, and disposal of carbaryl should be carefully managed to minimize contamination of the environment.

- Regularly exposed worker populations should receive periodic health evaluations.

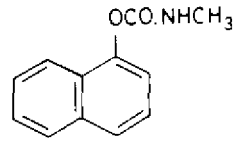
- The application of carbaryl should be timed to avoid effects on non-target species.

- Carcinogenicity studies that meet modern standards should be conducted.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Structural formula



Molecular formula:	$C_{12}H_{11}NO_2$
Common name:	Carbaryl (BSI)
CAS chemical name:	1-naphthalenylmethylcarbamate (9CI)
CAS registry number:	63-25-2
RTECS registry number:	FC5950000

Common synonyms:

alpha-naftyl-*N*-methylkarbamat, alpha-naphthalenyl methylcarbamate, alpha-naphthyl methylcarbamate, alpha-naphthyl *N*-methylcarbamate, carbamic acid, methyl-, 1-naphthyl ester, *N*-methyl-alpha-naphthyl-urethan, *N*-methyl-1-naftyl-carbamaat, *N*-methyl-1-naphthyl-naphthyl carbamate, *N*-methyl-1-naphthyl-carbamat, *N*-methylcarbamate de 1-naphtyle, *N*-metil-1-naftil-carbammato, 1-naphthol *N*-methyl-carbamate, 1-naphthyl methylcarbamate, 1 naphthyl-*N*-methyl-karbamat

The most commonly used chemical name is 1-naphthyl-*N*-methyl-carbamate.

Common trade names:

Arilat, Arilate, Arylam, Atoxan, Bercema, Caprolin, Carbacine, Carbatox, Carbavur, Carbomate, Carpolin, Denapon, Dicarbam, Dyna-carbyl, Karbaryl, Karbatox, Karbosep, Menaphtam,

Monsur, Mugan, Murvin, Oltitox, Panam, Pomex, Prosevor, Ravyon, Seffein, Sevimol, Sevin, Vioxan

The most commonly used trade name is Sevin.

Previous codes:

Compound 7744, ENT 23,969, ENT 23969, Experimental insecticide 7744, Germain's HSDB 952, NAC, NMC 50, Union Carbide 7744

Purity:

The technical product is principally manufactured in the USA; however, there are other minor sources in other parts of the world.

The technical product manufactured in the USA is produced to a minimum purity of 99% w/w carbaryl with a $<0.05\%$ w/w content of the 2-naphthyl carbamate isomer (sometimes known as "beta-carbaryl").

FAO specifies a minimum purity of 98% w/w carbaryl with $<0.05\%$ w/w content of the 2-naphthyl carbamate isomer.

2.2 Physical and chemical properties

Some of the physical properties of carbaryl are listed in Table 1.

Pure carbaryl is a white crystalline solid without odour.

The explosion limit for dust (finely divided particles) in air is 20.3 g/m^3 (approximately 2500 ppm). It is non-corrosive (Weston, 1982).

The volatility may increase 4-fold when the relative humidity is increased from 8 to 80%.

Table 1. Physical properties

Melting point (°C)	142
Boiling point (°C)	decomposing
Solubility in water (30 °C)	40 mg/litre
Specific density (20 °C)	1.23
Relative vapour density	-
Vapour pressure	1.17×10^{-6}-3.1×10^{-7} mmHg at 24-25 °C
Flash point	193 °C
Octanol/water partition coefficient (log K_{ow})	1.59-2.3
Flammability (explosive) limits	-
Relative molecular mass	201

The solubility of carbaryl increases with temperature (Bowman & Sans, 1985). In sea water at 18 °C, the solubility is 31 mg/litre (Karinen et al., 1967). Carbaryl is soluble to some extent in most organic solvents, and it is soluble in corn oil. It is lipophilic (Kanazawa, 1981).

It is stable to light and heat (up to 70 °C) and acids, but easily hydrolysed by alkaline materials (Dittert & Higuchi, 1963). It is a strong oxidizer.

The quality of carbaryl depends upon the purity of the precursor, 1-naphthol. The amount of the 2-naphthylcarbamate isomer found as a contaminant in the final product is directly related to the purity of this precursor. 1-Naphthol, free of 2-naphthol (undetectable), is produced in the USA today through the catalytic conversion of naphthalene. However, 1-naphthol produced by other manufacturing processes may contain 2-naphthol as a byproduct.

High pressure liquid chromatography (HPLC) has been used to determine 1- and 2-naphthol in their mixtures in ratios 500:1, in order to check for traces of contamination in samples of a commercially important insecticide. The results have been summarized in Table 2 (Argauer & Warthen, 1975).

Table 2. 2-Naphthol recovered from carbaryl samples[a]

Sample and size	Amount of 2-naphthyl methylcarbamate added for recovery check	Amount of 2-naphthol found
USA produced		
250 mg Union Carbide 99.66% active	None	Undetectable
500 mg Ortho Sevin 50% wettable powder	None	Undetectable
570 mg Union Carbide 44% aqueous slurry	None	Undetectable
310 mg Union Carbide 80% wettable powder	None	Undetectable
310 mg Union Carbide 80% wettable powder	2.5 mg	1.7 mg
310 mg Union Carbide 80% wettable powder	0.50 mg	0.33 mg
Foreign origin		
250 mg Sample A-technical	None	2.3 mg
250 mg Sample B-technical	None	14 mg
500 mg Sample C-50% wettable powder	None	12.4 mg
500 mg Sample D-50% wettable powder	None	1.3 mg

[a]From: Argauer & Warthen (1975).

2.3 Conversion factors

1 ppm = 8.22 mg/m^3 of air;
1 mg/m^3 = 0.12 ppm.

2.4 Analytical methods

The methods used to determine carbaryl are summarized in Table 3. They vary considerably in relation to the equipment used. As an alternative to chemical analysis, Bowman et al. (1982) used a simple bioassay system procedure to determine foliar residues for a safe re-entry period and to screen food for residues. *Daphnia* and *Hyalella* were used as highly sensitive test organisms.

The Joint FAO/WHO Codex Alimentarius Commission has given recommendations for the methods of analysis to be used for the determination of carbaryl residues (FAO/WHO 1986a).

Table 3. Methods of analysis

Medium	Sampling preparation	Analytical methods	Detection limit	Comments	Reference
Meat	extraction by acetone	paper test based on ChE determination; butyryl choline as a substrate and phenol red as an indicator	0.5 mg/kg		Filatov & Brytskov (1972)
Air		thin-layer chromatography	0.2 ng qualitative 0.5-50 ng quantitative		Wagner (1973)
Air (carbaryl and 1-naphthol)	absorption in methanol	UV spectrophotometry	1 mg/kg	carbaryl λ max. 281 nm 1-naphthol λ max. 296 nm	Klisenko (1965)
Soil plant	extraction by hexane, acetone, chloroform	thin-layer chromatography	0.1 μg	recovery 80-95% sensitivity 0.02 mg/kg	Kovaleva & Talanov(1978a)
Cow's milk and tissues		spectrophotometry *p*-nitrobenzene diazonium fluoborate coupling method	0.002 mg/litre - milk 0.02 mg/kg - tissues	recovery 79-81% fortification 9.5-5 μg	Hurwood (1967)
Urine 1-naphthol	extraction with benzene	gas chromatography tritium detector	0.02 mg/litre	recovery 89-95%	Shafik et al. (1971)

Table 3 (continued)

Air of working environment	absorption in sodium hydroxide solution with simultaneous hydrolysis to 1-naphthol; derivatization by 1-fluoro-2-4 dinitro-benzene	gas chroma-tography, electron capture detector			Krechniak & Foss (1981)
Spinach Chicory	sulfuric acid for hydrolysis to methylamine salt; 4-bromobenzoyl chloride used to produce derivative 4-bromo-*N*-methyl benzamide	electron capture for chroma-tography	0.2 mg/kg in fortified crop extract; 20 pg for pure standards		Tilden & van Middelem (1970)
Water carbaryl and 1-naphthol	extraction with dichloromethane	gas chroma-tography H-3 source electron capture detector or ^{63}Ni detector	0.2 µg/litre	recovery for carbaryl, 100%; for naphthol, 90%	Deuel et al. (1985)
Soil carbaryl and 1-naphthol	extraction with 20% diethylester in dichloromethane		0.01 mg/kg for fortified soil samples	recovery for carbaryl, 89.8%; for 1-naphthol, 79.4%	

Table 3 (continued)

Medium	Sampling preparation	Analytical methods	Detection limit	Comments	Reference
Air ambient	series of gas scrubbers charged with methanol; particulate deposit on Teflon discs	HPLC with ultra-violet detection at 220 nm			Currier et al. (1982)
Pads	methanol ethanol extraction; selective absorption and elution of reversed phase solid support	HPLC	50 ng/pad (103.2 cm^2)	sensitive, inexpensive procedure	Bogus et al. (1985)
Post-mortem specimens	extraction procedure on Extrelut column; protein precipitation with acetonitrile	HPLC ultraviolet detection reversed phase		recovery: blood and urine 99%; liver and stomach tissue 95%	Duck & Woolias (1985)
Foliage	surface extraction by trichloromethane	HPLC		recovery: at 5 ng/kg fortification level	Pieper (1979)
Grass, etc.	extraction by CH_3CN			grass 89.5%; geranium 86.5%	
Water	extraction by CH_2Cl_2			aspen 75%; Douglas fir 49.8%; at 0.1 mg/litre level	
Soil	extraction by acetonitrile + water			soil 103%; stream water 99.7%; sediment 101%	

Table 3 (continued)

Water, soil, cow's milk, tissue (liver, kidney, heart, lungs, etc.)	extraction by benzene (*n*-hexane, diethyl ether)	thin-layer chromatography	0.5 mg/kg qualitative	carbaryl and 1-naphthol	Klisenko et al. (1972)
Vegetables and fruits	extraction by methanol (10% in petroleum ether) or acetonitrile clean-up on a florasil column	HPLC		Recovery 83-97% at 0.5 mg/kg fortification level. Detailed description of the method is given	Ting et al. (1984)
Water and Serum	single extraction by methanol after 1 ml of C_{18} solid-phase extraction columns	HPLC	0.5 ng/ml	Analysis time is 10 min Recovery in water > 99%	Strait et al. (1991)
Plants	methanol and mechanical ultrasonic homogenizer used for extraction	liquid chromatography reverse phase; LC column using acetonitrile - water mobile phase	0.01 mg/kg	Recovery varies from 86 to 121%	Krause (1985a,b)

Table 3 (continued)

Medium	Sampling preparation	Analytical methods	Detection limit	Comments	Reference
Marion-berries	extracted by Luke procedure (Luke et al., 1975, 1981) cited by Cairns (1983); eluted through florisil using 50% mixed petroleum ethers	chemical ionization mass spectrometry with both methane and ammonia as reagent gases		Recommended when GC retention data are inconclusive	Cairns et al. (1983);
Honey-bees	extraction by diethyl ether clean-up using silica cartridge	gas chromatography, nitrogen-phosphorous ionization detector	0.03-0.10 mg/kg	Recovery 95-100%	Kendrick et al. (1991)

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

Carbaryl was first synthesized in 1953 and, in 1958, the Union Carbide Corporation began its commercial production. Carbaryl is now processed by more than 290 formulators into 1537 different registered products (Harry, 1977, unpublished report). Carbaryl is formulated as a 50 and 85% wettable powder, 1.75-50% dust, oil- and water-based 4% liquid suspension, and 5 and 10% granules and baits. Annual production is of the order of 10 000 tonnes. It is produced by the reaction of 1-naphthol with methylisocyanate.

Carbaryl is widely used, in many countries, as a broad spectrum contact and ingestion insecticide with some systemic properties, and is recommended for use at 0.25-2.7 kg active ingredient per hectare to control various insect pests. Up to 10 kg/ha per season can be used on tree fruits. In the USA, carbaryl is registered for the control of about 560 different pests. It is used on more than 115 food and fibre crops, trees, and ornamentals. About 40% of the quantity used is applied to cotton (Kuhr & Dorough, 1976; Mastro & Cameron, 1976; Payne et al., 1985). In combination with other substances, or alone, carbaryl is used as a plant regulator for apple thinning (Looney & McKellar, 1984; Looney & Knight, 1985).

In veterinary practice, carbaryl is used on cattle, poultry, and pets, especially to control flies, mosquitos, ticks, and lice, some of which are vectors of disease.

Carbaryl (5% formulation Carbacide) is used to treat human body louse infestation (Sussman et al., 1969).

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

4.1 Volatilization and air transportation

Carbaryl has a low volatility and a low air-water partition coefficient. Thus, only limited evaporation can be anticipated after treatment. Some traces of carbaryl in the air and in fog, resulting from spray drift, may be detected at a certain distance from the treated areas. A maximum level of 0.09 mg/m^3 in the air has been reported.

The dimensionless air-water partitioning constant (Henry's Law Constant) for carbaryl has been evaluated to be 5.3×10^{-6} (Schomburg et al., 1991).

Deuel et al. (1985) studied the persistence of carbaryl in paddy water. Results indicated that no measurable dissipation could occur as a result of volatilization. In contrast to the results from Deuel, using the BAM model, Lee et al. (1990) calculated that 50 days after treatment, 0.63% of the carbaryl applied to soil could have been volatilized and 78.84% degraded.

4.2 Water

4.2.1 Hydrolysis

In pure, sterilized water, kept in the dark, the persistence of carbaryl is pH-dependent. Carbaryl is rather stable in acidic conditions. Its half-life at pH 7 is 10-16 days, and at pH 8 it is 1.3-1.9 days only. At pH levels higher than 8, its half-life is in the range of a few hours, or even less (Aly & El Dib, 1971a).

Carbaryl is an example of an *N*-substituted carbamate that hydrolyses readily in water. In this mechanism, an acid-base equilibrium is established and the conjugate carbamate undergoes an elimination type reaction to give an unstable carbamic acid that decomposes to the primary amine and CO_2. Initially, the principal non-biological degradation pathway of carbaryl in water, however, involves base-catalysed hydrolysis to 1-naphthol (Khasawinah, 1977).

Aly & El Dib (1971a,b, 1972) conducted studies to determine the physical factors that may influence the degradation of carbamates, including carbaryl, in aquatic systems. Hydrolysis of carbaryl in alkaline medium was a function of hydroxyl ions in solution and was first order with respect to these ions. Carbaryl was so sensitive to hydroxide ions that, at high base concentrations, the liberation of 1-naphthol was too fast (few minutes) to be measured by conventional methods. Carbaryl was stable to hydrolysis at the acid pH range of 3-6. At pH 7, a rise in the hydrolysis rate was observed, which increased with increase in pH. Carbaryl was very susceptible towards hydrolysis in aqueous solutions at neutral and alkaline pH values. A series of kinetic studies was carried out at different temperatures (3-33 °C) to study the temperature dependence of the rate of hydrolysis. Results showed that an increase in temperature resulted in an increase in the reaction velocity.

Wauchope & Haque (1973) reported that, in weak acidic solutions, carbaryl and 1-naphthol were stable for several weeks, in the dark or under laboratory light. In basic solutions, the basic form of 1-naphthol (1-naphthoxide) was light sensitive. 1-Naphthoxide ion was transformed into 2-hydroxy-1,4-naphthoquinone; this was confirmed by mass spectrometry.

Khasawinah (1977) carried out the hydrolysis of carbaryl in the dark, in aqueous buffer solutions at temperatures of 25 and 35 °C. Increasing the pH and temperature of the buffer accelerated the disappearance of carbaryl and the formation of 1-naphthol.

Rate constants (at 20 °C) were determined for the purely chemical hydrolysis of carbaryl in water containing solvents at pH values ranging from 4 to 8 (Chapman & Cole, 1982). The solvent composition (water/ethanol = 99/1) was close to pure water and the solutions were sterilized to ensure that only chemical reactions were taking place. The half-lives for carbaryl were calculated from pseudo-first order disappearance rate constants (Table 4).

Table 4. Half-life of carbaryl at different pH values and temperatures in aqueous solution (days)

pH								Temperature	References
3	4	5	6	7	8	9	10	(°C)	
				10.5	1.3	0.1	0.01		Aly & El Dib (1971a, 1972)
						0.12	0.01	25°	Wauchope & Haque (1973)
stable			stable			0.14		25°	Khasawinah (1977)
stable			29			0.02		35°	
		1500		15		0.15		27°	Wolfe *et al.* (1978)
	2100[a]		406	14	1.9			20°	Chapman & Cole (1982)
	104		71.6		1.4				Fisher & Lohner (1986)
			171.4	16.5				25°	Larkin & Day (1986)
		stable		11.6		0.13			Carpenter (1990)
				12.5					

[a] pH 4.5

Fisher & Lohner (1986) conducted tests on the environmental fate of carbaryl as a function of pH. In both a microcosm and abiotic studies, greater amounts of carbaryl were detected in water at pH 4, than at pH 6 or 8.

Hydrolysis of labelled carbaryl in aqueous solution was conducted by Carpenter (1990) under dark conditions. When degradation occurred, the major degradation product of significance was 1-naphthol. No other degradation product accounted for more than 2% of the radioactivity and no volatile products were generated during the hydrolysis reaction. The test systems were sterile and the transformation/degradation mechanism was purely chemical hydrolysis.

Carbaryl half-lives in aqueous solution observed by different authors are summarized in Table 4.

4.2.2 Photolysis

There is sufficient evidence to suggest that photodecomposition will account for some loss of carbaryl in clear surface waters exposed to sunlight for long periods. In turbid waters, light penetration is greatly reduced, thus photolysis will play only a minor role in the decomposition of carbaryl.

The primary effect of ultraviolet light radiation (UVR) seems to be cleavage of the ester bond, however, other modifications in the carbaryl molecule occur. Crosby et al. (1965) studied the photodecomposition of carbaryl and found several other cholinesterase inhibitory substances, in addition to 1-naphthol, indicating that these substances retained the intact carbamate ester group, and that irradiation resulted in changes at other positions in the molecule. Both UVR and natural sunlight caused decomposition of carbaryl, however, the extent of photodecomposition was not the same under the different conditions of irradiation. Intense UV irradiation generally resulted in the formation of a greater number of degradation products. It is expected that the effects of natural sunlight UVR (292-400 nm) on the photodegradation rate and the nature of the degradation products would differ from those of the shorter wavelength irradiations used above.

The effect of UVR on the photodegradation of carbaryl was studied by Aly & El Dib (1971b, 1972). Generally, the concentration of carbaryl decreased with time, however, the photolysis rate gradually decreased. Photodecomposition proceeded at increasing rates as the pH values of solutions increased. After an exposure time of 60 min, the decomposition rates of carbaryl at pH 5, 7, and 8 were 50, 57, and 78%, respectively. The half-life at pH 8 was <20 min while, at pH 5, it was approximately 80 min. The main decomposition product after 5 min of exposure in all irradiated solutions was 1-naphthol. However, its concentration also decreased as the irradiation time was increased, indicating that 1-naphthol also underwent photolysis, as soon as it appeared in solution. The photodecomposition of 1-naphthol was also affected by the pH of the medium. The half-lives of carbaryl and 1-naphthol were 39 and 60 min, respectively, at pH 7 and 8, and 43 min at pH 8.

The photochemistry of carbaryl was studied by Addison et al. (1975) in aerated and pure ethanol, cyclohexane, isopropyl alcohol, and *tert*-butanol. Irradiation of carbaryl produced 1-naphthol and small amounts of naphthamides, naphthalene, and β-napthyl-1-naphthol. In cyclohexane, 1-naphthol was the only decomposition product.

Khasawinah (1977) conducted a photolysis study on labelled carbaryl in an aqueous solution buffered at pH 6. The study terminated before the actual half-life was reached. The half-life was calculated to be 40-50 days. The author stated that under field conditions it is expected that carbaryl will photodegrade slowly and that photodegradation does not play a major role in the environmental degradation of carbaryl.

The direct photolysis half-life of carbaryl in sunlight was 6.6 days in distilled water (Wolfe et al., 1978). On the basis of the results of the methods of Zepp et al. (1976) and Zepp & Cline (1977), the calculated half-life for direct photolysis was about 50 h in a clear water body, near the surface. The annual variation of the photolysis half-life of carbaryl according to season of the year was calculated. As the intensity of the sunlight increases, so do photolysis rates. Carbaryl absorbs UV-B radiation most strongly, and, thus, can also be photolysed under overcast conditions (cloudy days). UVR is absorbed by water, and the photolysis rate decreases

as the water deepens. In spring and summer, when carbaryl is applied, the rate of photolysis is about four times that in winter months. In distilled water under the June midday sunlight at pH 5.5, the half-life of carbaryl was 45 h.

Deuel et al. (1985) studied the photodecomposition of carbaryl in deionized water. They confirmed that carbaryl could be photodecomposed in an aquatic environment.

The influence of different aqueous systems (rivers, lakes, and seawater) on the photochemical degradation of some carbamate insecticides in Greece was studied by Samanidou et al. (1988). In lake and sea water, carbaryl was almost completely degraded by sunlight within 4 and 2 days, respectively, in the presence of oxygen. One day of UV irradiation in river, lake, and sea water, respectively, resulted in 98%, 87%, and 99% degradation. The high concentration of suspended matter in river and lake water influences the absorption of sunlight and consequently the degradation of carbaryl.

Das (1990a) exposed sterile water, buffered at pH 5, with labelled carbaryl to artificial sunlight (548.8 watts/m^2) for 360 h; 65% of the carbaryl had disappeared by the end of the 360-h period. The major degradation product was 1-naphthol. In control test solutions, incubated in the dark, changes in carbaryl concentrations were insignificant.

4.2.3 Degradation by microorganisms

A review of the chemical and microbial degradation of carbaryl in aquatic systems has been published by Paris & Lewis (1973).

The rate of hydrolysis of carbaryl in neutral and slightly basic conditions was so rapid that differences reported between sterilized and non-sterile water were usually were minor. Thus, it is generally considered that the microbial degradation of carbaryl in natural water plays only a secondary role in comparison with chemical hydrolysis.

The bacterial decomposition of 1-naphthol by ring cleavage was reported in farm pond water (Hughes & Reuszer, 1970). They studied bacterial populations in pond water containing drainage water from carbaryl-treated fields. Their data were the earliest to show that bacteria can adapt to live on carbaryl and that when this occurs one strain dominates. They also showed that there may be a minimum

period of time before bacteria can degrade carbaryl and a minimum concentration below which bacteria will not multiply rapidly enough to cause degradation.

Ahlrichs et al. (1970) found bacteria that could break the ring structure of carbaryl, however data concerning the role of microorganisms in the elimination of insecticides from surface water were variable.

In a study by Hughes (1971) a bacterium (*Flavobacterium* sp.) was isolated from pond water, which degraded 1-naphthol to *o*-hydroxycinnamic acid, salicylic acid, and an unidentified product. In this study, the bacteria cleaved the naphthalene ring, since both hydroxycinnamic acid and salicylic acid each have only a single phenol ring.

Aly & El Dib (1972) studied the biodegradation of carbaryl in Nile River water in 5-gallon containers, which was buffered to maintain a pH of 7.2 and held at 25±2 °C under aerobic conditions. The concentration of carbaryl in water decreased progressively with time and 89% of the added amount of carbaryl (4.75 mg/litre) degraded in 6 days. 1-Napthol, which appeared as a degradation product, did not result only from the chemical hydrolysis of carbaryl, since a sterile buffered solution showed negligible hydrolysis. 1-Naphthol was produced mainly as a result of the biological activity of microorganisms in river water. Subsequent additions of increasing concentrations of carbaryl disappeared in shorter periods of time, and there was no build-up of 1-naphthol. Carbaryl disappeared more rapidly in Nile River water containing sewage. Thus, the authors considered that natural waters and sewage contain microorganisms capable of degrading carbaryl and 1-naphthol.

A number of marine microorganisms, including algae, bacteria, fungi, and yeasts, were tested by Sikka et al. (1973, 1975) for their ability to metabolize carbaryl or 1-naphthol. None of them was able to degrade carbaryl to a significant extent. Only a very small amount of carbaryl was metabolized to form water-soluble metabolites by the algae *Cyclotella nana* and *Dunaliella tertiolecta*. 1-Naphthol was degraded to water- and ether-soluble metabolites by *Culcitalna achraspora, Halosphaeria mediosetigera, Humicola alopallonella, Aspergillus fumigatus, Serratia marina, Spirillum* sp., and *Flavobacterium* sp. The organisms differed greatly in their ability to convert carbaryl to water-soluble products, and also in their ability

to degrade 1-naphthol. Overall, 1-naphthol appeared more susceptible to degradation than carbaryl, and filamentous fungi appeared to possess a greater ability to degrade 1-naphthol than bacteria or yeast.

Bacteria isolated from river water were also capable of degrading 1-naphthol (Bollag et al., 1975; Czaplicki & Bollag, 1975). After 60 h of incubation with ^{14}C-labelled 1-naphthol, it was possible to trap 44% as CO_2 and 22% was recovered. The release of labelled CO_2 clearly indicated that complete biodegradation of carbaryl had taken place via rupture of the naphthyl ring. However, 15-20% of radioactivity remained in the growth medium. This suggests that at least 2 different pathways may be involved in the degradation of 1-naphthol by these bacteria. The radioactivity in the growth medium was partitioned and the dominant product was identified as 4-hydroxy-1-tetralone, which suggests an alternative pathway that involves hydroxylation of the naphthyl ring in the 4-position and conversion of an aromatic ring to an aliphatic cyclic compound. Walker et al. (1975a) confirmed this pathway with a soil pseudomonad.

Paris et al. (1975) found that, in heterogeneous bacterial cultures in water, bacteria did not significantly degrade carbaryl but did utilize 1-naphthol, produced from hydrolysis, as a carbon source. Products of the bacterial degradation of the 1-naphthol were 1,4-naphthoquinone and 2 unidentified compounds. Hydrolysis and photolysis contributed significantly to the degradation of carbaryl, since half-lives were short compared with those of biolysis.

Within 7 days of incubation in river water, 92% of carbaryl or 1-naphthol disappeared (Prima et al., 1976); 68% was removed by biochemical degradation, and 24% by a physico-chemical process.

Liu et al. (1981) measured the rate of carbaryl degradation at pH 6.8 both with, and without, bacteria obtained from lake sediment. Without the lake sediment inoculum, the half-life of carbaryl was 8.3 days under aerobic conditions and 15.3 days under anaerobic conditions. With bacterial metabolism, half-lives of 6.8 and 5.8 days, respectively, were measured. After the addition of cometabolites (glucose and peptone), the half-lives were further reduced to 3.8 and 4.2 days, respectively. Thus, bacterial degradation played a much

greater role in the degradation of carbaryl under anaerobic conditions.

Microbial activity was an important factor in the breakdown of carbaryl in water from a pond and creek (Szeto et al., 1979). Autoclaving prior to the addition of carbaryl and incubating for 50 days increased the recovery from 39 to 57% (creek water) and from 28 to 58% (pond samples containing sediment).

Boethling & Alexander (1979) studied the degradation of carbaryl in stream water (pH 7.5-8.6) at extremely low concentrations. They reported that, at initial concentrations of 30 and 300 mg/litre, more than 60% of the carbaryl was degraded to CO_2 within 4 days, but 10% or less was converted to CO_2 at 0.3 mg/litre and 0.0003 mg/litre. At these two latter concentrations, CO_2 was generated at rates not exceeding 3% of the starting material per day. The authors concluded that laboratory tests on biodegradation are usually conducted with concentrations of chemicals higher than those found in rivers, lakes, and marine waters and, therefore, will not accurately predict the environmental behaviour of microorganisms.

Sharom et al. (1980) compared the persistence of carbaryl in natural water, distilled water, sterilized natural water, and sterilized distilled water. Carbaryl disappeared from all four types of water, which was considered to show that chemical processes played a major role, and biological processes, a secondary role, in the degradation of carbaryl in water.

Chaudhry & Wheeler (1988) maintained a *Pseudomonas* sp. isolated from a pesticide waste disposal site on a medium containing normal and radiolabelled carbaryl. *Pseudomonas* sp. degraded carbaryl and the authors concluded that *Pseudomonas* sp. may have potential as biological treatments for waste and groundwater.

4.2.4 Persistence in surface water

The agricultural use of carbaryl may indirectly produce residues in surface water and in sediment, following application, as result of drift or from soil-bound particles. In general, carbaryl is not expected to persist in the aquatic environment. Although it is stable to hydrolysis in acidic water, at the pH of most surface fresh waters (7-8.2), it is highly susceptible to hydrolysis. Biologically-mediated

degradation and photolysis are secondary mechanisms; sediment and humic substances also influence the persistence of carbaryl in aquatic systems.

Half-lives of carbaryl in natural water, calculated from experimental results, are summarized in Table 5. In one case, with exceptionally cold and acidic conditions, the half-life was in the range of 70 days. In most cases, half of the carbaryl degraded in a few days, or even in less than one day.

Table 5. Percentage of carbaryl degraded in water, a certain number of days after treatment, and the corresponding approximate half-lives

Origin of water	Days after treatment	%	Half-life (days)	References
laboratory	7	95	1	Eichelberger & Lichtenberg (1971)
pond			< 0.5	Romine & Bussian (1971)
containers	8	89	2	Aly & El-Dib (1972)
microcosm			< 5	Kanazawa (1975)
river	7	92	2	Prima et al. (1976)
lab. pond water	42	80-82	18	Szeto et al. (1979)
lab. + sediment			< 2	
lab. creek water	42	80-83	30	
lab. + sediment			< 7	
lab. drainage	28	100	4	Sharom et al. (1980)
field, drainage	6	100	1	Osman & Belal (1980)
brooks, rivers, streams			1	Stanley & Trial (1980)
stream	17	100	3	Ott et al. (1981)
lab. sewage	42	100	11	Odeyemi (1982)
lab. fresh water	60	100	≤ 15	
rice irrigation	10	80	4	Thomas et al. (1982)
pond 1	60	100	8	Gibbs et al. (1981, 1984)
pond 2	138	77	2-3	
rice field				Deuel et al. (1985)
microcosm (pH 4-8)	7	31-73	13-4	Fisher & Lohner (1988)
stream			< 0.1	Sundaram & Szeto (1987)
stream	1-3	100	< 1	Springborn (1988b)
rice irrigation			< 1	Springborn (1988a)
ponds (18 °C)	4	100	1	Hanazato & Yasuno (1989)
ponds (4 °C)	10	30	20	
	45	95	10	
ponds (4-20 °C)			0.4-0.9	Hanazato & Yasuno (1990a,b)

[a]Rounded.

The behaviour and persistence of carbaryl in water from a pond and creek, with and without sediment, were studied under simulated conditions in the laboratory by Szeto et al. (1979). At 9 °C, carbaryl was less persistent in pond water (pH 7.5-7.8) than in creek water (pH 7-7.1). Carbaryl degraded to 18-20% of the initial amount after 42 days in pond water samples and to 37-40% of the initial amount in creek water samples after 50 days. The higher pH of pond water compared with creek water may have contributed to this effect. The presence of sediment did not affect the rate of loss of carbaryl, but approximately 50% of the remaining carbaryl was found in the sediment. Microbial activity was a major factor in the degradation of carbaryl in this study.

Eichelberger & Lichtenberg (1971) measured the persistence of carbaryl in river water at room temperature and pH 7.3-8. From an initial concentration of 10 μg/litre, only 5% could be detected after 1 week and none was detected at 2 weeks. At the time of disappearance of carbaryl, 1-naphthol could not be detected.

In Egypt, Osman & Belal (1980) mentioned that residues present in irrigation and drainage canals following application of carbaryl disappeared from the water 6 days after spraying.

The persistence of carbaryl was tested by Odeyemi (1982) who incubated water samples treated wtih 45 mg/kg under tropical greenhouse conditions (Nigeria). According to colorimetric measurements, carbaryl disappeared after 42 days of incubation in sewage water, and after 60 days in fresh water samples.

The impact of an experimental aerial application of carbaryl (Sevin-4-oil) on woodland ponds in Northern Maine (USA) was studied by Gibbs et al. (1981, 1984). Carbaryl was applied at the rate of 840 g/ha. Maximum residues levels of 734 μg/litre were detected in the water, and about 4860 μg/kg (dry weight) in the sediment. In one pond, carbaryl was not found after 62 days. Data from another pond showed residues equivalent to 23% of the initial residue after 138 days, and 13% of the initial residues persisting after 375 days. Investigators noted a rapid movement of carbaryl into bottom sediments with persistence up to 16 months in this compartment, compared with 14 months in the water. The anaerobic state of the organic substrate and acidic conditions in one pond may have contributed to greater persistence. The lower residue levels in the other pond were attributed to a greater flow of water.

Hanazato & Yasuno (1990a,b) conducted studies in experimental outdoor concrete ponds in Japan. Water received three treatments with carbaryl in order to produce a minimal concentration of 0.5 mg/litre on 12, 19, and 20 October. The water temperature, which was 20 °C at the start of the experiment, declined steadily to 4 °C in early December and then did not change. The pH increased from 7.3 on the third day after the start of the experiment to about 9 on the 13th day. It remained between 8-9 until the end of the experiment. The concentration of carbaryl in water decreased exponentially and it was no longer detected 4 days after the first and second treatments and 11 days after the third treatment. The half-lives for the three treatments were respectively 0.36, 0.40, and 0.86 days. The corresponding times for 90% degradation were, respectively, 1.18, 1.32, and 2.84 days.

Carbaryl was added to 60 litres of water and 15 kg of soil held in 110-litre, plastic, garbage containers, buried partially in open ground (Junk et al., 1984). Carbaryl was studied at the high and low concentrations of 4 g/litre and 0.2 g/litre, respectively. Additional variables studied included aeration (1 litre/min) and peptone nutrients (0.1% by weight). Data obtained from this experiment demonstrated that soil and water in an inexpensive container provide satisfactory conditions for the containment of pesticides so that chemical and biological degradation can occur. Hydrolysis of carbaryl was rapid.

Deuel et al. (1985) studied the persistence of carbaryl and the 1-naphthol metabolite in paddy water under flooded rice cultivation conditions. Persistence was evaluated with respect to time, application rates (1.1 and 5.6 kg/ha), and irrigation scheme (intermittent or continuous). Results showed that application rate and time of sample collection had a significant influence on the carbaryl residues recovered in paddy water during the 3-year study. They were found to be greater in plots under intermittent irrigation, but only in 2 of the 3 years. Carbaryl residues in water were greatest in years when rainfall occurred within 24 h of foliar application. Using intermittent treatment data, carbaryl was determined to dissipate to half the initial residue level within 48-59 h.

4.2.5 *Removal from water*

As already mentioned, Chaudhry & Wheeler (1988) proposed that *Pseudomonas* sp. may have potential as a biological treatment for waste and groundwater.

According to Miles et al. (1988a,b), the degradation rates of *N*-methylcarbamate insecticides, including carbaryl and its metabolite 1-naphthol, were more rapid in chlorinated water than in pure water. Half-lives of carbaryl were as follows:

carbaryl control pH 7:	10.3 days
carbaryl control pH 8:	1.2 days
carbaryl chlorinated pH 7:	3.5 days
carbaryl chlorinated pH 8:	0.05 days.

A separate experiment with 1-naphthol in chlorinated water showed that this product is highly unstable with a half-life of the order of minutes. A water source contaminated with carbaryl and treated by chlorination will have lower concentrations of the insecticide in the effluent.

Mason et al. (1990) studied the removal of carbaryl from drinking-water by the disinfectants, Cl_2, ClO_2, and O_3. Carbaryl did not react with chlorine or with ClO_2, but reacted very rapidly with O_3. Therefore removal/degradation of carbaryl can be achieved using ozonization.

4.2.6 *Persistence in sea water*

Under laboratory conditions, the persistence of carbaryl in sea water is slightly higher than that in freshwater and, according to temperature, lighting, and microbial presence, its half-life varies from a few days to about one month. The salt content of natural waters (ionic strength) may affect the rate of hydrolysis of carbamates (Christenson, 1964). Thus, carbaryl is expected to be more stable to hydrolysis in waters with a high salt content than in freshwater.

Carbaryl may enter marine systems when it is used to control oyster pests and predators, such as oyster drills, mud shrimp, ghost shrimp, and star fish (Loosanoff et al., 1960a,b; Lindsay, 1961; Loosanoff, 1961; Snow & Stewart, 1963; Haydock, 1964; Haven et

al., 1966). However, Hurlburt et al. (1989) stated that tidal action diluted the insecticide rapidly and that larvae are unlikely to be subjected to high concentrations of carbaryl for more than several hours.

The persistence of carbaryl in estuarine water was studied in the laboratory by Karinen et al. (1967). Samples of water containing 5, 10, or 25 mg carbaryl/litre and 3% NaCl were buffered at pH 8 and kept in aquaria at 8 °C. In the absence of mud, the concentration of carbaryl decreased 50% in 38 days, with most of the decrease accounted for by the production of 1-naphthol. In another experiment, naphthyl-^{14}C and carbonyl-^{14}C carbaryl (6.8-8.7 mC) were used with cold carbaryl at total concentrations of 15 and 25 mg/litre, respectively, and maintained at 20 °C. About 50% of the carbaryl was hydrolysed in 4 days and, after 17 days, the carbaryl had almost disappeared with 43% converting to 1-naphthol. Fluorescent light slightly accelerated the hydrolysis of carbaryl to 1-naphthol. When mud was added to the aquarium system, both carbaryl and 1-naphthol in sea water declined to less than 10% of the initial concentration in 10 days. Both compounds were adsorbed by the mud, where decomposition continued at a slower rate than in sea water. 1-Naphthol persisted in mud for a short period of time, but carbaryl could be detected for approximately 3 weeks. The naphthol moiety of the carbaryl molecule was converted to more persistent products. The experiment with labelled carbaryl demonstrated degradation by hydrolysis of carbamate and oxidation of the naphthyl ring to produce $^{14}CO_2$ and $^{14}CH_4$. In a preliminary field study, estuarine mud flats were treated with carbaryl at 11.2 kg/ha (dose used to control pests in oysters beds); carbaryl could be detected in the mud for up to 42 days. 1-Naphthol concentrations were found only after the first day, which may indicate that hydrolysis proceeds slowly in mud.

The fate of 1-naphthol was studied in simulated marine systems by Lamberton & Claeys (1970). 1-Naphthol was unstable in the alkaline environment of sea water, since light and microorganisms enhanced its degradation to CO_2 and other products. 1-Naphthol was relatively stable in an oxygen-free aqueous solution.

Odeyemi (1982) incubated water samples treated with 45 mg carbaryl/litre under tropical greenhouse conditions (Nigeria). According to colorimetric measurements, about 77% of the

insecticide had disappeared after 63 days of incubation in seawater, whereas it had completely disappeared after 42 days of incubation in sewage water, and after 60 days in freshwater samples.

4.2.7 Bioaccumulation/biomagnification

Because of its low persistence in water, and its even faster degradation by living organisms, carbaryl has very low bio-accumulation properties and presents no risk of biomagnification under practical conditions.

Kanazawa (1975) studied the uptake and excretion of carbaryl by *Pseudorasbora parva*. Fish were reared for 30 days in an aquarium containing carbaryl at about 1 mg/litre. In water, 95% of the carbaryl was degraded in 6 days. One day after treatment, residues of carbaryl in *P. parva* reached 7.5 mg/kg, which was the maximum uptake.

Kanazawa et al. (1975) studied the distribution and metabolism of ^{14}C-1-naphthyl-labelled methylcarbamate (carbaryl) in an aquatic model ecosystem containing 10 kg soil, 80 litre water, and catfish (*Ictalurus punctatus*), crayfish (*Procambarus* sp.), daphnids (*Daphnia magna*), snails (*Physa* sp.), algae (*Oedogonium cardiacum*) and duckweed (*Lemna minor*). After 20 days, 31% of the radioactivity was lost, 67.85% remained in the soil (about 45% unextractable residues), 1.1% was present in water, and only 0.1% was recovered in organisms. Bioaccumulation ratios were calculated from radioactivity recovery and were likely to be low in the case of animals. In the case of plants, they were apparently higher, but as they are based only on radioactivity, including normal synthesis reutilizing $^{14}CO_2$ and not on real carbaryl measurement, they should be considered as an overestimation of the true bioconcentration factor for carbaryl (Table 6).

A flow-through bioconcentration study was conducted with bluegill sunfish (*Lepomis macrochirus*) exposed to 0.093 mg carbaryl/litre for 28 days followed by a depuration phase in which bluegill were held for 14 days in untreated water (Chib, 1986a; Chib et al., 1986). Analysis of fillet, whole fish, and visceral portions indicated a rapid uptake of carbaryl. Bioconcentration factors ranged from 14× to 75×, for fillet and viscera, respectively. Data suggest

that fish stopped accumulating carbaryl after day 7 of uptake, indicating that a steady state had been reached.

Table 6. Accumulation of ^{14}C radioactivity expressed as carbaryl equivalent[a] by various aquatic organisms[b]

		Carbaryl
Concentration in water		1.66 (1 day)
µg/litre		9.45 (22 days)
Concentration in soil		2.43 (start)
mg/kg		2.55 (22 days)
Organisms	mg/kg	BAR[c]
Algae	37.9	4000
Duckweed	34.2	3600
Snail	2.81	300
Catfish	1.33	140
Crayfish	2.48	260

[a]Carbaryl not actually measured.
[b]From: Kanazawa et al. (1975).
[c]Bioaccumulation ratio calculated by dividing mg/kg of dried tissues by mg/litre in water at harvest.

By the end of the 14-day depuration period, over 90% of the accumulated carbaryl was eliminated.

The persistence and accumulation of radiolabelled carbaryl (technical, 99%), administered in either food or water (flow-through), was studied in catfish (*Ictalurus punctatus*) over a 56-day period (Korn, 1973). Fish were removed periodically for whole-body residue analysis. Intact carbaryl was not distinguished from 1-naphthol. Accumulation from dietary carbaryl (2.8 mg/kg per week) was 11 and 9 mg/kg tissue at 3 and 56 days, respectively. Fish accumulated 1% or less of the available pesticide via dietary exposure. The mean total accumulation of carbaryl (and/or metabolite residues) after 56 days of exposure to water containing 0.25 mg carbaryl/litre was 11 mg/kg. Fish exposed via the water retained 0.0001% carbaryl. Fish exposed to 2.8 mg/kg per week via diet eliminated residues rapidly after they were placed on a carbaryl-free diet for 28 days. However, residues remained constant for 28 days in fish previously exposed to 0.25 mg carbaryl/litre water for 56 days. The authors speculated that the greater persistence of

carbaryl residues from the water might be due to the persistence in fish of 1-naphthol.

The low accumulation and rapid elimination of carbaryl in fish were confirmed in other laboratory work (Kanazawa, 1975, 1981).

The biodegradation of carbaryl, was studied by Bogacka & Groba (1980) in a model system simulating the river-water and aqueous ecosystem conditions. The rate of pesticide decay in water depended on the initial concentration, temperature, and the kind of model. Lowering the temperature inhibited this process. The accumulation of carbaryl in bottom sediments or in aquatic organisms (algae, snails, and fish) was not observed at concentrations of 10 or 50 μg/litre. Trace quantities of 1-naphthol could be detected occasionally.

4.3 Soil

4.3.1 Adsorption, desorption

Carbaryl is adsorbed on soil. Most K_{oc} values were in the range of 100-600, which corresponds to medium to strong adsorption. Only in some soils from Eastern Australia was carbaryl apparently less tightly bound (K_{oc} 90-220). Taking into account both the adsorption/desorption properties and the short persistence of carbaryl in soil, it can be calculated that the compound has low to moderate mobility in soil and will remain in the top layers, when applied under actual agricultural conditions (normal dose rates). Leenheer & Ahlrichs (1971) stated that fast adsorption rates for carbaryl on soil particles were related to organic matter (OM) and were of the order expected for physical adsorption.

Carbaryl desorption and movement in the soil was studied in 1-m soil columns in glass tubes, which had a drain (LaFleur, 1976a). Desorption by added water was rectilinear for carbaryl (soil range 1-200 μmol/kg). The movement of carbaryl in the column was a function of the percentage of the organic matter. In soil containing 5.16% organic matter, carbaryl reached the 40-cm section of the column only. When the organic matter content of the soil was low (0.22-0.57%), about one-half of the added carbaryl moved through the column and was found in the effluent, after addition of a volume of water that was equal to six months' rainfall. Briggs (1981) also

reported that increasing levels of organic matter in soils resulted in an increase in the adsorption of carbaryl.

On the basis of the comparative mobility of carbaryl on soil thin-layer chromatography (TLC) plates using 4 US soils (silt loam, loam, Norfolk sandy loam, and silty clay loam), Chib & Andrawes (1985) concluded that the mobility of carbaryl is low to moderate. With water elution equivalent to about 580 mm of rainfall, the major portion of carbaryl was in the top 10 cm of soil, thus exhibiting low mobility. Only 0.6% of the applied ^{14}C was eluted with the water. Approximately 70% of the applied carbaryl was degraded to volatile gases during the 30-day incubation.

Aly et al. (1980) studied the adsorption of carbaryl at different temperatures on Ca-bentonite and on two Egyptian soils (Nile alluvial and a highly calcareous soil). Carbaryl adsorption increased as the temperature decreased. Ca-bentonite exhibited the highest degree of adsorption followed by the Nile alluvial soil and the calcareous soil. The factors that contributed most to the total adsorption of carbaryl were the soil contents of clay, calcium carbonate, and organic matter.

The adsorption-desorption and mobility of carbaryl in 3 soils, and in a stream sediment were studied by Sharom et al. (1980). The order of adsorptive capacity was organic soil (75.3% OM, pH 6.1) > sediment (2.8% OM, pH 6.6) > sandy loam (2.5% OM, pH 6.8) > sand (0.7% OM, pH 7). Desorption occurred in greatest amounts from sand > sandy loam > sediment. Leachability studies were consistent with the adsorption/desorption results and a water solubility of 40 mg/litre. Carbaryl leached more from the sand than from the organic soil.

In another adsorption/desorption study on carbaryl on sand, sandy loam, silt loam, silty clay loam, and on aquatic sediment using batch equilibrium techniques, Chib (1985a) concluded that carbaryl binds strongly to soil/sediment matrices. This depends on the carbaryl concentration in solution (the more in solution, the more on soil) and on the organic content of soil. Desorption isotherms for carbaryl at low concentrations were nearly flat with all soils, indicating that carbaryl was tightly bound to the substrates and difficult to move.

The transport of carbaryl in the soil was also studied under natural conditions. High-volume rainfall occurring shortly after carbaryl has been applied to a field can generate the low-level transport of the pesticide to non-target areas (Caro et al., 1974). Carbaryl is adsorbed on soil surfaces to a great extent. Laboratory measurements of absorption isotherms gave a Freundlich k value of 2.2. Of the 4 kg of carbaryl applied in a watershed, only 5.77 g (0.16%) were found in run-off water and sediment during the season; (75 and 25% of the seasonal loss, respectively). The distribution coefficient between sediment and water was 0.33. Carbaryl had completely disappeared from the sediment by day 70, but still remained in the water at low concentrations.

Carbaryl could still be found in the soil, 1-2 years after application at 2 kg 85% WP/ha. It is carried by rainfall and cultivation from the surface layers of the soil into the deeper layers. During the first few days after application, it was found in the root zone. After 3 months, 90% of the carbaryl was present in the surface layers, and, after 300 days, it was found in the soil at a depth of 60-70 cm. Rainfall was not specified (Molozhanova, 1968).

Carbaryl was applied to a sandy loam field plot at a dose of 25.4 kg/ha. A shallow water table was present at 1.1 m depth (LaFleur, 1976b). Rainfall during the following 16 months was 182 cm. After this length of time, the upper 1 m contained 6% of the applied carbaryl. No carbaryl was found in the 0-20 cm layer after the fourth month. The half-life of carbaryl in the upper 1 m was >1 month. Carbaryl appeared in the underlying groundwater within 2 months following treatment and could be detected through the eighth month. The maximum groundwater concentration occurred at the end of the second month (about 60 μg/litre). The dose rate was more than 10 times the usual one and the persistence was overestimated, as well as the residues that might be present in shallow groundwater.

Norris (1991) reported a terrestrial field soil dissipation study conducted with carbaryl under actual use conditions. Carbaryl was applied to broccoli in California at 2.24 kg/ha, five times, on a weekly schedule. It was also applied once to sweet corn in North Carolina at a rate of 7.12 kg a.i./ha. The half-life in soil was estimated to be 6-12 days at the California site and about 4.8 days at the North Carolina site. Carbaryl residues were found mainly at a

depth of 0-15 cm, which indicates that carbaryl has a low potential for leaching through the soil profile under typical agronomic practices.

4.3.2 Transformation

Degradation of carbaryl in soil occurs as a result of the activity of microorganisms, and through physical and chemical effects. It undergoes hydrolysis, oxidation, and other chemical processes and, on the surface of the soil, is subjected to photolysis. When applied at the usual doses, carbaryl has a short persistence in soil. In the field, under temperate and warm climatic conditions, the half-life of carbaryl in the soil does not exceed one month (Table 7).

4.3.2.1 Photolysis in soil

Studies have been conducted on the photolysis of carbaryl in soil. In one study, volatile substances were first identified and quantified and then soil TLC plates were used over a 30-day period to quantify degradation products (Chib, 1986b). The calculated half-life of carbaryl in sandy loam soil on TLC plates irradiated with a high-pressure mercury vapour lamp (200 watt, Hanovia) at 25 °C was 2.5 days. In controls kept in the dark, labelled carbaryl degraded with a half-life of >30 days. CO_2 was the only major volatile degradation product from all treatments. The other soil degradation products identified were 5-hydroxy carbaryl, *N*-hydroxymethyl carbaryl and 1-naphthol. Only carbaryl and 1-naphthol were present in control soil extracts. The degradation products in the irradiated soil extracts suggest that hydrolysis and oxidation are the main mechanisms in the degradation of carbaryl under soil photolysis conditions.

Das (1990b) also studied the photolysis of carbaryl in soil. Labelled carbaryl was applied to a sandy loam on plates (9.8 ± 0.3 mg/kg) and maintained in artificial sunlight, intermittently (12 h irradiation + 12 h darkness) for 30 days. The measured irradiance of the artificial sunlight (502.6 watts/m^2) was comparable to the natural sunlight (545.8 watts/m^2). The evolution of volatile substances was also monitored. Controls were incubated in the dark. The calculated half-life of irradiated samples was 41 days (each day

12 h irradiation + 12 h darkness). No major metabolites were formed under irradiated conditions.

4.3.3 Biotransformation in soil

The persistence and metabolism of ^{14}C-carbaryl (200 mg/kg) was studied in 5 different soil types by Kazano et al. (1972). Persistence was influenced by soil type, and the production of $^{14}CO_2$ varied from 2.2% (loamy sand) to 37.4% (clay loam) of the initial radioactivity during 32 days of incubation at 25 °C. The amount of radioactivity left in the soil after extraction was proportional to the soil organic matter content. A significant amount (17-57%) of the remaining radiolabel could not be extracted with organic solvents. Analysis of the extractable residues indicated the presence of 1-naphthyl *N*-hydroxymethylcarbamate, 4-hydroxy-1-naphthyl methylcarbamate and 5-hydroxy-1-naphthyl methylcarbamate, but these were not confirmed. The main pathway of degradation in soil was probably hydrolysis of the carbamate linkage, producing CO_2 and the corresponding phenol, though it is possible that hydroxylation of the ring or the methyl carbon precedes hydrolysis. 1-Naphthol decomposed more rapidly in clay than in sandy loam. Most of the radioactivity (83-92%) was recovered in the soils after 60 days of incubation. 1-Naphthol was immobilized on humic substances in the soil, not by mechanical adsorption, but by chemical bonding. Four metabolites (coumarin, the others not identified) were also produced by a soil *Pseudomonas*.

Gill & Yeoh (1980) studied the degradation of carbaryl in an extract of flooded paddy field soil (pH 3.7-4.8, organic matter content 0.5-3%, very high clay content) extract and in the paddy fish (*Trichogaster pectoralis*). Under flooded conditions, the soil half-life of carbaryl was about 7 weeks. The major significant metabolite was 1-naphthol. Soil moisture plays an important role in the extent of degradation since, under flooded conditions and 100% field capacity, the degradation of carbaryl was more extensive than under 0 and 50% field capacity, providing more evidence that microorganisms play an important role in carbaryl degradation in paddy-field soil. Where sufficient moisture is available, oxidative mechanisms become important giving rise to ring and *N*-methyl hydroxylation in addition to cleavage of the carbonyl moiety, a

common pathway of carbaryl metabolism. Carbaryl was also found to be more persistent in acidic soil than in alluvial soil.

Rajagopal et al. (1983) measured the residues of carbaryl and of the 1-naphthol metabolite in 3 flooded soils (organic matter 0.54-1.61%, pH 6.2-9.5) following three applications of the test substance. Samples received either 1, 2, or 3 applications of carbaryl in aqueous solution. The concentration of carbaryl decreased with incubation time in all soils. The disappearance of the first 50% of the substance in all soils ranged from 10 to 15 days. Subsequent samplings provided evidence for the enrichment of carbaryl-degrading microorganisms in retreated soils. Thus, the disappearance time for 75% of the compound was 20-26 days for 3 applications, 28-30 days for 2 applications, and >30 days for 1 application. It appears that carbaryl degradation under flooded conditions does not follow a clear kinetic pattern (e.g., first order). However, the first order degradation rates were similar for the first, second, and third applications for 0-10 days. Degradation proceeded by hydrolysis with 1-naphthol as the major product, the amounts formed decreasing with incubation time in 2 out of the 3 soils. The disappearance of 1-naphthol was faster in retreated soils and may not be attributed only to degradation, because significant amounts of 1-naphthol may be bound to humic substances, especially in soils with a high organic matter content.

The persistence of carbaryl was studied in 4 soils under flooded conditions by Venkateswarlu et al. (1980). They recovered a substantial portion of carbaryl from all soils 15 days after application. The recovery ranged from 37% in an alluvial soil to 73% in an acid sulfate soil. They concluded that flooded conditions enhance carbaryl degradation.

The metabolism of ^{14}C-carbaryl and ^{14}C-1-naphthol in moist and flooded soils was studied by Murthy & Raghu (1989) in a continuous flow-through system, over a period of 28 days, permitting a ^{14}C-mass balance. The percentage distribution of radiocarbon in organic volatile compounds, CO_2, and extractable and non-extractable (bound) fractions of soils was determined. Organic volatile compounds could not be detected in either carbaryl- or 1-naphthol-treated soils. More $^{14}CO_2$ (25.6%) was evolved from moist than from flooded soil (15.1%), treated with carbaryl. The mineralization of ^{14}C-1-naphthol was negligible. The level of extractable radiocarbon

was higher (5.5%) in flooded soil treated with carbaryl. Less than 1% was the parent compound, and carbaryl was mainly metabolized to 5-hydroxycarbaryl in moist soil and to 4- and 5-hydroxycarbaryl in flooded soil. The extractable radiocarbon amounted to 18.2% and 24.3% in moist and flooded soils, respectively, and there was less than 1% of the parent compound with 1-naphthol treatment. Most of the ^{14}C was found as soil-bound residues, levels being higher with 1-naphthol treatment than with carbaryl. The humus fraction of the soil organic matter contributed most to soil-bound residues of both carbaryl and 1-naphthol.

Aerobic and anaerobic soil metabolism studies were conducted with carbaryl applied to sandy and clay loam soils in the dark (Wilkes et al., 1977; Khasawinah, 1978). Under aerobic conditions at room temperatures (23-25 °C), the half-life of carbaryl was approximately 9-17 days in sandy loam soil (Texas) and 21-27 days in clay loam (California). Lower temperature (15 °C) nearly doubled its half-life. The only solvent-extractable apolar material was parent carbaryl. A major proportion of the radioactivity initially applied to the soil was lost as CO_2. It appears that, under aerobic conditions, carbaryl was degraded so that 1-naphthol carbon was lost as CO_2, or it was incorporated into the organic matter of the soil (1-naphthol was not detected). After 112 days, carbaryl levels declined to 3.6% (average in Texas soil) and 15% (average in California soil) of the initial application.

In an aerobic, soil study conducted by Miller (1990) with a sandy loam soil from North Carolina, soil was incubated with labelled carbaryl in the dark and maintained at 25±1 °C. The concentration of the parent compound rapidly decreased to a mean value of 11.9% of the applied dose by day 14. A significant amount of radioactivity was recovered as CO_2. The average maximum value of CO_2 was 59.8% by day 14. The only other major degradation product was 1-naphthol (maximum concentration of 34.9% of applied dose by day 1). Base hydrolysis released 41% of the unextractable residue. Carbaryl rapidly degraded under aerobic conditions with a half-life of 5.5 days.

Murthy & Raghu (1991) studied the fate of carbaryl in the soil environment as a function of pH, with respect to the formation of extractable and non-extractable (soil-bound) residues. Soil samples (sandy clay, sandy loam, and clay) containing C^{14}-carbaryl

(10 mg/kg) were incubated at 28-30 °C for periods ranging from 7 to 56 days. More ^{14}C-residues could be extracted from sandy clay and sandy loam than from clay soil, under both moist and flooded conditions. In general, flooding had no influence on the extractable ^{14}C-residues. Thin-layer chromatography of chloroform extracts revealed the presence of carbaryl and 1-naphthol. At the end of 56 days, the percentage of carbaryl recovered was 32.1, 6.4, and 1% in sandy clay (pH 4.2), sandy loam (pH 6.8), and clay soils (pH 8.3), respectively. The authors considered that there appeared to be a correlation between soil pH and soil-bound residue formation as an increase in soil pH was reflected in increased bound residues. The humin portion of soil organic matter accounted for most of the ^{14}C-residues. Low recoveries in sandy clay and in sandy loam soils may stem from the possible mineralization of carbaryl.

Carbaryl persistence in the soil was studied under normal conditions of application (Caro et al., 1974) of 5.03 kg/ha in granules applied in corn seed furrows. About 135 days were required for 95% of the carbaryl to disappear (Fig. 1). The pesticide remained stable in the soil for 25 days (in some cases, more than 116 days) and then decayed rapidly. This decay is an indirect indication of microbiological degradation.

This hypothesis is sustained by the finding that the stability of carbaryl in the soil is affected by the nature of the treatments applied during the period preceding its application. In soil that had been treated with carbaryl 6 months before sampling, more than 70% of the added radiolabelled carbaryl was degraded after 4 days, measured by the disappearance of radioactivity. Only 10% was lost in orchard soil that had been treated for 15 years with various pesticides, and only 3% was lost in soil that had never been treated with pesticides. It appeared that soil that was treated with carbaryl for 6 months increased the ability of the microorganisms to degrade carbaryl (Rodriguez & Dorough, 1977).

Carbaryl was applied in soil at an agricultural rate and incorporated to a depth of 6 inches (15 cm) (Heywood, 1975). At 28 days after treatment, 63% of the applied dose appeared as CO_2 and the identifiable residual carbaryl was about 6% of that applied.

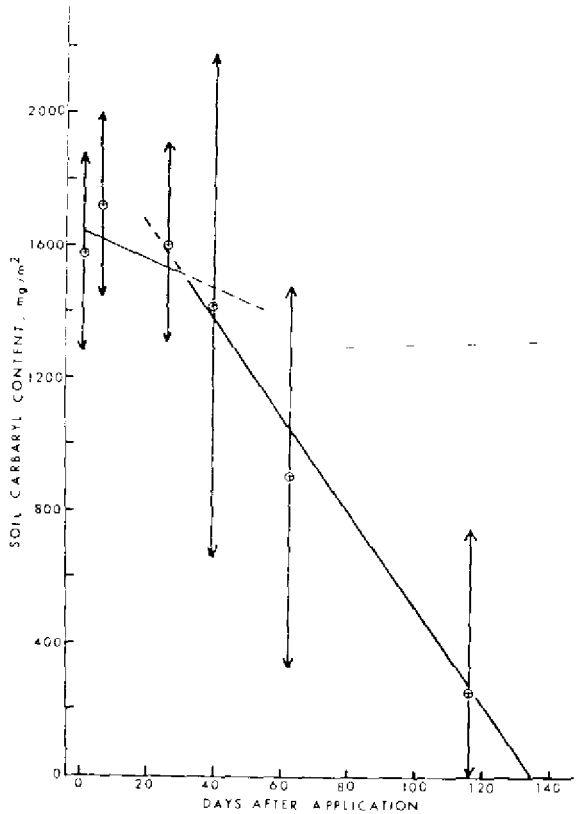


Fig. 1. The disappearance curve for carbaryl in loam soil. The circled crosses designate the analytical means for each sampling day. The vertical arrows on each of the means designate one standard deviation about the mean. From: Caro et al. (1974).

In India, degradation of carbaryl was studied in a greenhouse by Brahmaprakash & Sethunathan (1984, 1985). Since a soil planted with crops may be more dynamic and complex than unplanted soil,

because of increased microbial activity, they studied carbaryl persistence in soil (pH 6.2, organic matter 1.6%) planted with rice in a greenhouse, under flooded and non-flooded conditions. Carbaryl disappeared more rapidly from soils planted with rice than from those without rice, under both flooded and non-flooded conditions. The amount of carbaryl decreased to between 30.2 and 32.1% of the original level within 30 days in unplanted soil under both flooded and non-flooded conditions. During this same period, the carbaryl concentration decreased to 17-18% of the original level in planted soil under both water regimes. Degradation occurred by hydrolysis, but there was no appreciable difference in the rates of degradation between flooded and non-flooded soils. The rate of degradation of carbaryl was little affected by moisture. Further degradation of 1-naphthol was slow in both planted and unplanted systems. A significant portion of the ring-^{14}C accumulated in the soil as 1-naphthol and soil-bound residues. Evolution of $^{14}CO_2$ from the labelled side-chain and ring was negligible, even in soil planted to rice.

4.3.4 Degradation by microorganisms

Many studies have demonstrated the great ability of microorganisms to degrade carbaryl in the soil, and for some of them, to use it as a sole source of carbon. The most frequently identified organisms are bacteria (*Pseudomonas phaseolicola, P. cepaphia, Rhodococcus* sp., *Nocardia* sp., *Xanthomonas* sp., *Achromobacter* sp.) and fungi (*Aspergillus niger, A. terreus, Fusarium solani, Gilocladium roseum, Rhizoctonia solani, R. practicola, Penicillium* sp., *Mucor* sp., *Rhizopus* sp.). In many cases, it was demonstrated that the persistence of carbaryl in the soil decreased after a first application, which was interpreted as the selection and build-up of strains more capable of degrading the product. The same process may also explain that, in some studies, the rapidity of degradation suddenly rose after a lag period during which only minor amounts of carbaryl degraded.

Tewfik & Hamdi (1970) mentioned that carbaryl was decomposed into 4 distinct compounds by a soil bacterium designated as S-1. They considered that this soil bacterium might utilize carbaryl in a similar way to *Pseudomonas* sp., which metabolize naphthalene via the salicylate pathway.

Zuberi & Zubairi (1971) also reported that carbaryl is degraded by soil microflora. *Pseudomonas phaseolicola* and *Aspergillus niger* hydrolysed carbaryl to 1-naphthol. In the case of *P. phaseolicola*, an unidentified minor metabolite was also detected.

Larkin & Day (1986) reported that 2 bacteria isolated from garden soil, *Pseudomonas* sp. (NCIB 12042) and *Rhodococcus* sp. (NCIB 12038), could grow on carbaryl as the sole source of carbon and nitrogen at pH 6.8, but failed to metabolize carbaryl rapidly. Both could use 1-naphthol as the sole source of carbon and metabolize it via salicylic acid. Strain NCIB 12038 produced also gentisic acid. *Pseudomonas* sp. (NCIB 12043), in a soil perfusion column enrichment at pH 5.2, metabolized carbaryl rapidly to 1-naphthol and methylamine. 1-Naphthol itself was metabolized via gentisic acid. A possible pathway for the catabolism of carbaryl and 1-naphthol was proposed.

Walker et al. (1975a), working with *Pseudomonas* sp., observed degradation of 1-naphthol and suggested that carbaryl could serve as the sole source of nitrogen and carbon for bacteria. It was also noted that the presence of another nitrogen source in the media seemed to have a delaying effect on metabolism of carbaryl.

Bacterial communities of at least 12 and 14 members were selected in continuous culture using carbaryl as the sole source of carbon and nitrogen at pH 6. These communities were supported by the slow formation of hydrolysis products and no carbaryl-degrading bacterium was selected after more than 83 days. When using equimolar 1-naphthol and methylamine as the sole source of carbon and nitrogen, a bacterial community of at least 8 members was selected. After a lag of 10-50 days, soil perfusion columns (pH 5.2) and continuous culture enrichments (pH 5) led to the selection of a *Pseudomonas* sp. that could utilize carbaryl as its sole carbon and nitrogen source (Larkin & Day, 1985).

Sud et al. (1972) showed that *Achromobacter* sp. also utilized carbaryl as the sole source of carbon in a salt medium. Four degradation products of carbaryl were 1-naphthol, hydroquinone, catechole, and pyruvate. The organism also grew well in the first 3 degradation products.

The rate of degradation of carbaryl after 1, 2, and 3 applications to 3 submerged soils was examined by Rajagopal et al. (1983). Soils

that had been pretreated with carbaryl were able to degrade carbaryl more rapidly than those without pretreatment. The enrichment culture was inactivated upon autoclaving. The concentration of carbaryl decreased in the mineral medium inoculated with the enrichment cultures from the 3 soils, especially when it served as the sole source of both carbon and nitrogen.

Rajagopal et al. (1984) studied the metabolism of side-chain and ring ^{14}C-labelled carbaryl in a mineral salts medium by soil enrichment cultures. Hydrolysis was the major route of microbial degradation. During carbaryl degradation by enrichment cultures and *Bacillus* sp., 1-naphthol and 1,4-naphthoquinone accumulated in the medium.

Rajagopal et al. (1986) also observed that carbaryl disappeared more rapidly from a laterite soil pretreated with 1-naphthol than from a control soil never exposed to 1-naphthol. The accumulation of 1-naphthol and bound residues formed from added ^{14}C-carbaryl was greater in soils pretreated with 1-naphthol than in untreated soils.

In experiments with the soil fungus *Rhizoctonia practicola*, Bollag et al. (1976) found that it could transform 1-naphthol from an ether-extractable to a water-soluble product. It was also observed that, after removal of the fungal cells, the growth medium possessed the ability to transform 1-naphthol, indicating activity of an extracellular enzyme. Attempts to analyse the labelled material in the aqueous phase indicated that the radioactivity was associated with a compound of comparatively high relative molecular mass.

Czaplicki & Bollag (1975) exposed 1-naphthol to *Rhizoctonia solani*, isolated from soil, and found that it was completely transformed to a compound not extractable with ether.

Working with the soil fungus *Aspergillus terreus*, Liu & Bollag (1971b) investigated the metabolic transformation of carbaryl through 1-naphthyl-*N*-hydroxymethylcarbamate and tried to clarify the pathway of the side-chain. The next intermediate in biological transformation was 1-naphthyl carbamate, which was further degraded to 1-naphthol. Within one week, approximately half the amount of carbaryl was transformed to these other metabolic products. No attempt was made to clarify whether the formation of 1-naphthol was the result of the biological or the chemical

degradation of 1-naphthylcarbamate, but there were clear indications that 1-naphthol was metabolized further in the presence of *A. terreus*.

In vitro studies were carried out to investigate the degradation of carbaryl by soil microorganisms. Three isolates from soil, including *Fusarium solani*, a Gram-negative coccus, and a Gram-positive rod, accelerated the hydrolysis of carbaryl to 1-naphthol and other intermediates. *Fusarium solani* was the most effective in decomposing the ^{14}C-labelled compound. Radioactivity decreased by 24% during the first 5 days and by 82% during 12 days in a growing culture after inoculation. A mixture of two or three of the microorganisms was more effective in decomposing carbaryl and 1-naphthol (Bollag & Liu, 1971).

Bollag & Liu (1972a) studied the biological degradation of ^{14}C-1-naphthol during growth, with replacement cultures and cell extracts of *Fusarium solani*. The radioactivity of 1-naphthol disappeared partially during growth, but it was completely dissipated by cell extract activity. The cell extract of *F. solani* degraded more than 80% of the 1-naphthol to form CO_2 within 60 min of incubation, but it was not possible to identify intermediates. This implies rupture of the naphthol ring. No difference in activity could be observed between cell-free extracts from the spores or the mycelium of the fungus at pH 5.7 and 7.2. The enzyme system was relatively stable since there was no decrease in activity after the cell extract was stored at -10 °C during 4 months. The enzyme that participated in the degradation reaction was constitutive (always present) as shown by cell extracts prepared from cells grown in a medium with, or without, carbaryl as substrate.

The fungus *Gliocladium roseum*, isolated from soil by Liu & Bollag (1971a), metabolized carbaryl to 3 metabolites which were identified as 1-naphthyl-*N*-hydroxy methylcarbamate, 4-hydroxy-1-naphthyl methylcarbamate, and 5-hydroxy-1-naphthyl methylcarbamate. It was therefore considered that *N*-alkyl- and aromatic ring-hydroxylation of carbaryl were important detoxication reactions of *G. roseum*. About 70% of the radioactivity was recovered as carbaryl from an 11-day-old culture. The decrease in radioactivity from the growth medium containing side-chain labelled carbaryl indicated that a further degradation of the formed metabolites occurred, or that an additional pathway was involved in the degradation of carbaryl by *G. roseum*.

Bollag & Liu (1972b) reported that most soil fungi (*Penicillium* sp., *Mucor* sp., *Rhizopus* sp., and *Aspergillus* sp. except *A. fumigatus*), could hydroxylate carbaryl at different positions, but that the products differed qualitatively as well as quantitatively with the various fungi.

In a different study, the enzyme or protein fraction (extracellular phenol oxidase) of the culture filtrate from *Rhizoctonia practicola* as chromatographed on a column of Sephadex G-200 and fractions were obtained that were able to transform 1-naphthol as a substrate (Sjoblad et al., 1976). The enzyme catalysed the polymerization of 1-naphthol to several products.

Biological oxidation and coupling of phenols are key reactions in nature, that result in the formation of products such as lignins, melanins, tannins, alkaloids, and humus compounds. Thus, it can be assumed that enzymes interact with xenobiotic phenols that are incorporated into soil or sediment organic matter. *Rhizoctonia practicola* (and an extracellular enzyme) was able to polymerize 1-naphthol (dimers, trimer, tetramer) (Bollag et al., 1978).

Rodriguez & Dorough (1977) studied the persistence of carbaryl in culture media in the presence of mixed and pure cultures of bacteria and fungi isolated from soil. All fungi (*Fusarium, Penicillium, Aspergillus*, and one unidentified species), isolated from a soil treated with carbaryl six months before sampling, produced at least one metabolite from carbaryl. After 14 days of incubation, 54-79% of the carbaryl was recovered intact, and there was little formation of carbon dioxide by the fungi. In contrast, related experiments with bacterial isolates (*Arthrobacter, Nocardia, Pseudomonas, Xanthomonas*, and *Bacillus*) from the same soil showed that only 1-9% of the added carbaryl remained unconverted (*Arthrobacter* was the exception with 59.1% remaining carbaryl). Controls showed that non-biological degradation also occurred. Bacteria, like fungi, metabolized carbaryl qualitatively in the manner observed with natural soil populations. However, quantitative differences were so great that the use of isolates may be of little value in estimating the degradation rate of carbaryl and other pesticides in field soil. This is important to note when conducting microbial degradation studies in the laboratory.

Bollag (1979) summarized the transformations of carbaryl by microbial activity. It was possible to isolate several microorganisms capable of hydrolising carbaryl to 1-naphthol. In addition, *Gliocladium roseum* showed the formation of:

4-hydroxy-1-naphthyl *N*-methylcarbamate
5-hydroxy-1-naphthyl *N*-methylcarbamate
1-naphthyl *N*-hydroxy-methylcarbamate.

Other terrestrial fungi hydroxylated carbaryl at different positions, but the products differed quantitatively and qualitatively with the various fungi. Subsequent metabolic transformation of the hydroxylated products differed considerably. With *A. terreus*, the following products were obtained:

1-naphthyl *N*-hydroxy-methylcarbamate → 1-naphthyl-carbamate → 1-naphthol

Several bacteria isolated from river water were capable of degrading 1-naphthol. At least two different pathways were involved. The first was a complete degradation with the release of CO_2, the second produced principally 4-hydroxy-1-tetralone, which may involve hydroxylation of the naphthyl ring in the 4 position and conversion to an aliphatic cyclic compound. Such a pathway has also been described with a soil *Pseudomonas* by Walker et al. (1975a) and Davis & Evans (1964).

4.3.5 *Persistence in soil*

Carbaryl is not usually applied as a soil treatment, therefore, the amounts of carbaryl that may reach the soil come principally from spray drift, or from washing off treated crops by rain.

When applied at the usual doses, in the laboratory, carbaryl has a short persistence (half-life < 40 days and usually from 6-20 days), but this may increase when the soil is flooded, or when the dose is increased. In field studies, the half-life of carbaryl, applied at the usual dose rates, in warm or temperate climatic conditions, did not exceed one month in the soil. The results of laboratory and field studies on the persistence of carbaryl in soil are summarized in Table 7.

Table 7. Half-life of carbaryl in soil, calculated from experimental laboratory and field results

Origin of soil	Number of days	Degradation (%)	Half-life (days)	References
Laboratory	40	100	8	Johnson & Stansbury (1965)
Laboratory 0.5 mg/kg	45	77	20	Molozhanova & Kanevskij (1971)
Laboratory 1 mg/kg	45	53	40	
Laboratory 10 mg/kg	45	13		
Laboratory	30	55-63	≤ 20	Flores-Ruegg et al. (1980)
Laboratory (flooded)	15	63-27	10-40	Venkatesvarlu et al. (1980)
Laboratory	53	100	≤ 8	Odeyemi (1982)
Orchard	184	99	30	Ivanova & Molozhanova (1973)
Corn	135	95	30	Caro et al. (1974)
Pretreated soil	4	70	≤ 3	Rodriguez & Dorough (1977)
Grain crop[a]	30	53-31	27-55	Gangwar et al. (1978a)
Corn soil[b]	5	42-56	5	Kavadia et al. (1978)
Potatoes	50	≤ 99	≤ 7	Kovaleva & Talamov (1978b)
	30	96	6	

Table 7 (continued)

Origin of soil	Number of days	Degradation (%)	Half-life (days)	References
Unspecified			90	Czaplicki (1979)
Tropical			7	Rajukkannu et al. (1985)
Sesamum	60	56	50	Yadav et al. (1985)
Bare soil			≤ 4	Davis (1986a)
Bare soil			1-13	
Forest			1.5	Sundaram & Szeto (1987)
Forest	90	≤ 78	≤ 38	Springborn (1988b,c)
Forest	90	≤ 90	≤ 24	
Flooded rice	180	(56)		Springborn (1988a)
Flooded rice	180	(52)		
Broccoli			6-12	Norris (1991)
Sweet corn			5	

[a] 20-60 kg/ha.
[b] 15-45 kg/ha.

Johnson & Stansbury (1965) calculated a half-life of approximately 8 days in an agricultural soil (sandy loam, pH 5.5) treated at 3 concentrations. Residues of carbaryl appeared to be completely degraded within 40 days.

The considerable influence of the dose rate on the persistence of carbaryl in soil was demonstrated by Molozhanova & Kanevskij (1971). The percentages of the initial quantities that were degraded 45 days after treatment are shown in Table 8.

Table 8. Degradation rate of carbaryl in relation to the dose

Initial dose (mg/kg)	Degradation (%)
0.5	77
1	53
1.5	37.3
2	30
2.5	27
3	23
4	20
6	16.7
8	15
10	13.2

The same authors also demonstrated the influence of the type of soil on the degradation of carbaryl. Forty-five days after treatment, about 50% degradation was observed in light grey forestry soil, and only about 20% in peat. The ability of soils to degrade carbaryl could be ranked as follows: light grey > grey forestry > turf podzol > southern chernozeme > ordinary chernozeme > meadow > peat.

Ivanova & Molozhanova (1973) calculated that application of 1.36 kg carbaryl/ha in an orchard resulted in 19.7% being retained

in the soil; 99% of the carbaryl present in soil disappeared within 184 days.

Czaplicki (1979) conducted studies in Poland. The soil half-life of carbaryl was about 3 months and 90% degradation occurred within 18 months. From October to March, when the soil temperature was <5-8 °C, the disappearance of the insecticides in the soil almost stopped.

Rajukkannu et al. (1985) studied the persistence of 4 products in the red and black soils of Tamil Nadu (India), where the tropical climate in conjunction with the soil properties shortened the persistence of insecticides. The half-life of carbaryl was 6.7-7 days and 95% degradation was achieved after 90 days.

It was reported by Odeyemi (1982) that carbaryl disappeared from soil samples treated with 45 mg/kg after 53 days incubation in a greenhouse under tropical conditions (Nigeria).

4.3.6 *Interaction with other physical, chemical, or biological factors*

Nitrogen fertilizers (ammonium sulfate and urea) increased the persistence of carbaryl in flooded laterite soil with a low native content of nitrogen (0.04%). In the alluvial soil with 0.11% total nitrogen, the persistence of the insecticides was little affected. The rates of degradation in the two soils treated with nitrogen fertilizers were almost identical. The authors speculated about the mechanism of this effect, which was possibly due to the preferential utilization of inorganic nitrogen by microorganisms, or to the inhibition of soil hydrolase activity (Rajagopal & Sethunathan, 1984).

4.3.7 *Vegetation*

4.3.7.1 *Uptake and transformation in plants*

Carbaryl from soil treated at about 50 times the usual dose penetrated into apple trees and couch-grass (Molozhanova, 1968). Three months after application of carbaryl (85%) to soil at a dose of 100 mg/kg, residues of carbaryl were detected in the roots and stems in apples (39-13 mg/kg) and in couch-grass (50-38 mg/kg). Under the same conditions, no residues were detected in tomato fruits or in wheat grain, but 5.9 mg/kg were detected in potatoes (Table 9).

Table 9. Migration of carbaryl from the soil into apple trees at different times following application[a]

Experimental conditions	Sampling day after application	Carbaryl content of samples[b] (mg/kg)		
		Soil	Foliage	Fruits
85% WP carbaryl applied under each tree at a rate of 10 mg a.i./kg soil	5	9.3	0	-
	12	6.8	0	-
	19	6.0	5.0	-
	56	4.4	0.04	4.4
	138	2.1	0	-

[a]From: Molozhanova (1968).
[b]Average data from 18 samples are given for each case.

Huque (1972) reported that ^{14}C-labelled carbaryl was readily taken up from granules by 2-week-old rice plants. After 3 days, a level of about 100 mg/kg was determined in the plant (excluding the roots). Residues then decreased to about 15 mg/kg after 18 days.

Ferreira & Seiber (1981) studied the uptake and distribution of carbaryl in rice seedlings following exposure of the roots to the insecticide. Carbaryl was rapidly absorbed and transported upwards to the leaves and stems. After exposure was terminated, the major route of loss of carbaryl was through root exudation (22%) rather than volatilization from the leaves (4.2%). However, since most of the remaining carbaryl in the plant was present on the leaf surfaces, the authors surmised that volatilization might play a greater role in pesticide loss over longer periods of time.

^{14}C-carbaryl and ^{14}C-1-naphthol from soil-bound residues were partially released when barley was grown (Murthy & Raghu, 1988). ^{14}C-residues could be detected in both shoots and roots in the case of carbaryl treatment, while only roots showed ^{14}C-residues in the case of 1-naphthol.

The rate of decomposition of carbaryl in plants depends on the climatic conditions. It is more rapidly decomposed in hot climates, at high temperatures, and by intensive ultraviolet radiation. Thus, residual levels in feed plants were lower in regions with a hot climate than in other regions (Atabaev, 1972).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

5.1.1 *Air*

Ambient air concentrations of carbaryl were measured before and after a treatment of a large area of forest in Maine, USA, to control spruce budworm. Concentrations in air ranged from less than 0.0035 to 0.107 $\mu g/m^3$ several miles away (Shehata et al., 1984).

Room concentrations of airborne carbaryl were measured following application for pest control as a 5% dust at an undetermined rate. The levels detected on the day of application, and 1, 2, or 3 days after application were 1.3, 0.2, 0.1, and 0.01 $\mu g/m^3$, respectively (Wright et al., 1981).

5.1.2 *Water*

Carbaryl concentrations in water from different sources in the USSR were studied by Molozhanova (1970). Data are presented in Table 10.

Table 10. Concentrations of carbaryl in water[a]

Type of sample	Number of samples		Mean concentrations (mg/litre)
	Total	Carbaryl-containing samples (%)	
Well	114	87	0.13
Artesian water	64	70	0.16
Ground water	24	75	0.27
Dam	90	47	0.02
River	77	62	0.044
Lake	84	85	0.03

[a]From: Molozhanova (1970).

According to an earlier report by Molozhanova (1968), carbaryl was present in trace amounts up to a maximum level of 1 mg/litre in well water and reservoirs during carbaryl application (6 kg/ha, 85% WP).

Water irrigation channels, situated at a distance of 200-300 m from a carbaryl-treated cotton field, contained from 0.01 to 0.25 mg/litre up to 18 days after spraying at a dose of 2 kg/ha (Guseynov, 1970).

Residues of pesticides were monitored in the aquatic system of Ioannina basin (Greece) and its natural outlet, Kalamas River, for the period September 1984-October 1985 (Albanis et al., 1986). The carbaryl concentration in water was found to follow a seasonal fluctuation with maxima during summer and minima during winter months. Mean and range values are summarized in Table 11.

Table 11. Mean and range values of carbaryl (ng/litre) on different sampling dates in the Ioannina basin

Month of sampling	River	Canal	Lake
September	0.5		
November	ND[a]		ND[a]
March	ND[a]		
May	ND		
June			ND[a]
July	23.7		21.7
August			2.3
September	1.7		ND[a]
April		ND[a]	
July		8.8	

[a]ND = not detected.

An oil-based, carbaryl formulation (Sevin-2-oil) was applied twice to a coniferous forest in New Brunswick (Canada). At a dose rate of 280 g/ha, the highest concentration in stream water was

0.314 mg/litre and only 0.123 mg/litre 0.5 h after spraying. More than 50% of the initial residues dissipated within 1 h (Sundaram & Szeto, 1987).

Carbaryl was applied aerially as Sevin-4-oil (1.12 kg/ha) to a forest in Montana. Field samples of water were collected to study persistence. Residue levels in 4 streams sampled were variable (3-6, 3-175, 2-260, 4-108 μg/litre) 1.3-2.8 h after application (Pieper & Roberts, 1978; Pieper, 1979). Local accumulations of floating oil-based spray may have caused this variation. Grantham (1980) reported that carbaryl (Sevin-4-oil) levels were generally highest directly after spraying, but increased at some stream sites for 1-2 days after application. This was attributed to light rains, which washed the spray residue off the foliage and into the stream channel. However, Brown (1980) concluded that carbaryl enters streams in periodic doses and that rainfall dates are not related to the presence of residues in streams. Maximum residues of 26.32 μg/litre were found in water 12 h after spraying, with no residues detectable in samples taken hourly until 36 h. Residues were found again in samples taken 2.5-3 days and 5.5-6.5 days after spraying.

In a study where carbaryl (Sevin-4-oil) was applied aerially (0.84 kg/ha) to a forest in Maine, in 1978, samples were collected in 9 streams (Stanley & Trial, 1980). Peak concentrations occurred shortly after spraying and maximum residue levels ranged from 0.93 to 7.8 μg/litre in brooks and from 0.44 to 2 μg/litre in rivers. In one stream, the maximum concentration was 16 μg/litre. Ott et al. (1981) reported that carbaryl levels were highest on the day of spraying (2.7 μg/litre), declined to about 0.7 μg/litre by the third day, but increased again to about 1.2 μg/litre on day 5. No residues were detected in stream water samples taken on the 17th day.

Thomas et al. (1982) treated planted rice fields with carbaryl at rates of 0.63, 0.94, and 1.85 kg a.i./ha, either as a high volume spray (500 litre/ha) or as a low volume spray (150 litre/ha), and monitored the residues. In irrigation water sampled one hour after treatment, carbaryl levels amounted to 0.15-0.30 and 0.07-0.18 mg/litre, under high and low volume spraying, respectively. During the first 24 h after spraying, the concentration in the irrigation water remained fairly constant, but, by the fourth day, it had decreased significantly. By the tenth day after spraying

the residues in water had decreased to 0.02-0.05 and 0.03-0.04 mg/litre, respectively.

A rice field dissipation study was conducted in Arkansas (USA) by Springborn (1988). Carbaryl (Sevin XLR) was applied 3 times at 14-day intervals to an irrigated field plot in which rice was planted. In irrigation water, carbaryl residues disappeared with a half-life of < 1 day after each treatment. The maximum concentration in water was 1466 μg/litre and, by day 3 following each treatment, the concentration was < 121 μg/litre. In a similar study conducted in California, Springborn (1988a) found that carbaryl dissipated rapidly in irrigation water with a half-life of < 1 day. The maximum concentration in water was 648 μg/litre. By day 3 following each treatment, the concentration was < 27 μg/litre.

Residues of 1-naphthol were found in the water collected from wells and ponds in and around Bhopal (India). The residues of 1-naphthol in well water (near a manufacturing plant) ranged from 0.002 to 0.024 mg/litre. In pond waters, the levels were found to be between 0.036-0.098 mg/litre. The level of 1-naphthol in soil samples was of the order of 0.153-0.656 mg/kg (Dikshith et al., 1990).

5.1.3 Soil

Contamination of the soil occurs when carbaryl is used in agriculture. During the treatment period, levels of 1-3 mg carbaryl/kg were measured in the surface layer of the soil in the USSR (Molozhanova, 1968). Concentrations of 0.03-0.35 mg/kg were found in the surface layer of the soil up to 52 days after a single application of carbaryl at a rate of 2 kg/ha (Guseynov, 1970). Carbaryl levels in the soil varied depending on the type of soil (Table 12).

Potatoes were sprayed with carbaryl at 4.25 kg/ha (5 kg Sevin WP, 85%/ha). One day, 10 days, and 2 months after treatment, residues in the soil under the potatoes were, respectively, 1.9, 9.55, and 0.02 mg/kg (Kovaleva & Talamov, 1978b). When the soil was sprayed before sowing, the residues in the soil 1 day, 1 month, 4 months, and 15 months after treatment were 1.5-2, 0.05-0.07,

Table 12. Carbaryl content in different types of soil during harvesting[a]

Type of soil	Number of samples	Carbaryl concentration (mg/kg)
Meadow-chernozem	200	2.22 ± 0.5
Chernozem southern	766	1.01 ± 0.23
Chernozem ordinary	288	1.09 ± 0.26
Chenozem podzol	100	0.15 ± 0.04
Turf-podzol	150	0.04 ± 0.01
Grey-woodland	246	0.0

[a]From: Molozhanova (1970).

0.02-0.08, and 0.06 mg/kg, respectively. Within 100 and 150 days following soil incorporation of carbaryl (Sevin, 10 kg/ha), residues in non-planted soil decreased to 0.05 and 0.02 mg/kg, respectively (Kovaleva & Talanov, 1980).

Yadav et al. (1985) detected 0.22 mg carbaryl/kg in the soil at harvest time, when sesamum (*Sesamum indicum*) was sprayed twice with carbaryl (0.2%) on days 45 and 60 of crop growth (21 August and 5 September). As residues in the soil after the first spray were about 0.65 mg/kg, the rate of reduction of residues in soil was 56% within 2 months. Shilova et al. (1973) measured about 0.1 mg carbaryl/kg soil one month after treatment with carbaryl (5 kg/ha) against blood sucking insects in the subarctic.

Gangwar et al. (1978b) applied a 4% granular formulation to sandy loam planted with a grain crop (bajra) at very exaggerated application rates of 20, 40, and 60 kg a.i./ha. Initial residues of 140-354 mg/kg decreased by a total of 31 to 53% within 30 days and 95 to 98% within 90 days. Residues at 90 days were 2.68-17.49 mg/kg.

Application of carbaryl granules at very high doses of 15, 30, and 45 kg/ha resulted in deposits of 232, 397, and 525 mg/kg, respectively, in soils cultivated with corn, and in 104-109, 168-217, and 304-422 mg/kg, respectively, in clay loam soils cultivated with root crops (beet, radish, carrot). The dissipation rate of carbaryl residues from clay loam soil, in 5 days following the treatment, was 42-56% during autumn and 55-69% during spring. The highest residue levels sampled from all plots decreased to 229.7, 142.9,

73.8, 33.8, 6.7, and 1.3 mg/kg on days 5, 10, 15, 30, 60, and 100, respectively. Residues were below detectable levels in several plots by day 60 and in most plots by day 100 (Kavadia et al., 1978).

According to Kuhr et al. (1974), the dissipation of carbaryl in the soil of apple orchards is rapid. Soil residues of carbaryl had almost completely disappeared from the top 2 inches of soil in 2 weeks. They were 13.8 mg/kg immediately after application and 3 mg/kg, 1-2 days later.

An oil-based carbaryl formulation (Sevin-2-oil) was applied twice by a fixed-wing aircraft to a coniferous forest in New Brunswick (Canada). Initial residue levels 1 h post-spray in litter and soil for both applications were, respectively, 1.21 and 0.86 mg/kg and 0.78 and 0.48 mg/kg (Sundaram & Szeto, 1987). Relative to the amount sprayed, only a small amount of the chemical reached the litter and soil, probably because of canopy filtration. Within 1 day, an average of 40-45% of the initial residues was lost from litter and soil, respectively, indicating a rapid dissipation time of 1.5 days for the disappearance of 50% of the initial maximum concentration. Beyond 5 days, an average of 12% of the initial concentration remained in both the substrates.

As already reported, two field dissipation studies were conducted by Springborn (1988b,c) with carbaryl (Sevin-4-oil) applied twice with a seven-day interval to forest. The first study was conducted in a coniferous Oregon forest. In soil from the treated site, carbaryl levels decreased from 0.196-3.877 mg/kg following the first application to 0.130-1.87 mg/kg, 3 days after treatment, and from 0.079-5.323 mg/kg following the second application to 0.242-1.187 mg/kg at 90 days. The second study was conducted in Pennsylvania. Carbaryl levels in soil decreased from 0.022-0.068 mg/kg following the first application to <0.012-0.075 mg/kg, 3 days after treatment, and from 0.11-0.932 mg/kg following the second application to 0.01-0.099 mg/kg at 90 days.

A rice field dissipation study was conducted in Arkansas (USA) by Springborn (1988a). Carbaryl (Sevin XLR) was applied 3 times, at 14-day intervals, to an irrigated field plot in which rice was planted. In flooded soil, the concentration of carbaryl varied from <11 to 309 μg/kg throughout the study and was not directly related

to application date. The carbaryl level was < 11-309 μg/kg in soil following the first application and < 11-129 μg/kg following the third application; 180 days later, carbaryl concentrations in the soil were 11-56 μg/kg.

In a similar study conducted in California, under the same conditions, Springborn (1988) found that carbaryl dissipated rapidly in flooded soil. The concentration of carbaryl ranged from < 11 to 198 μg/kg throughout the study. Carbaryl was < 11-23 μg/kg in soil at sampling intervals following the first application, and increased to < 11-180 μg/kg following the third application; 180 days after the third application, carbaryl concentrations in the soil were 11-88 μg/kg.

A soil dissipation field study was conducted in 1985/1986 in California (sandy loam, pH 6.3) and Iowa (silt loam, pH 6.5) with carbaryl 80 S formulation (Davis, 1986a). Carbaryl was applied to strip plots of bare soil, 6 weeks later, 7 applications were made with intervals of about 5 days between applications. Soil sampling was performed before treatment, during treatment, and up to 6 months after the last application. No carbaryl residues were found in California pretreatment samples. After the last application, residues reached a maximum of 1.61 and 0.29 mg/kg in the 0-15 and 15-30 cm samples, respectively. Fourteen days after the last application, carbaryl residues below the 15-cm level were less than the limit of quantification.

It took 28 days for residues to dissipate completely from the top 15 cm. The half-life in California soil was calculated to be 2.7-3.8 days.

5.1.4 Food and animal feed

5.1.4.1 Fruit, vegetables, and grain

Contamination of vegetation by carbaryl occurs, either during spraying, or, by its migration through contaminated soil into the roots of plants.

Residual levels of carbaryl after the spraying of plants depend on the type and species of the plants sprayed. Carbaryl levels of up to 30 mg/kg have been found in plants during the treatment period (Molozhanova, 1968). It has been found to be rather persistent in

vegetables and fruits. Concentrations of 0.6-3.9 mg/kg were measured in lettuces 1 week after single or repeated sprayings, and levels up to 1 mg/kg were found in tomatoes treated according to requirements (Antonovich, 1970). In cabbage, initial residues after spraying ranged from 14.8 to 33.9 mg/kg, depending on the concentration used. After 7 days, the residues decreased to 2.5-5.13 mg/kg. In eggplant, the initial concentrations were 8.3-16.9, and 7 days later, 3.05-5.4 mg/kg. After washing, the concentrations decreased considerably to less than 3 mg/kg after day 7 (Mann & Chopra, 1969).

Following application of carbaryl on cauliflower, in the form of dust (10%) at 1.5-2 kg a.i./ha or wettable powder (50%) at 0.75-1 kg a.i./ha, the residues of carbaryl declined to 3.64-9.59 mg/kg within 8 days of treatment. The carbaryl deposits on leaves were between 19.45 and 42.08 mg/kg. Washing of cauliflower with plenty of water reduced the residues of carbaryl by 36-95%. A waiting period of 8 days has been suggested for cauliflower (Singh et al., 1978).

Persistence of carbaryl in brinjals and peas after spraying at 1 and 2 kg a.i./ha was found to be 3.42 and 5.03 mg/kg respectively. Washing of vegetables with water within one hour and after a day of spraying reduced the level of deposits of carbaryl to about 1.0 mg/kg level. In the case of pea pods, the levels of residues dropped to 0.20 mg/kg within 5 days. In pea seeds, the residue levels ranged between 0.03 and 0.09 mg/kg, after 8 days (Krishnaih et al., 1978).

Measurements of carbaryl in different fruits were taken at intervals of 5-10 days after plants had been treated with a 0.2% suspension of carbaryl at 1000 litre/ha during the vegetation period (Bogomolova, 1968, 1970). The initial amount of carbaryl, 2 days after the treatment, varied in different fruits from 2.3 to 2.7 mg/kg. Ten days later, the concentrations were reduced by 50-70%, and, after 20 days, the levels were within the range of 0.2-0.8 mg/kg, depending on the species (Table 13). According to Mann & Chopra (1969), the dissipation of carbaryl from plants after the first day of spraying was about 40-45% of the initial residue.

In apples, concentrations of 2.5-2.9 mg/kg, 0.4-2.4 mg/kg, and 0.15 mg/kg were found on days 7, 10, and 38, respectively, after spraying. One to two months after spraying apples with a 0.1%

suspension at a dose of 2000 litre/ha, residues of 0.08-0.10 mg/kg were measured (Antonovich, 1970). Four months after spraying with a 0.06% suspension at a dose of 9 kg a.i./ha, levels in the range of 0.09-0.24 mg/kg were found in apples, depending on the spraying procedure. Fine-droplet spraying resulted in residue levels 2.5-3 times lower levels than those with coarse-droplet sprays (Atabaev, 1972).

Table 13. Carbaryl levels in different fruits after spraying during vegetation (mg/kg)[a]

Kind of fruit	Day after spraying		
	2	10	20
Strawberries	2.3	1.25	
Gooseberries	2.5	0.90	0.6
Blackcurrants	2.4	1.10	0.8
Cherries	2.7	1.90	0.2-0.4
Plums	2.4	1.40	0.2-0.4

[a]From: Bogomolova (1968).

A survey of apples grown in Ontario, Canada, between 1978 and 1986 showed that out of 22% of carbaryl-treated apples (1.67 kg/ha) sold, 3.6% had detectable carbaryl residues (detection limit of 0.01 mg/kg), and that the average residue level was 0.03 mg/kg, with a maximum of 0.04 mg/kg (Frank et al., 1989).

Prolonged storage of apples reduced the carbaryl residues only slightly (Bogomolova, 1968). The initial level (2.4-2.8 mg/kg) changed little during the first 3 months of storage at a temperature of +5 to +10 °C. A slight reduction was observed during the fourth month of storage. During the process of storage, carbaryl migrated inwards from the surface, so that the concentration in the skin was reduced, while that in the pulp was increased (Table 14).

Residues on lemon foliage on day 0 of treatment were 4.6 ± 0.3 $\mu g/cm^2$. Five days after treatment, levels of 2.4 $\mu g/cm^2$ and 5.6 $\mu g/cm^2$ were found on lemon and orange foliage, respectively; on the 60th day, the residual values were 0.41 and 0.36 $\mu g/cm^2$, respectively. Persistence half-lives were 22 days (lemons) and 14 days (oranges) (Iwata et al., 1979).

Table 14. Carbaryl content in apples during storage (mg/kg)[a]

Part of apple	Day of storage								
	10	20	30	40	50	70	80	100	110
Skin	2.40	1.80	2.00	1.80	1.92	1.72	1.60	1.45	1.22
Pulp	0.35	1.00	1.02	1.10	1.00	1.10	1.34	1.42	1.30
Total	2.75	2.80	3.02	2.90	2.92	2.82	2.94	2.87	2.52

[a]From: Bogomolova (1968).

Carbaryl is persistent, particularly in citrus fruits and grapes. Residues of 3-6 mg/kg were measured in lemons and oranges 2.5-3 months after treatment of trees with 3-10 kg carbaryl/ha, and amounts of 3.6, 1.9, and 0.4 mg/kg were found in grapes on days 7, 14, and 40, respectively, after repeated spraying of vineyards with a 0.12% suspension. The half-life of carbaryl in grapes was 29 days, compared with 2-9 days in cherries and cabbage (Antonovich, 1970).

Washing and peeling reduced carbaryl levels in fruits and vegetables by 40%; thermal processing by 45-90%, and preparation of juices by 53% (Molozhanova, 1970). Canning also reduced carbaryl residues. Thus, canning of different fruits (strawberries, black currants, gooseberries) containing carbaryl in the range of 0.25-0.45 mg/kg, resulted in a reduction to 0.17-0.29 mg/kg; when the initial contents were higher (3-7 mg/kg) the levels after canning dropped to 1.4-2.2 mg/kg and 2.1-2.5 mg/kg, respectively, i.e., from 30 to 70%. Storage of canned fruit further reduced carbaryl residues by 2-3 times after 12 months (Bogomolova, 1968).

Boiling vegetables (e.g., cabbage) reduced carbaryl residues by approximately 50%; however, the residues in pickled cabbage, 5 months after preparation, were only 25% less than the initial amount (Antonovich, 1970).

Elkins (1989) reported that washing during the commercial processing of produce removed 97, 87, and 77% of the carbaryl residues from tomatoes, spinach, and broccoli, respectively. Blanching (short treatment with hot water) was stated to result in 68% removal of carbaryl from green beans, while blanching, in addition to washing, resulted in the removal of over 97% of carbaryl from both spinach and broccoli.

After a single application of carbaryl (Sevin 50 at 2.5 kg/ha), residues in cauliflower decreased from 16.75 mg/kg on the day of application to 0.87 mg/kg, 15 days afterwards (Yadav & Jaglan, 1982). Washing further reduced the detectable residues at 15 days to 0.67 mg/kg, while no detectable residues were present after boiling.

Carbaryl was found in vegetation adjacent to treated fields. Grass growing at a distance of 250 m from a carbaryl-treated cotton field contained 0.18-0.25 mg carbaryl/kg wet weight up to 45 days after spraying (Gusseynov, 1970).

The results of the 1989 Pesticide Residue Monitoring Programme in California showed that carbaryl was detected in 2 samples of grape from 26 in quantities less than the accepted tolerance level. It was not found in oranges (Okumura et al., 1991). Summaries of residue data on different plants are given in Tables 15 and 16. Carbaryl residues were not detected in 44 samples of wheat in the United Kingdom analysed by the multiresidue method (Osborne et al., 1989).

Table 15. Comparison of carbaryl residues with different formulations[a]

Formulation use (kg a.i./ha)	Plant	Mean residues value (mg/kg)	Day after last application
44% SC 2×0.5	apple	0.25	7
	pears	0.16	7
50% WP 2×0.5	apple	0.15	7
	pears	0.09	7
44% SC 2×2	spinach	4.44	-
50% WP 2×2		2.38	14
44% SC 2x2	lettuce leaf	2.72	14
50% WP 2×2		1.55	
44% SC 2×2	barley	7.87	14
50% WP 2×2		4.63	
44% SC 2×2	wheat	0.96	14
50% WP 2×2		0.99	
44% SC 2×2	oats	0.22	14
50% WP 2×2		0.26	

[a]From: Davis (1987).

Davis (1987) studied the impact of different types of formulation on food residues, including carbaryl (44% w/w) oil-based liquid formulation containing a "sticker", in order to prevent bees from carrying carbaryl particles back to the beehive. The 50 W formulation was a "standard" wettable powder formulation. The results are given in Table 15. This work showed that the addition of a "sticker" increased levels of food residues to some extent.

Table 16. Carbaryl residues following different applications

Formulation use (kg a.i./ha)	Plant	Mean value residues (mg/kg)	Day after last application	Reference
44% SC	barley	5.4	14	Davis & Thomas (1987)
44% SC	sugar beet roots	0.07-1.04	14	Thomas (1986)
44% SC aerial ground	pasture grass	59.7-183	3	Davis (1986b)
Carbaryl	sweet cherries	0.33		Frank et al. (1987a)
Carbaryl	tomato	1.2 0.5 0.03	0 3 6-8	Frank et al. (1991)
	tomato juice	0.47 0.24 0.08	0 3 6-8	

Studies on the removal of carbaryl residues from tomatoes, green beans, spinach, and broccoli by commercial and home preparation procedures (Elkins et al., 1968; Farrow et al., 1968, 1969; Lamb et al., 1968) showed a considerable decrease in the residues with treatment (Table 17).

For pre-harvest use on grain, the rate of application of carbaryl ranges from 2 to 9.5 kg/ha, depending on the degree of infestation, density of foliage, and the stage of the life cycle of the pest. Carbaryl, usually applied at a rate of 5 mg/kg, is also used to protect stored grain. Studies on stored wheat, barley, oats, and rice indicated that carbaryl residues on grain have a half-life of between 26 and 80 weeks, depending on the temperature (FAO/WHO, 1976). Residues of carbaryl in baked bread are then of the order of 1-1.5 mg/kg.

Table 17. Removal of carbaryl after preparation procedures

Vegetable	Initial residues (mg/kg)	Percentage removal				References
		Commercial procedure		Home procedure		
Tomatoes	5.2	washing	82-99	washing	77	Farrow et al. (1968)
		canning	98-99	canning	92	
		juicing	98	juicing	77	
Green beans	7.6	blanching & canning	68-73	washing	52	Elkins et al. (1968)
				blanching	81	
				freezing	94	
				canning	100	
Spinach	20.8	washing	66-88	washing	70	Lamb et al. (1968)
		blanching	96-97			
Broccoli	12.4	washing	77	washing & cooking	55	Farrow et al. (1968)
		blanching	82-97	washing, blanching, & freezing	90	

5.1.4.2 *Animal products*

Technical carbaryl was fed to dairy cows of the Brown Swiss, Jersey, Holstein, and Ayrshire breeds at 50, 150, and 450 mg/kg of their average total daily roughage intake (dry weight) for a period of 2 weeks. Samples of milk were taken at regular intervals and the cream was analysed for carbaryl by means of the *p*-nitrobenzene-diazonium fluoborate coupling method. The concentration of carbaryl, if present, was below the sensitivity of the analytical method (0.01 mg/kg) (Gyrisco et al., 1960).

Residues resulting from a single application and repeated applications of carbaryl spray on cattle were rapidly eliminated from body tissues. On days 1 and 3 after application, carbaryl was detected in the liver (0.05 mg/kg), muscles (0.04 mg/kg), and perirenal fat (0.16 mg/kg). Seventy-two hours after treatment, no residues were found in the tissues studied. The excretion in milk persisted for at least 69 h after spraying, the highest concentration being 0.075 mg/litre, 5 h after exposure (Hurwood, 1967).

Data concerning the composition and levels of milk and tissue residues in cows after continuous feeding with 100 mg ^{14}C-carbaryl/kg diet are shown in Tables 18 and 19.

Table 18. Metabolites in tissues after continuous 28-day feeding of 100 mg ^{14}C-carbaryl/kg diet[a]

Metabolite (mg/kg)	Kidney	Liver	Muscle
carbaryl	0.03	0.04	0.02
5,6-dihydrodihydroxycarbaryl	0.05	0.01	0.04
5,6-dihydrodihydroxynaphthol	0.02	0.02	0.0
naphthyl sulfate	0.29	0.02	0.0
water-soluble unknowns	0.43	0.13	0.03
unextractable unknowns	0.18	0.19	0.01

[a]From: Dorough (1971).

Table 19. Composition of milk residues after continuous 28-day feeding with 100 mg ^{14}C-carbaryl/kg diet[a]

	Percentage	mg/kg
Organic phase		
5,6-dihydrodihydroxycarbaryl	38.5	0.11
carbaryl	8.4	0.02
3,4-dihydrodihydroxycarbaryl	4.0	0.01
5,6-dihydrodihydroxynaphthol	1.0	0.01
Water soluble		
5-methoxy-6-hydroxycarbaryl	25.6	0.07
unknowns	10.6	0.03
1-naphthol	5.5	0.02
5-hydroxycarbaryl	3.1	0.01
carbaryl	1.2	0.01

[a]From: Dorough (1970a).

Effective horn fly control for a period of 15 days was obtained by spreading carbaryl down a cow's back. Results indicated that, if applications of a 0.5% spray or a 50% dust were made immediately after the morning or evening milking, no residues of carbaryl would result in subsequent milkings (Eheart et al., 1962). The results obtained by Petrovski (1970) were similar. After treating cows with a 0.85-1% suspension of carbaryl, residues of from 0.1 to 0.3 mg/litre were found in milk, 20 h after application. On the third day, only trace amounts of carbaryl were found. After treatment with a 0.5% suspension of carbaryl, no traces were found in the milk.

5.1.4.3 *Animal feed crops*

Generally, animal feed crops contain less carbaryl than fruit and vegetables. Mean levels of 0.82 mg/kg were found in 80 samples of animal feed plants (Molozhanova, 1970). Levels of 0.3 mg/kg were found in maize stems at harvest, 70 days after spraying (Antonovich, 1970).

Studies on the carbaryl content of animal feed plants in hot climates showed that carbaryl can be detected 3-3.5 months after treatment, depending on the dose and the number of applications. Thus, after repeated applications of 50% carbaryl dust at a rate of 0.5 g/m^2, the carbaryl content in animal feed plants was in the range of 1-1.8 mg/kg wet weight, but, after a single application of 0.7 g/m^2, concentrations of 0.10-0.31 mg/kg were found (Atabaev, 1972).

5.1.5 Other products

Measurement of carbaryl residues in tobacco plants showed that, 15 days after field spraying with 950 g/ha, the content of carbaryl in green tobacco leaves was 10.1 mg/kg. Drying leaves by hot air decreased carbaryl residues by only 10% (Antonovich, 1970).

Application of carbaryl at a rate of 2.2 kg/ha resulted in carbaryl residues on cotton foliage of 7.2 μg/cm^2 on the day of spraying (Estesen et al., 1982). Levels decreased to 5.9, 0.58, and 0.26 μg/cm^2 after 3, 6, and 8 days, respectively.

Carbaryl was found in the foliage of cotton plants in concentrations of 0.03-1 mg/kg from 10 days to 2.5 months after treatment. Carbaryl penetrated the plant through foliage and roots and contaminated the cotton and the seeds. Cotton harvested from treated fields 2 weeks to 1 month after treatment contained 0.015 mg/kg. Trace amounts of carbaryl were found in cotton oil (Guseynov, 1970).

After treatment with a 2% suspension of carbaryl against mountain pine beetle, residues in bark disks after 1 year were 359 mg/kg. In another case, residues in bark disks were 890$\pm$146 mg/kg, after spraying, and 531$\pm$178 mg/kg 16 months later (Page et al., 1985).

5.1.6 Terrestrial organisms

The quantities of carbaryl that were absorbed by songbirds, either by contact or by eating food from a sprayed area, were studied by Kurtz & Studholme (1974). Towhees (American finches) were collected 3 days after the forest had been sprayed for gypsy moths at a rate of 1.1 kg/ha. The amounts of carbaryl found in the towhees

were small, even though the samples were taken close to the spraying time. Trace amounts of carbaryl were found in three samples out of five, compared with two samples out of five control birds. The minimum level of detection was 0.1 μg/g. The low levels of carbaryl found in "sprayed" birds were explained by the fact that towheeds are groundfeeders and that only a small amount of carbaryl might have passed through the trees to the ground.

5.2 General population exposure

5.2.1 *Exposure through the food*

The daily intake of carbaryl was studied for several years in the USA (see Table 20).

Table 20. Carbaryl daily intake in the USA

Year	Positive samples (%)	Daily Intake (mg/day per person)		References
1964-65	7.4	0.15		Duggan et al. (1971);
1965-66	2.7	0.026		Duggan & Corneliussen
1966-67	1.1	0.007		(1972)
1968-69	0.8	0.003		
1969-70	0	-		
		Infant	*Toddler*	
1978	-	0.088	0.05	Gartrell et al. (1986)
1979	-	-	0.049	
1980	-	0.06	0.035	Reed et al. (1987)
1981-82	-	0.129	0.127	
1982	-	-	0.012	
1982-84	-	0.117	0.017-0.0315	Gunderson (1988)

Carbaryl residues in total diet samples in the USA are relatively low (Table 21). Carbaryl is found in potatoes, leguminous vegetables, root vegetables, and fruit. In foods processed in the usual manner, i.e., by peeling, stripping outer leaves, and cooking, when appropriate, carbaryl residues usually decreased to undetectable levels or traces (Manske & Corneliussen, 1974).

Table 21. Carbaryl residues in food in the USA

Number of composites analysed	Number of composites with residues	Number of composites with traces	Range in mg/kg	References
270, from 30 grocery stores in 27 cities June 1970-April 1971	20	15	trace to 0.5	Manske & Cornefiussen (1974)
420, from 35 market baskets, 6 June 1971-July 1972	6	5	0.02	Manske & Johnson (1975)
360, 12 August 1972-July 1973	12	10	0.05-1.10	Johnson & Manske (1976)
360, August 1973-July 1974	8	2	0.001-0.284	Manske & Johnson (1977)
1044, 1978-82	11 (1%)	[a]	[a]	Yess et al. (1991a)
3744, 16 market basket collections 1982-86	135 (4%)	[a]	[a]	Yess et al. (1991b)

[a] No figures given.

During a 5-year period, from 1982 to 1986, the Los Angeles District Laboratory analysed 19 851 samples of domestic and imported food and feed commodities for pesticide residues. A single, rapid, multiresidue method was used. Carbaryl was detected in 164 samples from the total 19 851 samples analysed. Not one sample exceeded the US Federal tolerance levels (Luke et al., 1988). In another publication, the same authors reported comparative studies on US and imported food. Carbaryl was found in 21 samples from a total 6391 US samples in quantities ranging from 0.1 to >2.0 mg/kg, but less than 10 mg/kg. From 12 044 imported agricultural commodities 132 were contaminated by carbaryl, and levels in 14 of them exceeded the tolerance levels (Hundley et al., 1988).

5.2.2 Exposure during insect control

Exposure to carbaryl, used to control the gypsy moth in camping and picnic areas, was monitored on the day of application and then weekly for 3 weeks. Carbaryl was applied from the air at a rate of 1.12 kg/ha. Exposure was measured using dermal pads. Extrapolating from the most contaminated group of pads (they contained an average of 279 μg/pad), the authors calculated a "worst case" exposure of 0.54 mg/kg on the day of spraying. The authors concluded that the risk to those who use public areas during, and after, carbaryl application to trees is negligible (Cameron et al., 1985).

A 5% spray of carbaryl 85% wettable powder (WP) was applied for insect control in homes (Vandekar, 1965), as a surface application, at the rate of 2 g/m^2. Urine samples taken from villagers 1 week after spraying showed a significant increase in 1-naphthol levels from 30.5 μg/ml baseline to 50.3 μg/ml. Inhibition of plasma ChEA was found in 48 out of 63 subjects, 1 week after spraying.

During a monitoring study carried out from 1976 to 1980 in the USA, 1-naphthol was found in 1.4% of the urine samples from persons between 12 and 74 years old. The source was thought to be carbaryl and naphthalene (Carey & Kutz, 1985).

5.3 Occupational exposure during manufacture, formulation, or use

Harry (1977) estimated that about 13 million people in the USA were potentially exposed to carbaryl during its manufacture, formulation, packing, transportation, storage, and during and after application, and while working with treated crops or during harvest.

Best & Murray (1962) published a survey on the exposure of plant workers during the production of carbaryl. Air concentrations varied from 0.23 to 31 mg/m^3. Urine samples contained an excess of 1 mg total 1-naphthol per 100 ml of urine. During air blast spraying of orchards, Jegier (1964) found air concentrations of 0.6 mg/m^3 (0.18-0.81 mg/m^3). The mean respiratory exposure, measured by the respirator pad technique was 0.29 mg/h (0.24-0.53 mg/h) and mean dermal exposure, measured by skin pads, was

25.3 mg/h (18.5-30.3 mg/h). The maximum total exposure was 31 mg/person per h, or 0.025% of the toxic dose. Simpson (1965) estimated that the amount of dermal exposure was less than 0.1% of the toxic dose in orchard sprayers. During cotton spraying by aircraft, Yakim (1965) found 4 mg carbaryl dust/m^3 in the breathing zone of flagmen, 1 mg/m^3 during preparation of the solution, and 0.7 mg/m^3 in the pilot's cabin. Adylov (1966) reported the following air concentrations found during the aerial application of a water solution: flagmen's breathing zone 1.92 (0.64-2.84) mg/m^3; pilot cabin, trace amounts, workers on the ground (preparation of solution, etc.,) 6.28 (0.48-19.2) mg/m^3. In the urine samples of carbaryl formulators, 1-naphthol levels varied from 6.2 to 78.8 mg/litre. Agricultural workers who used carbaryl for pest control excreted from 0.07 to 1.7 mg/litre in their urine (Shafik et al., 1971).

Exposure studies were completed for pesticide application and formulating plant workers by the biological monitoring of 1-naphthol in the urine, dermal pads, and respirator filter pads (total 480 samples of dermal pads and 73 respirator pads). Workers operating tractor-drawn airblast equipment applied carbaryl at 0.045-0.06% as spray (Comer et al., 1975). An estimate of the amount of dermal and respiratory exposure that could occur was made using the procedures described by Durham & Wolfe (1962). The results are presented in Table 22.

Table 22. Potential dermal and respiratory exposure of formulating plant workers and field spraymen to carbaryl[a,b]

Subject	Route of exposure	Exposure situations studied	Exposure (mg/h)	
			Range	Mean
Formulating plant workers[c]	dermal	48	0.80-1209.30	73.90
	respiratory	48	0.03-4.10	1.90
Field spraymen[d]	dermal	32	1.70-211.80	59.00
	respiratory	25	0.01-1.08	0.09

[a]From: Comer et al. (1975).

[b]Calculated on the basis of the worker wearing a short-sleeved, open-necked shirt, no gloves or hat, with his clothing protecting the areas covered.

[c]Workers on mixing and bagging operations (4 and 5% dust).

[d]Operating power air-blast spray machines in fruit orchards (0.045-0.06% solution spray).

The concentration of 1-naphthol in the urine varied from 0.2 to 65 mg/litre with a mean of 9 mg/litre. The rate of excretion per hour varied from 0.004 to 3.4 mg with a mean of 0.5 mg/h. The maximum level during the working day was reached by late afternoon. An approximate calculation of the excreted carbaryl (0.5 mg 1-naphthol/h = 0.7 mg/h excretion of carbaryl), and potential exposure, 75 mg/h, shows great differences. About 1/100 part of possible absorption occurs.

Exposure to carbaryl during agricultural application was studied by Leavitt et al. (1982). WP 80 carbaryl was used (0.45 kg in 200 litre water) to spray trees, lawns, and gardens. The mean dermal exposure was 128 mg/h and the mean inhalation exposure was 0.1 mg/h. The maximum percentage of the toxic dose that the applicators received was 0.12%/h. No symptoms or inhibition of ChE were reported. In another group of applicators, the mean dermal exposure was 59.4 mg/h and inhalation exposure 0.1 mg/h.

Dermal exposure is influenced by the type of spray equipment. The dermal deposit and respiratory intake of carbaryl in humans was monitored during home garden spray operations using compressed air or garden hose-end sprayers (Puech, undated). The greatest mean dermal deposit in cm^2/min was received on the feet. When the spray target was above shoulder height the next highest dermal spray was received on the forearm (Table 23). Exposure through inhalation was insignificant.

Table 23. Human exposure during spray operations

Type of spray equipment	Mean deposit ($\mu g/cm^2$ per min)	Total exposure ($\mu g/kg$ per min)
Compressed air sprayer		
below waist	0.030	4.3
above shoulder height	0.096	5.6
Hose-end sprayer		
below waist	0.154	18.3
above shoulder height	0.353	24.4

A study of the urban application of carbaryl was performed by Gold et al. (1982). The maximum dermal exposure recorded in this study was 2.86 mg/kg per h. The maximum air concentration was 0.28 μg/litre. An insignificant decrease in ChEA in serum and erythrocytes was found in some of the applicators. The mean dermal carbaryl exposure of the applicator, expressed as a percentage of toxic dose per h, was 0.01%, with a maximum of 0.08%. This exposure rate is below the risk rate for applicators. No symptoms of intoxication were reported by the authors. During the urban application of carbaryl to trees and ornamental shrubs using hand-held equipment, air concentrations measured at the breathing zone in full-shift samples, of 0.010-0.070 mg/m^3, were detected in only 30% of the samples (Leonard & Yearly, 1990).

Dermal exposure to carbaryl in harvesters of strawberries was studied by Zweig et al. (1984, 1985). They observed dermal exposure on the hands and forearms, and to a much lesser degree, on the lower legs. The first day, 3 mg carbaryl/h was found on cotton gloves, 0.66 mg/h on pads on the forearms, and 0.07 on the lower legs. The following day, the values were 1.23, 0.41, and 0.07 mg/h for gloves, forearms, and lower legs, respectively. The ratio of dermal exposure to dislodgeable foliar residues (DFR) was 4.34, 2.82, and 6.17, for 3 consecutive days. The half-life of carbaryl on strawberry leaves was 4.1 days. Dislodgeable carbaryl residues on cotton foliage, expressed as μg/cm^2 of cotton leaf (one surface only), following application by man-pulled ground rig were 7.2, 5.9, 0.58, and 0.26 at 0, 72, 144, and 192 h after application, respectively (Estesen et al., 1982). Approximate dermal exposure rates may be calculated using the following expression, proposed by Zweig et al. (1985). Dermal exposure rate (mg/h) = $5 \times 10^3 \times$DFR (in μg/cm^2). This method is suggested to obtain the exposure rate of fruit harvesters, in order to establish safe re-entry periods without human studies.

Factors affecting the levels of exposure during the agricultural application of pesticides were analysed by Wolfe et al. (1967). Wind is the most important environmental condition. The type of activity, equipment used, the duration of exposure, formulation, individual protection, including attitude, are also discussed. Carbaryl deposits from air jet application on orchards were found at 500 m downwind in the presence of inversion, and at 300 m, in its absence. Ground application results gave deposits at 150 and 50 m, respectively

(MacCollom et al., 1985, 1986). Air concentrations were 17.88 $\mu g/m^3$ during spraying above the orchard downwind edge, 9.5 $\mu g/m^3$, 30 min after spraying, and 8.17 $\mu g/m^3$, 1 h after spraying.

Airborne and deposit levels of carbaryl were measured after three applications by air to an apple orchard (Currier et al., 1982). Samples of air were taken at distances of from 12.2 to 3994 m from the target orchard. At a distance of 12.2 m, the concentration in air was between 3.3 and 76.2 $\mu g/m^3$. One hour later it was between 2.5 and 11.3 $\mu g/m^3$. At a distance of 3.2-3.3 km, the initial concentration was between 9 and 28.8 $\mu g/m^3$ during spraying and 0.9-14.4 $\mu g/m^3$, one hour after treatment. Because the area of the study was one of concentrated agriculture, it is possible that carbaryl could have been used on other orchards and gardens near to the sampling point.

6. KINETICS AND METABOLISM

6.1 Absorption

When only 0.1 ml of carbaryl solution (0.025-0.05 mmol/litre) was administered into the lungs of anaesthetized rats, it was rapidly absorbed. About 50% of the dose was absorbed in 2.6 min. The amount of carbaryl absorbed per unit time was directly proportional to the administered dose (Hwang & Shanker, 1974). Blase & Loomis (1976) demonstrated that carbaryl could be taken up and metabolized by the isolated perfused rabbit lung. Retention by rats of ^{14}C-labelled carbaryl, inhaled as vapours during a 1-h exposure period, was 75.4% of the total dose inhaled, which did not exceed 50 μg (Dorough, 1982).

When a dose of 7.5 μmol radiolabelled carbaryl/kg body weight was administered intragastrically to fasted, anaesthetized, female rats, 22 and 67 min after dosing, the proportions absorbed were $52.6 \pm 14.1\%$ (n=3) and $81.7 \pm 15.7\%$ (n=3), respectively; 89.3% of the radiolabelled material in the collected portal blood was [1-naphthyl-1-^{14}C]*N*-methyl carbarmate (Casper et al., 1973).

Absorption from the small intestine was studied in anaesthetized rats with a ligature around the pylorus and an ileocecal junction with major blood vessels not occluded. A concentration of carbaryl of 0.005-0.1 mmol/litre was used. The absorption half-time was 6.4 min (Hwang & Schanker, 1974).

On the basis of ligation studies on mice, Ahdaya & Guthrie (1982) determined that the absorption of carbaryl from the stomach was relatively low compared with that from the entire gastrointestinal tract (29%), but was relatively high in comparison with that of other pesticides.

Variation in the digestive absorption kinetics, according to the vehicle used, was reported in studies on female Wistar rats (Cambon et al., 1981). The results indicated that carbaryl was absorbed more rapidly in the intestine when either DMSO or tragacanth was used as

a vehicle. It seems that milk does not facilitate carbaryl absorption. Inhibition of ChEA was closely related to the absorption rate.

The rate of dermal penetration of carbaryl (in acetone solution) into mammals, birds, amphibia, and insects was studied by Shah et al. (1983). The half-time of penetration of ^{14}C-labelled carbaryl was 317 min in Japanese quail, 12.8 min in mice, 6.4 min in grass frogs, 4576 min in American roaches, and 791 min in tobacco horn worms.

In an *in vitro* study, only about 1% of an applied dose of carbaryl penetrated through the skin of the rat over an 8-h period (MacPherson et al., 1991). Using two different methods, Shah & Guthrie (1983) measured the half-time for penetration of carbaryl, applied dermally at a rate of 4 $\mu g/cm^3$, and found 10.34 h and 4.75 h, respectively. Shah et al. (1987) compared the rate of dermal penetration of carbaryl in young, versus adult, Fischer 344, female rats and did not find any consistent age-related differences.

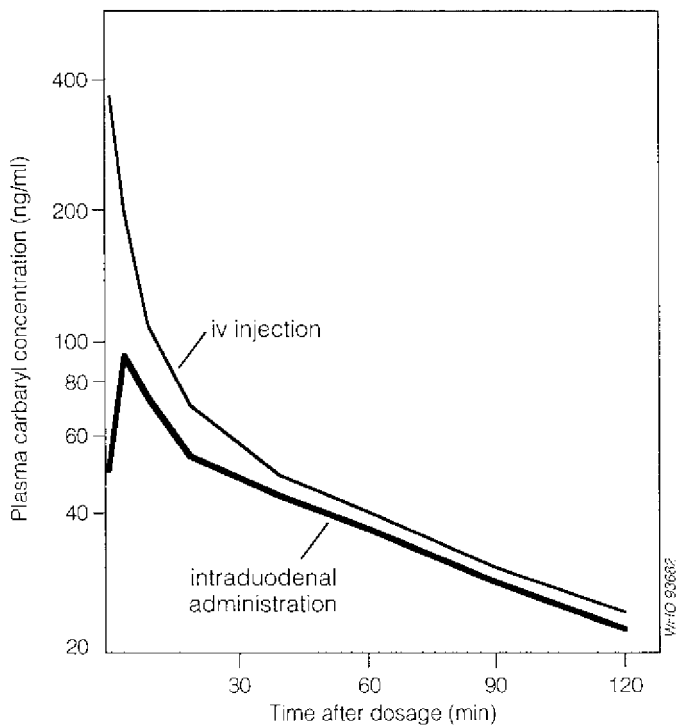
Percutaneous absorption of carbaryl in rats was also studied by Knaak et al. (1984). Carbaryl dissolved in acetone was applied to back skin (not occluded) at 43.4-48 $\mu g/cm^2$. Recovery studies indicated that 57.7% of the applied carbaryl was absorbed. Approximately 5.8% of carbaryl penetrated the skin within 1 h, the rate of absorption being 0.18 $\mu g/h$ per cm^2. The half-life of absorption by blood was 1.26 h, and that for elimination, 67 h.

Carbaryl labelled with radioactive carbon (^{14}C), dissolved in acetone, was applied to the skin of six volunteers, in order to study percutaneous penetration (Maibach et al., 1971; Feldmann & Maibach, 1974). The results showed almost complete penetration of carbaryl on the forearm and jaw angle. After a 24-h application, the cumulative urinary excretion over 5 days was 74%. According to other authors using the same data, the estimated cumulative absorption over 5 days, as a percentage of the applied dose, was 63% (Fisher et al., 1985), 45% of this occurring 8 h after the onset of penetration, which had a lag of 3.5 h.

Comparing the different studies, it is clear that some solvents can facilitate the dermal penetration of carbaryl.

6.2 Distribution

Plasma levels of carbaryl in rats were compared after iv, intraduodenal, or hepatic portal administration of 0.5 mg/kg (Houston et al., 1974). In Fig. 2, it is shown that plasma concentrations were lower after intraduodenal application, when carbaryl was subjected to the liver's first pass metabolizing effect. Plasma concentrations following portal application were also lower (approximately 80% of the concentration after the systemic route of application).



Adapted from: Houston et al. (1974)

Fig. 2. Metabolism of carbaryl.

The distribution of carbaryl in rat tissues after a single oral administration of 144.2 mg/kg body weight (0.2 LD_{50}) was studied (Klisenko & Yakim, 1966) at 5 and 30 min, and 1, 2, 4, 24, 48, and 72 h. Carbaryl and 1-naphthol were identified by thin-layer chromatography with a sensitivity of 0.5 μg/g. At 5 min, carbaryl was found in all organs. Thirty min after administration of carbaryl, peak concentrations found were: muscle, 35 μg/g, brain, 16 μg/g, spleen, 25 μg/g, and erythrocytes, 120 μg/g; at 60 min, a level of 45 μg/g was found in the liver. After 24 h, levels of only 1-4 μg carbaryl/g were detected in the liver, kidney, muscles, and skin. At 48 h, no residues were found. The authors suggested that carbaryl is rapidly distributed and excreted. 1-Naphthol was found in the liver, stomach, intestines, kidneys, and lungs. Other non-identified metabolites were present in the liver and lungs.

Levels of carbaryl in the tissues of rats poisoned with oral doses of 800 and 1200 mg/kg, respectively, were as follows: liver, 7-58 and 52-80 μg/g; heart, 3.5-31.3 and 40.6-45.9 μg/g; brain, 3-26.8 and 25.9-30.9 μg/g. Higher concentrations were found in animals that died from poisoning than in animals killed, even though they were treated with the same doses (Mount et al., 1981).

Yakim (1970) studied the distribution of carbaryl and 1-naphthol after 6-month oral administration of 0.2, 0.1, or 0.05 LD_{50} carbaryl in rats. Carbaryl was found in the intestines (20-40 μg/g), liver (4-20 μg/g), and kidneys and lungs (in trace amounts); 1-naphthol was found in the kidneys (20-50 μg/g), and in the liver (5-10 μg/g) in groups treated with 0.2 LD_{50}. The carbaryl level was < 1 μg/g in the organs studied in the group treated with 0.1 LD_{50}; no traces of carbaryl were found in the group treated with 0.05 LD_{50}. The author suggested that a higher quantity of carbaryl is found 30 min after a single oral application, which corresponds to the highest percentage of ChE inhibition.

Two to 6 h after a single dermal application of 500 mg carbaryl/kg to cats, the compound was found in plasma at 15 μg/ml and in erythrocytes at 25 μg/ml. Inhalation studies were also performed on cats (Table 24). The author stressed that carbaryl was present in smaller amounts in plasma than in erythrocytes because of the more active metabolism by blood proteins. More 1-naphthol and other unidentified metabolites were present in plasma.

Table 24. Relation between carbaryl inhalation and resulting cholinesterase (ChE) inhibition[a]

Experimental conditions	Carbaryl and 1-naphthol		ChE inhibition in %	
	Plasma	Erythrocytes	Plasma	Erythrocytes
Single 6 h exposure to 80 mg/m^3 8 cats	2.5-5 µg/ml after exposure; no traces 4 h later	5-10 µg/ml (after exposure) 10-15 µg/ml (4 h later) 2-2.5 µg/ml (24 h later)	39-80 (after 4 h)	52-84 (after 4 h)
Single 6 h exposure to 20 mg/m^3 8 cats		0-10 µg/ml in single animal 0 after 48 h		28-44 in blood (after 4 h); 0 (after 48 h)
4-Month exposure to 16 mg/m^3 4 cats		traces in single animal in blood		
1-Month exposure to 63 mg/m^3 4 cats	5-15 µg/ml, 0 on the 6th day after the end of exposure	5-15 µg/ml, 0 on the 6th day after the end of exposure	44 on the day of exposure	62 on the 7th day of exposure
4-Month exposure to 38 mg/m^3 4 cats	5 µg/ml on the third day of exposure	10 µg/ml on the third day of exposure	-	-

[a]From: Yakin (1979)

Elimination of carbaryl and normalization of ChE activities occurred in 48-70 h with all routes of administration of carbaryl. Carbaryl has a low cumulation capacity.

In a study in which the abilities of several pesticides to bind to potential carriers isolated from human blood were compared, carbaryl was much more effectively bound by albumin than by either high- or low-density lipoproteins (Maliwal & Guthrie, 1981).

Levels of carbaryl in some tissues of male, albino, Fisher Strain 344 rats, after single and multiple oral administration (Table 25) were reported by Hassan (1971).

Table 25. Tissue levels of carbaryl[a]

Treatment	Time after administration	Concentration of carbaryl		
		Whole blood (μg/ml)	Heart (μg/g)	Brain (μg/g)
Single dose 80 mg/kg	2 h	16.2	2.6	3.45
Rats fed 700 mg/kg diet	90 days	4.8	0.85	0.68
Rats fed 100 mg/kg diet	90 days	2.7	< 0.5	< 0.5

[a]From: Hassan (1971).

Andrawes et al. (1972) studied the ^{14}C residues in hen tissues following the feeding of 1-naphthyl-^{14}C-carbaryl at 70 mg/kg for 4 days (Table 26).

Radiolabelled carbaryl naphthyl ^{14}C (6600 dpm/μg) and carbaryl carbonyl ^{14}C (4000 dpm/μg) were administered intratracheally to rats as aerosols for 15 seconds. The maximum concentration in blood occurred after 2-5 min. Distribution of the residues in the organs, 1 h after inhalation, was highest in the lung (9.2-10.5%), liver (4.7-9.2%), bladder (2.7-5.9%), and kidney (2.5-3.7%) (Nye & Dorough, 1976).

Distribution of ^{14}carbon after intraperitoneal and oral administration of 7.4 μmol carbaryl/kg body weight to rats was studied by Krishna & Casida (1966) (Table 27). Carbaryl was found in all tissues analysed. No marked differences with sex and

Table 26. Concentration of ^{14}C residues in hen tissues after feeding 1-naphthyl-^{14}C carbaryl at the level of 70 mg/kg for 4 days[a]

Sample	μg/kg at indicated times after last treatment	
	16 h	7 days
Brain	17.3	6.8
Heart	47.5	20.9
Kidney	405.5	80.7
Pancreas	69.6	15.6
Skin	86.6	22.4
Fat	25.2	5.2
Gizzard	43.0	13.9
Thigh	28.6	10.1
Breast	25.9	12.7
Leg muscle	29.1	9.0
Blood	197.2	152.2
Lung	138.5	122.5
Liver	332.6	33.4
Spleen	108.7	74.2
Intestine and contents	300.1	< 5.0
Intestinal wall	44.0	11.1
Oviduct	50.5	6.7
Developing egg (small)	534.3	7.4
Developing egg (large)	508.1	35.5
Remaining carcass	35.5	< 5.0

[a]From: Andrawes et al. (1972).

administration route were noted. On the basis of the rate of excretion of radioactivity following an intraperitoneal injection of labelled carbaryl, Shah & Guthrie (1983) calculated a half-time for clearance of label of 6.46 h.

Distribution of carbaryl was studied in 7 Sprague-Dawley rats and Swiss mice on day 18 of pregnancy. Whole-body autoradiography was performed after oral application of 13.5 μCi carbaryl methyl ^{14}C/kg. The transfer to the placenta began in the first hour. Distribution of the carbaryl occurred in the excretory organs, fetus, digestive tract, and the bone marrow and brain. The major portion was quickly eliminated. A more stable localization occurred in highly active protein-building organs, such as the fetus, digestive tract, and bone marrow. The ^{14}carbon concentration in the eye, liver, and brain of the fetus was relatively constant from 8 to 96 h (Declume & Derache, 1976, 1977; Declume & Benard, 1977a,b, 1978).

Table 27. Distribution of ^{14}carbon in various tissues in rats, 48 h after ip administration of carbaryl and its hydrolysis product, in μmol equivalent/kg of fresh tissue, based on total ^{14}C[a]

Labelled position	Blood		Bone	Brain	Fat	Heart	Kidney	Liver	Lung	Muscle	Spleen	Testes
	Corpuscle	Plasma										
Carbonyl ^{14}C	0.38	0.16	0.26	0.33	0.16	0.39	0.47	0.63	0.32	0.18	0.33	
Methyl ^{14}C	0.51	0.22	0.47	0.67	0.19	1.23	1.37	1.78	0.97	0.47	0.97	
1-Naphthyl-1-^{14}C	0.02	0.19	0.19	0.03	0.18	0.06	0.17	0.09	0.05	0.03	0.26	0.09
1-Naphthol-1-^{14}C (hydrolysis product)	< 0.01	0.06	0.03	0.01	0.04	0.01	0.05	0.14	0.02	1.16	0.13	

[a]Adapted from: Krishna & Casida (1966).

Fernandez et al. (1982) determined that the elimination of label following intravenous administration of 20 mg ^{14}C carbaryl/kg to rats could be best described by a three compartment model, with 73% of the label excreted within 24 h.

Strother & Wheeler (1976, 1980) reported that ^{14}C-carbaryl rapidly crossed the rat placenta and was distributed in all fetal tissues. Fetal brain, heart, and lung contained more ^{14}C on a weight basis than the maternal counterpart.

6.3 Metabolism

The metabolism of carbaryl has been studied extensively, and its complexity and the need for additional studies are recognized. As with other carbamates (WHO, 1986), the principal metabolic pathways are hydroxylation, hydrolysis, and epoxidation, resulting in numerous metabolites subjected to conjugation, forming water-soluble sulfates, glucoronides, and mercapturates (Carpenter et al., 1961; Dorough et al., 1963; Dorough & Casida, 1964; Knaak et al., 1965; Menzie, 1969; Bend et al., 1971).

Hydrolysis of carbaryl results in the formation of 1-naphthol, carbon dioxide, and methylamine (Fig. 3) (Carpenter et al., 1961; Sakai & Matsumura, 1971).

The first evidence for carbaryl hydroxylation was reported by Hodgson & Casida (1961). Carbaryl is metabolized by a rat liver microsome system, requiring $NADPH_2$ and oxygen, to form a formaldehyde-yielding derivative.

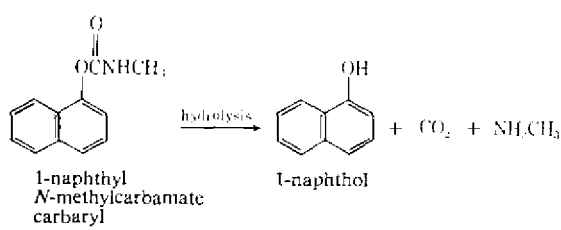


Fig. 3.Hydrolytic pathway for carbaryl.
From: Dorough (1970b).

The use of ^{14}carbon-labelled carbaryl (Fig. 4) and thin-layer chromatography contributed to further studies on carbaryl metabolism (Skraba & Young, 1959; Krishna et al., 1962). Chin et al. (1974) used *in vitro* techniques on tissues from animals and human beings.

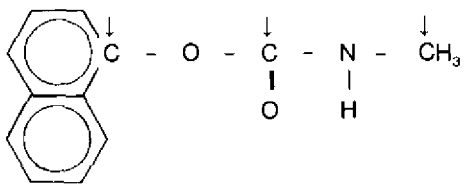


Fig. 4. Site of ^{14}carbon-label intrastructural formula of carbaryl. From: Dorough & Casida (1964).

Reviews on carbamate and carbaryl metabolism have been published (Lykken & Casida, 1969; Kuhr, 1970; Knaak, 1971; Kuhr, 1971; Ryan, 1971; Fukuto, 1973; Dorough, 1973; Kuhr & Dorough, 1976).

6.3.1 In vitro *studies on animal tissues*

An investigation of the individual metabolism of carbaryl in the liver, lung, and the kidney of rat was conducted using the tissue explant maintenance technique. Hepatic tissue of the rat, incubated with carbaryl, actively performed demethylation, hydrolysis, hydroxylation, and oxidation, followed by sulfate and glucuronide conjugations (Chin et al., 1979b).

Rat liver microsomes fortified with reduced nicotineamide-adenine dinucleotide phosphate were used to study the hydroxylated products of carbonyl ^{14}C, methyl ^{14}C, and naphthyl ^{14}C carbaryl (Dorough & Casida, 1964). The metabolites were identified as *N*-hydroxymethylcarbaryl, 4-hydroxycarbaryl, and 5-hydroxycarbaryl. At least 2 unidentified metabolites had the C-O-C(O)-N-C structure intact. 1-Naphthol and at least two unidentified metabolites without the carbamyl groups were formed as a product

of hydrolysis. The nature of carbaryl metabolites in liver microsomes in mice, rats, and rabbits was studied by Leeling & Casida (1966) and in guinea-pigs and rats by Knaak et al. (1965). Two more metabolites were identified (Table 28): 5,6-dihydro-5,6-dihydroxycarbaryl, and 1 hydroxy-5,6-dihydro-5,6-dihydroxy-naphthalene. It was suggested that hydrolysed metabolites are probably conjugated as glucoronides and sulfates (Knaak et al., 1965; Hassan et al., 1966; Leeling & Casida, 1966). A study on rat liver microsomes and small intestine later showed (Mehendale & Dorough, 1971) that about 90% of 1-naphthol and *N*-hydroxymethylcarbaryl and about 40% of 5-hydroxycarbaryl and 4-hydroxycarbaryl were conjugated as glucuronides. The presence of thioether conjugates in incubation mixtures of mouse liver homogenates with carbaryl has been confirmed (Bend et al., 1971; Ryan, 1971).

The *in vitro* technique for metabolic studies using liver tissues qualitatively reflects the *in vivo* metabolic processes of carbaryl in animals and human beings (Sullivan et al., 1972) and their similarity (Matsumura & Ward, 1966).

Methylmercury hydroxide pretreatment in rats (10 mg/kg daily for 2 days) decreased the hepatic microsomal cytochrome P-450 content and aminopyrine demethylase by 50%, as well as the microsomal hydroxylation reaction *in vitro* of carbaryl to form 4-hydroxycarbaryl and *N*-hydroxymethylcarbaryl. Chlordane pretreatment increased both cytochrome P450 and hydroxylation (Lucier et al., 1972). However, there were no quantitative changes in the metabolite pattern.

When the metabolism of carbaryl in rat intestine was studied *in vitro*, hydrolysis and the synthesis of 1-naphthyl glucuronide were reported to occur mainly in the first third of the intestine (Pekas & Paulson, 1970; Pekas, 1972).

MacPherson et al. (1991) studied the metabolism of carbaryl using a rat skin preparation *in vitro*. A post-mitochondrial fraction was able to catalyse hydrolysis and sulfation and glucuronidation conjugation reactions, but not ring hydroxylation. The activities were very small in comparison with activities in liver microsomes.

The degradation of carbaryl by an esterase of the American cockroach (*Periplaneta americana*) was reported by Matsumura & Sakai (1968).

Table 28. Carbaryl naphthyl-1-^{14}C metabolism by liver microsomes from mice, rabbits, and rats, in the presence of $NADPH_2$[a]

Substance determined	Total radiocarbon (%) using liver microsomes from:		
	Mice	Rabbits	Rats
Ether extract			
Carbaryl	32.1	19.4	46.9
Hydroxylated metabolites			
1-naphtyl *N*-hydroxymethylcarbamate	11.9	6.3	11.7
4-hydroxy-1-naphthyl methylcarbamate	6.7	8.1	6.1
5-hydroxy-1-naphthyl methylcarbamate	2.4	1.7	1.3
5,6-dihydro-5,6-dihydroxy-1-naphthyl methylcarbamate	5.3	9.1	3.8
1-hydroxy-5,6-dihydro-5,6-dihydroxy-naphthalene	1.9	2.7	1.5
1-Naphthol	7.2	6.3	5.8
Unidentified metabolites			
Metabolite A	4.0	4.5	3.5
Metabolite C	0.6	2.0	0.8
Aqueous fraction	28.5	39.6	19.4

[a]From: Leeling & Casida (1966).

6.3.2 In vivo *studies on animals*

The metabolism of carbaryl has been studied in a variety of mammals including rat, rabbit, guinea-pig, monkey, sheep, cow, pig, and dog. Although many organs have been shown to be able to metabolize carbaryl, the most important one is the liver.

The metabolism of 1-naphthyl-^{14}C carbaryl was studied in male and female Beagle dogs following a single, oral administration of 2.5 or 25 mg/kg. The metabolic pathways identified involved hydrolysis, *N*-methyl oxidation, ring hydroxylation, and conjugation. No significant qualitative differences were found between male and female dogs or between high and low dosage levels. Faecal elimination accounted for 30-66% of the applied dose and was found to be primarily the result of incomplete absorption from the intestinal tract of the solid material and subsequent elimination of unchanged carbaryl. The metabolic pathway defined is illustrated in Fig. 5 (Andrawes & Bailey, 1978c).

The metabolism of 1-naphthyl-^{14}C carbaryl was studied in male and female Sprague-Dawley rats following a single, oral administration of 2.5 mg/kg. The metabolic pathways identified in the rat involved hydrolysis, *N*-methyl oxidation, ring hydroxylation, and conjugation. New metabolites identified, previously unknown in the rat, were: 1,5-naphthalenediol, 1,6-naphthalenediol, 3,4-dihydro-3,4-dihydroxy-1-naphthol, and 3-hydroxy-1-naphthyl methylcarbamate. These new metabolites had been previously identified in the dog. The metabolic pathway defined is illustrated in Fig. 5. Faecal elimination accounted for only 2-7% of faecal ^{14}C as carbaryl, indicating more complete absorption of the test material than in the dog (Andrawes & Bailey (1978a).

Conjugated metabolites of 1-naphthyl-^{14}C carbaryl excreted in rat and dog urine, after similar single oral treatments of 2.5 mg/kg, were separated and compared as intact conjugates using gel permeation and thin layer chromatography. The metabolic products were found to be qualitatively similar in the two animal species, with evidence of glutathione conjugation in the dog. Urinary metabolites only differed quantitatively between species. The rat appeared to be considerably more active in hydrolysing carbaryl to 1-naphthol followed by conjugation, whereas, in the dog, the principle urinary metabolites

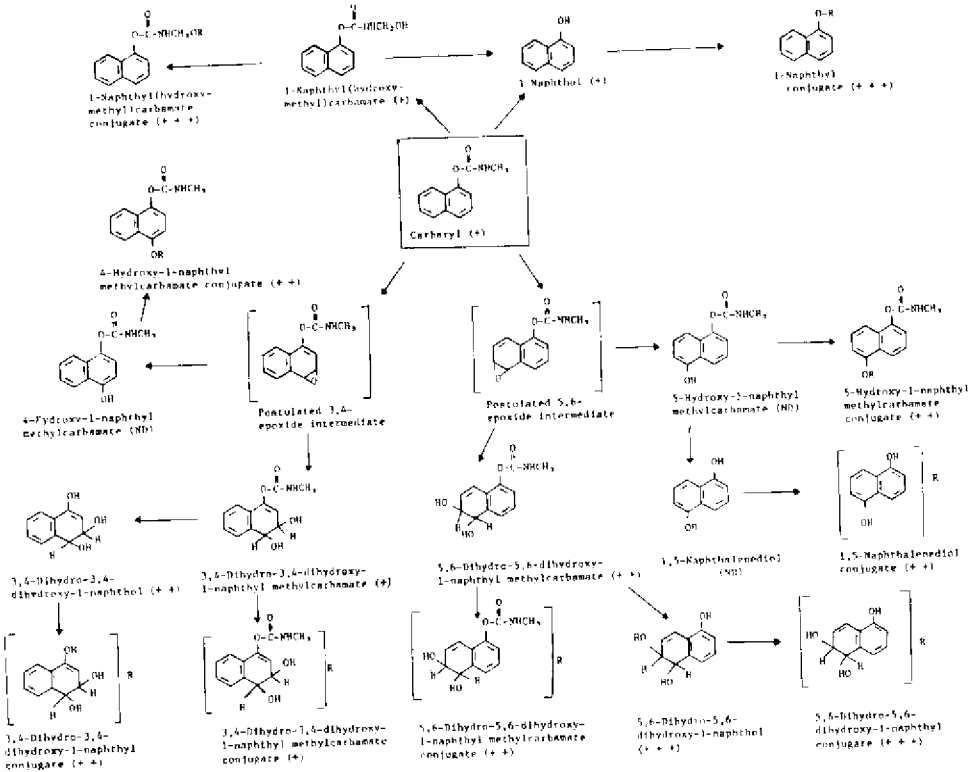


Fig. 5. A proposed metabolic pathway for carbaryl in man. From: Andrawes & Myers (1976).

were formed through direct conjugation of carbaryl itself. A significant amount of urinary radioactivity in both species remained unidentified, i.e., 27 and 34% in the rat and dog, respectively (Andrawes & Bailey, 1978b). Tables 29 and 30 illustrate the quantitative urinary metabolic differences in rats and dogs. Note that "Free" refers to unconjugated metabolites whereas "Acid" and "Enzyme" refer to acid- and enzyme-hydrolysed conjugates.

Table 29. Metabolic products present in a 24-h sample of urine of a rat treated orally with 2.5 mg 1-naphthyl-^{14}C carbaryl/kg in corn oil

Products	Percentage of total radioactivity in urine			
	Free	Enzyme	Acid	Total
1-Naphthol	0.26	15.86	0.49	16.61
Carbaryl	0.14	0.45	4.22	4.81
Methylol	ND[a]	ND[a]	0.64[b]	0.64
1,5-Naphthalenediol	0.17	1.12	0.08	1.37
1,6-Naphthalenediol	0.03	0.42	ND[a]	0.45
5-Hydroxy carbaryl	7.76	3.07	0.24	11.07
5,6-Dihydrodihydroxy naphthol	1.16	4.99	[b]	6.15
5,6-Dihydrodihydroxy carbaryl	5.66	7.75	[b]	13.41
1,4-Naphthoquinone[c]	0.03	1.12	0.10	1.25
4-Hydroxy carbaryl	2.30	2.76	0.19	5.25
3-Hydroxy carbaryl	ND[a]	ND[a]	0.06	0.06
3,4-Dihydrodihydroxy naphthol	0.71	1.53	[b]	2.24
Unknown 1	0.25	2.95	0.06	3.26
Unknown 2	ND[a]	3.46	ND[a]	3.46
Other unknowns	0.37	1.92	0.38	2.67
Highly polar materials	ND[a]	6.99	20.31	27.30

[a]ND = none detected.
[b]Acid hydrolysis degrades the methylol to desmethyl carbaryl and the dihydrodihydroxy derivatives to phenols.
[c]A decomposition product of 1,4-naphthalenediol during work-up.

Table 30. Metabolic products present in a 24-h sample of urine of a female dog treated orally with 25 mg 1-naphthyl-^{14}C carbaryl/kg

Products	Percentage of total radioactivity in urine			
	Free	Enzyme	Acid	Total
1-Naphthol	0.38	2.74	1.47	4.59
Carbaryl	1.71	0.16	9.90	11.77
Methylol	ND[a]	ND[a]	0.22	0.22
1,5-Naphthalenediol	0.21	1.83	1.14	3.18
1,6-Naphthalenediol	ND[a]	1.62	ND[a]	1.62
5-Hydroxy carbaryl	1.61	1.67	0.20	3.48
5,6-Dihydrodihydroxy naphthol	1.12	9.79	ND[a]	10.89
5,6-Dihydrodihydroxy carbaryl	3.80	3.09	ND[a]	6.89
1,4-Naphthoquinone[b]	ND[a]	1.24	1.36	2.60
4-Hydroxy carbaryl	0.64	5.30	0.44	6.38
3-Hydroxy carbaryl	ND[a]	0.04	0.01	0.05
3,4-Dihydrodihydroxy naphthol	ND[a]	0.50	ND[a]	0.50
Unknown 1	ND[a]	0.20	0.62	0.82
Unknown 2	ND[a]	1.30	ND[a]	1.30
Other unknowns	ND[a]	1.26	0.43	1.69
Highly polar materials	ND[a]	9.06	34.96	44.02

[a]ND = none detected.
[b]A decomposition product of 1,4-naphthalenediol during work-up.

The above work supersedes the work by Knaak & Sullivan (1967), who mistakenly concluded that the Beagle dog metabolic pathway was qualitatively different from that of the rat, because of poor absorption of solid/slurry test material. The marked emphasis on differences in metabolic pathways between species, together with the analytical techniques available at the time of the study contributed to their conclusions.

Studies on the nature of the biliary, water-soluble metabolites of carbaryl were conducted by Bend et al. (1971) on 19 male Wistar rats, using a technique with the bile duct cannulated. Water-soluble conjugates of carbaryl with sulfur-containing amino acid were found

in the urine as well as the bile of treated rats: *S*-(4-hydroxy-1-naphthyl) cysteine and *S*(5-hydroxy-1-naphthyl)-cysteine. Biliary secretion of 5,6-dihydro-5,6-dihydroxycarbaryl glucuronide following an infused dose was found to be greatly reduced, from 10% to less than 1%, by pretreatment with antibiotics (Struble et al., 1983b). This indicates that bacteria play a role in the enterohepatic circulation and bilary secretion of this metabolite of carbaryl.

The functional activity of the reticulo-endothelial system (RES) can influence carbaryl metabolism (Pipy et al., 1980). The elimination of carbaryl from the blood decreased significantly in rats (24 male Sprague-Dawley) with RES inhibited by colloidal carbon, and increased in those in which the RES was activated with glyceryl trioleate. Correlation of the activity of RES with the enzyme activity of monoxygenases of the hepatic microsomal fraction could possibly explain this effect of the RES in the toxicokinetics of carbaryl.

An intravenous injection of colloidal carbon, which inhibits liver microsomal metabolism, reduced biliary excretion of an iv dose of carbaryl given 18 h later (Pipy et al., 1981). Pretreatment of rats with 75 mg phenobarbital/kg per day, ip, for five days resulted in an increase in the rate of sulfate conjugation of carbaryl, following a high dose of carbaryl (16.4 mg/kg), but not a low dose (1.64 mg/kg) (Knight et al., 1987).

6.3.3 Metabolic transformation in plants

The formation of carbaryl metabolites in plants is primarily dependent on the hydrolytic, oxidative, and conjugative potential of the plant tissues, which are similar to the tissues of insects and mammals. The metabolism in plants is of a shorter duration than that in insects and mammals, and the tendency to accumulate metabolites is more pronounced. The carbamate ester bond appears to be quite stable in plants, which explains the small amount of recovery of 1-naphthol from treated plants. The extent of oxidation is generally higher in plants and insects than in mammals. Several hydroxymetabolites are formed by oxidation of the *N*-methyl group and naphthalene ring. They are conjugated as glycosides. Non-enzymatic factors, such as light, heat, and humidity may contribute to the degradation of carbaryl in plants as well (Kuhr, 1971).

The metabolism of carbaryl has been defined in a wide variety of plant species (Table 31). Metabolites were isolated in microgram quantities for mass and ultraviolet spectroscopic analyses (Mumma et al., 1971).

6.3.4 In vitro *studies with human tissues*

The metabolism of carbaryl in selected human tissues was studied *in vitro* by Chin et al. (1974). On the basis of the total anionic characteristics of the metabolites derived from each organ, metabolic activity occurred in the following organs in descending order: liver, lung, kidney, placenta, vaginal mucosa, uterus.

The metabolic profiles of carbaryl in human postembryonic fetal autopsy tissue were determined using 1-naphthyl-^{14}C or *N*-methyl-^{14}C-carbaryl. The anionics from fetal liver amounted to 20% of those found with the adult liver. Naphthyl glucuronide and naphthyl sulfate were produced in the kidney, whereas the lung produced naphthyl sulfate from carbaryl (Chin et al., 1979a).

Carbaryl was metabolized oxidatively by primary human embryonic cells in culture (Lin et al., 1975). Complete degradation occurred after 72 h of incubation. Unconjugated metabolites were identified as 1-naphthol, 5-hydroxycarbaryl, 4-hydroxycarbaryl, and 5,6-dihydro-5,6-dihydroxycarbaryl. The water-soluble components were identified as 4-hydroxycarbaryl, 1,4-naphthalenediol, and 5,6-dihydro-5,6-dihydroxycarbaryl. The primary human embryonic lung cells did not convert carbaryl to carbon dioxide. They may not possess the enzyme system that is necessary to break down the naphthalene ring of carbaryl to form carbon dioxide.

Sakai & Matsumura (1971) studied the degradation of carbaryl by brain esterases. Carbaryl was degraded by band $E_4$and E_6, whereas, in the mouse brain preparation, the compound was degraded by band E_8, E_9, and E_6.

Cell culture techniques were used to examine the products of carbaryl degradation by cultures of an L-132 cell line derived from normal human embryonic lung. The data indicated that detoxification was similar to that observed in animals and in *in vitro* enzyme systems (Baron & Locke, 1970).

Table 31. The composition of water-soluble metabolites of carbaryl in plants.
(% distribution of released aglycones 21 days after treatment (for apples, 53 days))

Metabolite	Bean[a] (mature foliage)	Bean[a] (shell only)	Wheat[b] (seedlings)	Potato[c] (mature foliage)	Corn[d] (seedlings)	Rice[d] (seedlings)	Tomato[c] (mature foliage)	Apples[e]
5,6-Dihydrodihydroxycarbaryl	2.5	12.7	2.1	ND[d]	1.3	2.9	ND	2.1
Methylol carbaryl[e]	29.9	47.9	10.5	16.2	13.3	7.8	25.4	2.8
7-Hydroxycarbaryl	24.2	trace	ND	ND	ND	ND	ND	0.8
4-Hydroxycarbaryl	15.0	4.1	23.6	4.1	8.9	3.7	13.8	13.7
5-Hydroxycarbaryl	7.3	9.4	21.3	4.1	12.9	5.6	3.4	9.2
1-Naphthol	13.8	21.0	1.1	5.8	3.2	3.5	8.1	11.3
5,6-Dihydrodihydroxynaphthol	ND	ND	ND	ND	0.5	1.0	ND	
Carbaryl	0.3	0.8	20.8	27.0	24.1	42.8	16.8	33.3
Unknown(s)	ND	ND	3.2	ND	2.9	2.2	5.2	3.0
Unhydrolysed conjugates	7.1	4.1	17.4	42.8	33.0	30.4	27.3	12.6

References: [a]Wiggins & Weiden (1969); [b]Andrawes & Chancey (1970); [c]Chancey & Andrawes (1971b); [d]Chancey & Andrawes (1971a); [e]Chancey (1974).
[f]ND = not detected.

Studies on the *in vitro* metabolism of carbaryl by a human liver fraction indicated that there was a difference in the metabolic pattern compared with that in the rat liver. The human liver produces at least two more metabolites (Strother, 1970).

6.3.5 In vivo *studies on humans*

The metabolism of carbaryl in humans appears to be qualitatively similar to that previously reported in other mammals. Metabolic reactions include: hydroxylation, hydrolysis, and conjugation. Metabolites of carbaryl were identified in the urine of human volunteers after ingestion of a 2 mg/kg dose (Andrawes & Myers, 1976). Only traces of the unchanged carbaryl could be detected in the urine indicating rapid metabolism. From the spectrum of the metabolites identified, a metabolic pathway of carbaryl in humans is proposed and shown in Fig. 6.

The only detectable metabolites in urine samples taken from workers exposed to carbaryl dust were 1-naphthylglucoronide and sulfate (Knaak et al., 1965). Later 1-naphthyl and 4-hydroxycarbaryl, as conjugates of glucuronic and sulfuric acid, were found in a study on volunteers.

Human exposure to carbaryl during aerial application for Gypsy moth control was assessed by Schulze et al. (1979). The results of this study indicated a strong positive correlation between carbaryl exposure and the excretion of urinary 1-naphthol within 24 h of known exposure and a total lack of 1-naphthol in pre-exposure samples.

The presence of these metabolites has been confirmed in six urine samples of workers with high exposures to carbaryl (Andrawes & Myers, 1976).

One major and three minor interfering chemicals were detected in no-exposure samples as well as the maximum exposure samples. These interfering materials developed a colour similar to that of carbaryl metabolites upon spraying the chromatograms with *p*-nitrobenzene diazonium fluoborate. It is estimated that the major interfering pigment accounted for as much as one-third of the total colour observed on thin-layer chromatograms. These interfering

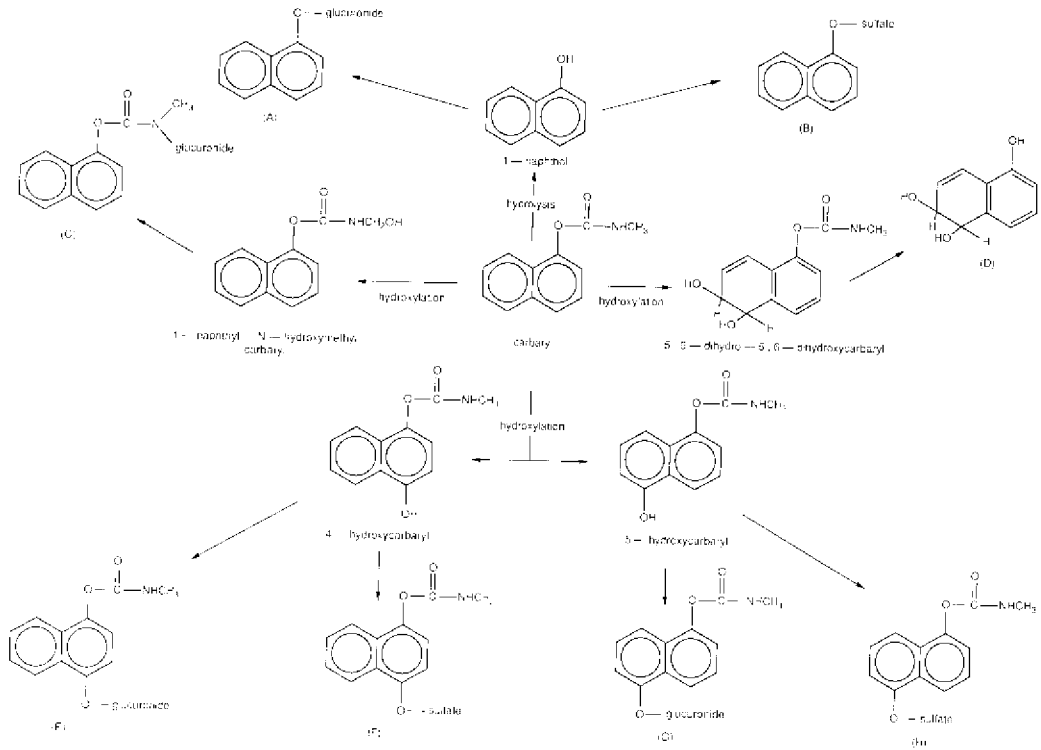


Fig. 6. Primary carbaryl metabolites in mammals and routes of formation (hydrolysis or hydroxylation). From: US EPA (1980).

chemicals may also be the cause of high blank values often encountered during the routine analysis of urine samples (Andrawes & Bailey, 1979).

6.4 Elimination and excretion in expired air, faeces, urine, milk, and eggs

The elimination of metabolized carbaryl is rapid, and accumulation in animals seems unlikely, under normal exposure conditions. Carbaryl is generally excreted entirely within 24-96 h of intake. Elimination takes place mainly through the urine, faeces, and respiration, and, to a lesser extent, through the milk of dairy animals and the eggs of poultry.

Carbaryl is mainly excreted as its product of hydrolysis, 1-naphthol, which is detoxified to water-soluble glucuronide (Carpenter et al., 1961), and sulfate (Whitehurst et al., 1963), and only in trace amounts as 1-naphthol or unchanged.

The average percentage of metabolites recovered after orally administered doses of 1-naphthyl ^{14}C, methyl ^{14}C, and carbonyl ^{14}C carbaryl to rats was 94% over a 7-day period (Knaak et al., 1965). Only residues from carbaryl methyl ^{14}C were detected after that, since the methyl moiety is incorporated in tissue (2-3%). Liberated naphthol is conjugated and excreted, while the liberated carbonyl groups are disposed of as respiratory $^{14}CO_2$ (Knaak et al., 1965). Forty-seven to 57% of the metabolites excreted retain the intact C-O-C(O)N-C structure, indicating a nonhydrolytic pathway for carbaryl. Monkeys and pigs (2 young females) excreted carbaryl as a conjugate of intact carbaryl and 4-hydroxycarbaryl, mainly glucuronides. Sheep also excreted 1-naphthyl glucuronide and sulfate and 4 (methylcarbamoyloxy)1-naphthylsulfate (Knaak et al., 1968).

Myers (1977) studied the correlation between the amount of carbaryl ingested and urinary metabolites levels. Metabolites were measured as three groups:

I. naphthyl sulfate;
II. free and sulfated 5,6-dihydrodihydroxycarbaryl and dihydrodihydroxynaphthol;
III. other conjugated (glucuronides) of naphthol, 5,6-dihydrodihydroxycarbaryl, and 5,6 dihydrodihydroxynaphthol.

The amounts in groups I and II were 25.5-36.5% of the dose. When all three groups of metabolites were analysed, the amounts of metabolites for the same period represented 41.5-52.7% of the dose. Naphthol was the major metabolite found in Group III (mean 75% of all metabolites of the group). A good correlation was found between the amount ingested and urinary metabolites.

Rats treated orally with naphthyl^{14}C carbaryl (2.3 μci) excreted 90% of the administered radioactivity in the urine within 3 days. During the 72-h sampling period, the faeces contained only 2-5% of the radioactivity (Lucier et al., 1972).

Eighty per cent of 5 mg of ^{14}C naphthyl carbaryl, given intraperitoneally to rats, (see section 6.3.2) was eliminated in the 24-h urine and 10% in the faeces (Bend et al., 1971). Enzymatic hydrolysis and reverse isotope dilution showed that 10% of the dose was excreted as 1-naphthyl-glucoronide, 5%, as 1-naphthylsulfate, 3%, as conjugates of 4-hydroxycarbaryl, 5%, as 1-naphthylsulfate, 3%, as conjugates of 4-hydroxycarbaryl, and 5% of 5-hydroxycarbaryl. About 2% of the carbaryl appeared unchanged in urine. Other radioactive metabolites were not identified.

Following a single, ip injection in albino rats of both sexes, of methyl ^{14}C and carbonyl ^{14}C carbaryl at 30 mg/kg, 75-80% was recovered after 48 h in the expired air and urine. Liberated by hydrolysis, *N*-methyl carbamic acid was spontaneously decomposed to methylamine and carbon dioxide (43.5%). The methylamine moiety was later demethylated to $^{14}CO_2$, which was eliminated in the expired air and ^{14}C formate (9.2%), which was excreted in the urine (Hassan et al., 1966).

In the study of Nye & Dorough (1976), 2.5% of the endotracheally administered carbaryl dose was exhaled as ^{14}C-carbon dioxide. More than 90% of the dose was eliminated in the urine during 3 days. The faeces contained 2-5%.

A comparative study on the excretion of carbaryl after a 7.5 μmol/kg, ip dose in rats was reported by Krishna & Casida (1966) who used three types of labelled carbaryl (Table 32).

Table 32. Fate of ^{14}carbon in male Sprague-Dawley rats after ip administration of carbaryl[a]

Labelled position	Administered ^{14}carbon recovered (%)			
	Expired $^{14}CO_2$	Urine		Faeces
		0-24 h	24-48 h	
Carbonyl ^{14}C	24.5	62.1	2.4	2.1
Methyl ^{14}C	12.3	54.6	3.4	3.9
Naphthyl ^{14}C	0.2	74.2	2.3	8.9
Hydrolysis product naphthol ^{14}C	< 0.1	86.4	3.3	1.4

[a]From: Krishna & Casida (1966).

Biliary excretion of carbaryl was studied in bile-duct cannulated rats. Naphthyl ^{14}C and methyl ^{14}C carbaryl (50 μg) were administered intravenously to rats (see section 6.3.2). During the first 2 h of collection, 90% of the total biliary radioactivity was eliminated (Bend et al., 1971). After oral application of 0.01 mg/kg naphthyl-^{14}C carbaryl to rats, 37.5% was excreted via the bile in the first 3 h and 45.4% (cumulative percentage) of the dose was eliminated within 48 h. Faecal elimination was 1.4% and urine elimination was 42.3% (Marshall et al., 1979). The results of Struble et al. (1983a), who used higher doses of carbaryl (1.5, 31, and 300 mg/kg) on male Sprague-Dawley rats were similar. Twelve hours after administration, 15-46% of the ^{14}C was excreted in the bile, 10-40% in the urine, and less than 1% was eliminated in faeces. Three metabolites were identified from the bile, the major one being 5-6-dihydro-5-6-dihydroxycarbaryl glucoronide (12-18% of the biliary ^{14}C).

On the basis of a study on 50, male, Sprague-Dawley rats, Borzelleca & Skalsky (1980) reported that carbaryl metabolites in the blood were also present in the saliva, at similar concentrations.

Leeling & Casida (1966) studied carbaryl metabolites in the urine of one male and one female New Zealand White rabbit. The ether-extractable metabolites found in the urine were: *N*-hydroxymethyl carbaryl, 4-hydroxycarbaryl, 5-hydroxycarbaryl,

5,6-dihydro-5,6-dihydroxycarbaryl, 5,6-dihydro-5,6-trihydroxy-1-naphthol, and 1-naphthol.

Thirty-five, adult, female American cockroaches (*Periplaneta americana*) were injected through the central abdominal wall with 5 μg of carbaryl-carbonyl ^{14}C, carbaryl methyl ^{14}C, or 2 μg carbaryl naphthyl ^{14}C. Metabolites similar to those appearing in rat liver microsomes were formed. About 19% of the radioactivity of carbaryl carbonyl ^{14}C was eliminated as ^{14}C-carbon dioxide in 24 h (Dorough & Casida, 1964).

Excretion of carbaryl in milk was studied by Baron (1968). Application of a total dose of 2 g carbonyl carbaryl ^{14}C to a lactating cow resulted in approximately 1% of radioactive residues in the milk. In skim milk, 87% of these residues were water-soluble and 13% chloroform-soluble. About 90-95% of the ^{14}C radioactivity in the soluble component was removed after crystallization of lactose.

The metabolism of carbaryl naphthyl ^{14}C was studied in one lactating Jersey cow (Dorough, 1967). Two consecutive single treatments at 6-day intervals with 0.25 mg/kg body weight (total 125 mg) and one single dose of 3.05 mg carbaryl naphthyl ^{14}C/kg body weight added to the feed, resulted in radiolabelled residues in the milk for as long as 60 h after treatment. The first sample of milk, taken after 6 h, showed maximum concentrations of chloroform extractables, water-soluble, and unextractable, residues in whole milk in the range of 0.063-0.95 mg/litre. Residues of only a slightly lower magnitude were detected in the 12-h milk samples and rapidly declined in 24-h samples. Thirty per cent of the residues in the 6-h sample was a chloroform-extractable metabolite, tentatively identified as 5,6-dihydro-5,6-dihydroxy-1-naphthyl-*N*-methylcarbamate. About 0.35% of the total dose was detected in the milk in both treatments, 70% in the urine, and 11% in the faeces in 0.25 mg/kg treatment, and 58% in the urine and 15% in the faeces in the 3.05 mg/kg treatment. The highest levels in the tissues of the cow, killed on an unspecified day after treatment, were found in the liver, kidney, and ovaries.

A single lactating cow was treated orally with a daily total dose of 518 mg ^{14}C-carbaryl (0.77 mg/kg body weight), given in two doses, 12 h apart. Results are shown in Table 33 (Dorough, (1969). Fifty-nine per cent of the radioactivity from a ^{14}C-labelled oral dose

of carbaryl administered to a cow was recovered from the urine within the first 24 h (Saini & Dorough, 1978).

The passage of ^{14}C into the milk and its presence in the suckling neonates has been studied by whole-body autoradiography in rats fed ^{14}C-methyl carbaryl. The highest concentrations in newborn offspring, after 48 h, were found in the stomach contents, the liver, the hair, and the bone marrow (Benard et al., 1979).

Table 33. Distribution and excretion of total-^{14}C equivalents in milk, urine, faeces, and tissues, 24 h after one-day oral application of carbaryl in a lactating cow

Sample	mg/kg	Dose recovered (%)
Milk	0.04	0.09
Urine	22.4	58.64
Faeces	0.47	1.65
Tissues:		
- liver	0.098	0.21
- kidney	0.382	0.17
- leg muscle	0.027	nil
- fat	0.014	nil

A Saanen goat was treated orally with 1.34 mg carbaryl carbonyl ^{14}C/kg. The excretion of radioactivity in the urine was 7.4% at 2 h, 24% at 4 h, and 45% at 24 h. In total, 47% of the radioactivity was excreted the urine. In the milk, the peak was 0.9 mg/litre at 8 h, dropping to 0.008 mg/litre 60 h after the administration of carbaryl (Dorough & Casida, 1964).

The excretion of carbaryl was studied in hens. Carbaryl-carbonyl^{14}C (10 mg/kg body weight) was given orally to Leghorn hens. Fifty per cent of the ^{14}C was expired within 48 h. When carbarylnaphthyl ^{14}C was applied at the same dose, no radioactivity was detected in the expired gases. The urine was the primary route of excretion. ^{14}Carbon remaining in the carcass, 48 h after dosing,

accounted for 1.4 and 7.1% of the dose given as the ring-labelled and carbonyl-labelled compound, respectively (Paulson & Feil, 1969). The main metabolites found in the urine of hens were: 1-naphthol, 1-naphthyl glucoronide, and sulfate esters of 1-naphthol, 4-hydroxycarbaryl, and 5-hydroxycarbaryl. Conjugates with other metabolites were also found in small quantities (Paulson et al., 1970). Mature hens were given a single oral dose of carbaryl naphthyl ^{14}C at 10 mg/kg body weight. Eggs collected for 12 days contained a total dose of 0.33% of the ^{14}C administered (Paulson & Feil, 1969).

The fate of naphthyl-1-^{14}C carbaryl in laying chickens was studied by Andrawes et al. (1972). Chickens (3 White Leghorn in each group) were fed 7, 12, or 70 mg/kg carbaryl in the feed twice daily for 14 days. They had been pretreated for 17 days with the same doses of nonlabelled carbaryl in feed. Residues reached maximum levels within 1 day in excrement, 2 days in egg white, and 6-8 days in egg yolk. After the end of dosing, the half-life of ^{14}C residues was < 1 day in the excrement and egg white, 2-3 days in the egg yolk, and 5 days in the carcass. Metabolites and carbaryl found in the eggs of hens, fed 70 mg carbaryl/kg averaged in total 19.7 μg of ^{14}C carbaryl equivalent per egg (16.3 μg in yolk and 3.4 μg in white), collected between the 9th and the 14th day of dosing. Naphthyl-1-sulfate was the largest single component of egg residues accounting for the higher concentration of residues in the egg yolk.

7. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

7.1 Microorganisms

7.1.1 Soil microorganisms

Studies of the effects of insecticides on soil microorganisms are complex and subject to many sources of variation. It is therefore difficult to assess the practical significance of the results of such studies.

Varsheny & Gaur (1972) studied the impact of carbaryl (as Sevin) on soil fungi. They determined the size of the fungal population and the species composition of the fungal community after plating out extracts of soil samples on various media. The authors suggested that, at very high rates of addition to the soil (up to 5000 mg/kg), there was evidence of a change in species composition and an increase in the total fungal population.

In laboratory cultures of saltmarsh protozoans (dominated by *Euplotes* sp.), Weber et al. (1982) found that both carbaryl and 1-naphthol caused dose-related mortality. For both compounds, mortality at 1 mg/litre was about 50%. There was almost 100% mortality at 10 mg/litre.

Carbaryl inhibited the growth of cultures of *Bacillus subtilis* (DeGiovanni & Donnelly, 1968).

7.1.2 Aquatic microorganisms

Edmiston et al. (1985) conducted a detailed study of the effects of carbaryl on *Paramecium multimicronucleatum*. The 24-h LC_{50} was 28 μg/litre in a static plate test. Effects on the oxygen uptake of cultures and effects on the cell surface were also reported, but these results were mostly obtained using concentrations in excess of the 24-h LC_{50}, and must be of limited value.

Murray & Guthrie (1980) studied the responses of bacterial cultures originating from Lake Houston. The respiratory rate of bacterial cultures was increased at water temperatures of between 23-33 °C. Plate counts of bacterial colonies suggested that carbaryl treated cultures contained more bacteria than control cultures on most days in a 26-day study.

7.2 Aquatic organisms

Aquatic toxicity studies have been conducted in the laboratory and field to define the biological effects associated with acute and long-term exposure to carbaryl and the degradation product, 1-naphthol, of aquatic vertebrates and invertebrates. More data are available for freshwater organisms than for saltwater organisms. In addition, actual and simulated field studies have been conducted to assess the impact of carbaryl exposure on freshwater invertebrates.

7.2.1 Aquatic invertebrates

Studies on the toxicity of carbaryl for non-target aquatic invertebrates have included investigations on molluscs, crustaceans, and insects, concentrating on organisms of commercial importance, organisms most likely to be exposed during a typical application of carbaryl, or on standardized test species typically used in aquatic toxicity tests. The acute and long-term laboratory studies under various environmental conditions (pH, temperature, water hardness, etc.) are briefly reviewed in Table 34.

Most of the studies on the toxicity of carbaryl for aquatic invertebrates have been conducted under laboratory conditions and, consequently, the results only yield data on the relative toxicity of the substance. They do not reflect realistic exposure in the environment. Most of the laboratory studies evaluate constant, short-term (less than 1 week) exposure to carbaryl under static or flow-through conditions. There are few long-term studies on the effects of carbaryl on aquatic invertebrates. Exposures in the environment are typically localized, at much lower concentrations than in aquatic toxicity tests and are not constant.

The toxicity of carbaryl on the early development of the sea urchin was studied by Hernandez et al. (1990). Developmental stages with active cleavage and cellular mobilization (blastula and gastrula) turned out to be more sensitive. The next two stages (prism and pluteus) were less sensitive and EC_{50} values were 8-26 times higher. This effect may be connected with increased detoxication processes by the cytochrome oxidase system.

Table 34. Acute toxicity of carbaryl for invertebrates

Organism	Test material	Size/age	Stat/ Flow[a]	Temp-erature (°C)	Hardness (mg/litre)[b]	pH	Parameter[c]	Concent-ration (µg/litre)	Reference
Crustacea (Freshwater)									
Water flea									
Daphnia magna	unknown		stat	16	42	7.4	48-h LC_{50}	5.6	Sanders et al. (1983)
Daphnia magna	technical						96-h LC_{50}	3280	Lejczak (1977a)
Daphnia magna	unknown						48-h EC_{50}	0.26	Rawash et al. (1975)
Daphnia magna	technical						21-day MATC 21-day NOEC (survival)	1.5-3.3 6.0	Surprenant (1985c)
Daphnia pulex	technical		stat	16	44	7.1	48-h LC_{50}	6.4	Mayer & Ellersieck (1986)
Simocephalus serrulatus	unknown		stat stat stat	10 16 21	44 44 44	7.1 7.1 7.1	48-h LC_{50} 48-h LC_{50} 48-h LC_{50}	11 7.6 8.1	Johnson & Finley (1980)
Ostracod									
Cypridopsis vidua	unknown	adult	stat	21	272	7.4	48-h LC_{50}	115	Mayer & Ellersieck (1986)
Sow bug									
Asellus brevicaudus	technical	adult	stat	18	44	7.1	96-h LC_{50}	280	Johnson & Finley (1980)

Table 34 (continued)

Organism	Test material	Size/age	Stat/ Flow[a]	Temp- erature (°C)	Hardness (mg/litre)[b]	pH	Parameter[c]	Concent- ration (µg/litre)	Reference
Crustacea (Freshwater)									
Amphipod									
Gammarus fasciatus	unknown	adult	stat	21	44	7.1	96-h LC_{50}	26	Johnson & Finley (1980)
Gammarus lacustris	unknown	adult	stat	21	44	7.1	96-h LC_{50}	22	Johnson & Finley (1980)
Gammarus pseudolimnaeus	unknown	adult	stat	12	40	6.5	48-h LC_{50}	8.13	Mayer & Ellersieck (1986)
		adult	stat	12	40	7.5	48-h LC_{50}	11.5	
		adult	stat	12	40	8.5	48-h LC_{50}	7.8	
Gammarus pulex	technical						48-h LC_{50}	29	Bluzat & Seuge (1979)
Gammarus pseudolimnaeus	technical						96-h LC_{50}	16	Sanders et al. (1983)
Gammarus pseudolimnaeus	technical						96-h LC_{50}	13	Woodward & Mauck (1980)
Glass shrimp									
Palaemonetes kadiakensis	unknown	adult	stat	21	272	7.4	96-h LC_{50}	5.6	Johnson & Finley (1980)
		25-31 mm	stat				96-h LC_{50}	120	Chaiyarach et al. (1975)

Table 34 (continued)

Crayfish									
Procambarus sp.	technical	immature	stat	12	42	7.5	96-h LC_{50}	1900	Mayer & Ellersieck (1986
Procambarus simulans	unknown	60-70 mm	stat				96-hLC_{50}	2430	Chaiyarach et al. (1975)
Procambarus acutus	technical						96-h LC_{50}	500	Cheah et al. (1978)
Crustacea (Freshwater)									
Prawn									
Macrobrachium lamarrei	technical						96-h LC_{50}	19	Omkar & Shukla (1985)
Upogebia pugettensis	wettable powder[d] 1-naphthol						48-h EC_{50} 48-h EC_{50}	90 4400	Stewart et al. (1967)
Callianassa californiensis	wettable powder[d] 1-naphthol						48-h EC_{50} 48-h EC_{50}	80 3500	
Hemigrapsus oregonensis	wettable powder[d] 1-naphthol						24-h EC_{50} 24-h EC_{50}	710 74 200	

Table 34 (continued)

Organism	Test material	Size/age	Stat/ Flow[a]	Temp-erature (°C)	Hardness (mg/litre)[b]	pH	Parameter[c]	Concent-ration (µg/litre)	Reference
Crustacea (estuarine & marine)									
Blue crab									
Callinectes sapidus	unknown	juvenile	flow	29	27s		48-h LC_{50}	320	Mayer (1987)
Brown shrimp									
Penaeus aztecus	unknown	juvenile	flow	30	28s		48-h LC_{50}	1.5	
Pink shrimp									
Penaeus duorarum	unknown	juvenile	flow	23	29s		48-h LC_{50}	32	
Grass shrimp									
Palaemonetes pugio	unknown	juvenile	flow	23	29s		48-h LC_{50}	28	
		3-4 days	stat	24	28-30s		96-h LC_{50}	22	Thursby & Champhon (1991)
Crustacea (estuarine & marine)									
Mysid shrimp									
Mysidopsis bahia	unknown		flow				96-h LC_{50}	> 7.7	Nimmo et al. (1981)

Table 34 (continued)

Mysidopsis bahia	technical						96-h LC_{50} NOEC	6.7 5.1	Surprenant (1985b)
Mysidopsis bahia		24 h 24 h 24 h	flow stat flow	25 24 26	31s 30s 31-32s		96-h LC_{50} 96-h LC_{50} 28-day LC_{50}	8.46 19 9.9	Thursby & Champhon (1991)
Ostracod									
Cypretta kawatai	technical						72-h LC_{50}	1800	Hansen & Kawatski (1976)
Insects									
Stonefly									
Isogenus sp.	unknown	larva	stat	7	35	7	96-h LC_{50}	2.8	Mayer & Ellersieck (1986)
Pteronarcys californica	technical						96-h LC_{50}	4.8	Johnson & Finley (1980)
Mosquito									
Culex pipiens	technical						24-h LC_{50}	75	Rawash et al. (1975)
Insects									
Midge									
Chironomus tentans	technical						24-h LC_{50}	7	Karnak & Collins (1974)
Chironomus tentans	technical						72-h LC_{50}	5900	Hansen & Kawatski (1976)

Table 34 (continued)

Organism	Test material	Size/age	Stat/ Flow[a]	Temperature (°C)	Hardness (mg/litre)[b]	pH	Parameter[c]	Concentration (μg/litre)	Reference
Chironomus plumosus	technical						48-h EC_{50}	10	Sanders et al. (1983)
Chironomus riparius	unknown	larva	stat	20		4	24-h LC_{50}	106	Fisher & Lohner (1986)
		larva	stat	20		6	24-h LC_{50}	133	
		larva	stat	20		8	24-h LC_{50}	127	
Back swimmer									
Notonecta undulata	technical						96-h LC_{50}	200	Federle & Collins (1976)
Water stick									
Ranatra elongata	wettable powder						96-h LC_{50}	624	Shukla et al. (1982)
Diptera									
Chaoborus	technical						48-h LC_{50}	296	Bluzat & Seuge (1979)
Ephemeroptera (Mayfly)									
Cloeon	technical						48-h LC_{50}	480	
Crawling water beetle									
Peltodytes sp.	technical						96-h LC_{50}	3300	Federle & Collins (1976)

Table 34 (continued)

Insects									
Stone fly									
Pteronarcella badia	unknown	larva	stat	16	44	7.1	96-h LC_{50}	1.7	Johnson & Finley (1980)
		larva	stat	12	38	6.5	96-h LC_{50}	11	Woodward & Mauck (1980)
		larva	stat	12	38	7.5	96-h LC_{50}	13	Mayer & Ellersieck (1986)
		larva	stat	12	38	8.5	96-h LC_{50}	29	
Claasenia sabulosa	unknown	larva	stat	16	44	7.1	96-h LC_{50}	5.6	Johnson & Finley (1980)
Molluscs									
Common mussel									
Mytilus edulis	unknown						48-h EC_{50} for byssal attachment	> 30 000	Roberts (1975)
Mytilus edulis	wettable powder	larva					48-h EC_{50}	2300	Stewart et al. (1967)
	1-naphthol						48-h EC_{50}	1300	
Giant oyster									
Crassostrea gigas	wettable powder	larva					48-h EC_{50}	2200	
	1-naphthol						48-h EC_{50}	800	
Clinocardium nuttallii	wettable powder	adults					24-h EC_{50}	7300	
	1-naphthol						24-h EC_{50}	6400	

Table 34 (continued)

Organism	Test material	Size/age	Stat/ Flow[a]	Temp- erature (°C)	Hardness (mg/litre)[b]	pH	Parameter[c]	Concent- ration (µg/litre)	Reference
Molluscs									
Eastern Oyster									
Crassostrea virginica		juvenile	flow	29	27s		96-h EC_{50}	> 2000	Mayer (1987)
Crassostrea virginica	technical						48-h EC_{50}	2700	Surprenant (1985a); Dionne et al. (1985)
Mactrid clam									
Rangia cuneata		35-50 mm	stat		5s		96-h LC_{50}	125 000	Chaiyarach et al. (1975)
Lymnaea stagnalis	technical						48-h LC_{50}	21 000	Bluzat & Seuge (1979)

[a]Stat = static conditions (water unchanged for the duration of the test).
Flow = flow-through conditions (carbaryl concentration in water continuously maintained).
[b]Hardness = expressed as mg $CaCO_3$/litre.
s = salinity (‰).
[c]EC_{50}s for oyster based on shell deposition.
[d]50-80% wettable powder.

Carbaryl is slightly toxic for freshwater and marine molluscs (clams, mussels, oysters). Acute toxicity typically occurs in adult molluscs at concentrations ranging from 1 mg carbaryl/litre to over 100 mg/litre. The major hydrolytic product of carbaryl, 1-naphthol, is slightly more acutely toxic for molluscs (mussel, pacific oyster) than the parent compound (Stewart et al., 1967). In addition, larvae and young juveniles are more sensitive to carbaryl exposure than older juveniles and adults.

There have been few studies on the effects of carbaryl on the growth of molluscs. Davis (1961) and Butler (1962) found that carbaryl (80% WP) concentrations of 1.0-2 mg/litre reduced the larval development and growth of oysters (*Crassostrea virginica*) and clams (*Venus mercenaria*).

The effects of a 1-h exposure to carbaryl (80% WP) and its hydrolytic product, 1-naphthol, were studied on six developmental stages of the mussel (*Mytilus edulis*) (Armstrong & Millemann, 1974c). The six stages included unfertilized eggs to the early veliger stage, 32 h after fertilization. Unfertilized eggs and the first polar body stage were exposed to carbaryl and 1-naphthol (separately). The acute toxicity values of carbaryl and 1-naphthol were similar for the first two stages, ranging from approximately 5 to 25 mg/litre. The stage of development most sensitive to carbaryl was the first polar body stage. Thereafter, susceptibility decreased as age of the larvae increased.

LC_{50} values for crustacea varied from 5 to 9 µg/litre (water fleas, mysid shrimps), 8 to 25 µg/litre (scud), and 500 to 2500 µg/litre for crayfish. The hydrolytic metabolite 1-naphthol was less toxic for daphnids and shrimps.

The effects of carbaryl (80% WP) on the life stages of crustacea have been studied in the Dungeness crab (*Cancer magister*) (Buchanan et al., 1970). Early larvae were more sensitive to carbaryl than juveniles and adults. Carbaryl (1.0 mg/litre) did not affect hatching of eggs but prevented moulting of all prezoeae to zoeae. The concentration that killed 50% of the first zoeae during a 96-h exposure was estimated to be 1 mg/litre.

Young juvenile crabs were more sensitive than older juveniles or adults. The 24-h EC_{50}s (death or irreversible paralysis) were estimated to be 0.076 and 0.35-0.62 mg/litre for second and ninth

stage juveniles, respectively. At 0.032 mg/litre, juvenile crabs were not affected when held in uncontaminated water after exposure. In adult crabs, the 24-h and 96-h EC_{50}s (death or paralysis) were 0.49 and 0.26 mg/litre, respectively. Post-larval Dungeness crabs had about the same sensitivity to carbaryl as other crabs. The 24-h EC_{50} (death or paralysis) of small stone crabs was 1.0 mg/litre (Butler, 1962), that of juvenile blue crabs, 0.55 mg/litre (Butler, 1963), and that of adult crabs, 0.06-1.05 mg/litre (Stewart et al., 1967).

As part of fresh water biota, daphnids have been used as assay organisms to determine toxic concentrations of a variety of pesticides. Laboratory bioassays were conducted with carbaryl to determine its toxicity and immobilization values for two species of daphnids, *Daphnia pulex* and *Simocephalus serrulatus*. The EC_{50}s for overt effects were 0.0064 mg/litre for *Daphnia pulex* and 0.0076 mg/litre for *Simocephalus serrulatus* (Sanders & Cope, 1966).

In a long-term study, *Daphnia magna* was exposed to technical carbaryl for 21 days; reproductive performance was the most sensitive indicator; the MATC was 1.5-3.3 μg/litre (Surprenant, 1985c).

Aquatic insects in the orders Plecoptera (stoneflies) and Ephemeroptera (mayflies) are generally highly sensitive to low levels of carbaryl.

The effects of 0.6-50.0 mg carbaryl/litre were studied on selected aquatic organisms, including: *Scanedesmus quadricauda, Lemna minor, Lebistes reticulatus* and *Daphnia magna* (Bogacka & Groba, 1980). Carbaryl depressed reproduction, biomass, and chlorophyll content in *Lemna minor* (vascular plant) after 24 h exposure at a concentration >6.6 mg/litre. An almost 100% decrease occurred at a concentration of 50 mg/litre. Inhibition of photosynthesis intensity in the alga *Scenedesmus quadricauda* was about 50% at a concentration of carbaryl in the water of 32 mg/litre, and 65% at a concentration of 56 mg/litre, after 24 h exposure. Less than 10% inhibition occurred at a concentration of 1.8 mg/litre. A decrease in the production of chlorophyll was demonstrated at 4.4 mg/litre.

Carbaryl applications of 5.7 or 11.4 kg/ha were effective in controlling ghost shrimp (*Callianassa californiensis*) as an oyster pest. The numbers of various clams in the mud were reduced by 22

and 38%, respectively. Clam species differed in susceptibility. For example, gaper clams (*Tresus capax*) were reduced by 58 and 69%. Polychaetes and nemertean worms were not affected during 30 days of observation (Armstrong & Millemann, 1974a,b).

7.2.2 Fish

7.2.2.1 Acute toxicity

Acute toxicity studies have been conducted with technical carbaryl, several formulations, and 1-naphthol to determine LC_{50} values for several freshwater and marine fish (Table 35). The results indicated that short-term exposure ($\leq$ 4 days) to carbaryl and its formulations showed some toxicity for fish (96-h LC_{50}s = 1-30 mg/litre). There were no differences in the toxicity of two formulations (4-oil-sevin and XLR) for rainbow trout and bluegill. The LC_{50}s for sheepshead minnow (exposed to technical material) and rainbow trout (exposed to 4-oil and XLR) were similar and both were generally more sensitive than bluegill. The toxicity of 1-naphthol for rainbow trout, bluegill, and sheepshead minnow was determined by Springborn (1988a); 96-h LC_{50} values for these species were 0.76, 1.4, and 1.2 mg/litre, respectively. The corresponding NOECs were < 0.43, 0.55, and 0.47 mg/litre. The metabolite, 1-naphthol, was more acutely toxic than the formulations for bluegill. However, the toxicities of 1-naphthol and the formulations were similar for rainbow trout and sheepshead minnows.

Few studies report acute toxicity values for fish that are lower than 1 mg/litre. Cold water fish (Salmonidae), such as Coho Salmon and trout, seem to be susceptible to carbaryl, while the catfish (Ictaluridae) is tolerant (Macek & McAllister, 1970; Post & Schroeder, 1971). Irritability, sluggishness, and loss of equilibrium were classical signs of acute intoxication. Rainbow trout (*Oncorhynchus mykiss*), exposed to 1 mg carbaryl/litre for 96 h, exhibited decreased swimming capacity and swimming activity; the capacity to capture and consume prey was also diminished (Little et al., 1990).

Other end-point concentrations have been established for carbaryl for various species. Reference should be made to the original documentation to obtain a fuller understanding of these measures of toxicity. The lowest no-observed-effect concentration (NOEC) was

Table 35. Acute toxicity of carbaryl for fish

Organism	Size/age	Stat/flow[a]	Temperature (°C)	Hardness (mg/litre)[b]	pH	Formulation[c]	Parameter	Concentration (mg/litre)	Reference
Freshwater									
Coho salmon (*Oncorhynchus kisutch*)	1 g	stat	13	44	7.1		96-h LC_{50}	4.3	Mayer & Ellersieck (1986)
		stat	13	42	7.1		96-h LC_{50}	2.4	
	4.6 g	stat	13	42	7.1		96-h LC_{50}	1.8	
	5.1 g	stat	13	42	7.1		96-h LC_{50}	2.7	
	10.6 g	stat	13	42	7.1		96-h LC_{50}	1.2	
	19.1 g					CT	96-h LC_{50}	0.8	Macek & McAllister (1970)
						CT	96-h LC_{50}	1.3	Post & Schroeder (1971)
Chinook salmon (*Oncorhynchus tshawytscha*)	fingerling	flow	13	314	7.5		96-h LC_{50}	2.4	Mayer & Ellersieck (1986)
Cutthroat trout (*Salmo clarkii*)	0.5 g	stat	12	40	7.5		96-h LC_{50}	7.1	
	0.5 g	stat	12	330	7.8		96-h LC_{50}	4.0	
	0.6 g	stat	7	42	7.5		96-h LC_{50}	6.0	
	0.7 g	stat	12	40	6.5		96-h LC_{50}	5.0	
	0.6 g	stat	12	40	8.5		96-h LC_{50}	1.0	
						CT	96-h LC_{50}	6.0	Woodward & Mauck (1980)
						C49	96-h LC_{50}	6.7	

Table 35 (continued)

Rainbow trout	1.5 g	stat	12	42	7.1		96-h LC_{50}	2.0	Mayer & Ellersieck (1986)
(*Oncorynchus*	1.5 g	stat	12	272	7.4		96-h LC_{50}	1.2	
mykiss)	1.2 g	stat	12	40	7.4		96-h LC_{50}	3.5	
	1.2 g	stat	12	320	7.4		96-h LC_{50}	3.0	
	1 g	stat	12	40	7.4		96-h LC_{50}	1.6	
	1 g	stat	17	40	7.4		96-h LC_{50}	1.1	
	1 g	stat	12	40	6.5		96-h LC_{50}	1.2	
	1 g	stat	12	40	7.5		96-h LC_{50}	0.8	
	1 g	stat	12	40	8.5		96-h LC_{50}	1.5	
	0.5 g	flow	17	314	7.5		96-h LC_{50}	1.3	
						CT	96-h LC_{50}	4.3	Macek & McAllister (1970)
						XLR	96-h LC_{50}	1.4	Springborn (1985)
						S4	96-h LC_{50}	1.3	
						CT	96-h LC_{50}	2.2	Sanders et al. (1983)
						CT	96-h LC_{50}	1.5	Post & Schroeder (1971)
Atlantic salmon	0.2 g	stat	7	42	7.5		96-h LC_{50}	0.3	Mayer & Ellersieck (1986)
(*Salmo salar*)	0.2 g	stat	12	42	7.5		96-h LC_{50}	0.9	
	0.2 g	stat	17	42	7.5		96-h LC_{50}	1.0	
	0.4 g	stat	12	42	8.5		96-h LC_{50}	1.3	
	0.4 g	stat	12	42	8.5		96-h LC_{50}	0.9	
Brown trout	0.6 g	stat	12	42	7.5		96-h LC_{50}	6.3	
(*Salmo trutta*)	fingerling	flow	12	314	7.5		96-h LC_{50}	2.0	

Table 35 (continued)

Organism	Size/age	Stat/flow[a]	Temperature (°C)	Hardness (mg/litre)[b]	pH	Formulation[c]	Parameter	Concentration (mg/litre)	Reference
Brook trout (*Salvelinus fontinalis*)	0.8 g	stat	12	42	7.5		96-h LC_{50}	2.1	Mayer & Ellersieck (1986)
	0.8 g	stat	7	42	7.5		96-h LC_{50}	3.0	
	1 g	stat	17	42	7.5		96-h LC_{50}	0.7	
	0.7 g	stat	12	42	6.5		96-h LC_{50}	4.6	
	0.7 g	stat	12	42	8.5		96-h LC_{50}	2.1	
	0.7 g	stat	12	42	9		96-h LC_{50}	1.1	
	0.8 g	stat	12	42	7.5		96-h LC_{50}	1.2	
	0.8 g	stat	12	300	7.5		96-h LC_{50}	1.3	
Lake trout (*Salvelinus namaycush*)	1.7 g	stat	12	40	7.5		96-h LC_{50}	0.7	
	1.7 g	stat	12	40	6		96-h LC_{50}	0.7	
	1.7 g	stat	12	40	9		96-h LC_{50}	0.9	
	0.5 g	stat	12	162	7.4		96-h LC_{50}	0.9	
	2.6 g	flow	12	162	7.4		96-h LC_{50}	2.3	
Gold fish (*Carassius auratus*)	0.9 g	stat	18	40	7.1		96-h LC_{50}	13.2	
	0.9 g	stat	18	272	7.4		96-h LC_{50}	12.8	
Common carp (*Cyprinus carpio*)	0.6 g	stat	18	40	7.1		96-h LC_{50}	5.3	
	fry					CT	96-h LC_{50}	1.7	Chin & Sudderuddin (1979)

Table 35 (continued)

Carp (*Cyprinus carpio communis*)						C50 WP	72-h LC_{50}	10.4	Toor & Kaur (1974)
(*Catla catla*)						S	96-h LC_{50}	6.4	Tilak et al. (1981)
(*Cirrhina mrigala*)						S50 WP	96-h LC_{50}	2.0	Verma et al. (1984)
Fathead minnow (*Pimephales promelas*)	0.5 g	stat	12	42	7.5		96-h LC_{50}	14.0	Mayer & Ellersieck (1986)
	0.8 g	stat	18	40	7.1		96-h LC_{50}	14.6	
	0.8 g	stat	18	272	7.4		96-h LC_{50}	7.7	
Sheepshead minnow (*Cyprindon variegatus*)						CT	96-h LC_{50}	2.2	Springborn (1985)
Black bullhead (*Ictalurus malas*)	1.2 g	stat	18	40	7.1		96-h LC_{50}	20.0	Mayer & Ellersieck (1986)
Channel catfish (*Ictalurus punctatus*)	1.5 g	stat	18	40	7.1		96-h LC_{50}	15.8	
	1.5 g	stat	18	272	7.4		96-h LC_{50}	7.8	
	fingerling	flow	12	314	7.5		96-h LC_{50}	17.3	
Freshwater catfish (*Mystus vittatus*)	1.1 g	stat	28			S50 WP	72-h LC_{50}	17.5	Arunachalam et al. (1980)
						S	96-h LC_{50}	2.4	Tilak et al. (1981)

Table 35 (continued)

Organism	Size/age	Stat/flow[a]	Temperature (°C)	Hardness (mg/litre)[b]	pH	Formulation[c]	Parameter	Concentration (mg/litre)	Reference
(*Mystus cavasius*)						S	96-h LC_{50}	4.6	
Freshwater catfish (*Clarias batrachus*)						CT	96-h LC_{50}	46.9	Tripathi & Shukla (1988)
						CT	96-h LC_{50}	107.7	
Catfish (*Lebistes reticulatus*)						CT	96-h LC_{50}	9.7	Lejczak (1977a)
Green sunfish	1.1 g	stat	18	40	7.1		96-h LC_{50}	11.2	Mayer & Ellersieck (1986)
(*Lepomis cyanellus*)	1.1 g	stat	18	272	7.4		96-h LC_{50}	9.5	

Table 35 (continued)

Bluegill (*Lepomis macrochirus*)	1.2 g	stat	18	40	7.1		96-h LC_{50}	6.8	
	1.2 g	stat	18	272	7.4		96-h LC_{50}	5.2	
	0.4 g	stat	12	44	7.4		96-h LC_{50}	7.4	
	0.4 g	stat	22	44	7.4		96-h LC_{50}	5.2	
	0.8 g	stat	12	40	7.4		96-h LC_{50}	16.0	
	0.8 g	stat	17	40	7.4		96-h LC_{50}	7.0	
	0.8 g	stat	22	40	7.4		96-h LC_{50}	8.2	
	0.4 g	stat	17	320	7.4		96-h LC_{50}	6.2	
	0.7 g	stat	17	40	6.5		96-h LC_{50}	5.4	
	0.7 g	stat	17	40	7.5		96-h LC_{50}	5.2	
	0.7 g	stat	17	40	8.5		96-h LC_{50}	1.8	
	0.7 g	stat	17	40	9.5		96-h LC_{50}	2.6	
	0.6 g	flow	12	314	7.5		96-h LC_{50}	5.1	
						XLR	96-h LC_{50}	9.8	Springborn (1985)
						S4	96-h LC_{50}	10	
Mosquito fish (*Gambusia affinis*)	30-40 mm	stat					96-h LC_{50}	31.8	Chalyarach et al. (1975)
Largemouth bass (*Micropterus salmoides*)	0.9 g	stat	18	40	7.1		96-h LC_{50}	6.4	Mayer & Ellersieck (1986)
Black crapple (*Pomoxis nigromaculatus*)	1 g	stat	18	40	7.1		96-h LC_{50}	2.6	

Table 35 (continued)

Organism	Size/age	Stat/flow[a]	Temperature (°C)	Hardness (mg/litre)[b]	pH	Formulation[c]	Parameter	Concentration (mg/litre)	Reference
Yellow perch (*Perca flavescens*)	1.4 g	stat	18	40	7.1		96-h LC_{50}	0.7	Mayer & Ellersieck (1986)
	0.6 g	stat	12	42	7.5		96-h LC_{50}	5.1	
	1 g	stat	7	42	7.5		96-h LC_{50}	13.9	
	1 g	stat	12	42	7.5		96-h LC_{50}	5.4	
	1 g	stat	17	42	7.5		96-h LC_{50}	3.4	
	1 g	stat	22	42	7.5		96-h LC_{50}	1.2	
	0.9 g	stat	12	42	6.5		96-h LC_{50}	4.0	
	0.9 g	stat	12	42	7.5		96-h LC_{50}	4.2	
	0.9 g	stat	12	42	8.5		96-h LC_{50}	0.5	
	0.9 g	stat	12	42	9		96-h LC_{50}	0.4	
	1 g	stat	12	42	8		96-h LC_{50}	3.8	
	1 g	stat	12	170	8		96-h LC_{50}	5.0	
	1 g	stat	12	300	8		96-h LC_{50}	3.8	
	fingerling	flow	12	314	7.5		96-h LC_{50}	1.4	
Snakehead fish (*Channa punctatus*)						CT	48-h LC_{50}	8.7	Rao et al. (1985a)
						C50 WP	96-h LC_{50}	19.5	Singh et al. (1984)
						C50 WP	48-h LC_{50}	8.1	Rao et al. (1985b)
(*Anabas testulus*)						S	96-h LC_{50}	5.5	Tilak et al. (1981)
Tilapid fish (*Sarotherodon mosambica*)						S50 WP	72-h LC_{50}	8.0	Koudinya & Ramamurthi (1980)

Table 35 (continued)

(*Tilapia* sp.)					C	48-h LC_{50}	5.5	Basha et al. (1983)
Estuarine teleost (*Therapon jarbua*)					C	96-h LC_{50}	2.2	Lingaraja & Venugopalan (1978)
(*Hetero-pneustes fossilis*)					C50 WP	96-h LC_{50}	20.1	Singh et al. (1984)
(*Macropodus*)					CT	96-h LC_{50}	3.5	Arunachalam & Palanichamy (1982)
(*Cyprinus*)					CT	96-h LC_{50}	4.0	
Estuarine & marine								
Longnose killifish (*Fundulus similis*)	juvenile	stat	28	19s		48-h LC_{50}	1.6	Mayer (1987)
Striped mullet (*Mugil cephalus*)	juvenile	stat	24	17s		48-h LC_{50}	2.4	

[a]Stat = static conditions (water uncharged for the duration of the test); Flow = flow-through conditions (carbaryl concentration in water continuously maintained).

[b]Hardness = expressed as mg $CaCO_3$/litre; s = salinity (‰).

[c]Formulation: C = carbaryl; CT = Carbaryl technical (> 95%); C50 WP = Carbaryl 50% wettable powder; S = Sevin; S4 = Sevin-4-oil; S50 WP = Sevin 50% wettable powder; XLR = Sevin (44% carbaryl); C49 = Carbaryl (49%). Where information on formulation is not given the carbaryl formulation used was mostly carbaryl technical.

found for rainbow trout at 0.065 mg/litre. Other NOECs were at least an order of magnitude greater. Maximum acceptable toxic concentrations (MATCS) have also been calculated. Bansal et al. (1980) estimated 30-day MATCs for 4 species of carp exposed to carbaryl (Sevin as a 50% wettable powder). For all species, the MATC was between 0.052 and 0.078 mg/litre. Verma et al. (1984) reported a 60-day MATC of between 0.09 and 0.11 mg/litre for another carp species, exposed to the same type of formulation of Sevin.

Exposure of *C. punctatus* to carbaryl at a concentration of 3 mg/litre for 48 h resulted in an increase in free fatty acids, cholesterol, and lipase activity in the liver (Rao et al., 1985b). However, the total lipid content was reduced.

The literature indicates that water temperature, hardness, and pH may influence the toxicity of carbaryl, as well as the size of the fish (Table 35).

In a study by Post & Schroeder (1971), water was supplied from a well, classified as very hard and highly alkaline at temperatures of 13.6-14.6 °C. Carbaryl was more toxic for cutthroat trout weighing 0.37 g than for those weighing 1-2 g (96-h LC_{50} 1.5 and 2.2 mg/litre, respectively) and more toxic for brook trout weighing 1.15 g than for those weighing 2.04 g (96-h LC_{50} 1.2 and 2.1 mg/litre, respectively).

A comparative toxicity study on carbaryl and 1-naphthol, under laboratory conditions showed that 1-naphthol was approximately 5 times more toxic than carbaryl for goldfish (*Carassius auratus*) and 2 times more toxic for killifish (*Fundulus heteroclitus*) (Shea & Berry, 1983).

Synergism of the effects of carbaryl and phenthoate on *Channa punctatus* was found (Rao et al., 1985a,b). Carbaryl produced potentiation of the effects of 2,4-D, *n*-butyl ester, dieldrin, rotenone, pentachlorophenol, and arecoline on trout (Statham & Lech, 1975).

Application of carbaryl to a forest resulted in a significant (15-34%) decrease in brain acetylcholinesterase activity in brook trout from a nearby stream (Haines, 1981). No other effects were observed.

7.2.2.2 Short-term and long-term toxicity

There is a limited data base on the effects of long-term carbaryl exposure on fish. In one study, juvenile spot *Leiostomus xanthurus* were exposed for five months to carbaryl (technical, 98%) at a level of 0.1 mg/litre in a flow-through system (Lowe, 1967). No carbaryl-related mortality was observed and there was no effect on growth.

Carlson (1972) conducted the only full life-cycle study on fish with carbaryl (80%), in which fathead minnows (*Pimephales promelas*) were exposed to five concentrations (0.008-0.68 mg/litre) for 9 months, beginning with the larvae. Survival of fatheads after 6 months at 0.68 mg/litre was lower than that in the controls. After 9 months at 0.68 mg/litre, the mean number of eggs produced per female was reduced, the mean number eggs per spawning was also affected and no hatching occurred. No other demonstrable effects were noted at 0.017, 0.062, and 0.21 mg/litre concentrations; thus, the maximum acceptable toxicant concentration (MATC) for fathead minnows, exposed to carbaryl in water, was between 0.21 and 0.68 mg/litre. The lethal threshold concentration for 2-month-old minnows was 9 mg/litre.

Kaur & Toor (1977) exposed different stages of the embryo of carp (*Cyprinus carpio*) to carbaryl through the hatching stage. There was 100% mortality of carp eggs and embryos at 2.5 mg/litre. There appeared to be no effect of carbaryl on hatching at 0.01-0.75 mg/litre. However, there was decreased hatching at 1.0 mg/litre and deformed larvae (3.3%) with enlargement of the pericardial sac and coiling of the posterior region of the embryo.

Thirty days exposure of *Channa striatus* to 10 or 20 mg carbaryl/litre retarded oocyte production, with an increase in the number of immature oocytes and a decrease in the number of mature oocytes (Kulshrestha & Arora, 1984).

Statistically significant reductions in gonadotropic hormone in the pituitary gland and plasma in *Channa punctatus* were observed following exposure to carbaryl at a concentration of 1.66 mg/litre (Ghosh et al., 1990). Gonadotropic hormone levels continued to decrease with continued exposure, with a 30% decrease in the pituitary gland and a 50% decrease in serum after 30 days of exposure.

Exposure of the freshwater fish *Puntius conchonius* to carbaryl at a concentration of 0.194 mg/litre for 15 days resulted in an increase in the incidence of lesions in the gill and liver (Gill et al., 1988). A higher level of exposure also resulted in lesions in the kidney.

A 27-day exposure to 12.5 mg/litre led to a decrease in the feeding and growth rate of the catfish (*Mystus rittatus*) (Arunachalam et al., 1980). Long-term toxicity of carbaryl for fish in most natural surface waters will not occur, since exposure would not be high enough or constant, because of the substance's degradation.

7.2.3 Amphibians

The LC_{50}s for bullfrog (*Rana tigrina*) 0.1 g tadpoles with 24, 48, 72, or 96 h of exposure were determined to be 12.8, 8.2, 6.7, and 6.3 mg/litre, respectively (Marian et al., 1983). Growth and feeding were decreased in a dose-dependent manner by doses ranging from 0.5 to 5 mg/litre.

7.3 Terrestrial organisms

7.3.1 Worms

Carbaryl was classified as extremely toxic for earthworms (LC_{50} = 9.1 $\mu g/m^2$) by Roberts & Dorough (1984). The LC_{50} value for the worm *Eisenia fetida-Savigny* was 14 $\mu g/cm^2$ (Neuhauser et al., 1985). The number of earthworms was reduced by 60% when carbaryl was applied at 0.5 kg (1.12 lb) a.i. per hectare (Thompson, 1971).

Exposure of earthworms to carbaryl (1-8 mg/kg) significantly increased the burrowing time, which was directly proportional to the dose and time of exposure, because of the AChE inhibition in the neural tissue (Gupta & Sundararaman, 1991).

7.3.2 Insects

Administration of carbaryl in sublethal doses produced death in the early embryonal stage of the silkworm (Kuribayashi, 1981).

The alfalfa leaf-cutting bee (*Megachile pacifica*), which is very important in the pollination of alfalfa, has been reported to be particularly tolerant to carbaryl (Lee & Brindley, 1974). Waller (1969) also classified carbaryl as relatively non-toxic for the alfalfa leaf-cutting bee. The carbaryl tolerance was related to sex and age. The LD_{50} was similar for 1-day-old males and 1-and 4-day-old females (240, 245, and 262 μg/g, respectively). However, four-day-old males were much more susceptible to carbaryl, and had an LD_{50} of 51 μg/g. Guirgius & Brindley (1975, 1976) showed that carbaryl toxicity in alfalfa leaf-cutting bees was controlled by the activity of mixed function oxidase or microsomal enzymes. This detoxification system varies with the age and sex of the bees and results in significantly different carbaryl persistence which, in turn, leads to differences in carbaryl toxicity. In the more tolerant groups, carbaryl metabolites were rapidly conjugated and moved to an aqueous fraction of the bee. Less tolerant insects (4-day-old males) accumulated these metabolites with time, indicating that the conjugation mechanisms had deteriorated with age.

Carbaryl is known to be highly toxic for honey-bees. When ingested, the LD_{50} was 0.18 μg/bee (Alvarez et al., 1970). The contact LD_{50} (approximately 10-15 mg/kg) for adult bees is approximately 1.3 μg (Stevenson et al., 1977; Stevenson, 1978).

The carbaryl residue content of bee bread was correlated with the amount of residue found in the bees and occurred at higher levels than in honey throughout the 56-day period (Winterlin & Walker, 1973).

7.3.3 Birds

The toxicity of carbaryl for birds appears to be low (Table 36). LD_{50}s for six species of waterfowl and game birds were all greater than 1000 mg/kg (Bart, 1979). There were some exceptions; thus the red-winged blackbird has an LD_{50} of 56 mg/kg (Schafer, 1972). In this study, 180 compounds were found to be toxic for the red-winged blackbirds and the LD_{50}s ranged between 0.24 and 100 mg/kg.

Table 36. Acute toxicity of carbaryl for birds

Species	Age	Parameter[a]	Concentration (mg/kg)	Reference
Japanese quail *Coturnix coturnix japonica*	2 months	LD_{50}	2290	Hudson et al. (1984)
	7 days	5 day-LC_{50}	> 10 000	Hill & Camardese (1986)
Bobwhite quail *Colinus virginianus*	23 days	5 day-LC_{50}	> 5000	Hill et al. (1975)
California quail *Callipepla californica*	10 months	LD_{50}	> 2000	Hudson et al. (1984)
Chukar *Alectoris chukar*	4 months	LD_{50}	1888	
Sharp-tailed grouse *Tympanuchus phasianellus*		LD_{50}	< 1000	
Pheasant	3-4 months	LD_{50}	707-> 2000	
Phasianus colchicus	23 days	LD_{50}	> 5000	Hill et al. (1975)
Mallard *Anas platyrhynchos*	3 months	LD_{50}	> 2564	Hudson et al. (1984)
	24 days	5 day-LC_{50}	> 5000	Hill et al. (1975)
Rock dove *Columbia livia*		LD_{50}	1000-3000	Hudson et al. (1984)
Canada goose *Branta canadensis*		LD_{50}	1790	
Red-winged blackbird *Agelaius phoeniceus*		LD_{50}	56	Schafer (1972)

[a] LD_{50} = single oral dose expressed as mg/kg body weight.
5 day-LC_{50} = 5-day dietary exposure (expressed as mg/kg feed) followed by 3 days on a "clean" diet.

Food intake, body weight, and locomotor activity were monitored in adult male bobwhites (*Colinus virginianus*), given diets that contained levels of carbaryl typical of normal exposure under agricultural conditions in Kansas. No changes were observed in diets containing 127 or 1235 mg carbaryl/kg (Robel et al., 1982).

Technical carbaryl fed to young Mallard ducks at dietary levels of 10, 100, 1000, or 3000 mg/kg, revealed dose-correlated signs of toxicity (reduced intake and/or body weight depression) at the 100, 1000, and 3000 mg/kg level (Fletcher & Leonard, 1986).

There was some tentative evidence that low dosages of carbaryl may increase the susceptibility of bobwhites (*Colinus virginianus*) to the protozoan parasite *Histomonas meleagridis*, to which they are usually resistant (Zeakes et al., 1981).

A study of the effects of carbaryl on forest birds was conducted in southern New York; plots had been treated 3-4 weeks previously with carbaryl at the normal rate of 1.1 kg/ha, and at 6 times the normal rate (6.6 kg/ha). In this study, carbaryl had little, if any, effect on birds. Young birds gained weight normally, adults continued nesting in the area, no changes were detected in song frequency, and there was no evidence of birds leaving the area to forage. This lack of detectable effects, despite the heavy dose (6.6 kg/ha), indicates that carbaryl applied at the normal rate (1.1 kg/ha) would have little if any adverse effect on birds (Bart, 1979).

The LC_{50} of carbaryl for mallard embryos, following field applications, was determined by Hoffman & Albers (1984) to be greater than 26.4 kg/ha or 118 μg/g egg. Carbaryl was estimated to be relatively nontoxic compared with other pesticides.

Inhibition of the brain ChE activity of birds from forests sprayed with carbaryl 1.13 (kg/ha) was found in 3 out of 12 species studied (Zinkl et al., 1977) up to 5 days after application.

7.3.4 Mammals

The effect of carbaryl on wild mice (*Clethrionomys glareolus* and *Apodemus sylvaticus*) in their natural environment was studied by Krylov (1970). Carbaryl-containing bait, each consisting of 2 kg grain treated with 50 g carbaryl in oil suspension, were distributed twice (in March and June) over 10 ha of woods, at a rate of 1 bait/ha. An adjacent territory of 10 ha was used as a control. Effects on mice, assessed 1½ months after the last application, were: reduction of the population by 31.5% compared with the control; changes in the reproduction system (e.g., decreased number of embryos *in utero*, and of corpora lutea, reduced weight of testicles), and increased weight of adrenal glands.

7.4 Effects on the population and ecosystem

The effects of carbaryl on terrestrial ecosystems have been studied by Stegeman (1964), Barrett (1968), and Spain (1974).

A large-scale study was performed by Barrett in 1968. It was designed to determine the effects of carbaryl on an intact ecosystem in a field that was planted with millet (*Panicum ramosum*). The area was sprayed with a single application of 2.24 kg carbaryl/ha. There was a highly significant decrease in litter decomposition in the treated area, 3 weeks after spraying, which was probably because of a reduction in microarthropods and other decomposers. After 5 weeks, there was a more than 95% reduction in the number of arthropods and in the total biomass. Phytophagous insects were severely affected, and predatory insects and spiders were less affected. The number of species was also reduced, but all species returned to control levels within 1-2 weeks, except Hemiptera and Hymenoptera. Reproduction of cotton rats was delayed by 4 weeks. However, the total mammal population was not affected, because of a compensating increase in the population of house mice. Old field mice did not seem to be affected.

The effects of carbaryl on forest soil mites and Collembola, the two most numerous soil arthropods, were studied by Stegeman (1964). Mites and Collembola are an important link in the decomposition process of dead plants and animal matter. They also are a natural means of decomposing the accumulating litter, and they provide nutrients for already existing or future crops and fungi. Application of carbaryl to a test plot in a red-pine plantation, at doses of 11.2 and 56 kg/ha, reduced the arthropod population proportional to the severity of the treatment. Neither mites nor Collembola were totally exterminated by any treatment. The rate of population increase of the mites, 4-5 months after treatment, was directly proportional to the dose applied. Collembola were more vulnerable to treatment than mites and did not recover as rapidly.

The effect of carbaryl at two application rates (0.11 and 1.13 g a.i. per m^2) on mixed species population of the litter fauna of a Corsican pine forest was studied by Spain (1974). He took a quantitative sampling of the fauna at intervals of 11, 106, 209, and 315 days after application to record the pattern and the time of the

recovery process (Table 37). The effect of carbaryl varied in different populations. For Collembola, there was a marked reduction at the two treatment levels. For Coccoidea and Symphyla, there was a slight effect at the lower level, and a marked decrease at the higher level. For Coleoptera, Diptera, Cryptostigmata, Mesostigmata, and Prostigmata, the effect was small or insignificant. The recovery process during the period of 315 days was not sufficient to reach the status of the untreated population.

Tagatz et al. (1979) studied the effects of carbaryl on animal communities that develop from planktonic larvae in aquaria containing sand and estuary water. Samples collected after 10 weeks of exposure were analysed. The numbers of animals and species were significantly less at 11.1 and 103 μg carbaryl/litre (Table 38) being decreased to nearly half (from 21 to 12). A carbaryl concentration of 1.1 μg/litre did not produce significant effects, except a decrease in the particularly sensitive amphiopod, *Coraphium acerusicum*. Carbaryl might have caused changes in biological interactions that affect the relative abundance of species. The annelid *Polydora ligni* increased at a concentration of 103 μg/litre, and there was a marked decrease in the number of other annelids and nemerteas.

There have been a number of field studies evaluating the impact of carbaryl applications on macroinvertebrate populations. In one study in New York State, carbaryl was applied aerially at a rate of 1.3 kg/ha, in fuel oil with a paraffin oil sticker, and its effects upon the aquatic fauna of two streams were studied (Burdick et al., 1960). The data indicated that carbaryl (in oil suspension) was toxic for mayflies (Ephemeroptera), stoneflies (Plecoptera) and caddisflies (Trichoptera). Other groups of insects were less affected and the application did not affect fish. Square-foot samples, collected before, and shortly after, spraying, showed reductions of from 50 to 97.2% in the weight of invertebrate (standing crop) fish food. A progressive effect from upstream to lower sections was correlated with increased 44-151 exposure time. No exposure concentrations in water were documented. Owen (1965) also reported a reduction of 54.2 to 62.8% in the standing crop of aquatic insects following aerial spraying with carbaryl (80 WP) (1.3 kg/ha). A control stream showed a 5.9% increase in the same period.

Table 37. Geometric means for assessed taxa (individuals/m^2), post-application sampling of carbaryl-treated plots[a]

Sampling day (after treatment)	Taxon	Control plot	High carbaryl	Low carbaryl
11	Coccoidea	272.9	90.8	129.4
	Coleoptera (imagines)	425.6	137.7	153.1
	Coleoptera (immature)	54.0	47.3	41.4
	Collembola	42 771.5	5033.4	9819.7
	Diptera	350.9	244.2	243.7
	Cryptostigmata	5707.3	3933.2	5863.5
	Mesostigmata	7239.5	3688.9	5038.2
	Prostigmata	1335.6	305.3	564.8
	Aranese	238.7	222.7	155.0
	Chilopoda	71.1	102.4	37.4
	Symphyla	872.1	359.0	388.9
106	Coccoidea	847.8	157.0	162.9
	Coleoptera (imagines)	41.9	379.1	170.7
	Coleoptera (immature)	41.9	31.7[b]	0.0[b]
	Collembola	18 185.1	1621.3	5205.9
	Diptera	264.0	173.8	160.5
	Cryptostigmata	5855.3	6237.9	6623.7
	Mesostigmata	8610.3	846.4	595.2
	Prostigmata	631.5	846.4	595.2
	Aranese	360.6	224.9	253.2
	Chilopoda	114.0	157.8	94.3
	Symphyla	317.5	47.0[b]	223.4

Table 37 (continued)

	Coccoidea	358.3	181.0	141.0
	Coleoptera (imagines)	520.0	86.6	232.6
	Coleoptera (immature)	289.6	125.9	74.1
	Collembola	41 198.7	3469.4	19 238.9
	Diptera	449.9	28.2[b]	209.5
209	Cryptostigmata	16 298.4	11 184.8	12 014.8
	Mesostigmata	16 150.0	7293.9	11 709.0
	Prostigmata	2721.6	2407.2	3152.4
	Aranese	264.7	108.3	220.2
	Chilopoda	241.9	28.2[b]	150.5
	Symphyla	357.3	78.3	174.4
	Coccoidea	142.0	207.5	51.5
	Coleoptera (imagines)	261.6	64.4	132.5
	Coleoptera (immature)	37.0	88.8	23.1[b]
	Collembola	40 139.5	4121.3	10 294.6
	Diptera	533.9	291.2	173.1
315	Cryptostigmata	10 889.3	12 743.6	10 506.6
	Mesostigmata	11 290.3	7762.7	14 912.0
	Prostigmata	2995.0	1944.7	4765.7
	Aranese	217.4	157.4	117.8
	Chilopoda	159.5	83.4	88.8
	Symphyla	349.6	85.4	158.8

[a]Source: Spain (1974).
[b]*95% confidence limits for the parametric mean include zero.*

Table 38. Animals and species, by phylum, collected from control aquaria and aquaria exposed to carbaryl[a]

	Control		Carbaryl					
			1.1 µg/litre		11.1 µg/litre		103 µg/litre	
Phylum	Number	Species	Number	Species	Number	Species	Number	Species
Mollusca	1691	3	1563	3	1340	3	1321	5
Arthropoda	380	7	339	8	336	2	269	2
Annelida	102	8	94	7	79	4	200	5
Nemerica	16	1	25	1	20	1	0	0
Coelenterata	3	1	5	1	0	0	0	0
Platyhelmintes	0	0	2	1	0	0	0	0
Echinodermata	0	0	0	0	1	1	0	0
All phyla	2192	20	2086	21	1776	11	1790	12

[a]From: Tagatz et al. (1979).

The effects on stream invertebrates of carbaryl, applied at a rate of 840 g a.i./ha for spruce budworm suppression, was studied. Benthos samples showed significant declines among Plecoptera, Ephemeroptera, and Trichoptera. Plecoptera had not repopulated any treated stream, 60 days after treatment (Courtemanch & Gibbs, 1980).

Gibbs et al. (1984) conducted a 42-month (1980-83) study on the occurrence/persistence of carbaryl residues in pond water and sediment as a result of an application of Sevin-4-oil (840 g a.i./ha). The immediate and long-term effects on pond macroinvertebrates and emerging aquatic insects were also evaluated. A preliminary study by these investigators in 1977 and others (Coutant, 1964) had shown that there were large increases in the number of drift organisms, several days after aerial spraying with carbaryl. Most drift was accompanied by dead Amphipoda, Ephemeroptera, Plecoptera, and Trichoptera, and carbaryl residues persisted longer than 30 days in pond sediment. The increase in the number of dead organisms was accompanied by a reduction in the standing crop of benthic macroinvertebrates. The most severe and persistent impact was on Amphipoda with *Hyallela azteca* and *Crangonyx richmondensis* reduced to almost 0/m^2; *C. richmondensis* failed to recolonize in one of the two treatment ponds, 42 months after treatment. The numbers of immature Ephemeroptera and Trichoptera were reduced immediately following spray application, but this effect did not persist throughout the season or into the following year. Immediate reduction in numbers of adult Ephemeroptera and Trichoptera emerging from the ponds was also found, but recovery of populations was observed. Numbers of immature Odonata were also reduced following treatment and remained low the following year. The Chironomidae populations did not appear to be affected, either as immatures or emerging adults.

The effects of two consecutive years of spraying with Sevin-4-oil on other aquatic systems appear similar to those observed in areas treated once (Courtemanch & Gibbs, 1978; Trial, 1978,1979).

In simulated aquatic field studies, 1 mg carbaryl (WP)/litre was applied to one outdoor concrete pond (4 x 5 x 1 m deep) (Hanazato & Yasuno, 1987). All zooplankton (Cladocera included) and Chaoborus larvae were killed. The zooplankton community recovered rapidly and Cladocera reappeared only two days after

application. Since Chaoborus populations are predators of crustacean zooplankton, their suppression may also have added to the recovery of increased populations of Cladocerans. Carbaryl exposure also changed the community from a rotifer-predominating zooplankton community to that of Cladocera-predominating. Rotifers in this study were also highly sensitive to carbaryl. The same phenomenon was observed again after the second application of carbaryl. Subsequent to this study, Hanazato & Yasuno (1989) applied carbaryl to simulated ponds in the same way as in the previous study, but in the spring when the water temperature was approximately 10 °C lower. Cladocerans never recovered to the density level of the pre-treatment period. The rapid recovery of Chaoborus seemed to interfere with the recovery of Cladoceran populations after treatment. The authors suggested that the different recovery patterns of the zooplankton community resulted from different temperatures in the ponds. In another study, Hanazato & Yasuno (1990a) examined Chaoborus density in relation to the effects of carbaryl (0.1 and 0.5 mg/litre) on zooplankton communities in ponds, where the abundance of Chaoborus larvae was controlled. They concluded that Chaoborus density and/or temperature may influence the recovery of the zooplankton community following the effects of carbaryl. The recovery of a zooplankton community may differ in different aquatic ecosystems (with different community structures) and under different temperatures, even when the same treatment is applied.

Hanazato & Yasuno (1990b) also studied the effect of the time of application of carbaryl (0.5 mg/litre) on recovery patterns of zooplankton communities in simulated ponds. The loss of carbaryl from pond water was rapid. The concentration decreased to less than 1% of its initial value, three days after the first or second application, and six days after the third application. This study also showed that applications of carbaryl at different times induced different zooplankton structures (and different recovery patterns), and, various factors other than toxicity of carbaryl, such as temperature, competitive interactions between zooplankters, and trends of zooplankton populations may play important roles in determining zooplankton community structure after chemical application. Furthermore, the significance of predators in the recovery process after chemical treatment was re-emphasized.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

Reviews of toxicological aspects of carbaryl were prepared by NIOSH (1976); US EPA (1977, 1980, 1982, 1984); USDHHS/USDL (1978); US EPA (1980b); Mount & Oehme (1981a); Weston (1982); and Cranmer (1986). Studies from the Soviet Union were reviewed by IRPTC (1982, 1989).

8.1 Single exposures

8.1.1 Oral toxicity

The oral LD_{50}s for the rat are given in Table 39 and for other mammals in Table 40. The values varied by about a factor of 4 depending on formulation, route of production, vehicle, and strain of rat. Interspecies differences were found. Cats are the most sensitive, with guinea-pigs, rats, mice, and rabbits showing more resistance in that order. Pigs and monkeys seem to be less sensitive (Carpenter et al., 1961; Gladenko & Malinin, 1970; Smalley, 1970).

Cattle are more sensitive than pigs. After a single oral application of carbaryl in cattle, symptoms appeared at a dose level of 25 mg/kg; 100 mg/kg was the minimum effective dose in pigs (Gladenko & Malinin, 1970).

Mount & Oehme (1981b) observed that the lethality of carbaryl, administered to sheep at doses ranging from 300 to 1000 mg/kg, was highly correlated with concentrations in the brain (> 1 mg/kg) and liver (> 3 mg/kg), and with inhibition of acetylcholinesterase (greater than 50% inhibition).

8.1.2 Acute inhalation toxicity

Acute toxic effects following inhalation at different concentrations are presented in Table 41.

Table 39. Acute oral LD_{50}s for the rat

Strain (sex)	Weight (g)	Formulation of carbaryl	Vehicle	LD_{50}(mg/kg body weight)	Symptoms	References
CF-N		technical	0.25% agar			Carpenter et al.
(male)	90-120			510 (360-650)	-	(1961)
(female)	90-120			610 (490-750)	-	
Sherman				850 (600 LD min)		Gaines (1969)
(male)						
(female)				500 (100 LD min)		
Inbred				721 (653-789)		Yakim (1965)
Inbred	120-200		sunflower oil	515		Rybakova (1966)
Sprague Dawley (male, female)	203-246	technical	carboxymethyl-cellulose in water	300		Hamada (1990)
Sprague Dawley (male, female)	112-173	technical	0.25% methyl-cellulose	685 (612-767)	death, 4-24 h	Field (1980b)
Sprague Dawley (male, female)	100-160	95% technical	0.25% methyl-cellulose	225 (202-321)	death, 2-24 h	Field (1980a)

Table 39 (continued)

Sprague Dawley (male)	200-264	40.38%	water	750 (467-1202)	tremor, prostration, laboured respiration, salivation	Hazleton Lab. American Inc. 10 February 1982
(female)				527 (257-977)	death, 4-3 days	
Harlem Sprague Dawley		Sevin XLR plus 44%	not diluted		death, 0.5 h-3 days	Kuhn (1991a)
(male)	229-286			867 (562-1336)		
(female)	182-219			575 (459-721)		
Harlem Sprague Dawley		Sevin-4-oil 47% (w/w)	not diluted	658 (456-979)	3 h-3 days	Kuhn (1991b)
(male)	229-286			963 (802-1160)		
(female)	182-219			473 (364-620)		
Hilltop Wistar (male)	200-250	98% technical	0.25% methyl-cellulose	283	death, 1.5-24 h	Bushy Run (1983b)
(female)				246		
Hilltop Wistar (male)	204-237	80% sprayable	water	406	death, 1 min-24 h	Bushy Run (1983c)
(female)				203		

Table 40. Acute oral toxicity for mammals other than rats

Species	Number of animals	Toxicity[a] (mg/kg body weight)	Reference
Mouse	6 per dose	363 (294-431)	Yakim (1965)
Mouse (female)	80 white	437 ± 70	Rybakova (1966)
Mouse	1310 white	206 (175-480)	Bukin (1965)
Guinea-pig	5 per dose	280	Carpenter et al. (1961)
Rabbit	4 per dose	710	
Rabbit	56	700 (LD_{100})	Bukin (1965)
Cat (female)	3	250 (LD_{100})	Carpenter et al. (1961)
Cat	no data	150	Yakim (1965)
Swine	3 per dose	800-1000	Gladenko & Malinin (1970)
Swine	1 per dose	1500-2000	Smalley (1970)
Monkey	no data	> 1000	FAO/WHO (1970)
Duckling	106	500 (LD_{15})	Bukin & Filatov (1965)
		6000 (LD_{100})	
Chick	48	250 (LD_{33})	
		1000 (LD_{100})	
Hen	12	> 1000 (no death)	
Hen	12	> 3000	Bukin (1965)

[a] LD_{50}, unless otherwise stated.

Table 41. Inhalation toxicity single exposure

Species	Concentration	Effects observed	References
Guinea-pig 6	390 mg 50% wettable powder/m^3 (average particle size 15 μm) 4 h	nasal and ocular irritation after 14 days - haemorrhage areas in the lungs	Carpenter et al. (1961)
Guinea-pig 6	230 mg carbaryl 85S/m^3 (average particle size 5 μm) 4 h	slight weight decrease; recovered by day 14	
Dog	75 mg carbaryl 85S/m^3 5 h	typical symptoms for ChE inhibition	
Cat 3 groups of 4 animals	82 mg/m^3 dust 6 h	tremor salivation, muscle fibrillation decreased ChEA by 39-55% serum; 53-71% red blood cells; normalization after 72 h	Yakim (1967, 1968)
	37 mg/m^3 dust 6 h	decreased ChEA by 23% in serum and 41% in red blood cells; recovery after 48 h	
	20 mg/m^3 dust 6 h	decreased ChEA by 11-27% in serum and 15.28% in red blood cells; recovery after 24 h	
Rat	20-23 mg/m^3 dust 98% particles less than 1.0 μm diameter	no effect	Weil & Carpenter (1974)
Rat	1800 mg/m^3 water aerosols	lacrimation, tremor with 1.5 h of exposure	Myers et al. (1975)
Rat Wistar Albino male 5 female 5	Aerosols Sevin XLR 44% 792 mg a.i./m^3 per 4 h (the highest attainable concentration) particle size 3.6 ± 2.64 μm	1/5 females died, tremor, ataxia, increased respiratory rate; recovery period 6 days	Fait (1984)

8.1.3 Dermal toxicity

A dose of 2500 mg/kg, applied as a 40% aqueous suspension of 50% wettable powder, killed 1 out of 4 rabbits (Carpenter et al., 1961). When 99% technical carbaryl was applied to male and female rabbits, the LD_{50} was >2000 mg/kg (Bushy Run, 1983b). In rats, the LD_{50} is thought to be >4000 mg/kg (Yakim, 1965; Gaines, 1969).

8.1.4 Other routes of exposure

Other routes of exposure are presented in Table 42.

Table 42. Toxicity following parenteral application

Species	Weight (g)	Vehicle	Route of administration	LD_{50} mg/kg body weight)	References
Rat female	10-107	propylene glycol	intravenous	18	Mellon Institute (1958)
Rat	92-126	polyethylene glycol 400	intravenous intravenous	24 (17-33)	
Rat	90-120	95% ethyl alcohol	intravenous	33 (26-41)	
Rabbit	1686-3544	0.25% agar	intraperi-toneal	223 (122-407)	
Rat	90-120	in lard	subcutaneous	1410	
Leghorn chick embryos (250)	10-11 days old		in alantoic cavity	3.44 mg per embryo	Tós-Luty et al. (1973)

8.2 Skin and eye irritation, sensitization

8.2.1 Skin and eye irritation

The results of several studies on skin irritation from carbaryl were negative (Carpenter et al., 1961; Yakim, 1965). Transient

erythema was noted after an application of 0.5 ml 43.4% carbaryl on occluded rabbit skin (Bushy Run, 1983a).

Carbaryl is a weak eye irritant (Table 43).

Table 43. Eye irritation

Species	Number	Formulation	Effects observed	Reference
Rabbit	5	technical grade 10% suspension in propylene glycol	mild injury in one of five eyes	Carpenter et al. (1961)
		25% aqueous suspension	no injury	
		50 mg dust	spots of corneal necrosis	
Rabbit New Zealand White	6	0.1 ml (90 mg) 99% technical product	conjunctival irritation after 2 days recovery	Bushy Run (1983b)
		0.1 ml 43.4% carbaryl	transient iritis in 2 of 6, conjunctival irritation in 6 of 6. Recovery in 3 days	Bushy Run (1983a)

8.2.2 *Sensitization*

The sensitization response following topical application of carbaryl was studied by Myers & Christopher (1987). The induction which consisted of an application of carbaryl to covered skin, once a week during 3 weeks, was followed by a 2-week incubation period. A single challenge dose of 50% (w/v) technical carbaryl in 0.25% aqueous methyl cellulose solution (0.1-0.3 ml) was administered. Carbaryl did not produce a positive response in any of the guinea-pigs tested.

Four out of 16, male, albino guinea-pigs were treated with 8 intravenous injections (3 per week) of 0.1 ml of a 0.1% dispersion of carbaryl in 3.3% propylene glycol. After a 3-week incubation period, a challenge dose was given, but did not cause sensitization (Carpenter et al., 1961). In a more recent study, a similar

procedure, but with 9 doses and a 2-week incubation period, was used. Although there was some skin irritation, it was considered that carbaryl had little or no sensitizing potential (Bushy Run, 1983a).

8.3 Short- and long-term oral exposure

Several short- and long-term feeding studies with carbaryl have been reported (Carpenter et al., 1961; Rybakova, 1967; Orlova & Zhalbe, 1968; Gladenko & Malinin, 1970; Dikshith et al., 1976; Hamada, 1991a). Results are shown in Table 44. Doses that do not show any effects are 200 mg/kg diet equal to 7.9 mg/kg body weight in rats, and 100 mg/kg diet for mice, and 1.8 mg/kg body weight for dogs (approximately 100 mg/kg diet).

The cumulation coefficient (LD_{50} for 3-month exposure/LD_{50} single application) was 18 (Kassin, 1968), demonstrating a very low cumulative potential for carbaryl.

8.4 Short- and long-term inhalation toxicity

Short-term and long-term inhalation toxicity data are given in Table 45.

8.5 Reproduction and developmental toxicity

The reproduction and developmental toxicity of carbaryl has been studied in many vertebrate species using a wide variety of study designs.

The data have shown that carbaryl can affect reproduction (Table 46) and embryo/fetal development (Table 47 and 48) in a number of species. The relevance of these studies for risk assessment is influenced by several factors related to experimental design, dose levels, and the types of effects noted. Shortcomings of the studies included small sample size; inappropriate dose selection; the variable degree of maternal toxicity (ranging from no effect to lethality); and a lack of historical data for some species. The following sections have been arranged according to end-point (reproduction and developmental toxicity) and species of animals studied (mammalian, non-mammalian). Studies that are of dubious value for risk

Table 44. Short- and long-term feeding and oral studies

Species	Sex	Number of animals	Dosage (mg/kg diet or mg/kg body weight)	Period of exposure	Effects observed	References
Mouse	male and female	48	100, 400 mg/kg diet	80 weeks	no changes in survival rate, pathology, and tumour incidence	FAO/WHO (1965)
Mouse	male and female	10/sex per group	100, 1000, 7000 mg/kg diet	53 weeks	at 7000 mg/kg diet: decreased survival, body weight gain and erythrocyte count; increased liver weight and decreased ovary weight; increased frequency and severity of chronic nephropathy in females; cholinesterase (plasma, RBC, and brain) depressed at 100 and 7000 mg/kg; NOEL 100 mg/kg diet	Hamada (1991b)
Rat	male	2 × 10	1500 (58.5 mg/kg body weight)	96 days	no changes	Carpenter et al. (1961)
	female	2 × 10	1500 (58.5 mg/kg body weight)	96 days	kidney weights significantly increased	
	male	2 × 10	2250 (87.5 mg/kg body weight)	96 days	increase in liver weight as a % of body weight, diffuse cloudy swelling in the kidney tubules in 4 animals (male and female)	
	female	2 × 10	2250 (87.5 mg/kg body weight)	96 days	decrease of body weight, increase in kidney weight	

Table 44 (continued)

Species	Sex	Number of animals	Dosage (mg/kg diet or mg/kg body weight)	Period of exposure	Effects observed	References
Rat CF-N	male and female	4×40	50, 100, 200 (2, 4, 7.9 mg/kg body weight)	2 years	no changes	Carpenter et al. (1961)
Rat CF-N	male and female	2×40	400 (15.6 mg/kg body weight)	2 years	weight depression in male, cloudy swelling of the hepatic cords, principally located around the central veins in both sexes; transitory diffuse cloudy swelling of the epithelial lining of the primarily convoluted proximal, and loop tubules	Carpenter et al. (1961)
Rat			75, 150, 300 mg/kg body weight	3 months	cytoplasmatic vacuolization in the proximal tubules	FAO/WHO (1970)
Rat	male and female	4×48	7, 14, 70 mg/kg body weight		weight depression at all dose levels; at 70 mg/kg, slight morphological liver changes; cloudy swelling in convoluted tubules; decreased motility of spermatocytes at all dose levels, more pronounced at 70 mg/kg; oedema in the interstitial tissue; desquamation of spermatogenic epithelium; destruction of parenchyma; decreased production of spermatocytes was found at 14 and 70 mg/kg dose levels; increased estral cycle; increased hypophysis gonadotropic function; decreased ascorbic acid contents; cell proliferation, hypertrophy, increased lipid content in suprarenal glands; decreased thyroid function; augmentation of follicles, colloid retention, thickness of follicular epithelium	Rybakova (1967)

Table 44 (continued)

Rat Sprague Dawley	male female	80-90/ group	250, 1500, 7500 mg/kg diet	52 weeks	body weight and food consumption lower at middle dose; significantly increased total cholesterol; increase in liver and kidney weight; NOEL 250 mg/kg diet	Hamada (1991c)
Rat	male and female	876	2, 5, 15 mg/kg body weight	1 year	changes in sex glands function at 15 and 5 mg/kg dose levels; enzymatic activity, spermatozoids and the estral cycle; reduced fecundity; no effect at 2 mg/kg dose level	Orlova & Zhalbe (1968)
Rat local strain	male	total 28	200 mg/kg body weight, 3 × per week in peanut oil	90 days	decreased AChE in blood with 33.8%; no histological changes	Dikshith et al. (1976)
Dog Basenji-cocker hybrids	male and female	total 14	0.45, 1.8, 7.2 mg/kg body weight in capsules, 5 days/week, to approximate levels of 24, 95, 414 mg/kg dry diet	1 year	diffuse cloudy swelling of proximal convoluted and loop tubules of kidney; local sudanophilic granules in the glomeruli at 400 mg/kg level; the same in control dogs to a lesser extent; transient hind leg weakness in 1 female after 189th dose at 0.45 mg/kg body weight	Carpenter et al. (1961)
Beagle dogs	male and female	24 + 24	125, 400, 1250 mg/kg diet	1 year	at 400 and 1250 mg/kg diet, decreased AChE in plasma, red blood cells, and in brain; increase in leucocyte count and segmented nitrophil count; increase in liver weight in male; no effect level 125 mg/kg diet	Hamada (1987)

Table 44 (continued)

Species	Sex	Number of animals	Dosage (mg/kg diet or mg/kg body weight)	Period of exposure	Effects observed	References
Beagle dogs	male female	24 24	0, 20, 45, 125 mg/kg diet	5 weeks	significant inhibition of cholinesterase activity in plasma at week 2 for males dosed 20 and 125 mg/kg	Hamada (1991a)
Monkey			150, 300, 600 mg/kg body weight	38 weeks	kidney alterations similar to those found in rats	FAO/WHO (1970)
Swine	male female	3 3	150 mg/kg body weight in diet	72-83 days until death	progressive myasthenia, incoordination ataxia, intentional tremor, chronic muscular contraction, terminal paraplegia and prostration; myodegeneration	Smalley et al. (1969)
Swine			5 and 10 mg/kg body weight	147-176 days	no changes	Gladenko & Malinin (1970)
Cattle (young)			1 and 4 mg/kg body weight	148 days	decreased Hb with 20%, and erythrocytes with 30% occasionally	

Table 45. Short- and long-term inhalation toxicity

Species	Number of animals	Concentration of carbaryl	Days of exposure	Effects	References
Cat	4	0.06 mg/litre	30	typical cholinergic symptoms, inhibition of ChE plasma 31-40%, erythrocytes 40-59%	Yakim (1968)
Cat	4	0.03-0.04 mg/litre	30	reaction time increased	
Cat	4	0.016 mg/litre	120	no symptoms, fluctuation in plasma ChE inhibition around 18%	
Rat	no data	10 mg/m^3 dust (85% suspension) 7 h/day 5 days per week	90 inhalation periods	no mortality no gross visible injury	Carpenter et al. (1961)

Table 46. Reproduction studies

Species (number)	Treatment	End-point(s)	Reference
Mouse			
Swiss Webster males 30-40 g (10 + animals/group)	0, 8.5, 17, 34 mg/kg body weight orally (5 days)	weight and uptake of testosterone: testes and accessory glands	Thomas et al. (1974)
Swiss Webster males 30-40 g (5 + animals/group)	0, 34, 68 mg/kg body weight orally (5 days)	biotransformation of testosterone-1,2-^{3}H	Dieringer & Thomas (1974)
C57Bl/6 x C3H 6-8 weeks of age (4 animals/group)	0, 12, 25, 50...800 mg/kg body weight per day 5 days i.p.	sperm morphology, testes weight on day 35	Osterloh et al. (1983) [route of administration]
Rat			
Osborne-Mendel (20 females and 1 male per group)	0, 2000, 5000, 10 000 mg/kg diet (3 generations)	fertility, litter size, and viability	Collins et al. (1971)
Wistar (13-21 animals/group)	0, 7, 25, 100, 200 mg/kg body weight per day in the diet	fertility, litter size, and viability	Weil et al. (1973)
	0, 3, 7, 25, 100 mg/kg body weight per day orally (3 generations)		
Male and female	0, 1, 5, 10, 20, 40, 50 mg/kg body weight per day orally (1 month)	general toxicity, serum protein, numbers of male reproductive cells, sperm viability, testicular histology, litter viability	Vashakidze (1975)

Table 46 (continued)

Wistar males (36 animals per group)	0, 12.5, 25.0, 250.0 mg/kg body weight per day	sperm morphology	Luca & Balan (1987)
Rats			
Male and female	0, 50, 100, 300 mg/kg body weight per day orally 2 weeks to 3 months	fertility indices	Vashakidze (1966) [insufficient data]
Male and female (total of 876 animals)	0, 2, 5, 15 mg/kg body weight per day orally 12 months for F_0 and 6 months for the F_1	fertility indices	Orlova & Zhalbe (1968); Zhalbe et al. (1968) [insufficient data]
Male and female	0, 2, 5 mg/kg body weight per day for 6 months (follow-up to Orlova & Zhable) 2 through 5 generations	fertility indices	Shtenberg & Ozhovan (1971) [insufficient data]
Male and female	0, 2, 5, 15 mg/kg body weight per day for 12 months	fertility indices	Shtenberg et al. (1973) [insufficient data]
Gerbil			
(32-80 animals per group)	0, 2000, 4000, 6000, and 10 000 mg/kg body weight diet (3 generations)	fertility, litter size, and viability	Collins et al. (1971)

Table 47. Developmental toxicity studies, mammalian

Species (number)	Treatment	End-points	References
Mouse			
CF-1 (23-44 in a group)	0, 100, 150 mg/kg body weight per day orally or 5660 mg/kg diet. Gestation day 6-15	fetal examination	Murray et al. (1979)
Swiss albino (10 per group)	0, 100, 150, or 200 mg/kg body weight per day orally. Gestation days 8, 12, or 6-15	fetal examination	Mathur & Bhatnagar (1991)
Charles River (8 per group)	0, 10, 20 mg/kg body weight. Gestation day 6-parturition	fetal examination	Benson et al. (1967) [doses too low]
CD-1 (23 animals)	100 mg/kg body weight per day orally. Gestation day 8-12	postnatal viability	Chernoff & Kavlock (1982) [teratology screen test]
CD-1 (30 animals)	200 mg/kg body weight per day orally. Gestation day 8-12	postnatal viability	Kavlock et al. (1987) [teratology screen test]
Rat			
Harlan Wistar (6 per group)	0, 20, 100, 500 mg/kg diet. Gestation days 1-7, 5-15, 1-21	fetal examination	Weil & Carpenter (1965); Weil et al. (1972)
Wistar (10 per group)	0, 200, 350 mg/kg body weight orally 40 mg/kg ip. Variety of gestation days.	fetal examination	Golbs et al. (1974)

Table 47 (continued)

Sprague-Dawley (6 or 7 per group)	0, 1, 10, 100 mg/kg body weight orally. 3 months before and during gestation	fetal examination	Lechner & Abdel-Rahman (1984)
Sprague-Dawley (22 or 23 per group)	0, 20, 37.5 mg/kg body weight per day. Gestation day 6-15	fetal examination	Hart (1972) [doses too low]
Rats	unknown dose (1/50 LD_{50}). Gestation days 9, 11, or 13	fetal examination	Dinerman et al. (1970) [insufficient data]
Rats	0, 10.6, 106 mg/kg body weight per day. Gestation day 1-20	fetal examination	Shtenberg et al. (1973) [insufficient data]
Guinea-pigs			
HRA/HART (9-4 per group)	0, 50, 100, 200 mg/kg body weight per day orally. 0, 100, 200, 300 mg/kg body weight per day in the diet	fetal examination	Weil et al. (1973)
Coulston strain (26 gestation day treatment 11-20; other treatments unknown)	300 mg/kg body weight per day. Gestation day 11-20 and a variety of other treatment periods within this time	fetal examination	Robens (1969) [insufficient data]

Table 47 (continued)

Species (number)	Treatment	End-points	References
Rabbit			
New Zealand White (15-20 per group)	0, 150, 200 mg/kg body weight per day orally. Gestation day 6-18	fetal examination	Murray et al. (1979)
New Zealand White (9-12 per group)	0, 10, 30 mg/kg body weight per day. Gestation day 9-16	fetal examination	Shaffer & Levy (1968) [doses too low]
New Zealand White (4-9 per group)	0, 50, 100, 200 mg/kg body weight per day orally. Gestation day 5-15	fetal examination	Robens (1969) [small number of animals]
Dog			
Beagle (6-13 per group)	0, 3.125, 6.25, 12.5, 25, 50 mg/kg per day in the diet throughout gestation	examination of pups	Smalley et al. (1968)
Beagle (7-9 per group)	0, 2.0, 5.0, 12.5 mg/kg per day in the diet throughout gestation	examination of pups	Imming et al. (1969)
Pig			
Hormel-Hanford (5-16 per group)	0, 4, 8, 16 mg/kg in the diet 20 days before/7 days after breeding throughout gestation	examination of fetuses (I) or piglets after birth (II)	Earl et al. (1973)
Pig (30)	up to 30 mg/kg body weight per day	?	Smalley (1968) [insufficient data]

Table 47 (continued)

Monkey			
Rhesus (4-6 per group)	0, 2, 20 mg/kg body weight per day orally throughout gestation	examination of gestational course and new born	Dougherty et al. (1971)
Rhesus (15-16 group)	0, 20, 32 mg/kg body weight per day orally. Gestation day 20-38	examination of gestational course and new born	Coulston et al. (1974)
Sheep			
(25 and 26 per group)	159, 297.5 mg/kg diet	examination of lambs after birth	Panciera (1967) [significance of defects impossible to assess]
Hamster			
Golden Syrian (6 or 8 per group)	125 mg/kg body weight per day on gestation day 6-8; 250 mg/kg body weight per day on gestation day 7 or 8	fetal examination	Robens (1969) [number tested too small]

Table 48. Non-mammalian studies

Species	Dosage	End-points	Reference
Fish			
Medaka *(Oryzias latipes)* 10 eggs per group	0.5, 1.0, 2.5, 5.0, 10.0, and 20.0 mg/litre, 4-cell through blastula	embryonic development	Solomon & Weis (1979)
Amphibian			
Xenopus laevis 10-12 per group	0.1, 1.0, 10.0 mg/litre; embryos to hatching or tadpoles for 24 h	embryonic development, posthatching activity	Elliott-Feeley & Armstrong (1982)
Birds			
Chicken 4-6 per group	0, 0.01, 0.1, 1.0, 10.0 mg/kg body weight	embryonic development	Olefir & Vinogradova (1968)
White Leghorn chicken 20 per group	0, 250, 500 mg/kg diet to pullets for 36 weeks and hatchlings for 4 weeks	egg production, embryonic development, hatchability, posthatching development	Lillie (1972)
White Leghorn chicken 38-40 per group	0, 1.0, 2.5, 5.0, and 10.0 mg/egg embryonic development injected into yolk sac after fertilization, prior to incubation for 5 or 12 days	embryonic development	Swartz (1981)
White Leghorn chicken 8 per group	10 mg/egg after fertilization prior to incubation	primordial germ cell migration	Swartz (1985)
White Leghorn chicken	1.0, 0.3 mg/egg and lower	examination of embryos	Eto et al. (1980) [insufficient data]

Table 48 (continued)

720 eggs	0, 1, 2, and 4 mg/egg	examination of hatchlings	Ghadiri & Greenwood (1966) [insufficient data]
Duck and chicken	10-1000 µg/egg 0, 4, 7, 10, and 13 day eggs	examination of embryos or hatchlings	Khera (1966) [insufficient data]
Chicken		examination of embryos	Dinerman et al. (1970) [insufficient data]
Quail			
Coturnix coturnix japonica 10 per group	0, 50, 150, 300, 600, 900, 1200 mg/kg diet from hatching through 14 weeks	growth, reproduction, post-hatching viability	Bursian & Edens (1977)
Colinus virginianus 36 per group	0, 300, 1000, 3000 mg/kg diet for 22 weeks	reproduction, post-hatching viability, gross pathology	Fletcher & Leonard (1986a)
Duck			
Anas platyrhyncos 36 per group	0, 300, 1000, 3000 mg/kg diet for 22 weeks	reproduction, post-hatching viability, gross pathology	Fletcher & Leonard(1986b)
	10-1000 µg/egg 0, 4, 7, 10, and 13 days eggs	examination of embryos or hatchlings	Khera (1966) [insufficient data]

assessment are listed at the end of the table sections, and are not discussed in the text. The reasons for such an evaluation are given below the references to the individual papers.

8.5.1 Mammalian reproductive toxicity studies

8.5.1.1 Mouse

Studies on the effects of carbaryl (8.5-34 mg/kg per day), given orally for 5 days, to mature male Swiss Webster mice, indicated no effects on the weights of testes and accessory sex glands or uptake of C^{14}-labelled testosterone by the prostate gland, as measured on the day after treatment (Thomas et al., 1974). These workers also examined the biotransformation of testosterone-1,2-^{3}H in animals given 34 or 68 mg/kg per day, orally, for 5 days. They found a significant decrease in androstenedione synthesis in the high-dose group, indicating increased hepatic androgen hydroxylase activity (Dieringer & Thomas, 1974).

8.5.1.2 Rat

Collins et al. (1971) studied the effects of carbaryl given in the diet (0, 2000, 5000, and 10 000 mg/kg) to Osborn-Mendel rats over 3 generations. The doses actually administered could only be estimated since there were no measurements of food intake. On the basis of a 15 g/day food intake and a 235 g rat, it can be estimated that animals received of the order of 125, 250, or 500 mg/kg per day. It should be noted, however, that the food intake of lactating rats greatly increases, so these figures may considerably underestimate carbaryl exposure during this critical time period. The author used the number of animals mated rather than the number giving birth as the number for litter size and viability, therefore their calculations are overestimates. Nevertheless, the data do show impaired fertility in the high-dose group (which also exhibited growth rate reduction) as well as reduced postnatal survival. The number of live-born offspring and growth rate were reduced in the 5000 and 10 000 mg/kg diet groups.

A three-generation study on Wistar rats was carried out by Weil et al. (1973) in which animals were given 0, 7, 25, 100, or 200 mg/kg per day in the diet or 0, 3, 7, 25, or 100 mg/kg per day

orally. Maternal toxicity was seen in the dietary study at 200 mg/kg per day (decreased weight) and in the gavage study at 100 mg/kg per day (decreased weight and mortality). Postnatal toxicity was noted in the 100 mg gavage group (reduced litter size and viability), but not in lower dose groups. The dietary study indicated fewer effects in the maternal animals with only an initial loss in weight. No perinatal effects were noted.

Vashakidze (1975) exposed male and female rats (number and strain unspecified) to 0, 1, 5, 10, 20, 40, and 50 mg carbaryl/kg, orally, for 1 month. Dose-related changes were noted in serum albumin (decrease), globulins (increase), ChE and AChE (decrease), aspartate transaminase (increase), and alanine transaminase (decrease). Reductions in stem cells as well as spermatozoa were noted at doses of 5 mg/kg or more. Adverse litter effects were seen in treated females. These effects included increased embryo/fetal death, decreased implantations, and prolonged estrus cycle.

Luca & Balan (1987) administered carbaryl-beta-naphthol to Wistar rats in the diet for up to 18 months. The treated groups showed an increase in sperm shape abnormalities, though there were no clear dose- or time-relationships with effects.

8.5.1.3 *Gerbil*

Collins et al. (1971) published the results of a 3-generation reproduction study in which animals were exposed to 0, 2000, 4000, 6000, or 10 000 mg/kg diet. Since all postnatal calculations used the number of animals mated rather than the number giving birth, the authors' data must be recalculated. When this is done, the magnitude of the effects reported is reduced. Adverse effects on various reproductive parameters are nevertheless seen, though the effects are not clearly related to dose levels in the 2000-6000 mg/kg diet groups. These data are difficult to interpret given the lack of information on maternal effects at doses other than the highest, where mortality was observed.

8.5.2 Mammalian developmental toxicity studies

8.5.2.1 Mouse

Murray et al. (1979) administered 100 or 150 mg carbaryl/kg per day, by gavage, or 5660 mg/kg diet (calculated to be 1166 mg/kg per day) to CF-1 mice on gestation days (g.d.) 6-15. Maternal toxicity was noted in the 150-mg group (ataxia, lethality). Litter effects were noted in the 150 mg/kg per day group, where an increase in entirely resorbed litters was seen, and in the dietary group where there was decreased fetal weight.

Pregnant mice were given 0, 100, 150, or 200 mg carbaryl/kg per day, orally, on gestation days 8, 12, or 6-15, and fetuses were examined at term (Mathur & Bhatnagar, 1991). Maternal death was noted at the high dose in the group receiving carbaryl on gestation days 6-15. Fetal weight reductions were seen at the high-dose levels in all groups, as was reduced ossification, open eyelids, and enlarged renal pelvis. These effects may be indicative of fetal growth retardation.

8.5.2.2 Rat

Carbaryl was administered to Harlan Wistar rats at 0, 20, 100, or 500 mg/kg per day, orally, on gestation days 1-7, 5-15, or 1-21 (Weil & Carpenter, 1965; Weil et al., 1972). Maternal toxicity was evident as was reduced weight gain in the high-dose groups receiving the chemical on gestation days 5-15 or 1-2. No adverse fetal effects were seen.

Golbs et al.(1975) treated Wistar rats with 0, 200, or 350 mg carbaryl/kg, orally, or 40 mg/kg ip on a variety of single or multiple gestation days. Reductions in fetal weight were seen in some groups. No other effects were noted.

Sprague-Dawley rats were treated orally with 0, 1, 10, or 100 mg carbaryl/kg per day, three months before and during gestation, and litters were examined at term (Lechner & Abdel-Rahman, 1984). Maternal weight gain was significantly less in the 100 mg/kg group than in controls. No compound-related effects on fetuses were noted.

8.5.2.3 Guinea-pig

Weil et al. (1973) administered carbaryl to guinea-pigs at dose levels of 0, 100, 200, or 300 mg/kg per day in the diet, or 0, 50, 100, or 200 mg/kg per day, orally. These dose levels were determined to be maximum non-maternally toxic doses in preliminary studies by the authors, though the 200 mg/kg dose did reduce maternal weight gain. No significant adverse embryo/fetal effects were seen in any treatment groups.

8.5.2.4 Rabbit

Murray et al. (1979) tested the effects of carbaryl on New Zealand White rabbits during gestation. Dams had diarrhoea at the high dose of 200 mg/kg per day and animals at this dose level as well as at the lower dose level (150 mg/kg per day) gained less weight during gestation than controls. A significant increase in umbilical hernia was noted in fetuses at the 200 mg/kg per day group.

8.5.2.5 Dog

Smalley et al. (1968) administered 3.125, 6.25, 12.5, 25, or 50 mg carbaryl/kg in the diet, throughout gestation, to beagle dogs. Maternal toxicity was noted at all dose levels. This toxicity was described by the authors as dystocia and symptoms included delayed delivery, anorexia, and restlessness. A variety of birth defects were found at doses of 6.25 mg/kg or more. The defects included ectopic intestines, brachygnathia, acaudia, polydactyly, and intestinal agenesis.

Another study was carried out by Imming et al. (1969) on the beagle dog. These workers used 0, 2.0, 5.0 or 12.5 mg/kg per day, orally, throughout gestation. As in the Smalley (1968) study, treated females exhibited toxicity during labour and single deaths were recorded at this time in all treated groups. Birth defects including umbilical hernia and gastrointestinal defects were seen at the 5.0 and 12.5 mg dose levels only.

8.5.2.6 Pig

Two studies on pigs were carried out by Earl et al. (1973). In the first study, fetal pigs were examined from dams given 0, 4, 8, or 16 mg carbaryl/kg per day in the diet; in the second, dams were allowed to farrow after receiving 0, 16, or 32 mg/kg per day in the diet. Animals were exposed throughout most or all of gestation. Effects noted were not consistent across the studies and increased prenatal lethality seen in the first was not noted in the second, even at a higher dose level. A small number of malformations were noted, but no characteristic dose-related pattern was evident.

8.5.2.7 Monkey

Dougherty et al. (1971) exposed a small number of female Rhesus monkeys to 0, 2, or 20 mg carbaryl/kg, throughout gestation. Of the 8 pregnant, treated females, 5 were reported as having aborted as opposed only 1 out of 5 in the controls. The Coulston et al. (1974) study included a larger number of animals per dose, an additional lower dose level (0.2 mg/kg per day), and a shorter dosage period (days 20-38 of gestation). No adverse effects were noted in the second study. These studies are not comparable for the evaluation of the abortifacient potential of carbaryl, since the dosing began later in gestation in the second study. The authors noted that the determination of abortion in the Rhesus monkeys may not have been reliable.

8.5.3 Reproductive and developmental toxicity studies in non-mammalian species

8.5.3.1 Fish

Medaka (*Oryzias latipes*) embryos were exposed to nominal carbaryl concentrations of 0.5, 1.0, 2.5, 5.0, 10.0, 20.0, or 30.0 mg/litre in the water from the 4-cell through to the blastula stages (Solomon & Weis, 1979). Exposure of the eggs resulted in increased cardiovascular anomalies (heart defects, circulatory defects, and edema) at dose levels of 5 mg/litre or more.

8.5.3.2 Amphibian

Elliott-Feeley & Armstrong (1982) treated both embryos and tadpoles of *Xenopus laevis* with nominal carbaryl concentrations in the water of 0.1, 1.0, or 10.0 mg/litre. Defects were seen in embryos exposed to 10 mg/litre, which also resulted in significant lethality. Embryo growth was reduced at all dose levels. Carbaryl-exposed tadpoles exhibited decreased activity at all dose levels.

8.5.3.3 Birds

Chicken eggs have been used by a number of workers to test the potential of carbaryl to affect avian development. Olefir & Vinogradova (1968) injected eggs with carbaryl at 0.01, 0.1, 1.0, or 10.0 mg/kg and examined embryos at different times after injection. Death and anomalies were recorded at 5, 10, 15, and 20 days of incubation at all doses above 0.01 mg/kg. Lillie (1973) administered 0, 250, or 500 mg/kg diet to pullets for 36 weeks beginning at 32 weeks of age. The adult birds showed reduced weights at both levels of carbaryl in the adults and at 500 mg in the progeny. No embryotoxicity or other effects were noted. Swartz (1981) examined the effects of carbaryl on chicken embryo development. They examined chick embryos at different days after injection, for 5 or 12 days post-fertilization. They found vehicle-related increased mortality (carbaryl was more toxic when administered in sesame oil than in acetone) for both periods of exposure. Scattered anomalies were recorded in surviving embryos. In another study (Swartz, 1985) primordial germ cell migration was followed after injection of 10 mg carbaryl per egg prior to incubation. Results did not indicate any significant adverse effects on the primordial germ cells or reproductive organs.

Bursian & Edens (1977) studied the effects of carbaryl on the fertility and post hatching viability of Japanese quail (*Coturnix coturnix japonica*). Birds were exposed from hatching to 14 weeks of age (breeding maturity). Fertility and the hatchability of eggs were measured. The animals received 0, 50, 150, 300, 600, 900, or 1200 mg carbaryl/kg diet. Growth of the adult birds was reduced at the 900 and 1200 mg/kg dose levels. There were no significant effects on any reproductive parameter.

Fletcher & Leonard (1986a) investigated the effects of carbaryl on reproduction in bobwhite quail (*Colinus virginianus*) exposed to 0, 300, 1000, or 3000 mg/kg diet for 22 weeks. No adverse effects were described in any factors related to hatchability, posthatching viability, or gross pathology of newly hatched birds. These workers used a similar protocol to study the effects of carbaryl on mallard ducks (*Anas platyrhyncos*) (Fletcher & Leonard, 1986b). The 3000 mg/kg diet level was toxic with some lethality, decreased numbers of eggs, and thinner egg shells. No effects were seen at the 300 or 1000 mg/kg diet levels.

8.5.4 *Appraisal*

In summary, mammalian studies on the reproductive or developmental toxicity of carbaryl clearly show that this compound is capable of inducing adverse effects *in utero* and during the reproductive process. These effects are always seen only at dose levels at which there is concurrent maternal toxicity, with the possible exception of a few studies on the rat which have not been replicated by other workers. For a number of species, the dams appear to be more sensitive than their litters. In general, the adverse effects noted in developmental toxicology studies cannot be simply attributed to maternal toxicity (Chernoff et al., 1990). However, the pattern of maternal and fetal toxicity occurring at the same dose levels indicates that the developing mammalian embryo/fetus is not especially susceptible to carbaryl.

Carbaryl has been shown to be embryotoxic for fish, amphibians, and birds, at some exposure concentrations.

8.6 Mutagenicity of carbaryl and *N*-nitrosocarbaryl

In this section on mutagenicity, and in the section on carcinogenicity (8.7.1), the two compounds, carbaryl and nitrosocarbaryl, are discussed (separately), since the formation of *N*-nitrosocarbaryl was reported to occur in the stomach of rats and guinea-pigs, in the presence of sodium nitrite and carbaryl, under acid conditions (Elespuru & Lijinsky, 1973; Beraud et al., 1979; Rickard & Dorough, 1984). See also section 8.9.3.

8.6.1 Genotoxicity assays in vitro

8.6.1.1 Primary DNA damage

(a) *Carbaryl*

Carbaryl did not cause DNA damage in different wild type strains and DNA recombination lacking strains of *Bacillus subtilis* (Table 49). Carbaryl was reported to be non-genotoxic for *B. subtilis* Marburg 17A Rec^+ and Marburg M45T Rec^- strains, highly sensitive to frameshift mutagens, even at the highest tested concentration of 10 mg/plate (Uchiyama et al., 1975).

Carbaryl (10^{-4} mmol/litre) did not affect the sedimentation profiles of DNA from human skin cells in culture (both normal and xeroderma pigmentosum), either immediately or 20 h after treatment (Regan et al., 1976).

There are two controversial reports on the genotoxicity of carbaryl, evaluated by the induction of mitotic gene conversion in the diploid strain of *Saccharomyces cerevisiae*, heteroallelic at the two different loci ade2 and trp5. Siebert & Eisenbrand (1974) used an assay system with a 16-h incubation time and a concentration of carbaryl of 4.97 mmol/litre and did not observe any changes in the control frequency of mitotic gene conversion. However, Jaszczuk & Syrowatka (1979), reported a weak positive response with a lower concentration of carbaryl (2.5 mmol/litre) and shorter (5 h) incubation time. No converting activity of *N*-hydroxy carbaryl (2.5 mmol/litre) was found under the same assay conditions.

Carbaryl was inactive in the rat primary hepatocytes unscheduled DNA synthesis assay (Cifone, 1989). It did not induce significant changes in the nuclear labelling of rat primary hepatocytes in two independent trials with applied concentrations ranging from 5 to 25 μg/ml.

No DNA-damaging properties of carbaryl, assessed by its capacity for inducing unscheduled DNA synthesis (UDS) in cultured human lymphocytes, were reported by Rocchi et al. (1980). However, the authors did not use a standardized test protocol meeting established criteria for the UDS assay performance. They tested only

Table 49. Bacterial assays of genetic toxicity of carbaryl

Test	Test organism	Concentration (μg/plate)	Genetic end-point	Metabolic activation	Result	Reference
DNA damage	*B. subtilis*	700 mg/litre	Rec assay	-	negative	DeGiovanni-Donnelly et al. (1968)
	B. subtilis	20	Rec assay	-	negative	Shirasu et al. (1976)
	B. subtilis	0.4, 4, 40, 400	Rec assay	-	negative	Eto et al. (1982)
Gene mutation	*B. subtilis*	up to 10 000	Rec assay	-	negative	Uchiyama et al. (1975)
	E. Coli WP2	1000	Try-	-	negative	Ashwood-Smith et al. (1972)
	E. Coli WP2	1000-3000	Try-	-	negative	Nagy et al. (1975)
	E. Coli WP2	10 000	Try-	-	negative	Uchiyama et al. (1975)
	H. influenzae	10 μmol/litre	Novobiocim	-	negative	Elespuru et al. (1974)
	S. typhimurium					
	TA 98	up to 2000	His-	-	negative	McCann et al. (1975)
	TA 98	up to 2000	His-	Rat	negative	
	TA 98	50 nmol/litre	His-	-	negative	Blevins et al. (1977)
	TA 98	10-1500	His-	-	negative	DeLorenzo et al. (1978)
	TA 98	10-1500	His-	Rat	negative	
	TA 98	0.25, 2, 5, 50, 1000	His-	-	negative	Jaszczuk et al. (1979)

Table 49 (continued)

TA 98	up to 5000	His-	-	negative	Moriya et al. (1983)
TA 98	up to 5000	His-	Rat	negative	
TA 98	0.2, 2, 20	His-	-	negative	Eto et al. (1982)
TA 98	0.2, 2, 20	His-	Rat	negative	
TA 98	5-2000	His-	-	negative	Lawlor (1989)
TA 98	5-2000	His-	Rat	negative	
TA 100	up to 2000	His-	-	negative	McCann et al. (1975)
TA 100	up to 2000	His-	Rat	negative	
TA 100	50 nmol/litre	His-	-	negative	Blevins et al. (1977)
TA 100	10-1500	His-	-	negative	DeLorenzo et al. (1978)
TA 100	10-1500	His-	Rat	negative	
TA 100	0.25, 2, 5, 50, 1000	His-	-	negative	Jaszczuk et al. (1979)
TA 100	0.2, 2, 20	His-	-	negative	Eto et al. (1982)
TA 100	0.2, 2, 20	His-	Rat	negative	
TA 100	5-2000	His-	-	negative	Lawlor (1989)
TA 100	5-2000	His-	Rat	negative	

Table 49 (continued)

Test	Test organism	Concentration (μg/plate)	Genetic end-point	Metabolic activation	Result	Reference
	TA 1535	up to 2000	His-	-	negative	McCann et al. (1975)
	TA 1535	up to 2000	His-	Rat	negative	
	TA 1535	2500	His-	-	positive	Marshall et al. (1976)
	TA 1535	1000	His-	Rat	negative	
	TA 1535	50 nmol/litre	His-	-	negative	Blevins et al. (1977)
	TA 1535	10-1500	His-	-	negative	DeLorenzo et al. (1978)
	TA 1535	10-1500	His-	Rat	negative	
	TA 1535	up to 5000	His-	-	negative	Moriya et al. (1983)
	TA 1535	up to 5000	His-	Rat	negative	
	TA 1535	5-2000	His-	-	negative	Lawlor (1989)
	TA 1535	5-2000	His-	Rat	negative	
	TA 1536	2500	His-	-	negative	Marshall et al. (1976)
	TA 1536	1000	His-	Rat	negative	
	TA 1537	up to 2000	His-	-	negative	McCann et al. (1975)
	TA 1537	up to 2000	His-	Rat	negative	
	TA 1537	50 nmol/litre	His-	-	negative	Blevins et al. (1977)

Table 49 (continued)

TA 1537	2500	His-	-	negative	Marshall et al. (1976)
TA 1537	1000	His-	Rat	negative	
TA 1537	10-1500	His-	-	negative	DeLorenzo et al. (1978)
TA 1537	10-1500	His-	Rat	negative	
TA 1537	0.25, 2, 5, 50, 1000	His-	-	negative	Jaszczuk et al. (1979)
TA 1537	up to 5000	His-	-	negative	Moriya et al. (1983)
TA 1537	up to 5000	His-	Rat	negative	
TA 1537	5-2000	His-	-	negative	Lawlor (1989)
TA 1537	5-2000	His-	Rat	negative	
TA 1538	100	His-	-	positive	Egert & Greim (1976)
TA 1538	100	His-	Mouse	positive	
TA 1538	50 nmol/litre	His-	-	negative	Blevins et al. (1977)
TA 1538	2500	His-	-	negative	Marshall et al. (1976)

Table 49 (continued)

Test	Test organism	Concentration (μg/plate)	Genetic end-point	Metabolic activation	Result	Reference
	TA 1538	1000	His-	Rat	negative	
	TA 1538	10-1500	His-	-	negative	DeLorenzo et al. (1978)
	TA 1538	10-1500	His-	Rat	negative	
	TA 1538	up to 5000	His-	-	negative	Moriya et al. (1983)
	TA 1538	up to 5000	His-	Rat	negative	
	TA 1538	5-2000	His-	-	negative	Lawlor (1989)
	TA 1538	5-2000	His-	Rat	negative	

one concentration of carbaryl (50 μg/ml), did not use any metabolic activation system, did not run negative and adequate positive controls concomitantly (other than the ultraviolet irradiation), and did not apply relevant criteria to assess data.

The lack of DNA-damaging properties of carbaryl, as measured by the induction of UDS, was confirmed by Probst et al. (1981). They used a standardized protocol and autoradiographic techniques in metabolically competent, cultured rat hepatocytes with test concentrations ranging from 0.5 to 1000 nmol/ml. In contrast, Ahmed et al. (1977a) reported that carbaryl induced the UDS of the ultraviolet type (long patch repair) in a cultured human fibroblast VA-4 cell line with, and without, metabolic activation in concentration ranges of 1, 10, 100, and 1000 μmol/litre. However, this study had several experimental shortcomings. The protocol, the control value, and the results of compounds tested were not in accordance with comparable assays by other authors.

(*b*) N-*nitrosocarbaryl*

The DNA-damaging properties of *N*-nitrosocarbaryl in *B. subtilis* have been reported (Table 50).

In one study (Uchiyama et al., 1975), more pronounced genotoxicity of *N*-nitrosocarbaryl to *B. subtilis* was registered compared with that of *N*-methyl-*N'*-nitro-*N*-nitrosoguanadine. However, the genotoxicity of *N*-nitrosocarbaryl was the lowest when compared with other concomitantly tested nitrocarbamates.

In contrast to carbaryl, *N*-nitrosocarbaryl showed pronounced genotoxicity toward *S. cerevisiae* D4 (Siebert & Eisenbrand, 1974).

N-nitrosocarbaryl, but not carbaryl, reacted with human DNA in cell culture to form alkaline-sensitive bonds (Regan et al., 1976). The DNA of nitrosocarbaryl-treated (10^{-4} mmol/litre) cells showed a substantial reduction in sedimentation rate immediately, and up to 20 h, after treatment. Presumably, the effect observed was related to the induction of numerous single-strand breaks in the DNA and the formation of DNA adducts. On the basis of selective labelling, the authors suggested that the methyl-containing moiety of nitrosocarbaryl was separated from the naphthalene ring in a human fibroblast culture and bound irreversibly to DNA (Regan et al., 1976).

8.6.1.2 Gene mutation assay

(*a*) *Carbaryl*

As summarized in Table 49, carbaryl did not exert a mutagenic effect in studies with *E. coli, H. influenzae,* or *Salmonella*. Among the many reports on *Salmonella*, only two indicated a positive effect. Thus, Marshall et al. (1976) observed increased mutagenicity at 1000 μg/plate with S9 mix for TA1535. An evaluation of this data is difficult because no negative and positive control data were presented. Egert & Greim (1976) reported a positive response for TA1538 by 100 μg/plate. The mutagenicity of carbaryl in this study greatly increased when a non-standard metabolic activation system (mouse liver microsome) was used.

Ahmed et al. (1977b) reported a positive mutagenic response to carbaryl in Chinese hamster V79 cells at a dose level of 0.01 mmol/litre, with no metabolic activation. There was a concentration-related effect of carbaryl on cell survival; less than 50% of the cells survived at concentrations >0.01 mmol/litre. Mutation studies carried out with a concentration of 0.01 mmol/litre showed an approximately 8-fold increase in ouabain resistance forward mutation in V79 cells as compared with the spontaneous mutation rate.

However, Wojciechowski et al. (1982) found no ouabain-resistance with carbaryl in a cell-mediated mutagenesis assay when they used an exogenous activating system in which irradiated fetal cells of Syrian hamsters were co-cultivated with cells of Chinese hamsters V79. No mutagenic response was observed for carbaryl at concentrations of 0.01, 0.05, 0.1 mmol/litre with, or without metabolic activation. The toxicity of carbaryl at these concentrations ranged from 7% at the lowest concentration to 23% at the highest.

Carbaryl produced a negative result for inducing forward mutations at the HPRT locus in Chinese hamster ovary cells both with, and without, metabolic activation (Young, 1990).

(*b*) N-*nitrosocarbaryl*

N-nitrosocarbaryl has shown a positive response in a number of bacterial assays (Table 50). In *Salmonella*, *N*-nitrosocarbaryl was

Table 50. Bacterial assays of the genetic toxicity of nitrosocarbaryl

Test	Test organism	Concentration (μg/plate)	Genetic end-point	Metabolic activation	Result	Reference
DNA damage	*B. subtilis*	0.4, 4, 40	Rec assay	-	positive	Eto et al. (1982)
	B. subtilis	up to 100	Rec assay	-	positive	Uchiyama et al. (1975)
Gene mutation	*E. Coli* 30 R	0.1 mmol/litre	Try-	-	positive	Elespuru et al. (1974)
	E. Coli WP2	5, 10, 50, 100	Try-	-	positive	Uchiyama et al. (1975)
	E. Coli K12	100	Try-	-	positive	Egert & Greim (1976)
	E. Coli K12	100	Try-	Mouse	positive	
	H. influenzae	10 μmol/litre	Novobiocin	-	positive	Elespuru et al. (1974)
	S. typhimurium					
	TA 98	0.001-11	His-	-	positive/ negative	Blevins et al. (1977)
	TA 98	10-1500	His-	-	negative	DeLorenzo et al. (1978)
	TA 98	10-1500	His-	Rat	negative	
	TA 98	0.25-1000	His-	-	positive	Jaszczuk et al. (1979)
	TA 98	0.02, 0.2, 2	His-	-	negative	Eto et al. (1982)
	TA 98	0.02, 0.2, 2	His-	Rat	negative	

Table 50 (continued)

Test	Test organism	Concentration (μg/plate)	Genetic end-point	Metabolic activation	Result	Reference
	TA 98	0.01-100	His-	-	negative	Rickard et al. (1982)
	TA 98	0.1-100	His-	Rat	negative	
	TA 100	0.001-11	His-	-	positive	Blevins et al. (1977)
	TA 100	0.02, 0.2, 2	His-	-	positive	Eto et al. (1982)
	TA 100	0.02, 0.2, 2	His-	Rat	negative	
	TA 100	0.1-100	His-	-	positive	Rickard et al. (1982)
	TA 100	0.1-100	His-	Rat	positive	
	TA 1535	0.5-100	His-	-	positive	Marshall et al. (1976)
	TA 1535	50-1000	His-	Rat	positive	
	TA 1535	0.001-11	His-	-	positive	Blevins et al. (1977)
	TA 1535	0.25-1000	His-	-	positive	Jaszczuk et al. (1979)
	TA 1535	0.1-100	His-	-	positive	Rickard et al. (1982)
	TA 1535	0.1-100	His-	Rat	positive	
	TA 1536	0.5-100	His-	-	negative	Marshall et al. (1976)
	TA 1536	50-1000	His-	Rat	negative	
	TA 1537	0.001-11	His-	-	negative	Blevins et al. (1977)

Table 50 (continued)

TA 1537	0.5-100	His-	-	positive	Marshall et al. (1976)
TA 1537	50-1000	His-	Rat	positive	
TA 1537	0.25-1000	His-	-	positive	Jaszczuk et al. (1979)
TA 1538	100	His-	-	positive	Egert & Greim (1976)
TA 1538	100	His-	Rat	positive	
TA 1538	0.001-11	His-	-	negative	Blevins et al. (1977)
TA 1538	0.5-100	His-	-	positive	Marshall et al. (1976)
TA 1538	50-1000	His-	Rat	negative	
TA 1538	0.25-1000	His-	-	negative	Jaszczuk et al. (1979)

mutagenic to strains responding to both base substitution (TA1535, TA100) and frame shift (TA1536, TA1537, TA1538, TA98). The mutagenic potential of *N*-nitrosocarbaryl toward *Salmonella* TA1535 was greatly diminished by the added exogenous activation system (Marshall et al., 1976). A decrease in mutagenic activity by the addition of S9 mix on frame shift mutagenesis has also been reported (Marshall et al., 1976; Jaszczuk et al., 1979).

8.6.1.3 *Chromosomal aberration assays and sister chromatid exchange*

(*a*) *Carbaryl*

Animals

Carbaryl induced a clastogenic response in the three *in vitro* bioassays (Ishidate & Odashima, 1977; Kazarnovskaya & Vasilos, 1977; Önfelt & Klasterska, 1983). All the positive responses were observed at toxic dose levels (30-80 μg/ml; 50, 100 μmol/litre); exogenous metabolic activation was not required for activity. Thus, Ishidate & Odashima (1977) observed a strong positive response for carbaryl (30 μg/ml) in a chromosomal aberration assay using a Chinese hamster fibroblast cell line. Carbaryl produced predominantly chromatid type gaps, breaks, translocations, rings, and fragmentation, 48 h after treatment.

Carbaryl was negative for inducing chromosomal aberrations in CHO cells without metabolic activation but was positive under metabolic activation conditions (Murli, 1989).

Kazarnovskaya & Vasilos (1977) reported a positive response for carbaryl in cultures of human embryonic fibroblast: levels of 40 and 80 μg/ml caused a 4-fold and 10-fold increase, respectively, in the frequency of chromosomal aberrations, at 24 h exposure time, compared with a control rate of 2% (without S9-mix). Again, the aberrations produced were mainly of a chromatid type; the type most frequently observed was single fragments. An increased number of paired fragments was found only at 80 μg carbaryl/ml. Carbaryl (80 μg/ml) increased the percentage of cells with chromosomal coiling (9.8% in the control group; 17.9% in the test group) and aneuploidy (3% in the control group; 29.2% in the test group). Previously, Kazarnovskaya & Vasilos (1977) had shown that carbaryl suppressed

mitosis, changed the rate of the mitotic phase, and significantly increased the number of pathological forms of mitosis in a human embryonic fibroblast culture, with a dose-time response. Onfelt & Klasterska (1983) observed induction of viable aneuploid/polyploid cells and multiple chromatid exchanges after treatment of V79 Chinese hamster cells with carbaryl. The compound exerted a pronounced chromosome-breaking effect, at a concentration of 100 μmol/litre, 26 and 50 h after treatment. There was an increased frequency of multiple chromatid exchanges and fragments, as well as pulverisation and more diffuse signs of chromosome damage. The effects of carbaryl on chromosome structure and distribution were almost abolished by the simultaneous addition of Aroclor-induced 2 or 10% rat S9-mix and glutathion.

In two *in vitro* assays for chromosome damage using Chinese hamster lung fibroblasts, carbaryl was found to be positive (Ishidate et al., 1981; Onfelt & Klasterska, 1984). In the latter study, the effect of carbaryl on the incidence of sister chromatid exchange was decreased by the addition of rat liver microsomes. Söderpalm & Önfelt (1988) related the mitotic aberrations in V79 Chinese hamster cells, in part, to a reduction in the intracellular levels of glutathione, and increased lipid peroxidation. They also hypothesized that the anticholinergic effects of carbaryl may play a role in the cleavage process.

Plants

A negative clastogenic response for carbaryl in a concentration range of 50-200 mg/litre was reported by Ma et al. (1984) who used the *Tradescantia micronucleus* test. At present, this test is considered the most established and standardized plant assay system for the purposes of *in situ* monitoring of environmental mutagen pollution (Ma et al., 1984).

Carbaryl induced chromosomal effects in different plant assays (Wuu & Grant, 1966; Amer & Farah, 1968; Brankovan, 1972). Carbaryl increased by approximately 10-fold the number of aberrant cells in the root tips of barley seedings (*Hordeum vulgare*) in C_1 and C_2 generations after the seeds were treated with concentrations of 500, 1000, or 1500 mg carbaryl/litre for 6 and 12 h. The cytogenetic effects induced included mostly metaphase and anaphase

fragments and anaphase bridges and were time-dependent (Wuu & Grant, 1966).

The mitotic, cytogenetic effects of carbaryl were seen in *Vicia faba* (Amer & Farah, 1968) and sugar corn (Brankovan, 1972). Carbaryl caused chromosomal abnormalities (chromosome lagging; stickiness, mainly in diakinesis, polyploidy, fragments, anaphase bridges) in different meiotic states in the pollen mother cells of *Vicia faba* after spraying flower buds of different ages (2 weeks, 1 month) with saturated aqueous solutions of a commercial carbaryl preparation. The percentage of the chromosomal aberrations increased with increase in the frequency of spraying (every week) or 2 weeks for 1 month; daily for 8 days) and then decreased when the recovery time was increased (Amer & Farah, 1968).

8.6.2 *Genotoxicity* in vivo

8.6.2.1 *Host-mediated assay*

(*a*) *Carbaryl*

Usha Rani et al. (1980) reported that carbaryl did not have a gene-mutation potential *in vivo*, when given orally in a toxic dose of 438 mg/kg, 3 times daily for 3 days, to 6 Swiss male mice, which were subsequently injected with *Salmonella* strain G46. These data are consistent with those that showed that carbaryl was not mutagenic for *Salmonella in vitro*.

8.6.2.2 Drosophila melanogaster *and other insects*

(*a*) *Carbaryl*

There are several reports of bioassays for carbaryl genotoxicity in which *Drosophila melanogaster* was used (Brzeskii, 1972; Brzeskii & Vaskov, 1972; Hoque, 1972; Woodruff et al., 1983; Omer et al., 1986).

In studies by Hoque (1972), carbaryl at 1.5 and 10 mg/litre was given to female *Drosophila*. It was reported that the treatment caused a changed sex ratio, changes in eye colour, and various chromosomal aberrations in the offspring. The small amounts of

material used and the lack of any detailed presentation of the findings preclude any evaluation or conclusion.

At high doses (0.3 ml from a 1% suspension of 85% commercial product in glucose), carbaryl caused a slight increase in mutation frequency in the F_1 generation males of a *Drosophila* line, which were studied at different stages of spermatogenesis. There were no deletions or disturbed fertility (Brzeskii, 1972; Brzeskii & Vaskov, 1972).

Woodruff et al. (1983), who used a sensitive experimental protocol that incorporated the mating scheme with repair-deficient females, reported that carbaryl was not mutagenic for *Drosophila*. F_1 male progeny of males that had ring X chromosomes and double marked Y chromosomes, were treated with carbaryl at 200 mg/litre and mated with mus-302, repair-deficient females of *Drosophila*. The male progeny did not show any induced complete (ring chromosome) or partial (Y chromosome markers) chromosome loss.

The mutagenic activity of carbaryl in *Drosophila melanogaster* was studied by Omer et al. (1986). The results indicated that carbaryl does not increase the rate of dominant and sex-linked recessive lethal mutations.

Carbaryl did not cause chromosome abnormalities in the meiotic cells of male grasshoppers, when they were given a single toxic dose (not precisely indicated) of 0.25 ml of the supernatant of an aqueous suspension/solution of carbaryl by ip injection; however, there were morphological disturbances in the spermatocytes (Venkat Reddy et al., 1974).

(*b*) N-*nitrosocarbaryl*

Results obtained by Omer et al. (1986) from the nitrosocarbaryl-treated populations of *Drosophila melanogaster* suggested that nitrosocarbaryl increased significantly the percentage of dominant lethal mutations above the spontaneous mutation frequency. The results obtained from the 0.05, 0.10, and 0.15% nitrosocarbaryl-treated populations also showed a significant increase in the percentages of sex-linked recessive mutations.

8.6.2.3 *Chromosomal aberrations and sister chromatid exchange*

(a) Carbaryl

There are several negative chromosomal studies on carbaryl and *N*-nitrosocarbaryl in somatic and germ cells *in vivo* in mammals (Venkat Reddy et al., 1974; Degraeve et al., 1976; Seiler, 1977, Usha Rani et al., 1980; Dzwonkowska & Hübner, 1986). In all these studies, sufficiently high dose levels of carbaryl were used (up to the LD_{50}) in order to define the negative cytogenetic responses.

Using the micronucleus test and the cytogenetic analysis of metaphase chromosomes, Degreave et al. (1976) found no clastogenic effects in the bone marrow of mice that had been given a single oral dose of carbaryl (0.2 ml), an intraperitoneal dose (0.5 ml) of carbaryl, or 7 oral doses of carbaryl solution (1×10^{-3} mg/litre) alone, or with sodium nitrite (2×10^{-3} mg/litre).

A negative response for a high dose of carbaryl (146 mg/kg, orally, 2 times per 24 h; 30-h sampling time) was reported by Usha Rani et al. (1980) with an adequate protocol for the mouse bone marrow micronucleous test.

No increase in the rate of the micronucleated, polychromatic erythrocytes in the bone marrow of mice was found during *in vivo* nitrosation of carbaryl after its oral administration at the maximum tolerated dose of 100 mg/kg, together with an excess of sodium nitrite (100 mg/kg) (Seiler, 1977).

A dose of 64 mg carbaryl/kg produced a negative result in an *in vivo* assay of chromosomal aberrations in the bone marrow cells of the Syrian hamster (Dzwonkowska & Hubner, 1986).

No chromosome aberrations were observed in the bone marrow of Syrian hamsters (6 per dose), given single intraperitoneal injections of doses up to the LD_{50} (64, 128, 320, and 640 mg/kg) of a commercial mixture of carbaryl/lindane (40:10) (Dzwonkowska & Hubner, 1986).

Daily oral doses of technical carbaryl (10 mg/kg) suspended in peanut oil were given to male, albino rats for a period of 5 days. There were no significant chromosomal changes in the bone marrow cells of the exposed animals (Dikshith, 1991).

8.6.2.4 Dominant lethal assays in rodents

(*a*) *Carbaryl*

Epstein et al. (1972) studied the mutagenicity of carbaryl using the dominant lethal test. In this assay, male ICR/Ha Swiss mice were treated orally with 1000 or 50 mg carbaryl/kg daily for 5 successive days and then caged with 3 untreated virgin females, which were replaced weekly for 8 consecutive weeks. The frequency of early fetal deaths and preimplantation losses in the test groups were within the limits of the control values. Therefore, dominant lethal mutations were not induced in mice given sufficiently high oral doses of carbaryl.

8.6.3 Other end-points

8.6.3.1 Cell transformation

(*a*) *Carbaryl*

Transformation of the fibroblast clone A31 of the BALB/3T3 mouse was not induced by carbaryl when given in non-toxic (1.5 and 10 μg/ml) or moderately cytotoxic (20 and 40 μg/ml) doses, over 24 h (Quarles & Tennant, 1975).

(*b*) N-*nitrosocarbaryl*

N-nitrosocarbaryl showed transforming activity, at concentrations of 10-20 μg/ml, which was cytotoxic for the BALB/3T3, A31 cells. That 3-10 cell passages are necessary for detecting the transforming event suggests that the transformation frequency for *N*-nitrosocarbaryl in this test system is low. Transformed cells showed morphological alterations, loss of contact inhibition, and growth in soft agar, as well as carcinogenic activity in normal newborn, irradiated, suckling, or athymic BALB/C mice. The tumour incidence (anaplastic sarcomas) was relatively low; in several instances, tumours regressed in normal mice, but not in athymic mice, after 2-3 weeks of growth. *N*-nitrosocarbaryl did not activate detectable amounts of the endogenous murine leukaemia viruses carried by the BALB/3T3 cells or viral protein. However, viral antigen production in the transformed cells was induced by iododeoxyuridin, which indicated

the presence of the viral genome. On the basis of this *N*-nitrosocarbaryl transforming activity in mammalian cells in culture, Quarles & Tennant (1975) suggested that the compound may be an active, though weak, carcinogen *in vivo*.

8.6.3.2 *Aneuploidy induction*

(*a*) *Carbaryl*

Tests of the chemical induction of spindle fibre inactivation and c-mitosis (colchicine-mitosis) in *Allium* revealed the existence of an unspecific physico/chemical mechanism, based on the partitioning of compounds into hydrophobic compartments of the cell. This means that chemical compounds, in general, cause c-mitosis according to their lipophilic characteristics, as indicated by the octanol/water partition coefficient. Thus, a close correlation exists between the lipophilicity of compounds and the dose at which spindle disturbance occurs. However, besides this unspecific effect on the spindle fibres mechanism, there are some compounds that exhibit specific effects causing inactivation of the spindle fibre mechanism at lower doses than indicated by their lipophilicity. This can occur via different mechanisms, such as specific binding to actin (colchicine) or binding to sulfhydryl groups (organic mercury). Onfelt (1987) analysed the c-mitotic effects of 22 compounds in V79 hamster cells. Five of these compounds fell outside the regression line for lipophilicity/c-mitosis, among them colchicine, methyl mercury, and carbaryl. Further analyses revealed that carbaryl owes its pronounced c-mitotic action to its reactivity with sulfhydryl groups. It is therefore not surprising that several authors have reported mitotic disturbances caused by carbaryl in various experimental systems. Onfelt & Klasterska (1983) reported that a significant increase in the aneuploidy/polyploidy cells was obtained with both 50 and 100 μmol carbaryl/litre, 26, 59, and 74 h after treatment. Carbaryl caused mitotic disturbances in *Allium cepa, Vicia faba, Gossypium barbadense, Nigella damascena* (Amer, 1965; Amer et al., 1971; Degraeve et al., 1976). Amer (1965) reported c-mitotic effects of carbaryl in the roots of *Allium cepa* that had been treated for 4 or 24 h with different concentrations of pure (0.5, 0.25%) and commercial products (85% sprayable powder). The increased rate of abnormal meta-telophases and ana-telophases depended on the concentration and temperature of the test solutions. The types of

induced abnormal metaphases included star-metaphases and a few prophase-metaphases. Two types of anaphases, the c-type and the multipolar type, as well as multinuclear interphase cells, were observed. Continuous treatment with carbaryl for 24 h nearly arrested mitosis. There was a full recovery of mitosis in 48 h and induced signs of polyploidy appeared.

Consistent with these findings are the c-mitotic effects of carbaryl in *Vicia faba* and *Gossypium barbadense* (Amer et al., 1971). The mitotic index of *Vicia faba*, after root treatment, decreased with increased concentrations of carbaryl (25, 50, or 100 mg/litre for 4 h. There was no effect from carbaryl after seed-soaking for different lengths of time. Mitotic anomalies (mostly disturbed meta- and anaphases) in the roots of *Vicia faba* and *Gossypium barbadense* showed a concentration-time response.

Carbaryl caused mitotic disturbances (c-mitotic effect, multipolar anaphases) or cytotoxicity (pycnotic nuclei, tissue degeneration) after root treatment of *Nigella damascena* with concentrations of 2.5×10^{-4} and 1×10^{-3} mg/litre. When $NaNO_2$ (2×10^{-3}) was added to carbaryl solutions of 1×10^{-2} and 1×10^{-3} mg/litre, the effects increased, possibly because of the formation of nitrosocarbaryl (Degreave et al., 1976). No effect was observed after grain treatment.

Soaking sugar corn seeds for 48 h with a 0.12 or 0.25% aqueous solution of 50% commercially prepared carbaryl, resulted in a dose-response induction of aberrations of anaphase chromosomes of types not seen in the controls (bridges with, or without, fragments, dicentrics). Repeated treatment of young plants with a 0.25% solution of carbaryl for 6 h during meiosis caused typical c-mitotic effects in metaphase and anaphase through the arrest of cell division and spindle inactivation. Some of the induced aberrations persisted until the generative stage. They were fixed and incorporated through the embryonal and generative development stages and thus increased pollen sterility (Brankovan, 1972).

Carbaryl was reported to increase the number of aberrant forms of mitosis (mostly c-mitotic effect) in the small intestine, cornea, and spleen of rats given oral doses of 400 mg/kg. The authors also reported that at lower doses of carbaryl (40 or 80 mg/kg), there was an increased incidence of bridge and chromosome lagging in anaphase and telophase, in addition to a high percentage of c-mitosis. The authors reported that there were no effects at 20 mg/kg. Only

the result following the 400 mg/kg dose was fully reported (Vasilos et al., 1975).

8.6.4 Appraisal

Carbaryl has been evaluated for its potential mutagenicity in a number of tests *in vitro* as well as *in vivo*, in bacterial, yeast, plant, insect, and mammalian systems, testing a variety of end-points.

The available evidence indicates that carbaryl has no DNA-damaging properties. No confirmed induction of mitotic recombination, gene conversion, and UDS in prokaryotes (*H. influenzae, B. subtilis*) and eukaryotes (*S. cerevisiae, A. nidulans*, cultured human lymphocytes, and rat hepatocytes) *in vitro* has been reported.

Negative results were obtained in tests for gene mutations in a number of bacterial assays, with the exception of two cases. In several studies of gene mutations in mammalian cells *in vitro*, carbaryl only produced one equivocal positive result in a cell culture study. However, the study had several shortcomings and the result has not been confirmed in any other comparable studies.

Chromosomal damage with high dosages of carbaryl, has been reported *in vitro* in human, rat, and hamster cells and in plants. No such effects have been observed in mammalian tests *in vivo*, even at doses as high as 1000 mg/kg.

Carbaryl has been shown to induce disturbances in the spindle fibre mechanism in plant and mammalian cells *in vitro*. The relevance of plant assays for extrapolation to humans is unclear.

It can be concluded that the available data-base does not support the presumption that carbaryl poses a risk of inducing genetic changes in either the somatic or the germinal tissue of humans.

The nitrosated product of carbaryl, *N*-nitrosocarbaryl, is capable of inducing mitotic recombination and gene conversion in prokaryotes (*H. influenzae, B. subtilis*) and eukaryotes (*S. cerevisiae*) *in vitro* and gave positive results in *E. coli* spot tests.

Furthermore, experimental results indicate that *N*-nitrosocarbaryl binds to DNA, causing alkali-sensitive bonds and single-strand breakage.

Nitrosocarbaryl has not been established as a clastogen *in vivo* (bone marrow and germ cells), even at high toxic doses.

8.7 Carcinogenicity

8.7.1 Carcinogenicity studies of carbaryl in rodents

8.7.1.1 Mouse

Seven early carcinogenicity studies with carbaryl have been reported (Table 51) involving different strains of mice, subcutaneous injection, skin painting, ip and oral routes of administration, different dose levels and dose schedules, and various lengths of exposure and observation. None of these negative studies (one marginal response) had sufficient data or data reporting and it was not possible to evaluate them.

Most of these studies involved the lung adenoma test in strain A mice. This test is no longer considered to be a satisfactory carcinogenicity bioassay because of the high rate of background tumours that occur in untreated animals (Clayson, 1987).

Carbaryl did not increase the incidence of lung tumours in two strains of male mice, A/Jax and C_3H, which were given 20 consecutive, weekly, subcutaneous injections of 10 mg carbaryl (Carpenter et al., 1961). As only one dose of carbaryl was tested and the initial number of animals entered was insufficient, no conclusion concerning the carcinogenic potential of carbaryl can be drawn from this study.

There was no tumour development in mice (unspecified strain and sex) after carbaryl application by skin painting for 24 months (dose not specified, 48% water suspension) (Weil & Carpenter, 1962). This study also lacked details about the experimental procedure and pathology used and, so, was placed in the inconclusive category.

Carbaryl did not induce tumours in the lungs, liver, kidney, heart, spleen, pancreas, and the thyroid and adrenal glands in two strains of mice, A and C_3HA, treated ip, once per week for about 2 years, with toxic doses of 60 mg/kg (Makovskaya et al., 1965). The

Table 51. Carcinogenicity studies on carbaryl in rodents

Chemical	Species, strain (number)	Sex	Route and mode of administration	Dose (mg/kg)	Duration of study	Significant tumour/organ	Evaluation of individual study	Reference
Carbaryl	Mouse, A/Jax, C_3H 30 in group	male	SC 1/week	200 mg (total)	20 weeks	none	inconclusive	Carpenter et al. (1961)
Carbaryl	Mouse, NS	not stated	skin painting	not stated	24 months	none	inconclusive	Weil & Carpenter (1962)
Carbaryl	Mouse, CD-1	male female	oral, diet	0.01% 0.04%	80 weeks 2 years	none	inconclusive	Mellon Institute (1969)
Carbaryl	Mouse, A,C_3,HA	not stated	intraperitoneal 1/week	50	2 years	none	inconclusive	Makovskaya et al. (1965)
Carbaryl	Mouse, (C_{57},$B1_6$x C_5H/Anf)F_1 (C_{57}B1/6xAKR)F_1 72	male female	oral gavage daily 7 days-4 weeks of age; in diet 4 weeks-18 months of age	4.64 14 mg/kg body weight	18 months	none	inconclusive	Innes et al. (1969)
Carbaryl	Mouse, A/He: 16	male	intraperitoneal 3/week for 4 weeks	6 mg (total)	20 weeks	marginal (±) lung tumours response	inconclusive	Shimkin et al. (1969)
Carbaryl	Mouse, A/J: 124	female	oral, diet	1000	10 weeks	none	inconclusive	Triolo et al. (1982)
Carbaryl technical	Mouse CD-1	male female	diet	100,1000 8000	53 weeks	none	no effect	Hamada (1991b)

Table 51 (continued)

Carbaryl	Rat, CF-N 120 per level	male female	oral, diet	0.005, 0.01, 0.02, 0.04% in diet	2 years	none	inconclusive	Carpenter et al. (1961)
Carbaryl technical	Rat, Sprague-Dawley 80 or 90 per group	male and female	diet	250, 1500 7500	52 weeks	none	negative	Hamada (1991b)
β-Carbaryl	Rat, mongrel 60 48 control	male	oral gavage twice a week	30	22 months	fibrosarcoma, skin; polymorphic cell sarcoma, stomach; osteosarcoma with multiple mestastases	positive but inconclusive	Andrianova & Alexeev (1970)
	48 48 control		single subcutaneous implantation	20 mg	22 months	fibrosarcoma, skin	positive but inconclusive	

study involved a sufficient number of animals in the carbaryl group (400), untreated control group (100), and urethan positive control group (150), killed at 1, 3, 6, 9, 12, 15, 18, and 24 months after the beginning of the study and studied histopathologically. However, no numerical data on the background lung tumours in the untreated control animals were presented. This lack of data, coupled with the absence of tumours in the lungs of the carbaryl-treated mice strain A, which are known for their high rate of naturally occurring lung adenomas, makes the negative response of little significance.

Carbaryl yielded a marginal tumour response in the pulmonary tumour induction test on mice (strain A) given a total dose of 6 mg by ip injections, 3 times per week for 4 weeks (Shimkin et al., 1969). Again, the lung adenoma test on strain A mice was not reliable for evaluating possible carcinogenicity and, thus, the results obtained from this study are not definitive.

No carcinogenic response was obtained with carbaryl administered orally, by gavage, and/or in the diet to four different strains of mice at doses ranging from 14 to 1000 mg/kg diet (Melon Institute, 1963; Innes et al., 1969; Triolo et al., 1982).

There was no increase in the total tumour incidence and no changes in tumour patterns in either sex of CD-1 mice fed diets containing doses of 0.01 or 0.04% (100 or 400 mg/kg) carbaryl for 80 weeks and 2 years, respectively (Mellon Institute, 1969). The survival rate in both test groups was too low for a response to be observed; no information was given for one-third of the animals; histopathology was performed only on animals that were suspected of having tumours. Because of these deficiencies, no conclusion can be drawn.

Carbaryl did not significantly increase the incidence of any type of spontaneously occurring tumours (hepatomas, lung adenomas, lymphoid sarcomas) in either sex of two hybrid strains of mice (C57B1/6×C3HAnf) F_1 and (C57B1/6×AKR) F_1, treated orally with 4.64 mg/kg by gavage (mice from 7 days to 4 weeks of age), and in the diet (mice from 4 weeks to 18 months of age) with 14 mg/kg diet (Innes et al., 1969).

Another inadequate feeding study of carbaryl carcinogenicity was conducted by Triolo et al. (1982), using the model of lung tumour induction in strain A/J female mice. In two studies, the feeding level

of 1000 mg carbaryl/kg, incorporated in the diet of mice for 20 weeks, did not cause a significant increase in the incidence of background lung adenomas, nor did it induce tumours in the glandular stomach or other tissues (spleen, intestinal tract). However, there were a number of confounding factors in defining the response in this study including: large variations in the incidence of lung adenomas in the four separate control groups; in particular, one such group had no tumours, despite high historical control levels in strain A mice. In addition, only one dose level was studied (1000 mg/kg), on the basis of which it is not possible to establish a dose-response relationship.

In the second study, in which the same feeding level and exposure period were used, carbaryl increased the lung benzo(*a*)pyrene hydroxylase activity, which was associated with a modest increase in the rate of lung tumours induced by the oral administration of 3 mg BP twice, on days 7 and 21, respectively of the study. However, there was great variability in the incidence of BP-induced lung adenomas in the 3 control groups; the first (7.2 ± 0.8) was well above the values presented for the test group carbaryl + BP (5.7 ± 1.4); and the second fell within the limits of the incidence of spontaneous tumours in the corn-oil control group, (1.17 ± 1.11), which make the results inconclusive.

A new mouse oncogenicity study is in progress, under proprietary sponsorship. The study design was as follows: carbaryl was administered in the diet to male and female CD^R-1 mice at rates of 0, 100, 1000, or 8000 mg/kg diet, for up to 104 weeks. Groups consisted of 80 mice/sex per group. Ten mice/sex per group were sacrificed for clinical pathology evaluation after 52 weeks of treatment. Results of this interim sacrifice are presented in section 8.3. The remaining animals were designated for continued exposure to the end of the 104-week treatment period. The study design and evaluation parameters are consistent with guidelines set out by the US EPA and OECD, with additional study parameters, for studies of this nature (Rhône-Poulenc, 1992).[a]

[a] Information to Task Group. These studies have not yet been reviewed by the IPCS. The company performing these studies has indicated that there is a significant increase in tumours at the highest dose in both species.

8.7.1.2 Rats

Two reports by Carpenter et al. (1961) and Andrianova & Alexeev (1970) are controversial. They studied the carcinogenicity of carbaryl given to rats by oral gavage, in the diet, or by subcutaneous implantation. Both studies had insufficiencies in the protocols used.

Carpenter et al. (1961) noted no significant increase in the total tumour incidence in either sex of CF-N rats fed a diet containing 0.005, 0.01, 0.02, or 0.04% carbaryl, for 2 years. Female mice had more pituitary tumours than male mice, but there was no significant difference in the incidence of tumours between the control and test groups. The small initial number of animals used, their relatively old age (60 days), their low survival rate, and the lack of detailed pathology are complicating factors in defining a negative response.

However, Andrianova & Alexeev (1970) reported that carbaryl, administered by both oral gavage and subcutaneous implantation, produced positive carcinogenic responses in mongrel rats. Male rats given oral doses of 30 mg carbaryl/kg, twice weekly for 22 months, developed skin fibrosarcoma, polymorphic cell sarcoma in the stomach, and osteosarcoma with multiple metastases. Carbaryl caused high lethality (80%) during the exposure period. The authors did not state whether the gross pathology was examined. One fibrosarcoma was discovered among 46 control animals, at 11 months. No data were presented on the number of control animals that lived for 22 months, so a comparison of survival rates in control and test groups could not be made.

In a parallel study, 20 mg of carbaryl in a purified paraffin capsule was implanted subcutaneously in 48 male rats. At the end of the 22-month exposure period, subcutaneous fibrosarcomas, in sites far from the implantation area, and on the back and neck, were diagnosed in 2 out of 10 surviving animals. There was no control group (Andrianova & Alexeev, 1970). The carbaryl used was obtained from a plant in the USSR and was of technical grade and 97.65% purity. No information about the chemical composition and impurities was given. Because of these deficiencies, this study is inconclusive.

A new combined long-term toxicity and oncogenicity study on rats is in progress, under proprietary sponsorship. The study design

is as follows: carbaryl was administered in the diet to male and female Sprague-Dawley rats at rates of 0, 250, 1500, or 7500 mg/kg diet, for up to 104 weeks. Groups consisted of 80 rats/sex per group for low- and middle-dose groups and 90 rats/sex per group for the high-dose and control groups. Ten animals/sex per group were sacrificed after 26 and 52 weeks exposure and evaluated for clinical pathology and histopathology. In addition, 10 animals/sex from the control and high-dose groups were used as a recovery group, kept on a basal control group diet before sacrifice at 56 weeks. The results of the interim sacrifices are presented in section 8.3. The remaining animals were designated for continued exposure to the end of the 104-week treatment period. The study design and evaluation criteria are consistent with guidelines set out by the US EPA and OECD, with additional study parameters, for studies of this nature (Rhône-Poulenc, 1992).[a]

8.7.1.3 *Overall appraisal of carbaryl carcinogenicity*

Carbaryl has been studied for its carcinogenic potential in numerous studies on rats and mice via various routes of administration. Most of these studies are old and do not meet contemporary standards.

Only one paper from the existing body of publications clearly reports a tumorigenic action of carbaryl. Carbaryl induced malignant tumours in an unidentified strain of rat by the oral and subcutaneous routes of administration. This study does not meet contemporary standards, because of insufficient reporting of control data.

New studies, designed to meet with contemporary standards, are in progress on rats and mice. Descriptions of the studies are given in sections 8.7.1.1 and 8.7.1.2.

8.7.2 *Carcinogenicity studies of* N*-nitrosocarbaryl*

Carbaryl is a secondary amine and is, therefore, capable of nitrosation in the presence of nitro donor groups, such as sodium

[a] Information to Task Group. These studies have not yet been reviewed by the IPCS. The company performing these studies has indicated that there is a significant increase in tumours at the highest dose in both species.

nitrate, to give a nitrosamide. This nitrosamide, nitrosocarbaryl, has been proved to be mutagenic and carcinogenic, at high doses in animals (see Table 52). A condition of this nitrosation is an acidic pH (less than 2), which is comparable to the one found in the human stomach. However, nitrosocarbaryl is not stable at this pH. Its maximum stability is between pH 3 and 5, at which pH no significant amount of carbaryl can be nitrosated. Carbaryl was nitrosated in several studies, *in vitro* as well as *in vivo*, in the guinea-pig, which has a stomach acidity similar to that of humans. See also section 8.9.3.

8.7.2.1 Rats

N-nitrosocarbaryl elicited a carcinogenic response in both sexes of two strains of rats (Wistar and Sprague-Dawley) by two routes of administration (oral gavage and subcutaneous injection) (Eisenbrand et al., 1975, 1976; Lijinsky & Taylor, 1976; Preussmann et al., 1976; Lijinsky & Schmähl, 1978).

A local carcinogenic effect of *N*-nitrosocarbaryl was reported by Eisenbrand et al. (1975) in Wistar rats given a single subcutaneous injection of 1000 mg/kg. Fifteen out of 16 treated animals developed sarcomas at the injection site; there was no histopathological evidence of any systemic carcinogenic effects. The dose of *N*-nitrosocarbaryl was highly toxic and 14 out of 16 animals had died by day 450. No spontaneous tumours were observed in control animals. When given to rats orally in single doses of 200-1500 mg/kg, *N*-nitrosocarbaryl did not induce tumours during 21 months of observation. No signs of toxicity were noted in any of the test groups.

Further studies involving repeated oral administration of *N*-nitrosocarbaryl to Sprague-Dawley rats gave unequivocal evidence of local carcinogenic effects, produced by both oral and subcutaneous routes of administration. (Eisenbrand et al., 1976; Lijinsky & Taylor, 1976, 1977; Preussmann et al., 1976; Lijinsky & Schmähl, 1978).

The nonglandular part of the stomach (forestomach) was the target organ of the local carcinogenic action of *N*-nitrosocarbaryl, when it was given orally to rats. All stages of malignant transformation in the forestomach, from hyperplasia to squamous cell carcinoma, were observed in male Sprague-Dawley rats treated with

Table 52. Carcinogenicity studies on *N*-nitrosocarbaryl in rodents

Chemical	Species, strain (number)	Sex	Route and mode of administration	Dose (mg/kg)	Duration of study	Significant tumour/organ	Evaluation of individual study	Reference
N-nitroso carbaryl	Rat, Wistar 8: male; 8: female	male female	subcutaneous, single injection	1000	450 days	polymorphic cell sarcoma at injection site; spindle cell sarcoma	positive	Eisenbrand et al. (1975)
	37	male, female	oral gavage, single	200-1500	21 months	none	inconclusive	
N-nitroso carbaryl	Rat, Sprague-Dawley 31	male	oral gavage, twice per week	130 (5000 total)	till spontaneous death	squamous cell sarcoma, papilloma, hyperkeratoses, forestomach	positive	Eisenbrand et al. (1976) Preussmann et al. (1976)
N-nitroso carbaryl	Rat, Sprague-Dawley 12	female	oral gavage, once a week for 10 weeks	50 mg (total)	110 weeks	squamous cell carcinoma forestomach, papilloma, oesophagus	positive	Lijinsky & Taylor (1976)
	12	male	oral gavage, twice a week for 20 weeks	300 mg (total)	90 weeks	squamous cell carcinoma forestomach, papilloma trachea		
N-nitroso carbaryl	Rat, Sprague-Dawley 16: male; 16: female	male female	oral gavage, once a week for 10 weeks	600 (total)	80 weeks	carcinoma forestomach	positive	Lijinsky & Schmahl (1978)

oral doses of 130 mg *N*-nitrosocarbaryl/kg, twice weekly, until spontaneous death. There was a substantial lowering of the survival rate of treated animals because of the pronounced toxicity. By the time of maximum increase of the tumour incidence (after 200 days), most of the animals were dead. The average survival time of tumour-bearing animals was 167 days after the onset of the study. The low background tumour incidence (3 out of 29) in control animals included lymphosarcomas and leukaemia.

In a comparative study of the carcinogenic potency of *N*-nitroso-*N*-alkylcarbamate esters, Lijinsky & Taylor (1976) showed that *N*-nitrosocarbaryl was a strong carcinogen, similar in action to its highly potent carcinogenic analogue *N*-nitrosomethylurethane. A high incidence (75-80%) of squamous-cell carcinomas in the forestomach was detected in female Sprague-Dawley rats given 10, weekly, equimolar oral doses (0.22 mmol) of both compounds. Nitrosomethylurethane was a more potent carcinogen, because the animals with tumours died earlier than those in the nitrosocarbaryl group. The same rate of carcinomas in the forestomach was induced in male rats treated orally with a considerably higher dose of *N*-nitrosocarbaryl (1.3 mmol total), over twice as long a period (20 weeks). The stronger carcinogenic effect of this dose in male animals was expressed by the shorter latent period of induced tumours and higher lethality compared with female animals. The local carcinogenic effect of *N*-nitrosocarbaryl in rats, the target organ being the forestomach, was seen in another oral carcinogenicity study of a series of nitroso-*N*-methylcarbamate insecticides carried out by Lijinsky & Schmähl, (1978). The oral gavage of 10 weekly doses of 60 mg nitrosocarbaryl/kg to both sexes of Sprague-Dawley rats led to a high incidence (over 70%) of carcinomas in the forestomach, with no evidence of other systemic carcinogenic effects.

No carcinogenic response for carbaryl was obtained with the transplacental carcinogenicity test after *in vivo* nitrosation in pregnant Sprague-Dawley rats (Lijinsky & Taylor, 1976). Pregnant animals were given 30 mg carbaryl/rat, orally, for 10 days (4-18 days of gestation). Two other groups of animals received the same dose of carbaryl, together with 0.6-1ml of 4% sodium nitrite on days 4-6 and 14-18 of pregnancy. The distribution of tumours in the rats of various groups was that normally seen in Sprague-Dawley rats. It is likely that an insufficient amount of nitrosocarbaryl was formed

under the conditions of *in vivo* nitrosation, or that no significant amount of nitrosocarbaryl crossed the placenta.

A low rate of *in vitro* nitrosation of carbaryl under conditions similar to those that exist in the human stomach was reported by Eisenbrand et al. (1975). The reaction of 10^{-3} mol/litre carbaryl with a 5-fold molar excess of sodium nitrite in 0.1N HCl (pH, 1) led, after 15-60 min, to yields of only 1.2 and 1.7% of the maximum possible conversion to nitrosocarbaryl. Reduction of the concentration of carbaryl and sodium nitrite by a factor of 10 decreased the yield of nitrosocarbaryl by about one-half. The yields of *N*-nitrosocarbaryl obtained by the *in vitro* nitrosation of carbaryl, under the described conditions, are low and the potential carcinogenic risk of *in vitro* nitrosation and similar nitrosation reactions *in vivo* is difficult to evaluate at present.

8.7.2.2 *Mice*

Nitrosocarbaryl administered for 104 weeks to the skin of female CFLP mice (65 mice per group) in three doses (12.5, 50, and 200 μg/mouse) was found to be more potent regarding dermal carcinogenic efficiency than nitrosomethylurea, applied under the same conditions, though not as effective as benzo-*a*-pyrene (Deutsch-Wenzel et al., 1985). Conclusions were drawn on the basis of the number of animals bearing carcinomas, total cases with local tumours, observed/expected ratios and dose-response relationships of incidences of malignant tumours. These results were found to be in contrast to the ones obtained by Lijinsky & Winter (1981), who used a single total dose of 23 mg and found that nitrosocarbaryl was a much less effective inducer of mouse skin tumours than nitrosomethylurea.

8.7.2.3 *Overall evaluation of the carcinogenicity of* N-*nitrosocarbaryl*

Sufficient evidence of carcinogenicity at the site of application was seen in multiple studies on both sexes of Sprague-Dawley rats, by different routes of administration (subcutaneous and oral gavage), using different dose levels. The non-glandular stomach was the target tumour site when nitrosocarbaryl was administered by oral gavage; subcutaneous injection of nitrosocarbaryl caused sarcomas at the injection site.

The local carcinogenic effect of *N*-nitrosocarbaryl in rats, and the lack of any systemic carcinogenicity, characterizes it as a direct-acting alkylating agent. *N*-nitrosocarbaryl was active as a direct bacterial mutagen and interacted with human DNA *in vitro*. These data agree with data that show that *N*-nitrosocarbaryl is an effective *in vivo* genotoxin.

8.7.3 Carcinogenicity of β-carbaryl

Beta-carbaryl (*N*-methyl β-naphthyl carbamate) was a component of technical carbaryl (∝-carbaryl), suspected of having a carcinogenic structure and a tumorigenic potential in mice and rats (Zabezhinski, 1970). In life-time studies on mice, strain CC57W (24 months), and mongrel rats (33 months), using two routes of administration, oral gavage (10 mg/kg in mice; 25 mg/kg in rats) and subcutaneous injection (20 mg/kg in mice; 50 mg/kg in rats), β-carbaryl showed a weak carcinogenic response. High rates of lethality (20-50%) were observed in both mice and rats, by the two routes of administration. No data for survival rates and the incidence of spontaneous tumours in control animals were presented. β-carbaryl caused a low rate of tumours in rats by both routes of administration. The types of tumours (21%) observed after subcutaneous injection of β-carbaryl included: fibrosarcoma at the injection site, subcutaneous rhabdomyosarcoma, intestinal sarcoma, leukaemia, reticuloses, and reticulosarcoma. The pattern of carcinogenic response after orally administered β-carbaryl (25%) involved sarcoma in the liver, fibroadenoma and adenocarcinoma in the mammary glands, carcinoma in the thymus, and granulocellular carcinoma in the ovaries. No local tumours at the injection site were observed in control animals after subcutaneous administration of corn oil. The other tumours (carcinoma in the mammary glands and thymus, haematopoietic system malignancies) were unusual for control animals, as well. β-carbaryl caused a higher tumour incidence in mice than in rats by both subcutaneous (60%) and oral (30%) routes. It should be mentioned, however, that most of the tumours observed (lung adenomas, leukaemia, and liver haemangiomas) occurred spontaneously in untreated mice. Since no control data were presented, the carcinogenic response to β-carbaryl in mice is of uncertain significance. Because of these deficiencies, this study is inconclusive.

8.8 Special studies

8.8.1 Neurotoxicity

The effect of carbaryl on the nervous system is primarily related to ChE inhibition.

Carpenter et al. (1961) studied the delayed neurotoxic potential of carbaryl in chickens (Rhode Island hens) compared with that of triorthocresyl-phosphate. Single doses of 250, 500, 1000, or 3000 mg/kg body weight, 25-40% in lard were administered subcutaneously to chickens. At 2000 mg/kg, weakness was observed on day 1 or 2 after dosing. In one case, the chicken was unable to walk for 3 days. No evidence of demyelination was observed in any brain sciatic nerve or spinal cord section examined microscopically. According to the authors, there was a transient cholinergic effect caused by the slow absorption of carbaryl.

The neurotoxic effect of carbaryl was studied in atropinized chickens (Gaines, 1969) to protect against acute effects of the subcutaneous injection of 800 or 1600 mg carbaryl/kg body weight. The higher dose caused leg weakness within 24 h, which recovered by day 24.

Carbaryl solution in corn oil at a daily dose of 100 mg/kg was administered orally for 7 consecutive days to 35, 6-day-old, female broilers, hybrids between Peterson strain roosters and Hubbard hens (Farage-Elawar, 1989). Altered locomotion and abnormally shortened gait were observed on the 7th day, and cases of delayed paralysis 20-40 days, after the last treatment. Locomotion changes were found to have no association with the activities of brain acetylcholinesterase and neuropathy target esterase, 24 h after the first, second, third, and fifth doses as well as 1, 3, 6, 10, 20, 30, and 40 days after the last treatment, when no statistical deviations from the control values of both enzymes were registered.

A similar, but lesser, effect on gait and stride length was observed when 45 mg carbaryl/kg was injected into chick eggs on day 15 of incubation (Farage-Elawar, 1990). This treatment resulted in significant inhibition of brain and plasma cholinesterase, and liver carboxylesterase. Administration of the same dose on day 5 of incubation resulted in 10% lethality. Brain NTE was not affected. The cause of this delayed alteration is not known.

Effects of long-term carbaryl exposure on the neuromuscular system of pigs were reported by Smalley et al. (1969). Six Yorkshire pigs, 3 male and 3 female, received carbaryl in their diet (150 mg/kg body weight); the male pigs for 72 days and the female pigs for 83 days. Three pigs from the same litter were fed carbaryl at 150 mg/kg body weight daily, for 4 weeks, and then 300 mg/kg body weight, daily, for 46 days (2 male pigs), and for 85 days (the female pig). The signs of intoxication started after about 1½ months, and were mostly typical of neuromuscular system damage (see Table 44; section 8.3). Microscopic examination of the skeletal muscle revealed myodegeneration. In the myelinated tracts of the cerebellum, brain stem, and upper spinal cord, moderate to severe edema was associated with vascular degenerative changes. No demyelination of nerve tissue was observed. When carbaryl feeding was stopped and hydrochlorothiazide applied as a diuretic, signs of toxicity of carbaryl, such as ataxia, and partial paralysis, disappeared.

Carbaryl disturbed the function of the myoneural synapses. It produced a decrease in the spontaneous activity and an increase in the permeability of the muscular fibre membrane for K^+ and Na^+ after multiple oral administrations of 8.5 mg/kg to rats(Kovtum & Sokur, 1970).

Kovtun (1970) while analysing the effects of carbaryl on myoneural formations, pointed out that, at a single intake (425 mg/kg), multiple intakes during 2 months, or 1/100 LD_{50}-8.5 mg/kg over 6 months, the frequency of tiny potentials of an edge plate was suppressed by 62-65%. On the basis of the data obtained it was concluded that carbaryl probably impairs the function of presynaptic nerve endings. At the same time, carbaryl does not affect the cholinereceptive membrane substance of muscular fibres. Carbaryl increases the rest potential of muscular fibres by 11-35%, depending of the carbaryl dose. This increase can be explained through high potassium ion accumulation inside the muscular fibres.

Three different laboratories examined the effects of carbaryl on motor activity in rats. All three reported decreased activity after intraperitoneal administration, with ED_{50}s that ranged from 13.3 to 17.6 mg/kg (Crofton et al., 1991).

Takahashi et al. (1991) compared the effects of carbaryl on both young (3 months) and old (12 months) rats. A dose of 50 mg/kg

decreased activity in an open field test, prolonged the duration of haloperidol-induced catalepsy, decreased body temperature, and increased the nociception threshold, as measured by a hot-plate test. A dose of 10 mg also prolonged haloperidol-induced catalepsy. The effects on body temperature and nociception were significantly greater in older rats.

Studies were carried out on the mechanical response characteristics of the soleus muscle *in situ*. Female Holtzman rats (6 treated-control pairs) were given 56 mg carbaryl/kg orally. Carbaryl increased the tension developed during complete tetanus (by electric stimulus) and decreased the time constant of tension development (Santolucito & Whitcomb, 1971). The more forceful and rapid contraction of the skeletal muscle is probably related to an accelerated catecholamine release.

EEGs on 4 Rhesus monkeys given 0.01 mg carbaryl/kg and on 3 given 1 mg/kg per day, orally, for 18 months, showed only a reduction in the amount of low-amplitude fast waves and an increased bilateral synchrony between the right and left hemispheres (Santolucito & Morrison, 1971). The authors did not relate these EEG changes to the dose.

Belonozhko & Kuchak (1969) found some changes in the EEG in rats, such as desynchronisation of rhythms after a single application of carbaryl at 100 mg/kg. During repeated doses of 35 mg/kg for 90 days, no changes in the EEG were noted, due (according to the authors) to adaptation of the nervous system. Oral doses of 72 mg carbaryl/kg, administered to rats for 10 days, caused a decrease in serotonin and an increase in dopamine levels in the brain (Kuzminskaya et al., 1984).

Morphological changes in the nervous system caused by carbaryl were dose-related. One to six months oral treatment of rabbits with 0.01 LD_{50} caused only haemodynamic disorders and cell infiltrations, a dose of 0.02 LD_{50} caused cell dystrophic changes, and a dose of 0.1 LD_{50} caused more progressive and serious disorders (Azizova, 1976).

The behavioural effects of carbaryl were studied in rats and monkeys. Disturbance of discrete (shock) avoidance behaviour by carbaryl in rats was reported at ip doses > 2.5 mg/kg, the LD_{50} being 8 mg/kg (Goldberg et al., 1965). Carbaryl administered at

doses of 8, 16, or 28 mg/kg, ip, decreased maze activity in CD male rats (10 in each group), whereas doses of 16 and 28 mg/kg reduced open field activity. After acute exposure, behavioural changes recovered within 60 min, whereas ChE of the blood and brain recovered after 240 min (Ruppert et al., 1983).

Carbaryl at 10 mg/kg administered subcutaneously in 16, male, Long Evans strain rats decreased the number of times they approached the novel stimuli and explored the exploratory box, and increased habituation. In familiar situations, carbaryl increased activity (Albright & Simmel, 1977).

Anger & Setzer (1979) studied the effects of oral and im administration of carbaryl on repeated chain acquisition in 5 male monkeys (*Macaccus mascicularis*). Oral doses of 50 mg/kg did not alter the performance of repeated acquisition tasks. The im injection resulted in consistent changes in performance at 5 and 10 mg/kg, but did not cause any changes at 1 mg/kg.

Carbaryl affected working memory (continuous delayed response and continuous non-match) in 28 male Sprague-Dawley rats (Heise & Hudson, 1985a,b). A dose of 10 mg carbaryl/kg, ip, affected performance of working memory procedures; with increasing dose, carbaryl nonselectively decreased response.

Administration of 2.24 mg carbaryl/kg, ip for 14 days, did not affect the performance of rats in activity wheel cages, 24 h after the last treatment. Acute ip administration of 0.54 or 2.24 mg/kg significantly decreased the motor activity of rats in activity wheel cages. This decrease was reversed by atropine sulfate (Singh, 1973). Doses as low as 7.76 mg/kg ip caused mild tremors.

Oral administration of carbaryl (200 mg/kg, 3 days/week) for a period of 90 days, though producing inhibition of ChE in blood (33%) and brain (11%), did not result in any kind of overt signs of toxicity in male albino rats (Dikshith et al., 1976).

Desi et al. (1974), in long-term studies, investigated the effects of carbaryl on the learning process, on the performance of previously learned tasks in mazes, and on the EEG in 40 male Wistar strain rats. Carbaryl was given at doses of 10 or 20 mg/kg body weight per day in the diet (100-200 mg/kg food), for 50 days. Mild, but permanent and increased, functional deviations of the nervous system were found. Because of increased irritability in the CNS, the treated

rats took less time than the untreated rats to find their food. Later, the task was performed with difficulty when the irritability of the CNS was reduced to below the normal level. The performance of the learned task was impaired. EEG deviations recorded at the end of the maze studies were slight, but permanent. They consisted of increased electric activity of the brain, increased number of moderately slow beta waves, and light flashes of 18 Hz accelerated electrical activity.

Viter (1978) found behavioural changes in rats treated via inhalation for several months with 12 or 23 mg carbaryl/m^3. The latency period of the conditioned reflex on nutrition was prolonged. Depression of investigative behaviour and spontaneous motor activity were noted.

The behavioural effects of carbaryl on rats were examined by Moser et al. (1988) using a functional observation battery. Carbaryl was administered at doses of 3-30 mg/kg, ip, and tested 0.5, 3, 24, and 48 h afterwards. Carbaryl decreased spontaneous activity, CNS excitability, motor and sensory function, and body temperature and weight. Effects indicative of AChE inhibition were also observed. All responses were dose dependent.

8.8.2 *Effects on the immune system*

8.8.2.1 *Appraisal on immunotoxicology*

The administration of carbaryl, or any other xenobiotic, at doses resulting in overt toxicity can be expected to result also in a variety of effects on the immune system. Carbaryl, when administered *in vivo*, at a dose not causing overt clinical signs has been reported to produce a variety of non-life-threatening effects on the immune system. The effects included cellular as well as humoral immunity, and several authors have suggested that they were was due to subtle, treatment-related stress. Many of the effects described were detected at doses close to the LD_{50}. Shortcomings of several of these studies were a lack of consistency and, sometimes, overt contradiction between results, which prevents the description of a defined immunotoxic mechanism.

Lifetime exposure to carbaryl did not result in increased occurrence of disease in rats or mice. No enhancement of viral

infections was found with carbaryl, even at dosages close to the LD_{50}. Most studies on rabbits and mice, at doses permitting survival, did not produce significant effects on the immune system.

In vitro, a number of researchers have demonstrated viral enhancement by prior incubation with carbaryl. *In vitro*, carbaryl can enhance herpes varicella-zoster, but not herpes simplex. In goldfish cell culture, carbaryl has been shown to permit viral enhancement by compromising interferon synthesis. Inhibition of human serum complement activity as well as interleukine-2 driven proliferation of large granular lymphocytes have been demonstrated *in vitro*. These actions could be mediated through the inhibition of serine esterases involved in the processes. No increased viral infections have been seen in long-term *in vivo* feeding studies, previously conducted or in progress at present. Carbaryl does not enhance transformation of BALB/53T fibroblasts in culture or the expression of endogenous murine leukaemia virus.

8.8.2.2 In vivo *studies*

Young mice weighing 10-12 g were infected with influenza by applying 3-4 drops (0.05 g) 1% influenza virus in physiological solution in the nose. The murine influenza virus strain A.P.R.8 was used in the primary dilution 1:32. After 2-3 days, this group of 30 mice was treated orally with carbaryl in sunflower oil, at a dose of 500 mg/kg (a dose that killed 3 out of 10 mice). Two control groups with the same number of mice, one treated with carbaryl alone, and one infected, were compared with the experimental animals for survival, blood biochemistry, and pathomorphological changes. The greatest number of mice dying were in the experimental group. AChE depression was more pronounced and recovery slower, and there were more histological changes in the livers of mice infected and intoxicated by carbaryl (Moreynis & Estrin, 1965). It is clear from this study that a summation of the effects of both factors occurred, but, because of the lack of statistical significance, it is impossible to judge the eventual effect of the enhancement.

The effect of carbaryl on an experimental *Erysipelothrix rhusiopathiae* infection in rats was studied by Shabanov et al. (1983). Rats, treated with doses that increased gradually every 6 days from 2 to 5 mg/rat (mean weight of rats, 50-60 g) during 30 days, were infected iv with *Erysipelothrix rhusiopathiae* at 1.5-108 cells/rat. The

mortality rate in carbaryl-treated rats was 36% versus 14% in control rats. Survival time was halved. Bacteraemia persisted for 10-12 days in treated groups, and only 5-6 days in the control group. Both the gross and the histopathological changes were more strongly manifested in the treated group.

Carbaryl, at 0, 2, 20, or 200 mg/kg was administered orally to rabbits, daily, for 6 months. A decrease in the phagocytic activity of leukocytes and antibody formation (4-5 times) after immunization with a murine type of typhoid vaccine, was reported at the dose level of 200 mg/kg. At the lower dose of 20 mg/kg, there were different phases of reactivity; at the beginning of the first 2 months, there was an increase and later a decrease in immunological reactivity (Perelygin et al., 1971).

The effects of oral ingestion of carbaryl on nonreaginic antibody production in BALB/c mice were studied after pretreatment with 150 mg carbaryl/kg diet for 10 weeks prior to commencement of the study. Carbaryl produced significant effects on systemic antibody production following oral immunization with sheep red blood cells (SRBC). It significantly increased both IgG1 and IgG2b titres. No reduction was seen in the synthesis of any antibody class. These results suggest that, at the doses used, carbaryl increased systemic antibody responses to orally ingested antigens (André et al., 1983).

Changes in the immunological structures of lymphatic follicles in the spleen during carbaryl administration were studied by Dinoeva (1974, 1982), who used a micrometric method. Albino rats (30 treated-control pair) were given 1.5 mg carbaryl/kg, orally, daily for 6 months. Plethora in the spleen and retardation in lymphatic follicles were observed, which were similar to effects seen in the positive control group treated with cyclophosphamide (2 mg/kg). There were no changes in the structure and weight of the thymus in carbaryl-treated rats, while in the cyclophosphamide positive control group, the weight of the thymus was reduced 2.5 times. The authors suggested that there is a different mechanism of the immuno-suppressive effect of carbaryl that needs further research.

A single dose of 500 mg carbaryl/kg inhibited the production of haemolysins and reduced the number of splenic germinal centres in White Leghorn chickens (Roszkowski et al., 1976). Dose-dependent immunosuppressive effects of continued dietary treatment of rabbits with carbaryl were studied (Street & Sharma, 1975). Rabbits (male

White New Zealand, 7 in each group) were fed 0, 4, 20, 45, or 150 mg carbaryl/kg diet (corresponding to 0, 0.23, 1.0, 2.3, or 8.38 mg/kg body weight per day) for 57 days. The treatment reduced the germinal centres in the spleen and caused atrophy of the thymus cortex. The antigen-induced increase in serum γ-globulin was decreased significantly (no dose relationship was noted), at 10 days. No changes were detected in the number of plasma cells in the lymph, haemolysin and haemoglutinin titres, skin sensitivity to tuberculin, leukocytes count, body weight, etc.

Rats pretreated, orally, with 0.05 LD_{50} carbaryl, daily, for 2.5 months, were immunized with typhoid antigen. Administration of carbaryl continued for an additional 2 months. Signs of insufficiency of the immune system, expressed as a reduction in specific globulin production, were observed 3.5 months after carbaryl application began. Carbaryl did not affect immunogenesis at a dose of 0.001 LD_{50}, daily, under the same exposure conditions. No overall evaluation was given (Olefir, 1977).

A humoral immunity study in female BALB/C mice after oral administration of carbaryl was performed by Wiltrout et al. (1978). The effects of humoral immune competence were measured by the immunoplaque in gel technique. The number of antibody plaque-forming cells (PFC) per plate was counted and the PFC/spleen calculated. Different groups of mice received carbaryl, orally, at about 1 LD_{50} (153 mg/kg body weight), 5 days before immunization (type of antigen not specified), on the day of immunization, and 2 days after. Only the last treatment resulted in significant suppression of the humoral immune response. The ratio (experimental: control) of antibody plaque-forming cells was 0.34. The oral administration of 0.1 LD_{50} for 8 and 28 days did not cause any significant effects on humoral immune competence. Depression of the PFC/spleen level corresponds to a decline in the total splenic lymphocyte population.

Akhundov et al. (1981) studied the effects of carbaryl on the immunological reactivity of 40 rabbits and 40 guinea-pigs given oral doses of 15 mg carbaryl/kg for 42 days. Heated vaccine *Salmonella typhimurium*, at doses of 250 or 500 million microbial cells, was applied 3 times at 7-day intervals, 21 days after the beginning of carbaryl administration. The auto-sensitizing effect of the vaccine was enhanced by carbaryl. Studies on guinea-pigs treated with

15 mg carbaryl/kg per day for 3 months showed decreased macrophagial migration activity.

Pipy et al. (1983) evaluated the cellular and humoral mechanisms of carbaryl-induced reticuloendothelial phagocyte depression. The function of the reticuloendothelial system (RES) involved in specific and non-specific aspects of host resistance to infection, neoplasma, etc., was quantitatively evaluated by the rate of disappearance of colloids injected into the blood. Colloid particles are extracted from the blood exclusively by the RES, in particular liver and spleen macrophages. Plasma or serum factors called opsonins have a strong stimulatory influence on inert particle phagocytosis. Male Sprague-Dawley rats (200-240 g) were given single, iv injections of labelled carbaryl at 0.5-32 mg/kg body weight (7 different doses). The iv LD_{50} determined by the authors was 50 mg/kg body weight. Colloidal carbon was administered simultaneously. In another group, carbaryl was incubated with serum from a normal rat for 20 min before the injection. The authors call this carbaryl "opsonized". The results showed the ability of carbaryl to induce a state of reticuloendothelial phagocytic depression, mediated through depletion of opsonins. Carbaryl inhibits the cell-bound aromatic amino acid esterase of the serine esterase class. The authors concluded that, apart from a slight deficiency in plasma opsonins, the inhibitory effect of carbaryl on the phagocyte function was primarily due to a selective hepatic and splenic macrophage impairment, which could be related to inhibition of a cell-bound serine esterase. In another study by Pipy et al. (1982), more details are given of this possible mechanism of phagocytoxic blockade by carbaryl. Rats were treated with iv carbaryl at 8 or 16 mg/kg body weight. The time-dependence of the effects on phagocytic function and the activities of liver serine esterases (*N*-benzoyl-DL-phenylalanine-β-naphthyl esterase and acethylcholinesterase) was studied. Macrophages of the RES had decreased phagocytic capacities after administration of carbaryl. Depression of the phagocytosis of colloidal carbon persisted from 1 to 7 h and 1 to 24 h after administration of 8 and 16 mg/kg carbaryl, respectively. Liver (*N*-benzoyl-DL-phenylalanine-β-naphthyl esterase (cell-bound serine esterase) was susceptible to reversible dose-related inhibition by carbaryl. A correlation between the reactivation kinetics of liver serine esterases and phagocytic activity was demonstrated.

8.8.2.3 In vitro *studies*

The replication of goldfish virus 2 (GFV-2) was enhanced *in vitro* by pre-treatment of a piscine culture with subtoxic concentrations (1 mg carbaryl/litre) (Shea, 1983). The mechanism of enhancement was studied *in vitro* in goldfish-derived cell lines and Air Bladder III infected with GFV-2 and pretreated with a carbaryl solution of 1 μg/ml. Interferon synthesis was studied as a possible mechanism of virus enhancement (Shea & Berry, 1984). The authors demonstrated that interferon synthesis was induced in CAR cells by GFV-2 cells. Antiviral protection provided by supernatants from infected CAR cultures with carbaryl, against infection of secondary CAR and Air Bladder III cultures was reduced. The authors interpreted this phenomenon as a result of general mild suppression of cellular metabolism, but other possible mechanisms, such as metabolic interaction, were not excluded. In another study, Shea (1985) demonstrated quantitative carbaryl inhibition of interferon synthesis. Supernatants from infected cultures, not treated with carbaryl, provided 10 times as much antiviral protection as compared with non-infected cultures. Carbaryl-treated infected culture provided only twice as much antiviral protection as uninfected cultures. A similar relationship was observed when comparing the amount of infectious viral progeny synthesized in the presence of supernatant from infected cultures not pretreated with carbaryl (10%), and from infected cultures pretreated with carbaryl (60% of the amount of virus synthesized in control cultures). The author speculated about the possibility of superimposition of a viral infection in a population exposed to pesticides.

Characterization of varicella zoster virus enhancement by carbaryl was carried out *in vitro* by Abrahamsen & Jerkofsky (1981) and Jerkovsky & Abrahamsen (1983). In previous studies, the authors demonstrated that the replication of varicella zoster virus (a human herpes virus) is increased 12 to 15-fold by pretreatment of cultures of human embryonic lung cells (HEL) with carbaryl, and, that different strains of this virus show differences in sensitivity to enhancement. Wild-type strains recently isolated from clinical materials are more sensitive than laboratory adapted strains. In this study, the authors demonstrated that the maximum enhancement occurred 48-72 h post-inoculation and that the optimal time for the pretreatment of monolayers of HEL is 20-24 h. 1-naphthol also

produced increased amounts of virus, but the treated cells cannot pass on to the daughter cells the ability to enhance virus replication.

Rodgers et al. (1986) determined that the EC_{50} for the inhibition of a T-cell-mediated cytolytic (CTL) response by carbaryl *in vitro* was 65.9 μg/ml. The addition of a supernatant containing liver enzymes reduced the effects of several organophosphorous pesticides on the CTL response, but had no significant effect on the potency of carbaryl.

Casale et al. (1989) compared the ability of carbaryl to interfere with the human serum complement mediated lysis of sheep blood cells. At a concentration of 3 mmol/litre and with 2-h preincubation, carbaryl inhibited lysis by 26-45%, depending on the antibody concentration. Carbaryl was a more potent lysis inhibitor than diisopropyl phosphorfluoridate or four other anticholinergic insecticides; the potency was not correlated with anticholinergic activity.

The effects of carbaryl at concentrations of 0.5-500 μmol/litre on lymphocyte proliferation were studied *in vitro* (Bavari et al., 1991). Carbaryl inhibited (^{3}H) thymidine incorporation, in a concentration-dependent manner, by as much as 50%. Alpha-naphthol also had a slight effect at 50 μmol/litre. The authors attributed the effect to inhibition of an esterase responsible for interleukin activation.

8.8.3 Effects in blood

Carbaryl affects the coagulation process. Hyper- and hypocoagulation were reported in different studies (Hassan & Cueto, 1970; Gapparov, 1974; Lox, 1984; Krug & Berndt, 1985; Krug et al., 1988).

Gapparov (1974) studied the indices of blood coagulation in dogs after oral treatment with a daily dose of 2 mg carbaryl/kg body weight, over 5 months. A clearly manifested hypercoagulation was established, which was connected with a rise in the general coagulation activity of the blood, higher thromboplastic activity, and prothrombin content, increased number of thrombocytes, accelerated coagulation time, and increased activity of the fibrinostabilizing factor. Also noted was a decrease in the recalcification time of blood plasma, fibrinogen concentration, and free heparin quantity, together

with an inhibition of the fibrolytic activity of the blood. The author interpreted all these changes as being connected with the arousal of the parasympathetic system.

The blood coagulation time was considerably shortened in rabbits that were given, orally, a mixture of carbaryl (5 mg/kg), DDT (5 mg/kg), and parathion (0.5 mg/kg), for 222 days. This effect corresponded to increased levels of 5-hydroxy-3-indolacetic acid (5-HIAA) and 4-hydroxy-3-methoxymandelic acid (VMA) in the urine, indicating an increased rate of metabolism of serotonin and catecholamine (Hassan & Cueto, 1970). The authors suggested that this effect was a manifestation of non-specific stress, since adrenocortical hormones shorten the coagulation time.

Fifteen male Sprague-Dawley rats (250-300 g) were given drinking-water containing 10 mg carbaryl/litre for 30 days. Platelet count, prothrombin time, partial thromboplastin time, fibrinogen, and clotting factor activity for coagulation factors II, V, VII, VIII, IX, X, and XII were determined. A significant decrease in platelet count and in the factor VII clotting activity was observed compared with those in the same number of control rats. Microscopic evaluation of the liver revealed hepatocyte degeneration, central vein congestion, some leukocytic infiltration, and vacuolization of the cytoplasm. The author suggested that carbaryl might have harmful effects on haemostasis (Lox, 1984).

Carbaryl has an *in vitro* inhibitory effect on arachidonic acid-induced platelet aggregation, which corresponds to its inhibition of thromboxane B_2-formation. The results suggest that carbaryl affected platelet aggregation by inhibition of cyclooxygenase (the key enzyme of prostaglandin synthesis) by carbamoylation (Krug & Berndt, 1985). At a concentration of 10 μmol/litre, carbaryl completely blocked platelet aggregation and cyclo-oxygenase activity (Krug et al., 1988). The carbamoylation of several platelet proteins, including cyclo-oxygenase, may be responsible for this effect.

Carbaryl produced, *in vitro*, a dose-dependent increase in methaemoglobin (Met Hb) formation at 10 and 100 mg/litre, as well as decreases in reduced glutathion levels in the erythrocytes of Dorset sheep with low erythrocyte glucoso-6-phosphate dehydrogenase (G-6-PD), which is similar to humans who have G-6-PD deficiency. Carbaryl posed oxidative stress to G-6-PD-deficient red cells, probably due to its major metabolite α-naphthol (Calabrese &

Geiger, 1986). Decreases in the K^+ ion concentration in erythrocytes (with more than 24%) and in haematocrits (from 43.5 to 38%) were found by Sokur (1971) in rats fed carbaryl 0.05 LD_{50}/day for 2 months.

In an *in vitro* study, Szczepaniak & Jeleniewicz (1981) found that carbaryl binds free blood amino acids (plasma and erythrocytes). These authors also performed a series of *in vitro* studies to investigate the effect of carbaryl on amino acids. A single application of 475 mg carbaryl/kg on 46 treated and 12 control rats produced significantly decreased amino acid values in the brain, except for valine and phenylalanine. All amino acids reached the control level after 72 and 120 h. Two hours after administration, erythrocyte amino acids also decreased >50% (Szczepaniak & Jeleniewicz, 1980; Jeleniewicz et al., 1984). A slight decrease in erythrocyte amino acid concentrations was observed after 30 days with 95 mg carbaryl/kg administered orally (Jeleniewicz & Szczepaniak, 1980). Blood serum amino acids in 24 rats decreased 4 h after a single application of 189.6 mg/kg. There was a larger decrease in valine, then in phenylalanine, alanine, aspergic acid, serine, and glycine (Szczepaniak et al., 1980). After 15-day dosing of 0.1 LD_{50}(94.8 mg/kg) per day to 12 rats, there were no changes in levels in serum and erythrocytes, but after 30-day dosing in 8 rats, there was a slight decrease in the alanine concentration of the erythrocytes (Jeleniewicz & Szczepaniak, 1980).

The effects of carbaryl on the thermoresistance and fractional content of blood serum proteins was studied by Subbotina & Belonozhko (1968). A single dose of 150 mg carbaryl/kg administered to rabbits and multiple applications of 100 mg carbaryl/kg for 2 months showed that, with a single application of carbaryl, there was an increase in protein thermocoagulation from 28% on day 1 to 67% on day 7, and with multiple applications of carbaryl there was a lowering of albumin levels and a rise in globulins (mostly α-globulins) in serum, on day 10. These changes were reversible. There was also a decrease in the coefficient of thermal dehydration. The changes in proteins in both studies show lowering of their lability.

Carbaryl inhibited the incorporation of ^{3}H-uridine and ^{14}C-labelled amino acids into RNA and proteins in cultures of HeLa cells. The effect was dose-dependent. Incorporation was inhibited

by 50% at a 150 μg/ml concentration after 30 min incubation. At a concentration of 350 μg/ml, only 10% of amino acids and 32% of uridine incorporation activity were retained (Myhr, 1973). Later, Blevins & Dunn (1975) showed that carbaryl caused general metabolic changes in Hela cells. A concentration of 1-2 mg carbaryl/litre stimulated all divisions and, at 4-8 mg/litre, inhibited growth. A decrease in cellular protein at 4 mg/litre was noted. Changes in the phospholipid fraction at 8 mg/litre were probably related to the alteration of the structure of cellular membranes. Disturbances in the development of human cells in culture were also reported by Shpirt (1973). An inhibitory effect of carbaryl on cell development was demonstrated in Ehrlich ascites tumours in mice. A reduced rate of incorporation of labelled uridine-5-^{3}H-thymidine methyl-^{3}H and L-leucine ^{14}C in the RNA, DNA, and proteins in Ehrlich cells *in vitro* was also reported (Walker et al., 1975b). The authors suggested that this effect could be a basis for investigating the mechanism of the adverse effects that carbaryl has on reproduction.

Carbaryl and *N*-nitrosocarbaryl appeared to have different action characteristics with regard to rat liver microsomal membrane alterations (Beraud et al., 1989b); carbaryl was ineffective on the lipoperoxidation indices while the nitroso compound had an inhibitory action on the formation of malonaldehyde and conjugated dienes as well as on the NADPH-dependent reductase activities.

8.8.4 *Effects on the liver and other organs*

Several authors reported data on disturbances in the carbohydrate, protein-forming, and detoxicating functions of the liver.

A single application of 300 mg carbaryl/kg in rats produced an increase in albumin and ∝-globulins, and a decrease in β-and γ-globulins (Zapko, 1970).

Kagan et al. (1970) studied the effects of carbaryl on the liver of 180 rats and 18 rabbits. During an 11-month study, they gave a daily, oral dose of 38 mg carbaryl/kg to rats. After 1 month, they observed a rise in the alanine-aminotransferase and alkaline-phosphatase activities in serum, and a decrease in succinic dehydrogenase and glycogen in the liver. Doses of 0.76 mg/kg and 0.38 mg/kg, given in the diet to rabbits, caused retention of

bromsulfophthaleine in the blood. The authors also reported a changed ratio in the protein fractions in serum and an increase in liver weight. The pathomorphological changes in the liver were destructive, necrobiotic, and proliferative. An effect on the liver was also demonstrated in the study of Lox (1987) (see section 8.8.3).

Pavlova et al. (1968) found that, with acute and long-term exposures, carbaryl affected the oxidative processes in tissues, because of its direct action on the enzymes of cell respiration and possible disturbance in the membrane processes. They performed studies on rats treated with 0.2 LD_{50} for 3 days and on rats treated with 0.01 LD_{50} for 20 weeks. At the higher dose, there were decreases in the cytochromoxidase and succinedehydrogenase activities in the liver and brain mitochondria. A histochemical examination revealed a rather high, irregular activity of the cytochromoxidase in the heart, as well as increased succinic dehydrogenase activity. With the long-term dosing, the changes were not significant, but there was a lowering of the cytochromoxidase and succinedehydrogenase activities in the heart mitochondria. Development of experimental cholesterol arteriosclerosis in rabbits was facilitated by the application of 20 mg carbaryl/kg for 2.5 months (Lukaneva & Rodionov, 1973). Changes were found in the following indices: general cholesterol, β-lipoproteins, ECG changes, and pathomorphological changes in the aorta and coronary vessels.

Carbaryl (100 mg/kg body weight) given to dogs in their diet for 45 days caused disturbances in the secretion of the intestinal enzymes. There was an increase in enterokinase secretion, as well as in the excretion of alkaline phosphates and lipase into the intestinal juice. The no-observed-effect level (NOEL) for these effects was 700 μg/kg body weight, which corresponds to 7 mg carbaryl/kg diet. Three dogs were used in each group (Georgiev, 1967).

8.8.5 *Effects on serum glucose*

Orzel & Weiss (1966) found that a rise in blood glucose correlated with the onset and duration of tremors and the degree of brain ChE inhibition in rats that were treated ip with 5 and 25 mg carbaryl/kg. The hyperglycaemic response is blocked by adrenalectomy and is unaltered by hypophysectomy. The authors suggested that the hyperglycaemia was related to increased secretion of epinephrine. Hyperglycaemia is thought to result from cholinergic

stimulations as it is also found in acute intoxications with organophosphorous compounds (Kaloyanova, 1963). In their studies, Orzel & Weiss did not find changes in liver glycogen. Muscle glycogen was decreased only in non-fasted rats. Elevated levels of blood glucose and slightly reduced immunoreactive insulin were found with repeated oral exposure of rats at 3 mg/rat, weekly, for one year (Wakakura et al., 1978). Glycogen disappeared in most of the hepatocytes. The cells mainly contained related granular endoplasmic reticulum with swollen mitochondria. A single application of 30 mg/rat produced transient hypoglycaemia at 20 h followed by hyperglycaemia at 44 h. The effects of carbaryl on respiration, glycolysis, and glycogenesis in isolated hepatocytes of male Wistar rats were studied by Parafita et al. (1984) and Parafita & Fernandez Otero (1984). The cells were treated with concentrations of carbaryl of 0.01, 0.1, and 1.0 mmol/litre dissolved in 1% dimethylsulfoxide (DMSO). DMSO slightly stimulates the respiratory coefficients. Carbaryl decreased the metabolic output of CO_2 at all concentrations; oxygen consumption was reduced by 40% in relation to the DMSO-treated groups only at the highest concentration (1.0 mmol/litre). Glucose remained unchanged in the presence of carbaryl. Endogenous production of lactic acid was not affected, and net metabolic production was strongly inhibited by both DMSO and carbaryl. At a maximum carbaryl concentration (1 mmol/litre), the net lactic acid production was completely blocked. Carbaryl inhibited lactate gluconeogenesis, and, to some extent, gluconeogenesis from fructose pyruvate and alanin. Glycerol glucogenesis was unaffected. Lactic dehydrogenase activity was reduced by 38% and glucose 6-phosphate synthetic activity was increased by 1.0 mmol carbaryl/litre. Aspartate aminotransferase activities (cytoplasmic and mitochondrial fractions) were inhibited by 0.1 and 1.0 mmol carbaryl/litre. The results indicated that carbaryl causes a decrease in glucose production by hepatic cells and suggested that carbaryl-induced hyperglycaemia in fasted animals is caused by deficiencies in the peripheral utilization of the glucose.

8.8.6 *Interactions with the drug metabolizing enzyme system*

Carbaryl is a weak inducer of hepatic microsomal drug-metabolizing activity. Cress & Strother (1974) reported depressed hexobarbital sleeping time in mice given 0.125 or 0.5 LD_{50} carbaryl, orally, for 10 days. These authors studied the effects of a 2-week

dietary administration of high levels of carbaryl (10 times higher than the dose given in the earlier study). Weanling male Swiss-Webster mice, weighing 17-20 g, were divided into 5 groups of 40 animals each. The daily consumption of carbaryl by each animal was approximately 119% of the acute LD_{50}. This dose was well tolerated with no deaths or overt symptoms of cholinesterase inhibition, probably because carbaryl was administered over a 24-h period, instead of in a single injection. Feeding carbaryl resulted in a 44% increase in the rate of *in vitro* *p*-hydroxylation of aniline, and increased *in vitro* demethylation of benzphetamine. The hepatic levels of cytochrome P-450 and b_5 were increased, but the microsomal protein concentration per gram of liver was not affected. No changes were reported in 1-naphthol-treated mice. Increased metabolic activity was demonstrated with phenobarbital and carbaryl. Phenobarbital sleeping time was shortened to 45 min (control 74 min) in carbaryl-fed mice. The rate of elimination for the carbaryl-treated animals was twice as high as that for control animals. The oral LD_{50} of carbaryl in carbaryl-pretreated animals (14 days feeding) was three times as high as in the control animals. 1-Naphthol did not affect the levels of cytochromes. Sleeping time and the LD_{50} for carbaryl were not different in control and 1-naphthol pretreated animals.

Liver weight was low in carbaryl-fed mice, but higher as a fraction of body weight. The authors concluded that the degree of the enzyme induction was not high, because most indicators exceeded the control values by 50% only, except for the lethal dose level.

The pretreatment of rats with 5 daily doses of 10 mg carbaryl/kg, administered ip, resulted in a 4.2-fold increase in the rate of benzo(*a*)pyrene metabolism (Lesca et al., 1984). Total microsomal P-450 content and benzphetamine demethylase activity were not significantly affected. The increased ability to hydroxylate aniline in mice under carbaryl treatment was reported by Guthrie et al. (1971).

Exposure of murine 3T3 fibroblasts to carbaryl at a concentration of 10^{-6} mol/litre was found to increase aryl hydrocarbon hydroxylase activity (Lahmy et al., 1988). The magnitude of the effect increased with the duration of exposure.

Carbaryl induction of microsomal enzyme systems in White Leghorn cockerels was demonstrated by Puyear & Paulson (1972). A decrease in phenobarbital sleeping time, an increase in liver weight

and elevation of liver aniline hydroxylase activity were found after oral treatment with carbaryl at 100 mg/kg per day (in gelatine capsules) for 3 or 6 days. No effect was observed at a dose of 50 mg/kg. Thus, the sleeping time data indicated that the NOEL of carbaryl for Leghorn cockerels was between 50 and 100 mg/kg per day. Higher doses caused an increase in liver aminopyrine demethylase activity (200 or more mg/kg per day) and in liver cytochrome P-450 content (300 or 400 mg/kg per day). Microsomal protein was not changed. All study parameters returned to control values by day 11 after the treatment was terminated (Puyear & Paulson, 1972).

El-Toukhy et al. (1989) reported that the administration by gavage of carbaryl to mice at a dose of 166 mg/kg resulted in small, but statistically significant (15-20%), decreases in liver pyridoxal phosphokinase and L-tryptophan 2,3-dioxygenase activity. Administration over a 5-day period of 83 mg carbaryl/kg per day had no significant effect. Hassan et al. (1990) administered 85 mg/kg, orally, either once or five times daily. Both the single and repeated regimens resulted in approximately 40% decreases in L-tryptophan 2,3-dioxygenase. Carbaryl was also found to be a competitive inhibitor of this enzyme *in vitro*.

Inhibition of monoamino-oxidase (MAO) was reported in the presence of carbaryl *in vitro* in liver homogenate (Hassan et al., 1966). The authors suggested that MAO and the catalase system are involved in oxidative demethylation during carbaryl detoxification.

Exposure of rat liver microsomes to carbaryl *in vitro* at a concentration of 0.5 mmol/litre resulted in decreases in the activities of several monooxygenases (Knight et al., 1986). The ability of carbaryl to inhibit the *N*-demethylation of ethylmorphine appeared to be competitive with a K_i of 2.4×10^{-4} mol/litre. However, when administered to rats at doses of up to 25 mg/kg, carbaryl did not have any significant inductive or inhibitory effect.

Lechner & Abdel-Rahman (1986a) reported that the *in vitro* incubation of 2 and 4 mmol carbaryl/litre for 60 min reduced glutathione levels and increased glutathione *S*-alkyltransferase in a rat liver homogenate in a dose- and time-dependent manner. Carbaryl had no apparent effect on glutathione levels in whole blood with 120 min of incubation. Carbaryl inhibited *N*-demethylation and

O-demethylation by rat liver microsomes with apparent Ki of 0.1 and 0.7 mmol/litre, respectively (Beraud et al., 1989a).

Carbaryl had an antagonistic action on the release of microsomal β-glucuronidase by malathion in a microsomal suspension *in vitro* (Lechner & Abdel-Rahman, 1985).

Jacob et al. (1985) studied the effects of carbaryl on the metabolic activation of the environmental, carcinogenic, polycyclic aromatic hydrocarbons. Carbaryl was a weak inducer of metabolism of benz(*a*)anthracence in the rat liver, and altered its metabolite profile by shifting from 10, 11-oxidation to 5, 6- and 8, 9-oxidation. Since carbaryl did not induce bay-region activation, the authors concluded that tumour-promoting activity could not be expected.

8.8.7 Effects on the endocrine system

The effect of carbaryl on the neuroendocrine system was studied in rats. Carbaryl was given, orally, at 7, 14, or 70 mg/kg body weight to male and female rats (each group contained 24 animals weighing 90-130 g) for a period of 1 year. Growth retardation, changes in the blood enzymes, and endocrine gland disturbances varied with the dosage, being especially marked at the end of the study in the group receiving 70 mg/kg body weight per day. Acetylcholinesterase and butylcholinesterase activities were inhibited significantly in these groups. Spermatozoon motility was reduced progressively with the duration of the exposure. In the prolonged estrus cycle, the diestrus period was particularly affected. An increase in the number of corpora lutea and atrophic follicles in the ovaries was correlated with this disturbance. There was a dose-dependent increase in the gonadotropic function of the hypophysis, which was determined by tests on immature mice. Hypophyseal homogenate from a rat given 70 mg carbaryl/kg increased the weight of the ovaries by 51.5%, and that of the uterus by 123%, compared with the weights in control mice. At all doses, histochemical studies of the hypophysis showed changes indicative of an increase in the activity of the cells producing a luteinizing gonadotrophy, i.e., an increase in the size of the cells, loss of granules, and hyalinization of the cytoplasm. Histological examination of the adrenal glands revealed an increase in the size and mitotic activity of cells in the zone glomerulosa. Enlarged cells with a large nucleus or two nuclei were present in the fascicular zone. Impairment of thyroid gland

functional activity in the test group was indicated by the reduction in the rate of absorption and excretion of ^{131}I and its rather low recovery, as well as by the corresponding histological findings, i.e., enlargement of follicles and more dense and basophilic colloid at all doses. Histological findings were more pronounced in the 70 mg/kg per day groups. It is likely that the effects of carbaryl on the reproductive organs is mediated by the endocrine glands. However, the possibility of a direct effect was not excluded by the authors (Rybakova, 1966; Shtenberg & Rybakova, 1968; Shtenberg et al., 1970).

The effect of carbaryl on the thyroid gland in rats was studied by Shtenberg & Hovaeva (1970). Rats were given carbaryl, orally, at 0.7, 2, 5, or 17 mg/kg per day for 6 months. They were fed a normal iodine diet or an iodine-deficient diet. There was an initial increase in function in the first 3.5 months of exposure and a decrease after 6 months of exposure. Recovery was complete 2 months after the end of the exposure. Decrease in iodine uptake and reduction of function was 26.5% in rats given 5 mg/kg and 29.5% in rats given 15 mg/kg. Rats fed an iodine-deficient diet were more sensitive to carbaryl-induced changes in the thyroid.

The functional states of the thyroid gland and adrenal cortex were affected by a daily administration of 36 mg carbaryl/kg to rats for 4 months. The maximum accumulation of ^{131}I occurred after 6 h and, in the control animals, after 12 h. The ^{131}I absorption rate normalized after 45 days, but its excretion was delayed. The concentration of sodium in the blood increased by 36.4% after day 15 and by 74% after 45 days, while the potassium concentrations were reduced. The daily excretion of 17-corticosteroids in the urine increased by 35.9%. The changes in the thyroid and adrenal glands were transient (Dyadicheva, 1971).

Hassan (1971) studied the effects of carbaryl on the synthesis and degradation of catecholamines in the rat. Rats were given carbaryl in the diet at concentrations of 100 or 700 mg/kg for 7 months, or in peanut oil at single oral doses of 50, 80, or 250 mg/kg, or 3 single doses of 80 mg/kg body weight. On day 30, the rats given 700 mg/kg diet eliminated amounts of urinary 4-hydroxy-3-methoxy mandelic acid (VMA) increased by more than 300%; levels returned to normal after 195 days. A similar effect was demonstrated after single oral doses with a dose-effect relationship.

The amount of 5-hydroxyindole acetic acid (5-HIAA) in the urine increased in rats that were treated with a single dose and 3 successive daily doses of 80 mg/kg per day. Adrenalectomy and hypophysectomy did not change the pattern of VMA excretion produced by carbaryl. There was an increased turnover rate (68%) of heart norepinephrine (NE-3H) in rats treated with 80 mg carbaryl/kg, 2 h before application of NE-3H. The corticosterone level was increased by about 125% at the same dose level. A carbaryl concentration of 16.2 μg/ml in the blood was enough to trigger maximal corticosterone secretion. The authors suggested a probable activation of the enzyme system involved in the catecholamine metabolism, because carbaryl may also directly affect the adrenergic nerve endings. Activation of the pituitary adrenal axis and an increase in sympaticoadrenergic activity with concomitant increased VMA elimination was a pharmacological effect due to carbaryl treatment.

The effect of a single oral dose of 60 mg carbaryl/kg body weight on serotonin (5-HT) metabolism in the male Holtzman Albino rat brain was studied by Hassan & Santolucito (1971); 2, 4, 6, and 24 h after carbaryl application, whole brain samples were analysed for serotonin, 5-HIAA, and corticosterone. The concentrations of 5-HT and 5-HIAA in the brain increased by 20-30% (5-HT from 0.61 to 0.8; 5-HIAA from 0.25 to 0.31 μg/g) from 2 to 6 h and returned to normal after 24 h. The plasma corticosterone level was also increased by about 125%, 1 h after oral administration of carbaryl, and returned to normal after 20 h. The inhibitory effect of *p*-chlorophenylalanine on brain 5-HT formation was diminished by carbaryl treatment. The serotonin level in the brain of carbaryl-treated animals pretreated with *p*-chlorophenylalanine was 72% higher than in the control animals. Increased 5-HIAA levels were probably a result of an increased rate of synthesis of serotonin. The authors suggested the possible role of the increased synthesis of serotonin and tryptophan-5-hydroxylase activity, which could be related to stress conditions. Carbaryl activation of MAO is probably related to the increased formation of cerebral 5-HIAA.

The uptake of noradrenaline *in vitro* by hypothalamic slices, isolated from rats exposed *in vivo* to near lethal levels of carbaryl, was increased in a dose-dependent manner (Jablonska & Brzezinski, 1990).

Oral administration of 200 mg carbaryl/kg to rats was reported to raise striatal levels of noradrenaline and homovanillic acid, a metabolic product of dopamine, when measured 0.5-2 h later (Ray & Poddar, 1985b).

The mechanism of the stimulation of corticosterone secretion is not clear.

In vivo studies on male mice receiving 38 and 68 mg carbaryl/kg showed that carbaryl can increase certain hepatic androgen hydroxylase activities. *In vitro* incubation of carbaryl with prostate tissue and testosterone 1,2-^{3}H stimulated the formation of dehydrotestosterone-^{3}H, thus, suggesting a direct action on steroidogenesis. Comparing these results with the effects of other toxic substances, the authors concluded that carbaryl cannot exert any major changes in steroid metabolism, nor can it reduce hormonal disturbances (Dieringer & Thomas, 1974).

Attia et al. (1991) studied the effect of carbaryl on rat melatonin production as alterations of the latter were found to have marked consequences in reproduction, immunology, and tumour growth. Male albino rats (*Rattus rattus*), 8 animals in a group, were exposed to light/dark cycles of 14/10 h. They were treated by gastric gavage with carbaryl dissolved in corn oil for 6 successive days. The total doses were 50, 125, and 250 mg/kg. The animals were killed 2 and 4 h after the onset of darkness, which was 8 or 10 h after the application of the insecticide. Carbaryl was found to bring about an augmentation of the pineal melatonin content 4 h after the onset of darkness, which coincided with the stimulated *N*-acetyltransferase levels and hydroxyindole-*O*-methyltransferase activity. However, at the same time, carbaryl treatment at all doses significantly lowered the circulating melatonin titres; this was supposed to be related to increased hepatic melatonin metabolism due to the increased activity of the liver drug metabolizing enzyme system (Gaillard et al., 1977). These results and the established carbaryl-induced elevated pineal 5-hydroxytryptophan, serotonin, and 5-hydroxyindole acetic acid contents in the course of the night cycle, support the concept that carbaryl has a significant effect on pineal melatonin synthesis and secretion.

Kadir & Knowles (1981) reported that carbaryl inhibited rat brain monamine oxidase activity *in vitro*.

8.8.8 Other studies

Human serum albumin reacted *in vitro* with the ester group of carbaryl and catalysed the hydrolysis and liberation of 1-naphthol. This reaction is similar to an "esterase type" action (Casida & Augustinsson, 1959) called carbamoylation (Oonnithan & Casida, 1968).

8.9 Factors modifying toxicity, toxicity of metabolites

8.9.1 Factors modifying toxicity

The toxicity of carbaryl can be modified by altering liver function by tranylcypromine treatment or 70% hepatectomy. A decrease in LD_{50} and increase in ChE activity were more pronounced after tranylcypromine treatment (Falzon et al., 1983).

The carbaryl LD_{50} in animals was increased three-fold by pretreating animals with small doses of carbaryl (Cress & Strother, 1974).

Phenobarbital, administered 24 h before carbaryl treatment, decreased the acute ip toxicity of carbaryl in mice, while 2-diethyl-amino-ethyl-2,2'-diphenyl-valerate-HCl (SKF 525-A), given 1 h before carbaryl treatment, increased its acute intraperitoneal toxicity (Neskovic et al., 1978). Enzyme-mediated binding of carbaryl to rat hepatic microsomal protein occurred *in vitro* in the presence of NADPH and oxygen. Incorporation of radioactivity of ^{14}C-ring labelled carbaryl was studied. A 2- to 3-fold increase in binding was produced by pretreatment of animals with MFO inducers, e.g., phenobarbital or 3-methylcholanthrene. SKF-525-A inhibited binding by approximately 77% of the radioactivity. It is likely that binding of active carbaryl metabolites formed by MFO occurs. The radiolabelled metabolic products were covalently bound to amino acid residues of microsomal protein: 99.3-99.7% of the bound radioactivity (Miller et al., 1979). A 50% decrease in microsomal β-glucuronidase activity was observed 1 h after a single oral administration of 50 mg carbaryl/kg to female, Sprague-Dawley rats. The whole liver homogenate β-glucuronidase content was reduced by 40% after daily treatment with the same dose of carbaryl for 7 days. This effect was attributed to the decreases in mitochondrial lysosomal and microsomal β-glucuronidase. The action of carbaryl in depleting

the endoplasmic reticulum of β-glucuronidase led to an increase in serum β-glucuronidase activity. This was demonstrated in an *in vitro* microsomal suspension study which showed that incubation of 4 mmol carbaryl/litre with microsomal suspensions effected a release of the β-glucuronidase enzyme. The effect on the endoplasmic reticulum was further exemplified by the induction in microsomal UDP-glucuronyl transferase activity after 7 days of daily treatment with carbaryl at a dose of 25 mg/kg. Thus, carbaryl modifies the enzyme activities associated with the endoplasmic reticulum by decreasing specific activity (90%) towards β-glucuronidase enzyme and activating the synthesis of endoplasmic reticulum protein connected with drug metabolism, such as the UDP-glucuronyl-transferase enzyme (Abdel-Rahman et al., 1985; Lechner & Abdel-Rahman, 1985).

Osman & Brindley (1981) conducted bioassays to determine the carbaryl susceptibility and synergism with piperonyl butoxide in natural populations of three species of Lobops grassbugs, in order to estimate monoxygenase detoxification. Pretreatment of the insects with piperonyl butoxide inhibited the mixed-function oxidase system and decreased the values of the LC_{50} for the insects (Osman & Brindley, 1981). Mixed-function oxydase involvement in the biochemistry of synergistic insecticides (including carbaryl) has been reviewed by Casida (1970).

Diet may modify carbaryl toxicity. Boyd & Boulanger (1968) reported an increased susceptibility to carbaryl toxicity in Albino rats (272 Wistar strain rats were used) fed a protein-deficient diet. Boyd & Krijnen (1969) also reported that the LD_{50} decreased from 589 mg/kg in rats fed an 81% casein diet to 67 mg/kg in rats fed a 0% casein diet; 285 male rats were used in this study.

The combined effects of different ambient temperature levels and carbaryl were studied by Ahdaya et al. (1976). The LD_{50} values in mice injected ip were 263 mg/kg at 1 °C and 122 mg/kg at 38 °C (588 mg/kg is the LD_{50} at 27 °C). The thermoregulation ability of mice treated with carbaryl was affected more than that of mice treated with parathion which is a stronger inhibitor of ChE. The authors suggested that this effect was due to an overall reduction in the basal metabolic rate.

Atropine sulfate decreased signs of parasympathetic stimulation in a group of pigs acutely poisoned with 1-2 g carbaryl/kg (Smally,

1970). During multiple administrations of carbaryl, drug-induced (hydrochlorothiazide) diuresis helped in the detoxification processes. ChE reactivations are contraindicated because they may aggravate the signs of carbaryl intoxication (Sanderson, 1961; Podolak & Warchocki, 1980).

Application of atropine or trepazin, 20 min before oral intoxication with carbaryl in mice, decreased toxicity about 2 times. The results were similar when cholinolytics were applied 2 min after administration of carbaryl (Vyatchanikov & Alexachina, 1968). Atropine administered iv to rats at a dose of 8 mg/kg increased the carbaryl ip LD_{50} by a factor of about 7 (70 to 460 mg/kg) (Harris et al., 1989). Co-administration of either of two different oximes (2-PAM and HI-6) with atropine was found to provide significantly less protection than that afforded by atropine alone, indicating that oxime therapy is not a useful treatment for carbaryl poisoning.

Co-administration of an oral dose of 10 mg malathion/kg in rats significantly reduced the rates of both absorption and elimination of an oral dose of 10 mg carbaryl/kg (Lechner & Abdel-Rahman, 1986a). Peak plasma levels of labelled carbaryl were observed about 1 h after the administration of carbaryl alone, and after 2 h when malathion was administered simultaneously. The terminal rate of elimination of carbaryl was decreased by a factor of about 4, with the half-life increasing from 16.96 h to 64.41 h.

Concentrations of cimetidine in the range of 60-240 μg/ml were observed to decrease the clearance rate of carbaryl by perfused rat liver in a dose-dependent manner (Ward et al., 1988).

Ray & Poddar (1985a,b, 1990) reported that the intraperitoneal administration of 1 mg haloperidol/kg, 12.5 to 100 mg 5-hydroxy-tryptamine (5-HTP)/kg, or 100 mg L-tryptophan/kg increased the incidence of tremors in rats following an oral dose of 50-200 mg carbaryl/kg. The potentiation of the tremorogenic effect of carbaryl by 5-HTP was demonstrated to be dose dependent. The potentiating effects of 5-HTP and haloperidol could be blocked by the coadministration of the serotonergic antagonist methysergide (20 mg/kg, ip) or the dopaminergic antagonist bromocriptine (10 mg/kg, ip), respectively. These results suggest the possible involvement of a central cholinergic, dopaminergic interaction in the carbaryl-induced tremor.

The effects of humic acids in the detoxification of carbaryl during oral application are very slight: only 9.9-18.6% decrease in toxicity was observed (Golbs et al., 1984).

The combined effects of carbaryl and sodium nitrite have been studied (Podolak-Majczak & Tyburczyk, 1984, 1986; Tyburczyk & Podolak-Majczak, 1984a,b; Tyburczyk & Podolak-Majczak, 1986). Dosing Wistar rats for 3 months with sodium nitrite at 20 mg/kg per day, and carbaryl at 0.1 LD_{50}/day (60 mg/kg), the brain γ-aminobutyryl acid level, methaemoglobin, blood serotonin, free blood tryptophan, serum and liver alanine amino-transferase activity levels increased and blood cholinesterase activity decreased. Decreases were observed in the vitamin E and A levels, glucose-6-phosphate dehydrogenase activity, and liver aminohexoses and hydroxyproline levels with a simultaneous increase in the serum aminohexoses level. This finding may indicate the increasing process of connective tissue catabolism and lisosomal membranes labilization.

8.9.2 Toxicity of metabolites

Hydrolysis of the carbamate ester bond of carbaryl results in detoxification. The carbamate moiety is decomposed to carbon dioxide and methylamine, and the phenolic part is conjugated and excreted. Kuhr (1971) summarized the data on the toxicity of carbaryl metabolites (Table 53).

Table 53. Toxicity of carbaryl and some of its metabolites[a]

	LD_{50} (mg/kg)		7-day NOEL[b] (mg/kg)	Molar i_{50} bovine anticholin-esterase
	Rat oral	Mouse Intraperitoneal	Rat	
Carbaryl	270	29-42	125-250	5×10^{-8}
4-Hydroxycarbaryl	1190	74	> 1000	4×10^{-7}
5-Hydroxycarbaryl	297	56	> 1000	4.6×10^{-8}
7-Hydroxycarbaryl	4760		> 1000	
Hydroxymethylcarbaryl	> 5000	630-780	250-500	1.4×10^{-5}
1-Naphthol	2570		500-1000	1×10^{-3}

[a]From: Kuhr (1971).
[b]NOEL = No-observed-effect level.

Many of the known metabolites are much less toxic than carbaryl. The pharmacological study of carbaryl in rats showed that the metabolites with a methylcarbamate moiety are inhibitors of plasma cholinesterase (Fernandez et al., 1982). None of the carbaryl metabolites was appreciably more active as a cholinesterase inhibitor than carbaryl itself (Oonnithan & Casida, 1968).

8.9.3 N-*nitrosocarbaryl*

Carbaryl is a secondary amine and is, therefore, capable of nitrosation in the presence of nitro donor groups, such as sodium nitrate, to give a nitrosamide. This nitrosamide, nitrosocarbaryl, has been proved to be mutagenic and carcinogenic, at high doses in animals. Conditions of this nitrosation include a strongly acidic pH (less than 2), which is comparable with the pH in the human stomach. However, nitrosocarbaryl is not stable at this pH. Its maximum stability is between pH 3 and 5, pHs at which no significant amounts of carbaryl can be nitrosated. Carbaryl has been nitrosated in several studies, *in vitro* as well as *in vivo*, in the guinea-pig, which has a stomach acidity close to that in man. If significant yields of nitrosocarbaryl have been shown in these circumstances, the significance of these findings is still not clear for human risk evaluation. The pH in the human stomach is variable during food intake and probably, more importantly, the stomach contains a lot of food, which will minimize the contact between naturally occurring nitrite and carbaryl residues, but which will also afford a lot of nucleophilic sites for nitrosocarbaryl to react with. It is also noteworthy that all studies that were conducted with jointly administered carbaryl and nitrite yielded negative results for oncogenicity. Cranmer (1986) estimated the potential intake of nitrosocarbaryl at 6×10^{-9} mg/kg per day. Using different mathematical models, Cranmer estimated a cancer risk for nitrosocarbaryl between 10^{-6} (one-hit model) and 10^{-9} (probit model). However, if such oncogenic nitroso-carbamates were to be found in such quantities in the human stomach, an increased incidence of stomach cancer would have been expected during the period when drug and pesticide carbamates were widely used. However, during this period, the incidence of gastric cancer in the USA declined considerably.

The bacterial metabolite *N*-nitrosocarbaryl may act as a noncompetitive inhibitor of the *in vitro* metabolism of aminopyrine, *p*-nitroanisole, and aniline by rat liver microsomes (Beraud et al., 1980, 1989a,b). *N*-nitrosocarbaryl was more effective as an inhibitor of microsomal activity than the parent compound.

8.10 Mechanism of toxicity - mode of action

The mechanism of toxicity and the mode of action of carbaryl and carbamates, in general, have been described in EHC 64 (WHO, 1986).

8.10.1 Inhibition of cholinesterase activity

As a carbamate compound, carbaryl is an inhibitor of cholinesterase (ChE) activity (for details see Reiner & Aldridge (1967) and Aldridge (1971)).

A number of studies have been performed by Carpenter et al. (1961) to assess the extent of ChE inhibition by carbaryl in mammals. A single oral dose of carbaryl of 560 mg/kg produced a 43% inhibition of the erythrocyte ChE in rats in 0.5 h, and a 30% inhibition in brain AChE. However, they returned to normal in rats that survived 24 h after administration of the dose. Carbaryl did not depress plasma ChE significantly. Two groups of Beagle dogs were injected once, iv, with 10 or 15 mg/kg as an 8% solution in 95% alcohol. No significant effects were found on either erythrocyte or plasma ChE. On the 5th day, several administrations of the same doses depressed plasma ChE by 24% and erythrocyte AChE by 40%. It is doubtful that a long incubation time for the samples (2 h for plasma) played a role in the slight depression of ChE. Comparative data on ChE inhibition in the brain, plasma, and erythrocytes of rats that received single doses of carbaryl were reported by Mount et al. (1981). As shown in Table 54, there was a dose-dependent decrease in ChE in the brain, plasma, and erythrocytes.

Brain AChE was significantly different in dead rats and in surviving rats given 800 mg/kg. AChE depression in the brain was >70% in the lethally poisoned rats. The inhibition of red blood cell AChE activity was the same as in plasma.

Table 54. Inhibition of ChE in % in comparison with the controls[a]

Sprague-Dawley rats	Post-dosing (h)	Brain	Red blood cells	Plasma
Controls 10 rats		0	0	0
450 mg/kg	0.5	56	44	51
(24 rats sacrificed)	1	74	29	53
	2	74	42	68
	4	66	48	61
	8	55	25	31
	24	27	60	38
	48	22	23	46
	96	6	19	-19
800 mg/kg	0.5	66	32	47
(34 rats sacrificed)	1	70	44	50
	2	79	73	69
	4	50	72	70
	12	50	72	50
	28	58	63	68
	48	17	26	40
	96	16	-6	16
800 mg/kg	3	80	-	-
(24 rats died)	4	85	-	-
	18	88	-	-
	25	71	-	-
	29	88	-	-
	30	84	-	-
1200 mg/kg (15 died)	1-36	88-91	-	-

[a]Adapted from: Mount et al. (1981).

The affinity of AChE of human brain caudate nucleus for carbaryl was studied *in vitro* and some inhibition constants were determined (Patocka & Bajgar, 1971). The value of the I_{50} affinity constant was calculated from the dependence of AChE inhibition on the molar concentration of the inhibitor in probit logarithm transformation. The Hill coefficient was obtained from Hill plots. The affinity constant for carbaryl pI_{50} was 5.59 and the Hill coefficient was 1.50. According to the authors, some results of this study suggest that AChE may be an allosteric enzyme.

Intravenous administration of colloidal carbon in the rat, inhibiting the phagocytic activity of the RES, prolonged the duration of the anticholinesterase effect of carbaryl (Pipy et al., 1979). The

authors speculated that the metabolism of carbaryl was decreased by the RES inhibition and, as a result, the reactivation speed of ChE was slower.

Pregnant rats were treated orally with 1 or 5 mg carbaryl/kg from day 11 to the last day of gestation (Declume & Benard, 1977b; Declume et al., 1979). No cholinesterase depression in blood, brain, and liver were observed in either the dams or the newborn offspring. However, after administration of 50 mg/kg from day 19 to the last day of gestation, ChE inhibition was seen in both the mother and newborn offspring.

Cambon et al. (1978) reported decreased cholinesterase activity in the blood, brain, and liver in the mother and the fetus after treatment of the dams at 6.25, 12.5, 25, and 50 mg/kg. Variability of cholinesterase levels in the controls and short-comings in the cholinesterase analysis protocol make these results difficult to interpret.

9. EFFECTS ON HUMAN BEINGS

9.1 General population exposure

9.1.1 Acute toxicity, poisoning incidents

The clinical picture of carbaryl intoxication results from the accumulation of ACh at nerve endings (WHO, 1986). The signs and symptoms can be categorized into the following 3 groups:

(*a*) *Muscarinic manifestations*
- increased bronchial secretion, excessive sweating, salivation, and lacrimation;
- pinpoint pupils, bronchoconstriction, abdominal cramps (vomiting and diarrhoea); and
- bradycardia.

(*b*) *Nicotinic manifestations*
- fasciculation of fine muscles (in severe cases, diaphragm and respiratory muscles also involved); and
- tachycardia.

(*c*) *Central nervous system manifestations*
- headache, dizziness, anxiety, mental confusion, convulsions, and coma; and
- depression of respiratory centre.

All these signs and symptoms can occur in different combinations and can vary in onset and sequence, depending on the chemical, dose, and route of exposure. The duration of symptoms is usually shorter than that observed in organophosphorus poisoning. Mild poisoning might include muscarinic and nicotinic signs only. Severe cases always show central nervous system involvement; the clinical picture is dominated by respiratory failure sometimes leading to pulmonary oedema, due to the combination of the above-mentioned syndromes.

A review of carbaryl-related poisoning from 1966 to 1980 was made by US EPA. During this period, 193 cases of over-exposure to carbaryl as the sole active ingredient in the poisoning and 144 cases of over-exposure to a combination of carbaryl with other active ingredients were recorded (Weston, 1982). Not all case histories have been confirmed. There were 5 deaths. There is no evidence

that carbaryl was involved in these deaths, except for one, which was acknowledged by the manufacturer.

Hayes (1963) reported two incidents of poisoning: one, a 19-month-old child who swallowed an unknown amount of carbaryl, and the other, a man who swallowed 250 mg of carbaryl. Both developed moderately severe ChE inhibition symptoms within 20 min: constricted pupils, salivation, muscular incoordination in the child, and epigastric pain, profuse sweating, lassitude, and vomiting in the man. Both recovered after atropine treatment. Blood cholinesterase was inhibited.

One death from carbaryl ingestion while drunk was reported by Farago (1969) who concluded that 2-PAM application hastened the fatal outcome (due to pulmonary oedema), 6 h after ingestion. Carbaryl was found in various tissues.

Acute intoxication during the loading of an airplane was reported by Long (1971).

In a case report of a suicide attempt involving about 25 g (500 mg/kg) of carbaryl, dicumarin and boric acid, Dickoff et al. (1987) described the occurrence of a peripheral neuropathy that resembled the syndrome observed following exposure to some organophosphorus compounds. Recovery continued for 9 months. Electrophysiological findings were consistent with axonal peripheral neuropathy. The cause-effect relationship was confounded because of combined exposure.

9.1.2 Controlled human studies

Wills et al. (1968) carried out controlled studies in human volunteers, aged 25-57 years. In a preliminary study, oral doses of 0.5, 1, and 2.0 mg carbaryl/kg in capsules (single application to 2 subjects) were tolerated without any subjective or objective symptoms. In the main study, one group (5 subjects) took 0.06 mg carbaryl/kg daily, and one group (6 subjects) took 0.13 mg carbaryl/kg for 6 weeks. Physical examination, BSP removal from blood, EEG examination, routine blood and urinalysis were performed, and ChE of plasma and red blood cells was examined. No changes were found in the low-dose group. An increase in the ratio of amino acid nitrogen to creatinine in the urine, at the high dose, may represent a decrease in the ability of the proximal

convoluted tubule to reabsorb amino acids. This change was reversible.

The urine of some subjects was analysed (Knaak et al., 1968). The overall recovery (by the fluorometric method) of the carbaryl equivalents in the urine was 26-28%, and, with the colorimetric method, 37.8%, in subjects treated with 2 mg carbaryl/kg. The following metabolites were found chromatographically in a 4-h urine sample: ∝-naphthol glucuronide (10-15%), and sulfate (6-11%) and 4-(methylcarbamoyloxy)-∝-naphthyl glucuronide (4%). Another metabolite, ∝-naphthyl methylimido-carbonate *O*-glucuronide, was identified by fluorometry.

A human ingestion study was conducted to determine the relationship between a single oral dose of carbaryl and the rate of its urinary excretion as metabolites. Elimination was apparently first order over the dosage range of the studies (0.25-1 mg/kg). The model predicts that, 24 h after ingestion, approximately 41% of the dose can be accounted for as urinary metabolites (Hansen, 1978).

In a study involving one subject, Ward et al. (1988) observed that pretreatment with a clinical regimen of cimetidine (3×200 mg over a three-day period) reduced presystemic (first-pass) clearance of a dose of 1 mg carbaryl/kg by about 46%.

A scientist studying the anthelminthic activity of carbaryl, tested its human safety by ingesting 250 mg (about 2.8 mg/kg). After 20 min, he experienced epigastric pain and began to sweat profusely. He was treated with a total dose of 3 mg atropine and recovered completely 2 h after taking the carbaryl. Another scientist ingested 420 mg carbaryl (4.45 mg/kg), and after 85 min he had vision troubles, weakness, profuse sweating, and felt lightheaded. He was treated with a total dose of 4.8 mg atropine and recovered 4 h after the onset of symptoms (Hayes & Laws, 1991).

9.1.3 Long-term exposure

Branch & Jacqz (1986a,b) reported the case of a 75-year-old man who was exposed to carbaryl for 8 months, inside his home, after repeated excessive applications of 10% dust formulation. He experienced a series of signs and symptoms compatible with cholinesterase depression in addition to a 40-lb (18-kg) weight loss. After exposure ceased, the patient's condition improved markedly.

However, a few months later he started to experience modification of his sleep pattern and peripheral neuropathy and cerebral atrophy were demonstrated. Other pathologies, such as recurrent gastric ulcer, cardiac fibrillations, a recent head injury due to an automobile accident, and other less defined pathologies were present in this patient which provide other, more likely, causes for these later symptoms.

The uncertainties associated with long-term exposure to levels sufficient to result in sustained suppression of plasma pseudocholinesterase activity and possible brain damage are discussed by Avashia (1987) and Branch (1987).

9.2 Occupational exposure

9.2.1 *Epidemiological studies*

The first report on workers exposed to carbaryl was published by Best & Murray (1962). For 19 months, from the start of carbaryl production, they studied men working on the production, handling, and shipping of carbaryl. The most exposed group were bagging workers occasionally exposed to carbaryl dust under abnormal conditions (40 mg/m^3). These showed a slight depression in blood ChE activity, but this was below the rate at which clinical symptoms might be expected. They found that 41% of 689 urine specimens contained >1000 μg/100 ml total 1-naphthol (>400 μg/100 ml indicates absorption), with no clinical or subjective symptoms. In cases of acute intoxication, 3140 μg 1-naphthol/100 ml urine were found. Knaak et al. (1965) using fluorometric analysis in conjunction with chromatographic separation, found 5 times more sulfate (25 mg/litre) than glucuronides (5 mg/litre) of 1-naphthol in the urine of exposed workers.

Vandekar (1965) in a village-scale trial in Nigeria, assessed the risk for the population of exposure to carbaryl. A slight depression of plasma ChE was found in all spraymen, the day after the spraying. Levels of 1-naphthol derivatives in their urine did not increase on days 1 and 2 after spraying but increased slightly on day 6.

In a study on 19 agricultural workers (Yakim, 1967), whole blood ChE activity was measured before, and after, 3-4 days exposure to airborne carbaryl. Men exposed to a mean airborne

carbaryl concentration of 2 mg/m^3 showed a decrease of 20-24% in ChE activity. Signalmen exposed to 4 mg/m^3 (mean) showed a 13-30% decrease in ChE activity. No objective signs of ill health were observed. In the same study, a mean carbaryl concentration of 0.7 mg/m^3 was reported in the cabin of an aeroplane used to apply carbaryl, but no changes were reported in the biological parameters of the pilots. During the agricultural application of carbaryl dust at a maximum exposure level of 19 mg/m^3 dust on cotton fields, Adylov (1966) reported a decrease in catalase activity, and a 20% decrease in ChE activity on day 14.

In cases of occupational overexposure to carbamates, mild symptoms appear long before a dangerous dose is absorbed, which is why severe occupational intoxications with carbaryl are rare. Tobin (1970) gives reasons for the lack of severe intoxications: (1) there is a very short time (½ h or less) between exposure to carbamates and the onset of symptoms; (2) lack of symptoms progression, because of a large margin between the median effective dose and the lethal dose of carbamates and the early detection of intoxication.

Workers exposed to carbaryl used on pets for flea control, experienced diarrhoea, increased salivation, cough, difficulty in breathing, and phlegm (Ames et al., 1989).

Vandekar (1965) reported a skin rash in a sprayman who was accidentally splashed with a carbaryl formulation. Although carbamate compounds generally have not caused dermatitis or allergic skin reactions, Vandekar suggested that they can appear in certain individuals after unusually heavy exposure.

One out of a group of 30 farmers with contact dermatitis was identified by a patch test as having a positive allergic reaction to a 1% solution of carbaryl (Sharma & Kaur, 1990). No allergic reaction were observed in a control population (No. = 20).

To identify possible effects on reproduction, Whorton et al. (1979) studied a cohort of 47 male workers who had worked for at least 1 year in the production and packaging of carbaryl. A semen sample was used for sperm count. Testosterone follicle-stimulating hormone, and luteinizing hormone were determined by radioimmunoassay. The range of airborne carbaryl concentrations in the workplace was 0.03-14.21 mg/m^3 with a mean of 4.9 mg/m^3. This cohort showed no seminal or blood abnormalities related to

carbaryl exposure. Although a small excess (not significant at $\alpha = 0.05$) was observed in a small number of oligospermic men in the exposed group, there was no evidence that testicular function or fertility in the male workers was affected under these conditions of exposure.

Wyrobek et al. (1981) used the same cohort of exposed workers to study sperm abnormalities. Semen was collected from 50 men, occupationally exposed to carbaryl for 1-18 years. Semen samples were analysed for changes in sperm motility, sperm count, morphology, and frequency of sperm-carrying double fluorescent bodies (YFF). The YFF test represents sperm with two Y chromosomes due to meiotic nondysjunction. The exposed workers showed changes in sperm morphology with a higher proportion of sperm with abnormal head shapes in comparison with the control group of newly hired unexposed workers. There was no dose dependence as judged by job classification. A negative correlation between number of years working in the carbaryl area and the percentage of abnormal sperm was observed. Workers who had once been exposed to carbaryl, but who had not been exposed for an average of 6.3 years, showed a marginally significant elevation in sperm abnormalities, possibly not reversible. MacLeod (1982) reviewed the Wyrobek et al. (1981) study and did not find any essential differences in the distribution of the sperm types in the control and the carbaryl-exposed groups. No significant changes in sperm count and fertility were reported in 100 workers (Thomas, 1981).

10. PREVIOUS EVALUATION BY INTERNATIONAL BODIES

The latest IARC evaluation of carbaryl was made during 1987 (IARC, 1987). It was concluded that there were no data on cancer in humans and inadequate evidence of carcinogenicity in experimental animals. Carbaryl could not be classified with regard to its carcinogenicity to humans (Group 3).

The FAO/WHO Joint Meeting on Pesticide Residues (JMPR) evaluated carbaryl at its meetings in 1963, 1965, 1966, 1967, 1968, 1969, 1970, 1971, 1973, 1975, 1976, 1977, 1979 and 1984 (FAO/WHO, 1964, 1965, 1967, 1968, 1969, 1970, 1971, 1972, 1974, 1976, 1977, 1978, 1980, 1985). Since 1973, an acceptable daily intake (ADI) of 0-0.01 mg/kg body weight has been established. This estimate is based on the following experimental data: no-effect level for rats: 200 mg/kg in the diet = 10 mg/kg per day; for dogs: 100 mg/kg in the diet = 1.8 mg/kg per day; and for human beings: 0.06 mg/kg per day (FAO/WHO, 1965, 1967, 1974).

Maximum residue levels (MRLs) for carbaryl were recommended by FAO/WHO (1986b) (see Table 55). The values recommended for tolerance levels represent the sum of free carbaryl, combined carbaryl, conjugated naphthol, and conjugated methylcarbaryl, expressed as total toxic residues of carbaryl.

A WHO study group on occupational health recommended 5 mg carbaryl/m^3 as a tentative, health-based, maximum permissible level in the working environment. A biological limit of 30% inhibition of ChE activity in whole blood, plasma, or red cells with respect to pre-exposure levels should not be exceeded (WHO, 1982).

In the WHO recommended classification of pesticides by hazard, technical carbaryl is classified in Class II as moderately hazardous in normal use (WHO, 1992). WHO/FAO (1975) issued a data sheet on carbaryl (No. 3).

IRPTC in its series "Scientific reviews of Soviet literature on toxicity and hazards of chemicals" has published a review on carbaryl (IRPTC, 1982, 1989).

Table 55. Maximum Residue Limits (MRLs) established by the Codex Alimentarius[a]

Commodity	MRL (mg/kg)
Animal feedstuffs (green alfalfa, clover, corn, forage, cow pea foliage, grasses, peanut hay, sorghum forage, soybean vines, sugarbeet tops, bean and pea vines)	100
Bran (wheat)	20
Apricots, blackberries, boysenberries, nectarines, peaches, raspberries, asparagus, okra, leafy vegetables (except brassica), nuts (whole), olives (fresh), sorghum grain, cherries, plums, kiwi fruit	10
Blueberries, citrus fruit, cranberries, strawberries	7
Apples, bananas (pulp), grapes, beans, peas (including pod), brassica, tomatoes, peppers, aubergines, pears, poultry skin, barley, oats, rice (in husk and hulled), rye, wheat	5
Cucumbers, melons (Cantaloupe), pumpkins, squash	3
Root crop vegetables (beets, carrots, radishes, rutabagas, parsnips), peanuts (ground-nuts, whole), wholemeal flour	2
Cottonseed (whole), sweet corn (kernels), nuts (shelled), olives (processed), soybeans (dry mature seed), cow-peas	1
Poultry meat, eggs (without shells)	0.5
Potatoes, meat of cattle, sheep, and goats, sugarbeets, wheat flour (white)	0.2
Milk and milk products	0.1

[a]From: FAO/WHO (1986b).

REFERENCES

Abdel-Rahman MS, Lechner DWH, & Klein KM (1985) Combination effect of carbaryl and malathion in rats. Arch Environ Contam Toxicol, **14**: 459-464.

Abrahamsen LH & Jerkofsky M (1981) Enhancement of varicella-zoster virus replication in cultured human embryonic lung cells treated with the pesticide carbaryl. Appl Environ Microbiol, **41**(3): 652-656.

Addison JB, Silk PJ, & Unger I (1975) The photochemistry of carbamates V. The photodecomposition of Sevin (1-naphthyl-*N*-methyl carbamate) and of Phenmec (phenyl-*N*-methyl carbamate). Int J Environ Anal Chem, **4**: 135-140.

Adylov MA (1966) [Sanitary hygienic assessment of the working conditions and health state of people working with Sevin in Uzbekistan.] Gig Primen Toxicol Pestic Klin Otrav, **1866**: 271-275 (in Russian).

Ahdaya SM & Guthrie FE (1982) Stomach absorption of intubated insecticides in fasted mice. Toxicology, **22**(4): 311-317.

Ahdaya SM, Shah PV, & Guthrie FE (1976) Thermoregulation in mice treated with parathion, carbaryl or DDT. Toxicol Appl Pharmacol, **35**: 575.

Ahlrichs JL, Chandler L, Monke EJ, & Reuszler HW (1970) Effect of pesticide residues and other organotoxicants on the quality of surface and ground water resources. Lafayette, Indiana, Indiana Water Research Center, 106 pp (Technical Report No. 10).

Ahmed FE, Hart RW, & Lewis NJ (1977a) Pesticide induced DNA damage and its repair in cultured human cells. Mutat Res, **42**: 161-174.

Ahmed FE, Lewis NJ, & Hart RW (1977b) Pesticide induced ouabain resistant mutants in Chinese hamster V79 cells. Chem-Biol Interact, **19**: 369-374.

Akhundov VY, Lurie LM, & Ismailova IM (1981) [Effect of Sevin on immunological reactivity.] Gig i Sanit, **46**(2): 25-28 (in Russian).

Albanis TA, Pomonis PJ, & Sdoukos AT (1986) Organophosphorous and carbamates pesticide residues in the aquatic system of Ionnina basin and Kalamas river (Greece). Chemosphere, **15**(8): 1023-1034.

Albright LM & Simmel EC (1977) Behavioural effects of cholinesterase inhibitor and insecticide carbaryl (Sevin). Paper presented at the 49th Annual Meeting of the Midwestern Physiological Association, Chicago, 5-7 May 1977.

Aldridge WN (1971) The nature of the reaction of organophosphorous compounds and carbamates with esterases. Bull World Health Organ, **44**: 25.

Alvarez CC, Shimanuki H, & Argauer RJ (1970) Oral toxicity of carbaryl to adult honey bees. J Econ Entomol, **63**(6): 1834-1835.

Aly OM & El Dib MA (1971a) Studies on the persistence of some carbamate insecticides in the aquatic environment. I. Hydrolysis of Sevin, Baygon, Pyrolan and Dimetilan in waters. Water Res, **5**: 1191-1205.

Aly OM & El Dib MA (1971b) Photodecomposition of some carbamate insecticides in aquatic environments. In: Faust SJ & Hunter JV ed. Proceedings of the Rudolfs Research Conference on Organic Compounds in Aquatic Environments. New York, Basel, Marcel Dekker, Inc., pp 469-493.

Aly OM & El Dib MA (1972) Studies on the persistence of some carbamate insecticides in the aquatic environment. In: Fate of organic pesticides in the aquatic environment. Washington, DC, American Chemical Society, pp 211-241 (Advances in Chemistry Series, Volume 111).

Aly MI, Bakry N, Kishk F, & El-Sebae AH (1980) Carbaryl adsorption on calcium-bentonite and soils. J Soil Sci Soc Am, **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 SM & Farah OR (1968) Cytological effects of pesticides. III. Meiotic effects of *N*-methyl-1-naphthyl carbamate "Sevin". Cytologia, **33**: 337-344.

Amer SM, Hammouda MA, & Farah OR (1971) Cytological and morphological effects of the insecticide *N*-methyl-1-naphthyl carbamate "Sevin". Flora (Jena), **160**: 433-439.

Ames RG, Brown SK, Rosenberg J, Jackson RJ, Stratton JW, & Quenon SG (1989) Health symptoms and occupational exposure to flea control product among California pet handlers. Am Ind Hyg Assoc J, **50**(9): 466-472.

Andrawes NR & Bailey RH (1978a) Metabolism of carbaryl in the rat. A reappraisal (File No. 25051). Research Triangle Park, North Carolina, Union Carbide Corporation (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Andrawes NR & Bailey RH (1978b) Conjugated metabolites of carbaryl: A comparison between rat and dog. South Charleston, West Virginia, Union Carbide Research and Development (Project Report No. 811C20) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Andrawes NR & Bailey RH (1978c) Metabolism of carbaryl in Beagle dogs. South Charleston, West Virginia, Union Carbide Research and Development (Project Report No. 811C20) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Andrawes NR & Bailey RH (1979) Carbaryl metabolites detected in the urine of plant workers (File No. 25957). South Charleston, West Virginia, Union Carbide Research and Development (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Andrawes NR & Chancey EL (1970) The metabolism of 1-naphthyl-C^{14} carbaryl in wheat and bean plants. Clayton, North Carolina, Union Carbide Corporation (Project Report No. 13749) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Andrawes NR & Myers WR (1976) Identification of carbaryl metabolites in human urine (File No. 22983). South Charleston, West Virginia, Union Carbide Corporation (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Andrawes NR, Chancey EL, Crabtree RJ, Herrett RA, & Weiden MHJ (1972) Fate of naphthyl-1-^{14}C carbaryl in laying chickens. J Agric Food Chem, **20**(3): 608-617.

André F, Gillon J, André C, Lafont S, & Jourdan G (1983) Pesticide-containing diets augment anti-sheep red blood cell nonreaginic antibody responses in mice but may prolong murine infection with *Giardia muris*. Environ Res, **32**: 145-150.

Andrianova MM & Alexeev IV (1970) [On the question of the carcinogenic properties of the pesticides Sevin, Maneb, Ziram and Zineb.] Vopr Pitan, **6**: 71-74 (in Russian).

Anger WK & Setzer JV (1979) Effects of oral and intramuscular carbaryl administrations on repeated chain acquisition in monkeys. J Toxicol Environ Health, **5**: 793-808.

Antonovich NA (1970) [On the residual quantities of Sevin in food products.] Gig Primen Toxicol Pestic Klin Otrav, **1970**: 176-179 (in Russian).

Argauer RJ & Warthen JD (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**(11): 2472-2474.

Armstrong DA & Millemann RE (1974a) Pathology of acute poisoning with the insecticide Sevin in the bent-nosed clam, *Macom nasuta*. J Invertebr Pathol, **24**(2): 201-212.

Armstrong DA & Millemann RE (1974b) Effect of the pesticide carbaryl on clams and some other intertidal mud flat animals. J Fish Res Board Can, **31**: 466-470.

Armstrong DA & Millemann RE (1974c) Effect of the insecticide Sevin and its first hydrolytic product 1-naphthol on some

developmental stages of the bay mussel *Mytilus edulis*. Mar Biol, **28**: 11-15.

Arunachalam S & Palanichamy S (1982) Sublethal effects of carbaryl on surfacing behaviour and food utilization in the air breathing fish, *Macropodus cupanus*. Physiol Behav, **29**(1): 23-27.

Arunachalam S, Jeyalakshmi K, & Aboobucker S (1980) Toxic and sublethal effects of carbaryl on a freshwater catfish, *Mystus vittatus* (Bloch). Arch Environ Contam Toxicol, **9**: 307-316.

Ashwood-Smith M, Trevino J, & Ring R (1972) Mutagenicity of dichlorvos. Nature (Lond), **240**: 418-420.

Atabaev ST (1972) [Carbamate compounds.] In: [Pesticides and hygiene of the environment in the conditions of warm climate.] Tashkent, Medizina, pp 114-121 (in Russian).

Attia AM, Reiter RJ, Nonaka KO, Mostafa MH, Soliman SA, & El-Sebae AH (1991) Carbaryl-induced changes in indoleamine synthesis in the Pineal gland and its effects on night-time serum melatonin concentrations. Toxicology, **65**: 305-314.

Avashia BH (1987) Is carbaryl safe as its reputation. Letter to the Editor. Am J Med, **83**: 1168-1169.

Azizova OM (1976) [Effect of Sevin and methyl-mercaptophos on different levels of the nervous system.] In: Medved' LI ed. [Current problems of the hygiene of application of pesticides in different climatic and geographical zones. Proceedings of the Itinerary Scientific Session of Vniigintoks, Erevan.] Kiev, Vniigintoks (in Russian).

Bansal SK, Verma SR, Gupta AK, & Dalela RC (1980) Predicting long-term toxicity by subacute screening of pesticides with larvae and early juveniles of four species of freshwater major carp. Ecotoxicol Environ Saf, **4**: 224-231.

Baron RL (1968) Radioactive lactose in skim milk following administration of carbonyl-^{14}C-carbaryl to a lactating cow. J Assoc Off Anal Chem, **51**: 1046-1049.

Baron RL & Locke RK (1970) Utilization of cell culture techniques in carbaryl metabolism studies. Bull Environ Contam Toxicol, **5**: 287-291.

Barrett GW (1968) The effect of an acute insecticide stress on a semi-enclosed grassland ecosystem. Ecology, **49**(6): 1019-1035.

Bart J (1979) Effects of acephate and Sevin on forest birds. J Wildl Manage, **43**(2): 544-549.

Basha SM, Rao KSP, Rao KRSS, & Rao KVR (1983) Differential toxicity of malathion, BHC, and carbaryl to the freshwater fish, *Tilapia mossambica* (Peters). Bull Environ Contam Toxicol, **31**(5): 543-546.

Bavari S, Casale GP, Gold RE, & Vitzthum EF (1991) Modulation of interleukin-2 driven proliferation of human large granular lymphocytes by carbaryl, an anticholinesterase insecticide. Fundam Appl Toxicol, **17**: 61-74.

Belonozhko GA & Kuchak JA (1969) [Electrocortical reactions to treatment with Sevin in rats.] Gig i Sanit, **34**(2): 111-113 (in Russian).

Benard P, Cambon C, & Declume C (1979) Passage of radioactivity into the milk of rats treated with [^{14}C] carbaryl. Toxicol Lett, **4**: 149-153.

Bend JR, Holder GM, Protos E, & Ryan AJ (1971) Water soluble metabolites of carbaryl (1-naphthyl *N*-methylcarbamate) in mouse liver preparations and in the rat. Aust J Biol Sci, **24**: 535-546.

Benson BW, Scott WJ, & Beliles RP (1967) Sevin teratological study in the mouse (Prepared by Woodard Research Corporation) (Union Carbide proprietary report, submitted to WHO by Rhône-Poulenc Agro, Lyon).

Beraud M, Pipy B, Derache R, & Gaillard D (1979) Formation d'un cancérigène, le N-nitrosocarbaryl, par interaction entre un insecticide de la série des carbamates, le carbaryl, et le nitrite de sodium de suc gastrique de rat. Food Cosmet Toxicol, **17**(6): 579-583.

Beraud M, Gaillard S, & Derache R (1980) Inhibition of two hepatic microsomal drug-metabolizing enzymes by a carcinogenic *N*-nitrosated pesticide: *N*-nitrosocarbaryl. Chem-Biol Interact, **31**: 103-112.

Beraud M, Forgue M-F, Pipy B, & Derache P (1989a) Interaction of carbaryl and *N*-nitrosocarbaryl with microsomal monooxygenase activities. Toxicol Lett, **45**(2-3): 251-260.

Beraud M, Forgue M-F, Pipy B, Didier A, & Carre P (1989b) Lipid peroxidation in rat liver microsomes: Influence of carcinogenic *N*-nitrosocarbaryl. Toxicology, **58**: 299-311.

Best EM & Murray BL (1962) Observations on workers exposed to Sevin insecticide: A preliminary report. J Occup Med, **4**(10): 507-517.

Blase W & Loomis TA (1976) The uptake and metabolism of carbaryl by isolated perfused rabbit lung. Toxicol Appl Pharmacol, **37**: 481-490.

Blevins RD & Dunn WC (1975) Effects of carbaryl and dieldrin on the growth, protein content and phospholipid content of Hela cells. J Agric Food Chem, **23**(3): 377-382.

Blevins RD, Lee M, & Regan JD (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 & Seuge J (1979) Effets de trois insecticides (lindane, fenthion et carbaryl): toxicité aiguë sur quatre espèces d'invertébrés limniques; toxicité chronique chez le mollusque pulmoné *lymnea*. Environ Pollut, **18**: 51-70.

Boethling RS & Alexander M (1979) Effect of concentration of organic chemicals on their biodegradation by natural microbial communities. Appl Environ Microbiol, **37**(6): 1211-1216.

Bogacka T & Groba J (1980) [Toxicity and biodegradation of chlorfenvinphos, carbaryl, and propoxur in water environment.] Bromatol Chem Toksykol, **13**(2): 151-158 (in Polish with English summary).

Bogomolova ZN (1968) [Changes in the content of Sevin in fruitberry cultures during the process of vegetation, storage and canning.] Gig Primen Toxicol Pestic Klin Otrav, **1968**: 363-367 (in Russian).

Bogomolova ZN (1970) [Content of Sevin in fruit cultures.] Gig Primen Toxicol Pestic Klin Otrav, **1970**: 197-180 (in Russian).

Bogus ER, Gallagher P, Cameron F, & Mumima R (1985) Analysis of pesticide exposure pads using selective absorption and elution of reversed-phase solid support. J Agric Food Chem, **33**: 1018-1021.

Bollag JM (1979) Transformation of xenobiotics by microbial activity. In: Proceedings of an EPA Workshop on Microbial Degradation of Pollutants in Marine Environments. Gulf Breeze, Florida, US Environmental Protection Agency, Environmental Research Laboratory, pp 19-27 (EPA 600/9-79-012).

Bollag JM & Liu SY (1971) Degradation of Sevin by soil microorganisms. Soil Biol Biochem, **3**(4): 337-345.

Bollag JM & Liu SY (1972a) Fungal degradation of 1-naphthol. Can J Microbiol, **18**(7): 1113-1117.

Bollag JM & Liu SY (1972b) Hydroxylations of carbaryl by soil fungi. Nature (Lond), **236**: 177-178.

Bollag JM, Czaplicki EJ, & Minard RD (1975) Bacterial metabolism of 1-naphthol. J Agric Food Chem, **23**(1): 85-90.

Bollag JM, Sjoblad RD, Czaplicki EJ, & Hoeppel RE (1976) Transformation of 1-naphthol by the culture filtrate of *Rhizoctonia praticola*. Soil Biol Biochem, **8**: 7-11.

Bollag JM, Sjoblad RD, & Liu S-Y (1978) Characterization of an enzyme from *Rhizoctonia praticola* which polymerizes phenolic compounds. Can J Microbiol, **25**: 229-233.

Borzelleca J & Skalsky HL (1980) The excretion of pesticides in saliva and its value in assessing exposure. J Environ Sci Health, **B13**(6): 843-866.

Bowman BT & Sans WW (1985) Effect of temperature on the water solubility of insecticides. J Environ Sci Health, **B20**(6): 625-631.

Bowman MC, Oller W, Kendall D, Dosnell A, & Oliver K (1982) Stressed bioassay systems for rapid screening of pesticide residues. Part II. Determination of foliar residues for safe re-entry of agricultural workers into the field. Arch Environ Contam Toxicol, **11**: 447-455.

Boyd EM & Boulanger MA (1968) Insecticide toxicology. Augmented susceptibility to carbaryl toxicity in albino rats fed purified casein diets. J Agric Food Chem, **16**: 834-838.

Boyd EM & Krijnen CJ (1969) The influence of protein intake on acute oral toxicity of carbaryl. J Clin Pharmacol, **9**(5): 292-297.

Brahmaprakash GP & Sethunathan N (1984) Mineralization of carbaryl and carbofuran in soil planted to rice. Rice Newsl, **5**(3-4): 2.

Brahmaprakash GP & Sethunathan N (1985) Metabolism of carbaryl and carbofuran in soil planted to rice. Agric Ecosyst Environ, **13**(1): 33-42.

Branch RA (1987) The reply. Letter to the Editor. Am J Med, **83**: 1169.

Branch RA & Jacqz E (1986a) Is carbaryl as safe as its reputation? Does it have the potential for causing chronic neurotoxicity in humans? Am J Med, **80**: 659-664.

Branch RA & Jacqz E (1986b) Subacute neurotoxicity following long-term exposure to carbaryl. Am J Med, **80**: 741-745.

Brankovan O (1972) Meiotic effects in corn in embryonic and generative stages induced by Sevin 50. Arhiv Poljopr Nauke, **90**: 125-132.

Briggs GG (1981) Adsorption of pesticides by some Australian soils. Aust J Soil Res, **19**: 61-68.

Brzeskii VV (1972) The study of the mutagenic properties of an insecticide from the carbamate group - Sevin. Sov Genet, **8**: 798-800.

Buchanan DV, Millemann RE, & Stewart NE (1970) Effects of the insecticide Sevin on various stages of the dungeness crab, *Cancer magister*. J Fish Res Board Can, **27**: 93-104.

Bukin AL (1965) [Toxicity of Sevin for mammalia and birds.] Gig Primen Toxicol Pestic Klin Otrav, **1965**: 431-435 (in Russian).

Bukin AL & Filatov GV (1965) [Sevin toxicity for mammalia and birds.] Veterinaria, **42**: 93-95 (in Russian).

Burdick GE, Dean HJ, & Harris EJ (1960) Effect of Sevin upon the aquatic environment. NY Fish Game J, **7**(1): 14-25.

Bursian SJ & Edens FW (1977) The prolonged exposure of Japanese quail to carbaryl and its effect on growth and reproductive parameters. Bull Environ Contamin Toxicol, **17**(3): 360-368.

Bursian SJ & Edens FW (1978) The effect of acute carbaryl administration on various neurochemical and blood chemical parameters in the Japanese quail. Toxicol Appl Pharmacol, **46**: 463-473.

Bushy Run (1983a) Acute toxicity and irritancy study. Export, Pennsylvania, Bushy Run Research Center (Project Report No. 46-96) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Bushy Run (1983b) Sevin 99% technical: Acute toxicity and irritancy study. Export, Pennsylvania, Bushy Run Research Center (Project Report No. 46-71) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Bushy Run (1983c) Sevin 80 sprayable. Acute toxicity and irritancy study. Export, Pennsylvania, Bushy Run Research Center (Project Report No. 46-97) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Butler PA (1962) Effects on commercial fisheries. In: Effects of pesticides on fish and wildlife: A review of investigations during 1960. Washington, DC, US Department of the Interior, Fish and Wildlife Service, pp 11-25 (Circular No. 143).

Butler PA (1963) Commercial fisheries investigations. In: Pesticide-wildlife studies: A review of Fish and Wildlife Service investigations during 1961 and 1962. Washington, DC, US Department of the Interior, Fish and Wildlife Service, pp 11-25 (Circular No. 167).

Cairns T, Siegmund GA, & Doose MG (1983) Potential identification problems with carbaryl. Bull Environ Contam Toxicol, **30**: 93-98.

Calabrese EJ & Geiger CP (1986) Low erythrocyte glusose-6-phosphate dehydrogenase (G-6-PD) activity and susceptibility to carbaryl induced methaemoglobin formation and glutathion depletion. Bull Environ Contam Toxicol, **36**(4): 506-509.

Cambon C, Declume Ch, & Derache R (1978) Inhibitions of acetylcholinesterase from foetal and maternal tissues after oral intake of carbaryl (1-naphthyl-*N*-methyl carbamate) by pregnant rats. Biochem Pharmacol, **27**: 2647-2648.

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

Cameron EA & Mastro VC (1976) Forest insect and disease management / Evaluation Report: Effectiveness of disparlure in combination with Sevin 4 oil for Gipsy moth suppression in Pennsylvania 1974. Upper Darby, Pennsylvania, US Department of Agriculture, Northeastern Area State and Private Forestry Service.

Cameron EA, Loerch CR, & Mumma RO (1985) Incidental and indirect exposure to three chemical insecticides used for control of the Gypsy moth, *Lymantria Dispar* (L.). Z Angew Entomol, **99**: 241-248.

Carey AE & Kutz FW (1985) Trends in ambient concentrations of agrochemicals in humans and the environment in USA. Environ Monit Assess, **5**(2): 155-164.

Carlson AR (1972) Effects of long-term exposure to carbaryl (Sevin) on survival, growth and reproduction of the fathead minnow (*Pimephales promelas*). J Fish Res Board Can, **29**(5): 583-587.

Caro HJ, Freeman HP, & Turner BC (1974) Persistence in soil and losses in run off of soil incorporated carbaryl in a small watershed. J Agric Food Chem, **22**(5): 860-863.

Carpenter M (1990) Hydrolysis of ^{14}C-carbaryl in aqueous solutions buffered at pH 5, 7, and 9. Columbia, Missouri, Analytical Bio-Chemistry Laboratories, Inc. (ABC final report No. 38380) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Carpenter CP, Weil CW, Palm PH, Woodside MW, Nair JH III, & Smith HF (1961) Mammalian toxicity of 1-naphthyl-*N*-methyl carbamate (Sevin insecticide). J Agric Food Chem, **9**: 30-39.

Casale GP, Bavari S, & Connolly JJ (1989) Inhibition of human serum complement activity by diisopropylfluorophosphate and selected anticholinesterase insecticides. Fundam Appl Toxicol, **12**(3): 460-468.

Casida JE (1970) Mixed-function oxidase involvement in the biochemistry of insecticide synergists. J Agric Food Chem, **18**: 753.

Casida JE & Augustinsson KB (1959) Reaction of plasma albumin with 1-naphthyl-*N*-methylcarbamate and certain other esters. Biochim Biophys Acta, **35**: 411-426.

Casper HH, Pekas JC, & Dinusson WE (1973) Gastric absorption of a pesticide (1-naphthyl *N*-methylcarbamate) in the fasted rat. Pestic Biochem Physiol, **2**: 391-396.

Chaiyarach S, Ratananun V, & Harrel RC (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.

Chancey EL (1974) Sevin carbaryl insecticide: metabolism of carbaryl in apple fruit (File No. 19496). Clayton, North Carolina,

Union Carbide Corporation (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Chancey EL & Andrawes NR (1971a) The absorption and metabolism of 1-naphthyl-C^{14} carbaryl in corn and rice plants. Clayton, North Carolina, Union Carbide Corporation (Project Report No. 15712) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Chancey EL & Andrawes NR (1971b) Metabolism and translocation of 1-naphthyl-C^{14} carbaryl in tomato fruit and foliage and potato foliage. Clayton, North Carolina, Union Carbide Corporation (Project Report No. 15715) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Chapman RA & Cole CM (1982) Observations on the influence of water and soil pH on the persistence of insecticides. J Environ Sci Health, **B17**(5): 487-504.

Chaudhry GR & Wheeler WB (1988) Biodegradation of carbamates. Water Sci Technol, **20**(11/12): 89-94.

Chernoff N & Kavlock RJ (1982) An *in vivo* teratology screen utilizing pregnant mice. J Toxicol Environ Health, **10**: 541-550.

Chernoff N, Setzer RW, Miller DB, Rosen MB, & Rogers JM (1990) Effects of chemically induced maternal toxicity on prenatal development in the rat. Teratology, **42**: 651-658.

Chib JS (1985a) The adsorption/desorption of 1-naphthyl methylcarbamate on five soils (File No. 33820). Research Triangle Park, North Carolina, Union Carbide Agricultural Products Co., Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Chib JS (1985b) Sevin: Aerobic aquatic metabolism of carbaryl (File No. 34234). Research Triangle Park, North Carolina, Union Carbide Agricultural Products Co., Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Chib JS (1985c) Sevin (1-naphthyl methylcarbamate): Anaerobic aquatic metabolism of carbaryl (File No. 34086). Research Triangle Park, North Carolina, Union Carbide Agricultural Products Co., Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Chib JS (1986a) Sevin brand carbaryl insecticide. Bioconcentration and fate of carbaryl in bluegill sunfish (*Lepomis macrochirus*). Research Triangle Park, North Carolina, Union Carbide Corporation (Report No. 801R10) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Chib JS (1986b) Sevin brand carbaryl insecticide: Photodegradation of carbaryl on soil (File No. 34598). Research Triangle Park, North Carolina, Union Carbide Agricultural Products Co., Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Chib JS & Andrawes NR (1985) Carbaryl (1-naphthyl methylcarbamate) - Soil mobility study (File No. 33770). Research Triangle Park, North Carolina, Union Carbide Agricultural Products Co., Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Chib JS, Noeth SP, & Smith BK (1986) Sevin brand carbaryl insecticide. Bioconcentration and fate of carbaryl in Bluegill Sunfish (*Lepomis Macrochirus*) (File No 34540). Research Triangle Park, North Carolina, Union Carbide Agricultural Products Co., Inc., Research and Development Department (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Chin YN & Sudderuddin KI (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 BH, Eldridge JM, & Sullivan LJ (1974) Metabolism of carbaryl by selected tissues using an organ-maintenance technique. Clin Toxicol, 7: 37-56.

Chin BH, Sullivan LJ, Eldridge JM, & Tallant J (1979a) Metabolism of carbaryl by kidney, liver, and lung from human postembryonic fetal autopsy tissue. Clin Toxicol, 14(5): 489-498.

Chin BH, Eldridge JM, Anderson JH, & Sullivan LJ (1979b) Carbaryl metabolism in the rat. A comparison of *in vivo, in vitro* (tissue explant), and liver perfusion techniques. J Agric Food Chem, **27**(4): 716-720.

Christenson I (1964) Alkaline hydrolysis of some carbamic esters. Acta Chem Scand, **18**: 904-922.

Cifone MA (1989) Mutagenicity test on carbaryl technical in the *in vitro* rat primary hepatocyte unscheduled DNA synthesis assay. Final report (HLA Study No. 10862-0-435). Kensington, Maryland, Hazelton Laboratories America, Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Clayson DB (1987) The need for biological risk assessment in reaching decisions about carcinogens. Mutat Res, **185**(3): 243-269.

Collins TFX, Hansen WH, & Keeler HV (1971) The effect of carbaryl (Sevin) on reproduction of the rat and the gerbil. Toxicol Appl Pharmacol, **19**: 202-216.

Comer SW, Staiff DC, Armstrong JF, & Wolf HR (1975) Exposure of workers to carbaryl. Bull Environ Contam Toxicol, **13**(4): 385-391.

Coulston F, Rosenblum I, & Dougherty WJ (1974) Teratogenic evaluation of carbaryl in the Rhesus monkey (*Macacca mulatta*). Holloman Air Force Base, New Mexico, International Center of Environmental Safety, Albany Medical College, 54 pp (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Courtemanch DL & Gibbs KE (1978) The effects of Sevin-4-oil on lenthic communities. In: Environmental monitoring of cooperative spruce budworm control projects, Maine 1976 and 1977. Augusta, Maine, Maine Department of Conservation, Forest Service, pp 141-150.

Courtemanch DL & Gibbs KE (1980) Short- and long-term effects of forest spraying of carbaryl (Sevin-4-oil) on stream invertebrates. Can Entomol, **112**: 271-276.

Coutant CC (1964) Insecticide Sevin: Effect of aerial spraying on drift of stream insects. Science, **146**: 420-421.

Cranmer MF (1986) Carbaryl. A toxicological review and risk analysis. Neurotoxicology, **7**(1): 247-332.

Cress CR & Strother A (1974) Effects on drug metabolism of carbaryl and 1- naphthol in the mouse. Life Sci, **14**: 861-872.

Crofton KM, Howard JL, Moser VC, Gill MW, Reiter LW, Tilson HA, & MacPhail RC (1991) Interlaboratory comparison of motor activity experiments: Implications for neurotoxicological assessments. Neurotoxicol Teratol, **13**: 599-609.

Crosby DG, Leitis E, & Winterlin WL (1965) Photodecomposition of carbamate insecticides. J Agric Food Chem, **13**(3): 204-205.

Currier WW, MacCollom GB, & Baumann GI (1982) Drift residues of air-applied carbaryl in an orchard environment. J Econ Entomol, **75**(6): 1062-1068.

Czaplicki E (1979) Persistence in the soil of some more important insecticides applied in Poland. I. Dynamics of insecticide disappearance in the soil. Pr Nauk Inst Ochr Rosl, **21**(2): 7-40.

Czaplicki EJ & Bollag JM (1975) Microbial degradation of 1-naphthol. Biul Inst Ochr Rosl, **59**: 241-248.

Das YT (1990a) Photodegradation of (1-naphthyl-^{14}C) carbaryl in aqueous solution buffered at pH 5 under artificial sunlight. Piscataway, New Jersey, Innovative Scientific Services, Inc. (Report No. 90060) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Das YT (1990b) Photodegradation of (1-naphthyl-^{14}C) carbaryl on soil under artificial sunlight. Piscataway, New Jersey, Innovative Scientific Services, Inc. (Report No. 90061) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Davies JI & Evans WC (1964) Oxidative metabolism of naphthalene by soil Pseudomonads. The ring-fission mechanism. Biochem J, **91**: 251-261.

Davis HC (1961) Effects of some pesticides on eggs and larvae of oysters (*Crassostrea virginica*) and clams (*Venus mercenaria*). Commer Fish Rev, **23**(12): 8-23.

Davis CW (1986a) Sevin brand carbaryl insecticide: Dissipation of soil residues under field use conditions (File No. 34620). Research Triangle Park, North Carolina, Union Carbide Agricultural Products Co., Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Davis CW (1986b) Sevin brand carbaryl insecticide: Magnitude of carbaryl residues on rangeland and pasture grasses (File No. 34821). Research Triangle Park, North Carolina, Union Carbide Agricultural Products Co., Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Davis CW (1987) Sevin brand carbaryl insecticide: Comparison of the magnitude of carbaryl residues resulting from applications of XLR plus and 50 W formulations to tree fruit, leafy vegetables, and cereals (File No. 35357). Research Triangle Park, North Carolina, Union Carbide Agricultural Products Co., Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Davis CW & Thomas SJ (1987) Carbaryl insecticide. Section D-Residues barley (File No. 40092). Research Triangle Park, North Carolina, Union Carbide Agricultural Products Co., Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Declume C & Benard P (1977a) Foetal accumulation of [^{14}C] carbaryl in rats and mice autoradiographic study. Toxicology, **8**: 95-105.

Declume C & Benard P (1977b) Etude autoradiographique de la distribution d'un agent anticholinestérasique, le 1-naphthyl-*N*-methyl [^{14}C] carbamate chez la ratte gestante. Toxicol Appl Pharmacol, **39**: 451-460.

Declume C & Benard P (1978) Etude de la pharmacocinétique du ^{14}C-carbaryl chez la souris gestante. Toxicol Eur Res, **1**: 174-180.

Declume C & Derache M (1976) Biodisponibilité du ^{14}C-carbaryl après l'administration oral à la ratte gestante. C R Acad Sci Paris, **D283**: 1799-1801.

Declume C & Derache M (1977) Passage placentaire d'un carbamate anticholinestérasique à activité insecticide: Le carbaryl. Chemosphere, **6**: 141-146.

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

Degraeve N, Moutschen-Dahmen M, Houbrechts N, & Colizzi A (1976) A propos des risques d'un insecticide: le carbaryl utilisé seul et en combinaison avec les nitrites. Bull Soc R Sci Liège, **45**(1-2): 46-57.

DeGiovanni-Donnelly R, Kolbye SM, & Greeves PD (1968) The effect of IPC, CIPC, Sevin and Zectran on *Bacillus subtilis*. Experientia (Basel), **24**: 80-81.

Desi I, Gonczi L, Simon G, Farkas I, & Kneffel Z (1974) Neurotoxicological studies of two carbamate pesticides in subacute animal experiments. Toxicol Appl Pharmacol, **27**: 456-476.

Deuel LE, Brown KW, Price JD, & Turner FT (1985) Dissipation of carbaryl and the 1-naphthol metabolite in the flooded rice fields. J Environ Qual, **14**(3): 349-354.

Deutsch-Wenzel P, Brune H, Grimmer G, & Misfeld J (1985) Local application to mouse skin as a carcinogen specific test system for non-volatile nitroso compounds. Can Lett, **29**: 85-92.

Dickoff DJ, Gerber O, & Turovsky Z (1987) Delayed neurotoxicity after ingestion of carbamate pesticide. Neurology, **37**(7): 1229-1231.

Dieringer CS & Thomas JA (1974) Effects of carbaryl on the metabolism of androgens in the prostate and liver of the mouse. Environ Res, **7**: 381-386.

Dikshith TSS (1991) Mutagenicity and teratogenicity of pesticides. In: Dikshith TSS ed. Toxicology of pesticides in animals. Boston, Boca Raton, Ann Arbor, CRC Press, pp 189-198.

Dikshith TSS, Gupta PK, Gaur JS, Datta KK, & Mathur AK (1976) Ninety-day toxicity of carbaryl in male rats. Environ Res, **12**: 161-170.

Dikshith TSS, Kumar SN, Raizada RB, Srivastava MK, & Ray PK (1990) Residues of 1-naphthol in soil and water samples in and around Bhopal, India. Bull Environ Contam Toxicol, **44**: 87-91.

Dinerman AA, Lavrent'eva NA, & Il'inskaia NA (1970) [The embryotoxic action of some pesticides.] Gig i Sanit, **35**: 39-42 (in Russian).

Dinoeva SK (1974) [Dynamics of the changes in the immunological structures of lymphatic follicles in spleen during pesticide poisoning.] Gig i Sanit, **39**(3): 85-87 (in Russian).

Dinoeva S (1982) Humoral immune response in 1st, 2nd and 3rd generations guinea-pigs in the period of reactivation after intoxication. In: Immunology of reproduction. Proceedings of the Fifth International Symposium, Varna, Bulgaria, 26-29 May 1982. Sofia, Bulgarian Academy of Sciences Press, pp 393-395.

Dionne E, Kendall TB, & Suprenant D (1985) Acute toxicity of carbaryl technical to embryos-larvae of Eastern oysters (*Crassostrea virginica*). Wareham, Massachusetts, Springborn Bionomics, Inc. (Report No. BW-85-7-1817) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Dittert LW & Higuchi T (1963) Rates of hydrolysis of carbamate and carbonate esters in alkaline solution. J Pharm Sci, **52**: 852-857.

Dorough HW (1967) Carbaryl-C^{14} metabolism in a lactating cow. J Agric Food Chem, **15**(2): 261-266.

Dorough HW (1969) Carbaryl cow study No. 2. Lyon, Rhône-Poulenc Agro (Unpublished proprietary information).

Dorough HW (1970a) Continuous feeding of carbaryl naphthyl-C^{14} to lactating cows. Progress report. Lyon, Rhône-Poulenc Agro (Document No. 25, Section C, Part III) (Unpublished proprietary information).

Dorough HW (1970b) Metabolism of insecticidal methylcarbamates in animals. J Agric Food Chem, **18**(6): 1015-1022.

Dorough HW (1971) Carbaryl residues in milk and meat of dairy animals. Presented at the International Symposium on Pesticide Terminal Residues, Tel- Aviv, Israel, 17-19 February 1971 (Document No. 27, Section C, Part III).

Dorough HW (1973) Metabolism of carbamate insecticides. Washington, DC, US Environmental Protection Agency, Office of Research and Development, 246 pp (EPA-650/1-74-002).

Dorough HW (1982) Inhalation toxicology: Starting with the environment. Environ Toxicol Chem, **1**(3): 213-220.

Dorough HW & Casida JH (1964) Nature of certain carbamate metabolites of the insecticide Sevin. J Agric Food Chem, **12**(4): 294-304.

Dorough HW, Leeling NL, & Casida JE (1963) Nonhydrolytic pathway in metabolism of *N*-methylcarbamate insecticides. Science, **140**: 170-171.

Dougherty WJ, Goldberg L, & Coulston F (1971) The effect of carbaryl on reproduction in the monkey (*Macacca mulatta*). Toxicol Appl Pharmacol, **19**: 365.

Duck BJ & Woolias M (1985) Reverse-phase high performance liquid chromatographic determination of carbaryl in postmortem specimens. J Anal Toxicol, **9**: 177-179.

Duggan RE & Corneliussen PE (1972) Dietary intake of pesticide chemicals in the United States (III). June 1968-April 1970. Pestic Monit J, **5**(4): 331-341.

Duggan RE, Lipscomb GQ, Cox EL, Heatwole RE, & Kling RC (1971) Residues in food and feed. Pesticide residue levels in foods in the United States from July 1, 1963, to June 30, 1969. Pestic Monit J, **5**(2): 73-124.

Durham WF & Wolfe HR (1962) Measurements of the exposure of workers to pesticides. Bull World Health Organ, **26**: 75-91.

Dyadicheva TV (1971) [Experimental data on thyroid and adrenal cortex function during prolonged effect of carbamine pesticides.] Vrach Delo, **2**: 120-123 (in Russian).

Dzwonkowska A & Hubner H (1986) Induction of chromosomal aberrations in the Syrian hamster by insecticides tested *in vivo*. Arch Toxicol, **58**(3): 152-156.

Earl FL, Miller E, & Van Loon EJ (1973) Reproductive teratogenic and neonatal effects of some pesticides and related compounds in beagle dogs and miniature swine. In: Deichman W ed. Pesticides and the environment: A continuing controversy. Proceedings of the 8th Inter-American Conference on Toxicology and Occupational Medicine, Miami, Florida, pp 253-266.

Edmiston CE Jr, Goheen M, Malaney GW, & Mills WL (1985) Evaluation of carbamate toxicity: Acute toxicity in a culture of *Paramecium multimicronucleatum* upon exposure to aldicarb, carbaryl, and mexacarbate as measured by Warburg respirometry and acute plate assay. Environ Res, **36**(2): 338-350.

Egert G & Greim H (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.

Eheart JF, Turner EC, & Dickinson J (1962) Residues of Sevin in whole milk from sprayed and dusted cows. J Entomol, **55**(4): 504-505.

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

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

Eisenbrand G, Schmähl D, & Preussmann R (1976) Carcinogenicity in rats of high oral doses of *N*-nitroso-carbaryl, a nitrosated pesticide. Can Lett, **1**: 281-284.

Elespuru RK & Lijinsky W (1973) The formation of carcinogenic nitroso compounds from nitrite and some types of agricultural chemicals. Food Cosmet Toxicol, **11**: 807-817.

Elespuru R, Lijinsky W, & Setlow JK (1974) Nitrosocarbaryl as a potent mutagene of environmental significance. Nature (Lond), **247**: 386-387.

Elkins ER (1989) Effect of commercial processing on pesticide residues in selected fruits and vegetables. J Assoc Off Anal Chem, **72**(3): 533-535.

Elkins ER, Lamb FC, Farrow RP, Cook RW, Kawai M, & Kimball JR (1968) Removal of DDT, malathion and carbaryl from green beans from commercial and home preparative procedures. J Agric Food Chem, **16**(6): 962-966.

Elliot-Feeley E & Armstrong JR (1982) Effects of fenitrothion and carbaryl on *Xenopus laevis* development. Toxicology, **22**(4): 319-335.

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

Estesen BJ, Buck NA, & Ware GW (1982) Dislodgeable insecticide residues on cotton foliage: carbaryl, cypermethrin, and methamidophos. Bull Environ Contam Toxicol, **28**(4): 490-493.

Eto M, Seifert J, Engel J, & Casida J (1980) Organophosphorous and methylcarbamate teratogens: Structural requirements for reducing

embryonic abnormalities in chickens and kynurenine formamidase inhibition in mouse liver. Toxicol Appl Pharmacol, 54: 20-30.

Eto M, Kuwano E, Yoshikawa M, Suiko M, Kohno M, Kamihata M, & Nakatsu S (1982) Mutagenicity and anticholinesterase activity of possible metabolites of aryl *N*-methylcarbamates. J Fac Agric Kyushu Univ, 26(4): 213-219.

Fait DW (1984) Sevin XLR acute inhalation toxicity test. Export, Pennsylvania, Bushy Run Research Center (Report No. 47-84) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Falzon M, Fernandez Y, Cambon C, Gros C, & Mitjavila S (1983) Influence of experimental hepatic impairment on the toxicokinetics and the anticholinesterase activity of carbaryl in the rat. J Appl Toxicol, 3(2): 87-89.

FAO (1982) Second Government Consultation on International Harmonization of Pesticides Registration Requirements, Rome, 11-15 October 1982. Rome, Food and Agriculture Organization of the United Nations.

FAO/WHO (1964) Carbaryl. In: Evaluation of the toxicity of pesticides residues in food. Report of a Joint Meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues, Geneva, 30 September-7 October 1963. Geneva, World Health Organization, pp 132-135 (FAO Meeting Report No. PL:1963/13; WHO/Food Add./23).

FAO/WHO (1965) Carbaryl. In: Evaluation of the toxicity of pesticide residues in food. Geneva, World Health Organization, pp 31-35 (FAO Meeting Report No. PL:1965/10/1; WHO Food Add./27.65).

FAO/WHO (1967) Carbaryl. In: 1966 Evaluation of some pesticide residues in food. Geneva, World Health Organization, pp 31-38 (FAO PL/CP/15; WHO Food Add./67.32)

FAO/WHO (1968) Carbaryl. In: 1967 Evaluation of some pesticide residues in food. Geneva, World Health Organization, pp 15-25 (FAO Report No. PL: 1967/M/11/1; WHO Food Add./68.30).

FAO/WHO (1969) Carbaryl. In: 1968 Evaluation of some pesticide residues in food. Geneva, World Health Organization, pp 35-38 (FAO PL:1968/M/9/1; WHO Food Add./69.35).

FAO/WHO (1970) Carbaryl. In: 1969 Evaluations of some pesticide residues in food. Geneva, World Health Organization, pp 45-57 (FAO PL:1969/M/17/1; WHO Food Add./70.38).

FAO/WHO (1971) Carbaryl. In: 1970 Evaluations of some pesticide residues in food. Geneva, World Health Organization, pp 3-6 (AGP 1979/M/12/1; WHO Food Add./71.42).

FAO/WHO (1972) 1971 Evaluations of some pesticide residues in food. Geneva, World Health Organization (WHO Pesticide Residue Series No. 1).

FAO/WHO (1974) Carbaryl. In: 1973 Evaluations of some pesticide residues in food. Geneva, World Health Organization, pp 141-176 (WHO Pesticide Residue Series No. 3).

FAO/WHO (1976) Carbaryl. In: 1975 Evaluations of some pesticide residues in food. Geneva, World Health Organization, pp 83-84 (WHO Pesticide Residue Series No. 5).

FAO/WHO (1977) Carbaryl. In: 1976 Evaluations of some pesticide residues in food. Rome, Food and Agriculture Organization of the United Nations, pp 95-123 (AGP 1977/M/14).

FAO/WHO (1978) Carbaryl. In: Pesticide residues in food. Evaluations 1977. Rome, Food and Agriculture Organization of the United Nations, pp 47-50 (FAO Plant Production and Protection Paper 10 Sup).

FAO/WHO (1980) Carbaryl. In: Pesticide residues in food. Evaluations 1979. Rome, Food and Agriculture Organization of the United Nations, pp 101-102 (FAO Plant Production and Protection Paper 20 Sup).

FAO/WHO (1985) Carbaryl. In: Pesticide residues in food - 1984. The monographs. Rome, Food and Agriculture Organization of the

United Nations, pp 79-83 (FAO Plant Production and Protection Paper 67).

FAO/WHO (1986a) Guide to Codex recommendations concerning pesticide residues. Part 8. Recommendations for methods of analysis of pesticide residues, 3rd ed. Rome, Food and Agriculture Organization of the United Nations, Codex Alimentarius Commission.

FAO/WHO (1986b) Codex maximum limits for pesticide residues, 2nd ed. Rome, Food and Agriculture Organization of the United Nations, Codex Alimentarius Commission (CAC/Vol. XIII).

Farage-Elawar M (1989) Enzyme and behavioural changes in young chicks as a result of carbaryl treatment. J Toxicol Environ Health, **26**(1): 119-131.

Farage-Elawar M (1990) Effects of *in ovo* injection of carbamates on chick embryo hatchability, esterase enzyme activity and locomotion of chicks. J Appl Toxicol, **10**(3): 197-201.

Farago A (1969) [Fatal suicidal case of Sevin (1-naphthol-*N*-methyl carbamate) poisoning.] Arch Toxicol, **24**: 309-315 (in German).

Farrow RP, Lamb FC, Cook RW, Kimball JR, & Elkins ER (1968) Removal of DDT, malathion and carbaryl from tomatoes by commercial and home preparative methods. J Agric Food Chem, **16**(1): 65-71.

Farrow RP, Lamb FC, Elkins ER, Cook RW, Kawai M, & Cortes A (1969) Effect of commercial and home preparative procedures on parathion and carbaryl residues in broccoli. J Agric Food Chem, **17**(1): 75-79.

Federle PF & Collins WJ (1976) Insecticide toxicity to three insects from Ohio ponds. Ohio J Sci, **76**(1): 19-24.

Feldmann RJ & Maibach HT (1974) Percutaneous penetration of some pesticides and herbicides in man. Toxicol Appl Pharmacol, **28**: 126-132.

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

Ferreira GAL & Seiber JN (1981) Volatilization and exudation losses of 3-*N* methylcarbamate insecticides applied systemically to rice. J Agric Food Chem, **29**(1): 93-99.

Field WE (1980a) Oral LD_{50} in rats of carbaryl, technical grade, made in West Virginia. Clarks Summit, Pennsylvania, Chemicals, Drugs and Cosmetics Research (Report No. CDC-UC-046-79) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Field WE (1980b) Oral LD_{50} in rats of carbaryl, technical grade, made in India. Clarks Summit, Pennsylvania, Chemicals, Drugs and Cosmetics Research (Report No. CDC-UC-047-79) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Filatov DV & Brytskov VE (1972) [Enzymic method of residue determination of chlorophos and Sevin by means of indicator paper.] Probl Vet Sanit, **XLI**: 233-241 (in Russian).

Fisher SW & Lohner TW (1986) Studies on the environmental fate of carbaryl as a function of pH. Arch Environ Contam Toxicol, **15**(6): 661-667.

Fisher HL, Most B, & Hall LL (1985) Dermal absorption of pesticides calculated by deconvolution. J Appl Toxicol, **5**(3): 163-177.

Fletcher DW & Leonard MI (1986a) Toxicity and reproduction study with carbaryl technical in Bobwhite quail. Neillsville, Wisconsin, Bio-Life Associate Ltd (Report No. 85-DR-15) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Fletcher DW & Leonard MI (1986b) 28-day dietary toxicity and reproduction pilot study with carbaryl technical in Mallard ducks. Neillsville, Wisconsin, Bio-Life Associate Ltd (Report

No. 85 DR P14) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Flores-Ruegg E, De Andrea MM, Helene CG, & Hirata R (1980) Persistence of pesticide residues in Brazilian soil samples related to organic matter and microbiological activity. In: Meeting of the Advisory Group on Agrochemical Residue Biota Interaction: Proceeding report. Sao Paulo, Brazil, Biological Institute, pp 181-187.

Frank R, Braun HE, & Ripley BD (1989) Monitoring Ontario grown apples for pest control chemicals used in their production, 1978-86. Food Addit Contam, **6**(2): 227-234.

Frank R, Braun HE, Ripley BD, & Pitblado R (1991) Residues of nine insecticides and two fungicides in raw and processed tomatoes. J Food Prot, **54**(1): 41-46.

Fukuto TR (1973) Metabolism of carbamate insecticides. In: Di Carlo FJ ed. Drug metabolism reviews. New York, Basel, Marcel Dekker, Inc., vol 1, pp 117-151.

Gaillard D, Chamoiseau G, & Derache R (1977) Interaction du carbaryl et du nitrite de sodium sur les activités enzymatiques de quelques mono-oxygénases microsomiques du foie de rat. J Pharmacol, **8**: 437.

Gaines TB (1960) The acute toxicity of pesticides to rat. Toxicol Appl Pharmacol, **2**: 88-99.

Gaines TB (1969) Acute toxicity of pesticides to rat. Toxicol Appl Pharmacol, **14**: 514-534.

Gangwar SK, Kavadia VS, Gupta HCL, & Srivastava BP (1978a) Persistence of carbaryl in sandy loam soil and its uptake in *bajra, Pennistetum typhoides* P. Ann Arid Zone, **17**(4): 357-362.

Gangwar SK, Kavadia VS, Srivastava BP, & Gupta HCL (1978b) Persistence of carbaryl residues in sandy loam soil and its uptake by root crops. Indian J Plant Prot, **8**(1): 11-18.

Gapparov Sh (1974) [Haemocoagulation indices in dogs chronically intoxicated with low doses of Sevin.] [Health Health Care Organ Uzbekistan], **11**: 146-149 (in Russian).

Gartrell MJ, Craun JC, Podrebarac DS, & Gunderson EL (1986) Pesticides, selected elements, and other chemicals in infant and toddler total diet samples, October 1980-March 1982. J Assoc Off Anal Chem, **69**(1): 123-145.

Georgiev IN (1967) [The effect of toxic and maximal permissible amounts of Sevin on intestinal secretion.] Gig i Sanit, **32**(8): 42-46 (in Russian with English summary).

Ghadiri M & Greenwood DA (1966) Toxicity and biologic effects of malathion, phosdrin and Sevin in the chick embryo. Toxicol Appl Pharmacol, **8**: 342.

Ghosh P, Bhattacharya S, & Bhattacharya S (1990) Impairment of the regulation of gonadal function in *Channa punctatus* by metacid 50 and carbaryl under laboratory and field conditions. Biomed Environ Sci, **3**(1): 106-112.

Gibbs E, Mingo TM, & Courtemanch DL (1981) The effect on pond macroinvertebrates from forest spraying of carbaryl and its persistence in water and sediment. Augusta, Maine, Maine Department of Conservation, Forest Service.

Gibbs KE, Mingo TM, & Courtemanch DL (1984) Persistence of carbaryl (Sevin-4-oil) in woodland ponds and its effects on ponds macro invertebrates following forest spraying. Can Entomol, **116**: 203-214.

Gill SS & Yeoh CL (1980) Degradation of carbaryl in three components of the paddy-field ecosystem of Malaysia. In: Meeting of the Advisory Group on Agrochemical Residue Biota Interaction: Proceeding report. Sao Paulo, Brazil, Biological Institute, pp 229-243.

Gill TS, Pant JC, & Pant J (1988) Gill, liver, and kidney lesions associated with experimental exposures to carbaryl and dimethoate in

the fish (*Puntius conchonius* Ham.). Bull Environ Contam Toxicol, **41**(1): 71-78.

Gladenko IN & Malinin OA (1970) [Toxicity of Sevin for livestock.] Gig Primen Toxicol Pestic Klin Otrav, **1970**: 188-193 (in Russian).

Golbs S, Kühnert M, & Leue F (1975) [Prenatal toxicological study of Sevin (carbaryl) for Wistar rats.] Arch Exp Veterinaermed, **29**: 607-614 (in German with English summary).

Golbs S, Kühnert M, & Fuchs V (1984) [Influence on the acute toxicity of selected pesticides by huminic acids.] Z Gesamte Hyg, **30**(12): 720-723 (in German).

Gold RE, Leavitt JR, Holcslaw T, & Tupy D (1982) Exposure of urban applicators to carbaryl. Arch Environ Contam Toxicol, **11**: 63-67.

Goldberg HI, Johnson HE, & Knaak JB (1965) Inhibition of discrete avoidance behaviour by three anticholinesterase agents. Psychopharmacologia, **7**(1): 72-76.

Guirguis GN & Brindley WA (1975) Carbaryl penetration into and metabolism by alfalfa leafcutting bees, *Megachile pacifica*. Agric Food Chem, **23**(2): 274-279.

Guirguis GN & Brindley WA (1976) Effect of chlorcyclizin, aminopyrine or phenobarbital on carbaryl metabolism in alfalfa leafcutting bees. Environ Entomol, **5**(3): 590-594.

Gunderson EL (1988) FDA total diet study, April 1982-April 1984. Dietary intake of pesticides, selected elements, and other chemicals. J Assoc Off Anal Chem, **71**(6): 1200-1209.

Gupta SK & Sundararaman V (1991) Correlation between burrowing capability and AChE activity in the earthworm, *Pheretima posthuma*, on exposure to carbaryl. Bull Environ Contam Toxicol, **46**: 859-865.

Guseinov MK (1970) [On the question of circulation of Sevin in environment.] Gig Primen Toxicol Pestic Klin Otrav, **1970**: 174-176 (in Russian).

Guthrie FE, Monro RJ, & Abernathy CO (1971) Response of laboratory mouse to selection for resistance to insecticides. Toxicol Appl Pharmacol, **18**: 92-101.

Gyrisco GG, Lisk DJ, Fertig SN, Huddleston EW, Fox FH, Holland RF, & Teimberger GW (1960) The effects of feeding high levels of Sevin on residue, flavour, and odour of the milk of dairy cattle. Agric Food Chem, **8**(5): 409-410.

Haines TA (1981) Effect of an aerial application of carbaryl on brook trout (*Salvelinus fontinalis*). Bull Environ Contam Toxicol, **27**(4): 534-542.

Hamada NN (1987) One year oral toxicity study in Beagle dogs with carbaryl technical. Vienna, Virginia, Hazleton Laboratories America, Inc. (Report No. 400-715) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Hamada NN (1990) Acute oral toxicity study in rats. Carbaryl technical. Vienna, Virginia, Hazleton Laboratories America, Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Hamada NN (1991a) Subchronic toxicity study in dogs with carbaryl technical. Vienna, Virginia, Hazleton Laboratories America, Inc. (Report No. N656-152) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Hamada NN (1991b) Oncogenicity with carbaryl technical in CD-1® mice. Vienna, Virginia, Hazleton Laboratories America, Inc. (Report No. N656-138) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Hamada NN (1991c) Combined chronic toxicity and oncogenicity study with carbaryl technical in Sprague-Dawley rats - 52 week interim report with 4-week recovery. Vienna, Virginia, Hazleton Laboratories America, Inc. (Study No. 656-139) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Hanazato T & Yasuno M (1987) Effects of a carbamate insecticide, carbaryl, on the summer phyto- and zooplankton communities in ponds. Environ Pollut, **48**: 145-159.

Hanazato T & Yasuno M (1989) Influence of over-wintering *Daphnia* on spring zooplankton communities: An experimental study. Ecol Res, **4**: 323-338.

Hanazato T & Yasuno M (1990a) Influence of *Chaoborus* density on the effects of an insecticide on zooplankton communities in ponds. Hydrobiologia, **194**: 183-197.

Hanazato T & Yasuno M (1990b) Influence of time in application of an insecticide on recovery patterns of a zooplankton community in experimental ponds. Arch Environ Contam Toxicol, **19**: 77-83.

Hansen JL (1978) Carbaryl: Human ingestion study statistical analysis (File No. 24971). Research Triangle Park, North Carolina, Union Carbide Corporation (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Hansen CR & Kawatski JA (1976) Application of 24-hour post-exposure observation to acute toxicity studies with invertebrates. J Fish Res Board Can, **33**: 1198-1201.

Harris LW, Talbot BG, Lennox WJ, & Anderson DR (1989) The relationship between oxime induced reactivation of carbamylated acetylcholinesterase and antidotal efficacy against carbamate intoxication. Toxicol Appl Pharmacol, **98**(1): 128-133.

Harry JB (1977) A review of human exposure to Sevin carbaryl insecticide with particular reference to the USA. Research Triangle Park, North Carolina, Union Carbide Agricultural Products Co., Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Hart ER (1972) Teratology study. Sevin, vitamin A, aspirin and malathion. South Charleston, West Virginia, Union Carbide Corporation, 8 pp (Prepared by Bionetics Research Laboratories) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Hassan A (1971) Pharmacological effects of carbaryl. The effect of carbaryl on the synthesis and degradation of catecholamines in the rat. Biochem Pharmacol, **20**: 2299-2308.

Hassan A & Cueto C Jr (1970) Biochemical effects in the rabbit of repeated administration of a mixture of DDT, carbaryl and parathion. Z Naturforsch, **B25**: 521-525.

Hassan A & Santolucito JA (1971) Pharmacological effects of carbaryl. II. Modification of serotonin metabolism in the rat brain. Experientia (Basel), **27**: 287- 288.

Hassan A, Zayed SMAD, & Abdel-Hamid FM (1966) Metabolism of carbamate drugs. I. Metabolism of 1-naphthyl-*N*-methylcarbamate (Sevin) in the rat. Biochem Pharmacol, **15**: 2045-2055.

Hassan AA, El Sewedy SM, Minatogawa Y, & Kido R (1990) Effects of some insecticides on several enzymes of tryptophan metabolism in rats. J Environ Sci Health, **B25**(3): 333-346.

Haven D, Castagna M, Chanley P, Wass M, & Whitcomb J (1966) Effects of the treatment of an oyster bed with polystream and Sevin. Chesapeake Sci, 7(4): 179-188.

Haydock CI (1964) An experimental study to control oyster drills in Tomales Bay, California. Calif Fish Game, **50**: 11-28.

Hayes WJ (1963) Clinical handbook on economic poisons. Emergency information for treating poisoning. Atlanta, Georgia, US Department of Health, Education and Welfare, Communicable Disease Center, pp 44-46.

Hayes WJ Jr & Laws ER Jr ed. (1991) Carbaryl. In: Handbook of pesticide toxicology. Volume 3 - Classes of pesticides. New York, San Diego, Academic Press, Inc., pp 1144-1189.

Hazleton Laboratories America, Inc. (1982) Acute oral toxicity study in rats - Sevin RF. Vienna, Virginia, Hazleton Laboratories America, Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Heise GA & Hudson JD (1985a) Effects of pesticides and drugs on working memory in rat: Continuous delayed response. Pharmacol Biochem Behav, **23**: 591-598.

Heise GA & Hudson JD (1985b) Effects of pesticides and drugs on working memory in rats: Continuous non-match. Pharmacol Biochem Behav, **23**: 599-605.

Hernandez DA, Lombardo RL, Ferrari L, & Tortorelli MC (1990) Toxicity of ethyl-parathion and carbaryl on early development of sea urchin. Bull Environ Contam Toxicol, **45**: 734-741.

Heywood DL (1975) Degradation of carbamate insecticides in soil. Environ Qual Saf, **4**: 128-133.

Hill EF & Camardese MB (1986) Lethal dietary toxicities of environmental contaminants and pesticides to Coturnix. Washington, DC, US Department of the Interior, Fish and Wildlife Service (Fish and Wildlife Technical Report No. 2).

Hill EF, Heath RG, Spann JW, & Williams JD (1975) Lethal dietary toxicities of environmental pollutants to birds. Washington, DC, US Department of the Interior, Fish and Wildlife Service (Special Scientific Report, Wildlife No. 191).

Hodgson E & Casida JE (1961) Metabolism of N:N-dialkyl carbamate and related compounds by rat liver. Biochem Pharmacol, **8**: 179-191.

Hoffman DJ & Albers PH (1984) Evaluation of potential embryotoxicity and teratogenicity of 42 herbicides, insecticides, and petroleum contaminants to mallard eggs. Arch Environ Contam Toxicol, **13**: 15-27.

Hoque H (1972) Radio tracer studies on chemical residues in food and agriculture. Proc. Comb. Panel Res. Coord. Meet. 1971.

Hoque MZ (1972) Carbaryl - A new chemical mutagen. Curr Sci, **41**(23): 855-856.

Houston JB, Upshall DG, & Bridges JW (1974) Pharmacokinetics and metabolism of two carbamates, carbaryl and landrin, in the rat. Xenobiotica, **5**(10): 637-648.

Hudson RH, Tucker RK, & Haegele MA (1984) Handbook of toxicity of pesticides to wildlife, 2nd ed. Washington, DC, US Department of the Interior, Fish and Wildlife Service (Resource Publication 153).

Hughes L Jr (1971) A study of the fate of carbaryl insecticide in surface waters. Lafayette, Indiana, Purdue University (Ph.D Dissertation) (University microfilms, High Wycombe, England).

Hughes LB & Reuszer HW (1970) A study of bacterial decomposition of carbaryl in farm pond waters. Lafayette, Indiana, Purdue University, Water Resources Research Center (Technical Report No. 10).

Hundley HK, Cairns T, Luke AM, & Masumoto HT (1988) Pesticide residue findings by the Luke method in domestic and imported foods and animal feeds for fiscal years 1982-1986. J Assoc Off Anal Chem, **71**(5): 875-892.

Huque H (1972) Preliminary report on the residues of carbaryl granules in rice plants. Radiotracer Stud. Chem. Residues Food Agr., Proc. Comb. Panel Res. Coord. Meet. 1971. Vienna, International Atomic Energy Agency, pp 107-109.

Hurlburt E, McMillan R, & Vialle M (1989) Supplemental environmental impact statement: use of the insecticide carbaryl to control ghosts and mud shrimp in oyster beds of Willapa Bay and Grays Harbour. Olympia, Washington, Washington State Department of Fisheries and Washington State Department of Ecology (Unpublished report submitted to WHO by Rhône-Poulenc Agro, Lyon).

Hurwood IS (1967) Studies on pesticide residues. 2. Carbaryl residues in the body tissues and milk of cattle following dermal application. Qld J Agric Anim Sci, **24**: 69-74.

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

IARC (1987) Overall evaluations of carcinogenicity: An updating of IARC monographs, volumes 1 to 42. Lyon, International Agency for Research on Cancer (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 7).

Imming RJ, Shaffer BC, & Woodard G (1969) Sevin, safety evaluation by feeding to female Beagles from day one of gestation through weaning of the offspring. (Prepared by Woodard Research Corporation for Union Carbide Agricultural Products Co., Inc., Research Triangle Park) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Innes JRM, Ulland MB, Valerio MG, Petrucel L, Fishbein L, Hart ER, Pallotta AJ, Bates RR, Falk HL, Gart JJ, Klein M, Mitchell I, & Peters H (1969) Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. J Natl Cancer Inst, **42**: 1101-1114.

IRPTC (1982) In: Izmerov NF ed. IRPTC scientific reviews of Soviet literature on toxicity and hazard of chemicals No. 7: Carbaryl. Moscow, Centre of International Projects, GKNT, 13 pp.

IRPTC (1989) In: Izmerov NF ed. [Scientific reviews of Soviet literature on toxicity and hazard of chemicals No. 7: Carbaryl], 2nd ed. Moscow, Centre of International Projects, GKNT, 82 pp (in Russian).

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

Ishidate M Jr, Sofuni T, & Yoshikawa K (1981) Chromosomal aberration tests *in vitro* as a primary screening tool for environmental mutagens and/or carcinogens. Gann Monogr Cancer Res, **27**: 95-108.

Ivanova LN & Molozhanova YG (1973) [Static and dynamic distribution of carbaryl in the environment.] Gig i Sanit, **38**(2): 24-28 (in Russian).

Iwata Y, Dusch ME, Garman GE, & Gunther FA (1979) Worker environment research: Residues for carbaryl, chlorobenzilate, dimethoate and trichlorfon applied to citrus trees. J Agric Food Chem, **27**(6): 1141-1145.

Jablonska J & Brzezinski J (1990) The influence of carbaryl on the uptake of (3H) noradrenaline (3H) NA by rat hypothalamic slices. Arch Toxciol, **64**(5): 417-419.

Jacob J, Schmoldt A, Raab J, Hamman M, & Grimmer G (1985) Monoxygenase induction by various xenobiotics and its influence on the rat liver microsomal metabolite profile of benza(a)anthracene. Cancer Lett, **27**: 105-113.

Jaszczuk E & Syrowatka T (1979) [Induction of mitotic conversion in *Saccharomyces cerevisiae* D4 with propoxur, carbaryl, dimethylnitrosamine and products of their metabolic activation.] Rocz Panstw Zakl Hig, **30**(4): 323-330 (in Polish).

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

Jegier Z (1964) Health hazards in insecticide spraying of crops. Arch Environ Health, **8**: 670-674.

Jeleniewicz KK & Szczepaniak St (1980) [Free aminoacids and amino nitrogen levels in serum and blood erythrocytes of rat exposed to subacute intoxication with carbaryl.] Bromatol Chem Toksykol, **13**(3): 237-240 (in Polish).

Jeleniewicz KK, Szczepaniak St, & Slenkiewicz E (1984) [Effect of acute intoxication with carbaryl on brain free aminoacids level in rat.] Bromatol Chem Toksykol, **17**(3): 225-227 (in Polish).

Jerkofsky M & Abrahamsen LH (1983) Variation on human herpes virus susceptibility to enhancement by the pesticide carbaryl. Appl Environ Microbiol, **45**(5): 1555-1559.

Johnson WW & Finley MT (1980) Handbook of acute toxicity of chemicals to fish and aquatic invertebrates. Washington, DC, US Department of the Interior, Fish and Wildlife Service (Resource Publication 137).

Johnson RD & Manske DD (1976) Pesticide residues in total diet samples (IX). Pestic Monit J, **9**(4): 157-169.

Johnson DP & Stansbury HA (1965) Adaptation of Sevin insecticide (carbaryl) residue method to various crops. J Agric Food Chem, **13**: 235-238.

Junk GA, Richard JJ, & Dahm PA (1984) Degradation of pesticides in controlled water-soil systems (treatment and disposal of pesticides wastes). Washington, DC, American Chemical Society, pp 37-67 (ACS Symposium Series No. 259).

Kadir HA & Knowles CO (1981) Inhibition of rat brain monoamine oxidase by insecticides, acaricides and related compounds. Gen Pharmacol, **12**(4): 239-247.

Kagan J, Rodionov G, Voronina L, Velitsco L, Kulagin O, & Peremitina A (1970) [Effect of Sevin on liver function and structure.] Pharmacol Toxicol, **33**: 219-224 (in Russian with English summary).

Kaloyanova F (1963) [Changes in the blood sugar in cases of intoxications with certain phosphorus organic compounds.] In: [Works of the Scientific Research Institute on Work Safety and Occupational Diseases - Volume X.] Sofia, Institute of Hygiene and Occupational Health, pp 63-67 (in Bulgarian).

Kanazawa J (1975) Uptake and excretion of organophosphorus and carbamate insecticides by freshwater fish, Motsugo, *Pseudorasbora parva*. Bull Environ Contam Toxicol, **14**(3): 346-352.

Kanazawa J (1981) Measurement of the bioconcentration factors of pesticides by freshwater fish and their correlation with physicochemical properties or acute toxicities. Pestic Sci, **12**(4): 417-424.

Kanazawa J, Isensee AR, & Kearney PC (1975) Distribution of carbaryl and 3,5-xylylmethyl carbamate in an aquatic model ecosystem. J Agric Food Chem, **23**(4): 760-763.

Karinen FJ, Lamberton JG, Stewart NE, & Terrier LC (1967) Persistence of carbaryl in the marine estuarine environment. J Agric Food Chem, **15**(1): 148-156.

Karnak RE & Collins WJ (1974) The susceptibility to selected insecticides and acetylcholinesterase activity in a laboratory colony of midge larvae, *Chironomus tentans* (Diptera: chironomidae). Bull Environ Contam Toxicol, **12**: 62-69.

Kassin VJ (1968) [Structural changes in endocrine organs under repeated action of Sevin.] Gig Primen Toxicol Pestic Klin Otrav, **1968**: 631-635 (in Russian).

Kaur K & Toor HS (1977) Toxicity of pesticides to embryonic stages of *Cyprinus carpio communis* Linn. Indian J Exp Biol, **15**: 193-196.

Kavadia VS, Gangwar SK, Srivastava BP, Kathpal TS, & Gupta HCL (1978) Persistence of carbaryl in clay loam soil and its uptake in maize and root crops. Indian J Entomol, **40**(3): 265-272.

Kavlock RJ, Short RD, & Chernoff N (1987) Further evaluation of an *in vivo* teratology screen. Teratog Carcinog Mutagen, **7**: 7-16.

Kazano H, Kearney PC, & Kaufman DD (1972) Metabolism of methylcarbamate insecticides in soil. J Agric Food Chem, **20**(5): 975-979.

Kazarnovskaya ML & Vasilos AF (1977) [The effect of Sevin on chromosomal apparatus of cells *in vitro*.] Zdravookhranenije, **20**(4): 14-16 (in Russian).

Kendrick PN, Trim AJ, Atwal JK, & Brown PM (1991) Direct gas chromatographic determination of carbaryl residues in honeybees (*Apis mellifera* L.) using a nitrogen-phosphorus detector with confirmation by formation of a chemical derivative. Bull Environ Contam Toxicol, **46**: 654-661.

Khasawinah AM (1977) Hydrolysis of carbaryl in aqueous buffer solutions (Project No. 111A12, File No. 23092). South Charleston, West Virginia, Union Carbide Corporation (Prepared in cooperation with the International Research and Development Corporation) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Khasawinah AM (1978) Fate of carbaryl in soils (Project No. 285). Monument, Colorado, Analytical Development Corporation (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Khera K (1966) Toxic and teratogenic effects of insecticides in duck and chick embryos. Toxicol Appl Pharmacol, **8**: 345.

Klisenko MA (1965) [Determination of Sevin in air and biological material.] J Anal Chim, **XX**(5): 634-636 (in Russian).

Klisenko MA & Yakim VS (1966) [Accumulation and excretion of Sevin from the body of warm-blooded animals.] Gig Primen Toxicol Pestic Klin Otrav, **1966**: 146-149 (in Russian).

Klisenko MA, Lebedeva TA, & Yurkova ZF (1972) [Chemical analysis of micro amounts of pesticides.] Moscow, Medizina, pp 197-201 (in Russian).

Knaak JB (1971) Biological and nonbiological modifications of carbamates. Bull World Health Organ, **44**: 121-131.

Knaak JB & Sullivan LJ (1967) Metabolism of carbaryl in dog. J Agric Food Chem, **15**(6): 1125-1126.

Knaak JB, Marilyn J, Tallant MJ, Bartley WJ, & Sullivan LF (1965) The metabolism of carbaryl in rat, guinea-pig, and man. J Agric Food Chem, **13**(6): 537-543.

Knaak JB, Tallant MJ, Kozbelt SJ, & Sullivan LJ (1968) The metabolism of carbaryl in man, monkey, pig, and sheep. J Agric Food Chem, **16**(3): 465-470.

Knaak JB, Yee K, Ackerman CR, Zweig G, Fry DM, & Wilson BW (1984) Percutaneous absorption and dermal dose - ChE response studies with parathion and carbaryl in the rat. Toxicol Appl Pharmacol, **76**: 252-263.

Knight EV, Chin BH, Ueng TH, & Alvares AP (1986) Differences in the *in vivo* and *in vitro* effects of the carbamate insecticide, carbaryl on rat hepatic monooxygenases. Drug Chem Toxicol, **9**(3-4): 253-273.

Knight EV, Alvares AP, & Chin BH (1987) Effects of phenobarbital pre-treatment on the *in vivo* metabolism of carbaryl in rats. Bull Environ Contam Toxicol, **39**(5): 815-821.

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

Koundinya PR & Ramamurthi R (1980) Toxicity of Sunithion and Sevin to the freshwater fish *Sarotherodon mossambicus* (Peters). Curr Sci, **49**: 875-876.

Kovaleva ES & Talanov GA (1978a) [Methods for determination of Sevin in soil and plants by means of thin-layer chromatography.] Gig i Sanit, 7: 69-70 (in Russian).

Kovaleva ES & Talanov GA (1978b) [Residual amounts of Sevin in plants and soil.] Khim Sel'sk Khoz, **16**(8): 77-79 (in Russian).

Kovaleva ES & Talanov GA (1980) [Plant and soil dynamics of Sevin residues and dithiocarbamic acid derivatives.] In: Bobovnikova TI & Malakhov SG ed. [Migration of contaminants in soil and contiguous media. Proceedings of the All-Union Congress, 2nd Meeting, 1978.] Leningrad, Gidrometeoizdat, pp 155-159 (in Russian).

Kovtun SD (1970) Analysis of the action exerted by Sevine on the myoneural formations. Pharmacol Toxicol, **35**(5): 543-545.

Kovtun SD & Sokur AI (1970) [The effect of Sevin on the spontaneous electrical activity of myoneural synaps and permeability

of the membrane of skeletal muscle in white rats.] Gig Primen Toxicol Pestic Klin Otrav, **1970**: 211-214 (in Russian).

Krause RT (1985a) Pesticide and industrial chemical residues. Liquid chromatographic determination of *N*-methylcarbamate insecticides and metabolites in crops. I. Collaborative study. J Assoc Off Anal Chem, **68**(4): 726-733.

Krause RT (1985b) Liquid chromatographic determination of *N*-methylcarbamate insecticides and metabolites in crops. II. Analytical characteristics and residue findings. J Assoc Off Anal Chem, **68**(4): 734-740.

Krechniak V & Foss W (1981) Gas chromatography determination of carbaryl. Pr Cent Inst Ochr Pr, **XXXI**(110): 183-188.

Krishna JG & Casida JE (1966) Fate in rats of the radiocarbon from ten variously labelled methyl- and dimethylcarbamate-C^{14} insecticide chemicals and their hydrolysis products. J Agric Food Chem, **14**(2): 98-105.

Krishna JG, Dorough HW, & Casida JE (1962) Synthesis of *N*-methylcarbamates via methyl isocyanate-C^{14} and chromatographic purification. J Agric Food Chem, **10**(6): 462-466.

Krishnaih K, Prasad VG, & Jagan Mohan N (1978) Carbaryl residues on brinjal and peas. In: Edwards CA, Veeresh GK, & Krueger HR ed. Proceedings of the Symposium on Pesticide Residues in the Environment in India, 7-10 November 1978. Hebbal, Bangalore, University of Agricultural Sciences, pp 229-231 (UAS Technical Series No. 32).

Krug HG & Berndt J (1985) Inhibition by pesticides of prostglandin formation in blood platelets. Blut, **51**: 19-23.

Krug HF, Hamm U, & Berndt J (1988) Mechanism of inhibition of cyclo-oxygenase in human blood platelets by carbamate insecticides. Biochem. J, **250**(1): 103-110.

Krylov DG (1970) [The effect of Sevin on red vole population.] Gig Primen Toxicol Pestic Klin Otrav, **1970**: 218-110 (in Russian).

Kuhn JO (1991a) Acute oral toxicity study in rats with Sevin XLR plus. Sugar Land, Texas, Stillmeadow, Inc. (Laboratory Study No. IV 8150-91) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Kuhn JO (1991b) Sevin-4-oil 47.0% (w/w). Acute oral toxicity study in rats . Sugar Land, Texas, Stillmeadow, Inc. (Laboratory Study No. N 7712-90) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Kuhr RJ (1970) Metabolism of carbamate insecticide chemicals in plants and insects. J Agric Food Chem, **18**(6): 1023-1030.

Kuhr RJ (1971) The formation and importance of carbamate insecticide metabolites as terminal residues. Pure Appl Chem, **Suppl**: 199-220.

Kuhr RJ & Dorough HW (1976) Carbamate insecticides: Chemistry, biochemistry and toxicology. Cleveland, Ohio, CRC Press, Inc., pp 125-200.

Kuhr RJ, Davis AC, & Bourke JB (1974) Dissipation of Guthion, Sevin, Polyram, Phygon and Systox from apple orchard soil. Bull Environ Contam Toxicol, **11**(3): 224-230.

Kulshrestha SK & Arora N (1984) Impairments induced by sublethal doses of two pesticides in the ovaries of a freshwater teleost *Channa striatus* Bloch. Toxicol Lett, **20**(1): 93-98.

Kuribayashi S (1981) Studies on the effect of pesticides on the reproduction of the silkworm, *Bombyx Mori* L. I. Effects of chemicals administered during the larval stage on egg-laying and hatching. J Toxicol Sci, **6**: 169-176.

Kurtz DA & Studholme GA (1974) Recovery of trichlorfon (Dylox) and carbaryl (Sevin) in songbirds following spraying of forest for Gipsy moth. Bull Environ Contam Toxicol, **11**(1): 78-84.

Kuzminskaya UA, Ivanitskij VA, & Shilina VA (1984) [The influence of pesticides having anticholinesterase effect upon the

content of biogenic amines in brain.] Gig i Sanit, **5**: 80-81 (in Russian).

LaFleur KS (1976a) Carbaryl desorption and movement in soil columns. Soil Sci, **121**(4): 212-216.

LaFleur KS (1976b) Movement of carbaryl through Congaree soil into ground water. J Environ Qual, **5**(1): 91-92.

Lahmy S, Salmon JM, & Viallet P (1988) Influence of long-term treatment with 3 methylcholanthrene or carbaryl on mixed function oxidase activity in 3T3 fibroblasts: studies by microspectrofluorimetry on single cells. Cell Biochem Funct, **6**(4): 275-282.

Lamb FC, Farrow RP, Elkins ER, Kimball JR, & Cook RW (1968) Removal of DDT, parathion and carbaryl from spinach by commercial and home preparative methods. J Agric Food Chem, **16**: 967-973.

Lamberton JG & Claeys RR (1970) Degradation of 1-naphthol in sea water. J Agric Food Chem, **18**(1): 92-96.

Larkin MJ & Day MJ (1985) The effect of pH on the selection of carbaryl- degrading bacteria from garden soil. J Appl Bacteriol, **58**(2): 175-186.

Larkin MJ & Day MJ (1986) The metabolism of carbaryl by three bacterial isolates, *Pseudomonas* spp. (NCIB 12042 & 12043) and *Rodococcus* sp. (NCIB 12038) from garden soil. J Appl Bacteriol, **60**(3): 233-242.

Lawlor TE (1989) Mutagenicity test on carbaryl (technical) in the Ames Salmonella/Microsome reverse mutation assay. Final report. Kensington, Maryland, Hazleton Laboratories America, Inc. (Report No. 10862-0-401) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Leavitt JRC, Gold RE, Holcslaw T, & Tupy D (1982) Exposure of professional pesticide applicators to carbaryl. Arch Environ Contam Toxicol, **11**(1): 57-62.

Lechner DMW & Abdel-Rahman MS (1984) A teratology study of carbaryl and malathion mixtures in rat. J Toxicol Environ Health, **14**: 267-278.

Lechner DMW & Abdel-Rahman MS (1985) Alterations in rat liver microsomal enzymes following exposure to carbaryl and malathion in combination. Arch Environ Contam Toxicol, **1**: 451-457.

Lechner DMW & Abdel-Rahman MS (1986a) The effect of carbaryl and malathion in combination on gamma glutamyl transpeptidase and glutathione-*S*-alkyltransferase activity *in vitro*. Arch Environ Contam Toxicol, **15**(6): 647-651.

Lechner DMW & Abdel-Rahman MS (1986b) Kinetics of carbaryl and malathion in combination in the rat. J Toxicol Environ Health, **18**(2): 241-256.

Lee RM & Brindley WA (1974) Synergist ratios, EPN detoxication, lipid and drug-induced changes in carbaryl toxicity in *Megachile pacifica*. Environ Entomol, **3**: 899-907.

Lee DY, Chen CT, & Houng KH (1990) Behaviour assessment of eight major pesticides used in Taiwan in soils by mechanistic models. In: Soils and fertilizers in Taiwan, pp 33-50.

Leeling NC & Casida JE (1966) Metabolites of carbaryl (1-naphthyl methyl carbamate) in mammals and enzymatic systems for their formation. J Agric Food Chem, **14**(3): 281-290.

Leenheer JA & Ahlrichs (1971) A kinetic and equilibrium study of the adsorption of carbaryl and parathion upon soil organic matter surfaces. Soil Sci Soc Am Proc, **35**: 700-705.

Lejczak B (1977) Effect of insecticides: chlorfenvinphos, carbaryl and propoxur on aquatic organisms. Pol Arch Hydrobiol, **24**(4): 583-591.

Leonard JA & Yearly RA (1990) Exposure of workers using hand-held equipment during urban application of pesticides to trees and ornamental shrubs. Am Ind Hyg Assoc J, **51**: 605-609.

Lesca P, Fournier A, Lecointe P, & Cresteil T (1984) A dual assay for the specific screening of 3 methylcholanthrene and phenobarbital like chemical inducers of cytochrome P450 monooxygenases. Mutat Res, **129**: 229-310.

Lijinsky W & Schmähl D (1978) Carcinogenicity of *N*-nitroso derivatives of *N*-methylcarbamate insecticides in rats. Ecotoxicol Environ Saf, **2**: 413-419.

Lijinsky W & Taylor HW (1976) Carcinogenesis in Sprague-Dawley rats on *N*- nitroso-*N*-alkylcarbamate esters. Cancer Lett, **1**: 275-279.

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

Lijinsky W & Winter C (1981) Skin tumours induced by painting nitrosoalkylureas on mouse skin. J Cancer Res Clin Oncol, **102**: 13-20.

Lillie RJ (1973) Studies on the reproductive performance and progeny performance of caged white leghorns fed malathion and carbaryl. Poult Sci, **52**: 266-272.

Lin TH, North HH, & Menzer RE (1975) Metabolism of carbaryl (1-naphthyl *N*-methylcarbamate) in human embryonic lung cell cultures. J Agric Food Chem, **23**(2): 253-256.

Lindsay CE (1961) Pesticide tests in the marine environment in the State of Washington. Proc Natl Shellfish Assoc, **52**: 87-97.

Lingaraja T & Venugopalan UK (1978) Pesticide induced physiological and behavioural changes in an estuarine teleost *Therapon jarbua* (Forsk). Fish Technol, **15**: 115-119.

Little EE, Archeski RD, Flerov BA, & Kozlovskaya VI (1990) Behavioral indicators of sublethal toxicity in rainbow trout. Arch Environ Contam Toxicol, **19**(3): 380-385.

Liu SY & Bollag JM (1971a) Metabolism of carbaryl by a soil fungus. J Agric Food Chem, **19**(3): 487-490.

Liu SY & Bollag JM (1971b) Carbaryl decomposition to 1-naphthyl carbamate by *Aspergillus terreus*. Pestic Biochem Physiol, **1**(3-4): 366-372.

Liu D, Thomson K, & Strachan WMJ (1981) Biodegradation of carbaryl in simulated aquatic environment. Bull Environ Contam Toxicol, **27**(3): 412-417.

Long KR (1971) Pesticides and occupational hazards on farms. Am J Nurs, **71**(4): 740-743.

Looney NE & Knight JN (1985) Effects of initial set and carbaryl treatment in final fruit set on "Greensleeves" apple. Hortic Sci, **20**(3): 400-401.

Looney NE & McKellar JE (1984) Thinning Spartan apples with carbaryl and 1-napthaleneacetic acid: influence of spray volume and combinations of chemicals. Can J Plant Sci, **64**: 161-166.

Loosanoff VL (1961) Recent advances in the control of shellfish predators and competitors. Proc Gulf Caribb Fish Inst, **13**: 113-128.

Loosanoff VL, MacKenzie CL Jr, & Shearer LW (1960a) Use of chemical barriers to protect shellfish beds from predators. In: Fisheries: Fish farming. Volume 3 - Fisheries management. Olympia, Washington, Washington State Department of Fisheries, pp 86-90.

Loosanoff VL, MacKenzie CL Jr, & Shearer LW (1960b) Use of chemical to control shellfish predators. Science, **131**: 1522-1523.

Lowe JI (1967) Effect of prolonged exposure to Sevin on an estuarine fish, *Leiostomus xanthurus* Lacépède. Bull Environ Contam Toxicol, **2**(3): 147-155.

Lox CD (1984) The effects of acute carbaryl exposure on clotting factor activity in rat. Ecotoxicol Environ Saf, **8**: 280-283.

Luca D & Balan M (1987) Sperm abnormality assay in the evaluation of the genotoxic potential of carbaryl in rats. Morphol Embryol (Bucur), **33**(1): 19-22.

Lucier GW, McDaniel OS, Williams C, & Klein R (1972) Effects of chlordane and methylmercury on the metabolism of carbaryl and carbofuran in rats. Pestic Biochem Physiol, 2: 244-255.

Lukaneva AM & Rodionov GA (1973) [Some experimental data on the effect of DDT and Sevin upon the development of cholesterin atherosclerosis.] Gig i Sanit, 9: 41-45 (in Russian).

Luke MA, Masumoto HT, Cairns T, & Hundley HK (1988) Levels and incidences of pesticide residues in various foods and animal feeds analyzed by the Luke multiresidue methodology for fiscal years 1982-1986. J Assoc Off Anal Chem, 71(2): 415-420.

Lykken L & Casida JE (1969) Metabolism of organic insecticide chemicals. Can Med Assoc J, 100: 145-154.

Ma TH, Harris MM, Anderson VA, Ahmed I, Mohammed K, Bare JL, & Lin G (1984) Tradescantia-Micronucleus (Trad-MCN) tests on 140 health-related agents. Mutat Res, 138: 157-167.

McCann J, Choi E, Yamasaki E, & Ames BM (1975) Detection of carcinogen as mutagens in the *Salmonella*/microsome test: Assay of 300 chemicals. Proc Natl Acad Sci (USA), 72(12): 5135-5139.

MacCollom GB, Currier WW, & Baumann GL (1985) Pesticide drift and quantification from air and ground applications to a single orchard site. In: Honeycutt RC, Zweg D, & Ragsdale N ed. Dermal exposure related to pesticide use. Washington, DC, American Chemical Society, pp 190-198 (ACS Symposium Series No. 273).

MacCollom GB, Currier WW, & Baumann GL (1986) Drift comparisons between aerial and ground orchard application. J Econ Entomol, 79(2): 459-464.

Macek KJ & McAllister WA (1970) Insecticide susceptibility of some common fish family representatives. Trans Am Fish Soc, 99(1): 20-27.

MacLeod J (1982) Report on UCC sperm morphology readings submitted to Union Carbide Agricultural Products Co., Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

MacPherson SE, Scott RC, & Williams FM (1991) Fate of carbaryl in rat skin. Arch Toxicol, **65**: 594-598.

Maibach HI, Feldmann RJ, Milby TH, & Serat WF (1971) Regional variations in percutaneous penetration in man - Pesticides. Arch Environ Health, **23**: 208-211.

Makovskaya EL, Rapoport MB, & Pintshuk VG (1965) [On the possibility of carcinogenic effect of some insecticides belonging to the carbamate group.] Vopr Exp Onkol, **1**: 67-74 (in Russian).

Maliwal BP & Guthrie FE (1981) Interaction of insecticides with human plasma lipoproteins. Chem-Biol Interact, **35**(2): 177-188.

Mann GS & Chopra SL (1969) Residues of carbaryl on crops. Pestic Monit J, **2**(4): 163-165.

Manske DD & Corneliussen PE (1974) Pesticides in food and feed. Pesticide residues in total diet samples (VII). Pestic Monit J, **8**(2): 110-124.

Manske DD & Johnson RD (1975) Residues in food and feed. Pesticide residues in total diet samples (VIII). Pestic Monit J, **9**(2): 94-105.

Manske DD & Johnson RD (1977) Residues in food and feed. Pesticide and other chemical residues in total diet samples (X). Pestic Monit J, **10**: 134-148.

Marian MP, Arul V, & Pandian TJ (1983) Acute and chronic effect of carbaryl on survival, growth, and metamorphosis in the bullfrog (*Rana tigrina*). Arch Environ Contam Toxicol, **12**(3): 271-275.

Marshall TC, Dorough HW, & Swin HE (1976) Screening of pesticides for mutagenic potential using *Salmonella typhimurium* mutants. J Agric Food Chem, **24**(3): 500-563.

Marshall TC, Dorough HW, & Swin HE (1979) Biliary excretion of carbamate insecticides in the rat. Pestic Biochem Physiol, **11**: 56-63.

Mason Y, Choshen E, & Rav-Acha C (1990) Carbamate insecticides: Removal from water by chlorination and ozonation. Water Res, **24**(1): 11-22.

Mastro VC & Cameron EA (1976) Control of *Archips semiferanus* on *Quercus*, spp with two chemical insecticides. J Econ Entomol, **69**(4): 554-556.

Mathur A & Bhatnagar P (1991) A teratogenic study of carbaryl in Swiss albino mice. Food Chem Toxicol, **29**(9): 629-632.

Matsumura F & Sakai K (1968) Degradation of insecticides by esterases of the American cockroach. J Econ Entomol, **61**(3): 598-605.

Matsumura F & Ward CT (1966) Degradation of insecticides by the human and the rat liver. Arch Environ Health, **13**: 257-261.

Mayer FL Jr (1987) Acute toxicity handbook of chemicals to estuarine organisms. Gulf Breeze, Florida, US Environmental Protection Agency, Gulf Breeze Laboratory (EPA 600/8-87/017).

Mayer FL & Ellersieck MR (1986) Manual of acute toxicity: Interpretation and data base for 410 chemicals and 66 species of freshwater animals. Washington, DC, US Department of the Interior, Fish and Wildlife Service (Resource Publication 160).

Mehendale HM & Dorough HW (1971) Glucuronidation mechanisms in the rat and their significance in the metabolism of insecticides. Pestic Biochem Physiol, **1**: 307-318.

Mellon Institute (1958) Acute toxicity of carbaryl. Pittsburgh, Pennsylvania, Mellon Institute (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Mellon Institute (1963) Results of the eighty weeks of inclusion of Sevin in the diet of mice. Pittsburgh, Pennsylvania, Mellon Institute, pp 1-12 (Special report No. 26-53) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Menzie CM (1969) Metabolism of pesticides. Washington, DC, US Department of the Interior, Bureau of Sport Fisheries and Wildlife, pp 72-76 (Special Scientific Report, Wildlife No. 127).

Miles CJ, Trehy ML, & Yost RA (1988a) Degradation of *N*-methylcarbamate and carbamoyl oximes pesticides in chlorinated water. Bull Environ Contam Toxicol, **41**(6): 838-843.

Miles CJ, Trehy ML, & Yost RA (1988b) Fate of pesticides in chlorinated water. Paper presented at the 195th Meeting of the American Chemical Society. Washington, DC, American Chemical Society (Abstract ENVR 139).

Miller NE (1990) Metabolism of C^{14}-carbaryl under aerobic soil conditions. Research Triangle Park, North Carolina, Rhône-Poulenc Ag Company (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Miller A III, Henderson MC, & Buhler DR (1979) Covalent binding of carbaryl (1-naphthyl-*N*-methylcarbamate) to rat liver microsome *in vitro*. Chem-Biol Interact, **24**: 1-17.

Molozhanova EG (1968) [Circulation of Sevin in compartments of the environment.] Gig Primen Toxicol Pestic Klin Otrav, **1968**: 355-362 (in Russian).

Molozhanova EG (1970) [Factual content of Sevin in compartments of the environment and quantities of the formulation apt at getting into human organism.] Gig Primen Toxicol Pestic Klin Otrav, **1970**: 170-174 (in Russian).

Molozhanova EG & Kanevskij AA (1971) [Application of mathematical analysis to modelling the behaviour of Sevin in soil.] Gig Primen Toxicol Pestic Klin Otrav, **1971**: 77-83 (in Russian).

Moreynis JA & Estrin IM (1965) [Sevin action on animals infected with the virus of influenza.] Gig Primen Toxicol Pestic Klin Otrav, **1965**: 435-442 (in Russian).

Moriya M, Ohta T, Watanabe K, Miyazawa T, Kato K, & Shirasu Y (1983) Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res, **116**: 185-216.

Moser VC, McCormick JP, Creason JP, & MacPhail RC (1988) Comparison of chlordimeform and carbaryl using a functional observational battery. Fundam Appl Toxicol, **11**(2): 189-206.

Mount ME & Oehme FW (1981a) Carbaryl. A literature review. Residue Rev, **80**: 1-64.

Mount ME & Oehme FW (1981b) Diagnostic criteria for carbaryl poisoning in sheep. Arch Environ Contam Toxicol, **10**(4): 483-495.

Mount ME, Dayton AD & Oehme FW (1981) Carbaryl residues in tissues in cholinesterase activities in brain and blood of rats receiving carbaryl. Toxicol Appl Pharmacol, **58**(2): 282-296.

Mumma RO, Khalifa S, & Hamilton RH (1971) Spectroscopic identification of metabolites of carbaryl in plants. J Agric Food Chem, **19**(3): 445-451.

Murli H (1989) Mutagenicity test on carbaryl technical in an *in vitro* cytogenetic assay measuring chromosomal aberration frequencies in Chinese hamster ovary (CHO) cells. Kensington, Maryland, Hazleton Laboratories America, Inc. (Report No. 10862-0-437) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Murray HE & Guthrie RK (1980) Effects of carbaryl, diazinon and malathion on native aquatic populations of microorganisms. Bull Environ Contam Toxicol, **24**: 535-542.

Murray FJ, Staples RE, & Schwets BA (1979) Teratogenic potential of carbaryl given to rabbits and mice by gavage or by dietary inclusion. Toxicol Appl Pharmacol, **51**: 81-89.

Murthy NBK & Raghu K (1988) Soil bound residues of carbaryl and 1-naphthol: release and mineralization in soil, and uptake by plants. J Environ Sci Health, **B23**(6): 575-585.

Murthy NBK & Raghu K (1989) Metabolism of ^{14}C-carbaryl and ^{14}C-naphthol in moist and flooded soils. J Environ Sci Health, **B24**(5): 479-491.

Murthy NBK & Raghu K (1991) Fate of ^{14}C-carbaryl in soils as a function of pH. Bull Environ Contam Toxicol, **46**(3): 374-379.

Myers WF (1977) Carbaryl insecticide. Estimation of carbaryl exposure to humans. South Charleston, West Virginia, Union Carbide Corporation (Project Report No. 111A12) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Myers RC & Christopher SM (1987) Sevin technical dermal sensitization study in the guinea-pig (Project No. ID-49-146). Export, Pennsylvania, Bushy Run Research Center (Proprietary report submitted to WHO by Rhône-Poulenc Agro, Lyon).

Myers RC, Weil CS, & Carpenter CP (1975) Sevin liquid, 44% carbaryl, range-finding toxicity studies. Pittsburgh, Pennsylvania, Carnegie-Mellon Research Institute (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Myhr S (1973) A screen for pesticide toxicity to protein and RNA synthesis in HeLa cells. J Agric Food Chem, **21**(3): 362-367.

Nagy Z, Mile I, & Antony F (1975) Mutagenic effect of pesticides on *Escherichia coli* WP2 try. Acta Microbiol Acad Sci Hung, **22**: 309-314.

Neskovic N, Terzic M, & Vitorovic S (1978) [Acute toxicity of carbaryl and propoxur in mice previously treated with phenobarbital and SKF-525-A.] Arh Hig Rada, **29**: 251-256 (in Croatian).

Neuhauser EF, Loehr RC, Malecki MR, Milligan DL, & Durkin PR (1985) The toxicity of selected organic chemicals to the earthworm *Eisenia fetida*. J Environ Qual, **14**(3): 383-388.

Nimmo DR, Hamaker TL, Matthews E, & Moore JC (1981) An overview of the acute and chronic effects of first and second generation pesticides on an estuarine Mysid. In: Vernberg FJ, Calabrese A, Thurberg FP, & Vernberg WB ed. Biological monitoring of marine pollutants. New York, Academic Press, Inc., pp 3-19.

NIOSH (1976) Criteria for a recommended standard ... Occupational exposure to carbaryl. Cincinnati, Ohio, National Institute for Occupational Safety and Health, 191 pp (DHEW (NIOSH) Publication No. 77-107).

Norris FA 1991) A terrestrial field soil dissipation study with carbaryl (Study No. EC 89-080, File No. 40862). Research Triangle Park, North Carolina, Rhône-Pouienc Ag Company (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Nye DE & Dorough HW (1976) Fate of insecticides administered endotracheally to rats. Bull Environ Contam Toxicol, **15**(3): 291-296.

Odeyemi O (1982) Relative stability of carbaryl in tropical ecosystems. Environ Pollut, **A29**(3): 207-213.

Okumura D, Melnicoe R, Jackson T, Drefs C, Maddy K, & Wells J (1991) Pesticide residues in food crops analyzed by the California Department of Food and Agriculture in 1989. Rev Environ Contam Toxicol, **118**: 87-150.

Olefir AI (1977) [Effects of pesticides on immunogenesis.] Vrach Delo, **9**: 121-123 (in Russian).

Olefir AI & Vinogradova VKh (1968) [A study of the embryotropic effect of the pesticides Sevin and Zyram.] Vrach Delo, **11**: 103-106 (in Russian).

Omer AA, Youssef MK, Abou-Youssef AY, & Khalil AM (1986) Mutagenicity of insecticide Sevin and its derivative nitrosocarbaryl on *D. melanogaster*. Alex J Agric Res, **31**(3): 239-248.

Omkar & Shukla GS (1985) Toxicity of insecticides to *Macrobrachium lamarrei* (H. Milne Edwards) (Decapoda, Palaemonidae). Crustaceana, **48**: 1-5.

Önfelt A (1987) Spindle disturbances in mammalian cells. III. Toxicity, c-mitosis and aneuploidy with 22 different compounds. Specific and unspecific mechanisms. Mutat Res, **182**: 135-154.

Önfelt A & Klasterska I (1983) Spindle disturbances in mammalian cells. II. Induction of viable aneuploid/polyploid cells and multiple chromatid exchanges after treatment of V-70 Chinese hamster cells with carbaryl. Modifying effects of glutathion and S9. Mutat Res, **119**: 319-330.

Önfelt A & Klasterska I (1984) Sister chromatid exchanges and thioguanine resistance in V79 Chinese hamster cells after treatment with the aneuploidy inducing agent carbaryl +/ S9 mix. Mutat Res, **125**: 269-274.

Oonnithan ES & Casida JE (1968) Oxidation of methyl- and dimethylcarbamate insecticide chemicals by microsomal enzymes and anticholinesterase activity of the metabolites. J Agric Food Chem, **18**(1): 28-44.

Orlova NV & Zhalbe EP (1968) [Experimental material contributive to the problem of maximal permissible amounts of Sevin in food products.] Vopr Pitan, **27**(6): 49-55 (in Russian).

Orzel RA & Weiss LR (1966) The effect of carbaryl (1-naphthyl-*N*-methylcarbamate) on blood glucose, and liver and muscle glycogen in fasted and nonfasted rats. Biochem Pharmacol, **15**: 995-998.

Osborne BG, Barrett GM, Laal-Khoshab A, & Willis KH (1989) The occurrence of pesticide residues in UK home-grown and imported wheat. Pestic Sci, **27**: 103-109.

Osman MA & Belal MH (1980) Persistence of carbaryl in canal water. J Environ Sci Health, **B15**(3): 307-311.

Osman DH & Brindley WA (1981) Estimating monoxygenase detoxification in field populations: toxicity and distribution of carbaryl in three species of *Labops* grassbugs. Environ Entomol, **10**(5): 676-680.

Osterloh J, Letz G, Pond S, & Becker Ch (1983) An assessment of the potential testicular toxicity of 10 pesticides using the mouse sperm morphology assay. Mutat Res, **116**(3-4): 407-415.

Ott FT, McCullogh R, & Stanley JG (1981) Effects of forest spraying on the ecology of brook trout. Report to the Maine Department of Conservation, Forest Service, Augusta.

Owen BB Jr (1965) Aquatic insect populations reduced by aerial spraying of insecticide Sevin. Philadelphia, Pennsylvania, Pennsylvania Academy of Science, pp 63-69.

Page M, Haverty MJ, & Richmond ChE (1985) Residual activity of carbaryl protected Lodgepole Pine against Mountain Pine Beetle, Dillon, Colorado, 1982 and 1983. Berkeley, California, US Department of Agriculture, Forest Service, Pacific Southwest Forest and Range Experiment Station (Research Note PSW-375).

Panciera RJ (1967) Determination of teratogenic properties of orally administrated 1-naphthyl-*N*-methylcarbamate (Sevin) in sheep. Research Triangle Park, North Carolina, Union Carbide Agricultural Products Co., Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Parafita MA & Fernandez-Otero P (1984) The interaction of carbaryl with the metabolism of isolated hepatocytes. II. Effect on glycogenesis. Gen Pharmacol, **15**(4): 333-337.

Parafita MA, Fernandez-Otero P, & Aldegunde MA (1984) The interaction of carbaryl with the metabolism of isolated hepatocytes. I. Effect on respiration and glycolysis. Gen Pharmacol, **15**(4): 327-331.

Paris DF & Lewis DL (1973) Chemical and microbiological degradation of ten selected pesticides in aquatic system. Residue Rev, **45**: 95-124.

Paris D, Lewis D, Barnett J, & Baugham G (1975) Microbial degradation and accumulation of pesticides in aquatic systems. Corvallis, Oregon, US Environmental Protection Agency, Office of Research and Development, National Environmental Research Center, pp 1-45 (EPA-660/3-75-007).

Patocka JJ & Bajgar J (1971) Affinity of human brain acetylcholinesterase to some organophosphates and carbamates *in vitro*. J Neurochem, **18**: 2545-2546.

Paulson GD & Feil VJ (1969) The fate of a single oral dose of carbaryl (1-naphthyl-*N*-methyl-carbamate) in the chicken. Poult Sci, **48**: 1593-1597.

Paulson GD, Zaylskie RG, Zehr MV, Portnoy CE, & Feil VJ (1970) Metabolites of carbaryl (1-naphthyl *N*-methyl-carbamate) in chicken urine. J Agric Food Chem, **18**: 110-115.

Pavlova II, Petrovskaya OG, & Ivanova SI (1968) [Biochemical and histochemical studies on the oxidative-reductive enzymes after an exposure to Sevin.] Gig Primen Toxicol Pestic Klin Otrav, **1968**: 625-630 (in Russian).

Payne JA, Dutcher JD, & Ellis HC (1985) Low pressure soil application of carbaryl for control of the pecan weevil, *Curculio carvae*. J Agric Entomol, 2(1): 1-5.

Pekas JC (1972) Intestinal hydrolysis, metabolism and transport of a pesticidal carbamate in pH G.5 medium. Toxicol Appl Pharmacol, **23**: 62-70.

Pekas JC & Paulson GD (1970) Intestinal hydrolysis and conjugation of a pesticidal carbamate *in vitro*. Science, **170**: 77-78.

Perelygin VM, Shpirt MB, Aripov OA, & Ershova VI (1971) [Effect of some pesticides on immunological response reactivity.] Gig i Sanit, **36**(12): 29-33 (in Russian).

Petrovski VV (1970) [The level of content and duration of excretion of Sevin in the milk of cows treated against ticks.] Gig Primen Toxicol Pestic Klin Otrav, **1970**: 193-196 (in Russian).

Pieper GR (1979) Residues analysis of carbaryl on forest foliage and in stream water using HPLC. Bull Environ Contam Toxicol, **22**(1-2): 167-171.

Pieper GR & Roberts RB (1978) Residue analysis of carbaryl on forest foliage and in creek water. US Department of Agriculture, Forest Service, Northern Region, pp 1-9 (Report No. 78-5).

Pipy B, Gaillard D, & Derache R (1979) Effect of blockage of the reticulo-endothelial system on the carbaryl toxicity in the rat. Toxicology, **12**: 135-142.

Pipy B, Gaillard D, Beraud M, & Derache R (1980) Phagocytic activity of the rat reticuloendothelial system and the pharmakokinetics of an anticholinesterasic insecticide: carbaryl. Xenobiotica, **10**(10): 785-793.

Pipy B, Gaillard D, & Derache R (1981) Phagocytic activity of the reticuloendothelial 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.

Pipy B, Gaillard D, Beraud M, & Derache R (1982) Enzymatic activities of liver serine esterases during the reticuloendothelial system phagocytosis blockade by carbaryl, an anticholinesterasic insecticide. Toxicol Appl Pharmacol, **62**: 11-18.

Pipy B, de Maroussem D, Beraud M, & Derache R (1983) Evaluation of cellular and humoral mechanisms of carbaryl-induced reticuloendothelial phagocytic depression. J Reticuloendothel Soc, **34**(5): 395-412.

Podolak M & Warchocki B (1980) [Effect of toxobidin on the kinetics of reaction of ChE inhibition by chlorfenvinfos and carbaryl.] Rocz Panstw Zakl Hyg, **31**(2): 125-131 (in Polish).

Podolak-Majczak M & Tyburczyk W (1984) Effect of joint action of sodium nitrite and carbaryl on rats organism. Bromatol Chem Toksykol, **XVII**(3): 211- 214 (in Polish with English summary).

Podolak-Majczak M & Tyburczyk W (1986) [Effect of joint action of sodium nitrite and carbaryl on rats organism. Part IV. Hepatotoxic action.] Bromatol Chem Toksykol, **XIX**(3): 164-166 (in Polish with English summary).

Post G & Schroeder TR (1971) The toxicity of four insecticides to four salmonid species. Bull Environ Contam Toxicol, **6**(2): 144-155.

Preussmann RG, Eisenbrand G, & Schmahl D (1976) Carcinogenicity testing of low doses of nitrosopyrrolidine and of nitrosobenzothiazuron and nitrosocarbaryl in rats. In: Walker EA, Bogovski P, & Griciute L ed. Environmental *N*-nitroso compounds analysis and formation. Proceedings of a Working Conference held at the Polytechnical Institute, Tallinn, Estonian SSR, 1-3 October 1975. Lyon, International Agency for Research on Cancer, pp 429-433 (IARC Scientific Publications No. 14).

Prima NG, Prima AP, Sem'yan AI, Solov'eva VG, & Bondarenko VF (1976) [Model studies of the rate of self-purification of river water from Sevin and 1-naphthol residues.] Probl Okhr Vod, **7**: 8-13 (in Russian).

Probst GS, McMahon RE, Hill LE, Thompson CZ, Epp JK, & Neal SB (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.

Puech AA (undated) A study of the potential for human dermal and inhalation exposure of Sevin, carbaryl insecticide during normal garden use. Research Triangle Park, North Carolina, Union Carbide Corporation (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Puyear RL & Paulson GD (1972) Effect of carbaryl (1-naphthyl-*N*-methylcarbamate) on phenobarbital-induced sleeping time and some liver microsomal enzymes in white leghorn cockerels. Toxicol Appl Pharmacol, **22**: 621-627.

Quarles JM & Tennant RW (1975) Effects of nitrosocarbaryl on Balb/3T3 cells. Cancer Res, **35**: 2637-2645.

Rajagopal BS & Sethunathan N (1984) Influence of nitrogen fertilizers on the persistence of carbaryl and carbofuran in flooded soils. Pestic Sci, **15**: 591-599.

Rajagopal BS, Chendrayan K, Reddy B, Rajasekhar-Reddy B, & Sethunathan N (1983) Persistence of carbaryl in flooded soils and its degradation by soil enrichment cultures. Plant Soil, **73**(1): 35-45.

Rajagopal BS, Rao VR, Nagendrappa G, & Sethunathan N (1984) Metabolism of carbaryl and carbofuran by soil-enrichment and bacterial cultures. Can J Microbiol, **30**(12): 1457-1465.

Rajagopal BS, Panda S, & Sethunathan N (1986) Accelerated degradation of carbaryl and carbofuran in a flooded soil pretreated with hydrolysis products, 1-naphthol and carbofuran phenol. Bull Environ Contam Toxicol, **36**(6): 827-832.

Rajukkannu K, Basha AA, Habeebullah B, Duraisamy P, & Balasubramanian M (1985) Degradation and persistence of DDT, BHC, carbaryl and malathion in soils. Indian J Environ Health, **27**(3): 237-243.

Rao KRSS, Rao KSP, Sahib IKA, & Rao KVR (1985a) Combined action of carbaryl and phenthoate on a freshwater fish (*Carina punctatus* bloch). Ecotoxicol Environ Saf, **10**(2): 209-217.

Rao KS, Rao KR, Sahib IK, & Rao KV (1985b) Combined action of carbaryl and phenthoate on a tissue lipid derivatives of murrel, *Channa punctatus* (Bloch). Ecotoxicol Environ Saf, **9**(1): 107-111.

Ray SK & Poddar MK (1985a) Central cholinergic dopaminergic interaction in carbaryl induced tremor. Eur J Pharmacol, **119**(3): 251-253.

Ray SK & Poddar MK (1985b) Effect of pentylenetetrazol on carbaryl induced changes in striatal catecholamines. Biochem Pharmacol, **34**(4): 553-557.

Ray SK & Poddar MK (1990) Interaction of central serotonin and dopamine in the regulation of carbaryl induced tremor. Eur J Pharmacol, **181**(3): 159-166.

Rawash IA, Gaaboub IA, El-Gayar FM, & El-Shazli AY (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**: 133-144.

Regan JD, Seltow RB, Francis AA, & Lijinsky W (1976) Nitrosocarbaryl: Its effect on human DNA. Mutat Res, **38**: 239-302.

Reiner E & Aldridge WN (1967) Effect of pH on inhibition and spontaneous reactivation of acethylcholinesterase treated with esters of phosphorus acids and of carbamic acids. Biochem J, **105**: 171-179.

Rickard RW & Dorough HW (1984) *In vivo* formation of nitrosocarbamates in the stomach of rats and guinea-pigs. J Toxicol Environ Health, **14**(2-3): 279-290.

Rickard RW, Walter-Echols G, Dorough HW, & Lawrence LJ (1982) Importance of pH in assessing the potential for nitrosocarbamate formation in the stomach. Pestic Biochem Physiol, **18**(3): 325-333.

Robel J, Felthausen RW, & Dayton D (1982) Effects of carbamates on bobwhite food intake, body weight and locomotor activity. Arch Environ Contam Toxicol, **11**(5): 611-615.

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

Roberts D (1975) The effect of pesticides on byssus formation in the common mussel, *Mytilus edulis*. Environ Pollut, **8**(4): 241-254.

Roberts BL & Dorough HW (1984) Relative toxicity of chemicals to the earthworm *Eisenia foetida*. Environ Toxicol Chem, **3**: 67-78.

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

Rodgers KE, Leung N, Imamura T, & Devens BH (1986) Rapid *in vitro* screening assay for immunotoxic effects of organophosphorus and carbamate insecticides in the generation of cytotoxic T-lymphocyte responses. Pestic Biochem Physiol, **26**(3): 292-301.

Rodriguez LD & Dorough HW (1977) Degradation of carbaryl by soil microorganisms. Arch Environ Contam Toxicol, **6**(1): 47-56.

Romine RR & Bussian RA (1971) Sevin Insecticide: The degradation of carbaryl after surface application to a farm pond (Project No 111A13, File No. 15265). South Charleston, West Virginia, Union Carbide Corporation (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Roszkowski J, Zadura J, & Skwarek P (1976) The effect of carbaryl on immune response in chickens. Bull Vet Inst Pulawy, **20**(3-4): 85-88.

Ruppert P, Cook L, Dean F, & Reiter W (1983) Acute behavioural toxicity of carbaryl and propoxur in adult rats. Pharmacol Biochem Behav, **18**(4): 579-584.

Ryan AJ (1971) The metabolism of pesticidal carbamates. CRC Crit Rev Toxicol, **1**: 35-54.

Rybakova MN (1966) [Toxic effect of Sevin on animals.] Gig i Sanit, **31**(9): 42-47 (in Russian with English summary).

Rybakova MN (1967) [Comparative toxic effect of Sevin and DDT used in the treatment of food crops.] Vopr Pitan, **26**: 9-15 (in Russian with English summary).

Saini ML & Dorough HW (1978) Metabolism of carbaryl-naphthyl-C^{14} in a lactating cow, when administered orally. In: Edwards CA, Veeresh GK, & Krueger HR ed. Proceedings of the Symposium on Pesticide Residues in the Environment in India, 7-10 November 1978. Hebbal, Bangalore, University of Agricultural Sciences, pp 74-87 (UAS Technical Series No. 32).

Sakai K & Matsumura F (1971) Degradation of certain organophosphate and carbamate insecticides by human brain esterases. Toxicol Appl Pharmacol, **19**: 660-666.

Samanidou V, Fytianos K, Pfister G, & Bahadir M (1988) Photochemical decomposition of carbamate pesticides in natural waters of Northern Greece. Sci Total Environ, **76**(1): 85-92.

Sanders HO & Cope DB (1966) Toxicity of several pesticides in two species of Cladocerans. Trans Am Fish Soc, **95**(2): 165-169.

Sanders HO, Finley MT, & Hunn JB (1983) Acute toxicity of six forest insecticides to three aquatic invertebrates and four fishes. Washington, DC, US Department of the Interior, Fish and Wildlife Service, 5 pp (Technical Paper 110).

Sanderson DM (1961) Treatment of poisoning by anticholinesterase insecticides in the rat. J Pharm Pharmacol, **13**: 435-442.

Santolucito JA & Morrison G (1971) EEC of Rhesus monkeys following prolonged low level feeding of pesticides. Toxicol Appl Pharmacol, **19**: 147-154.

Santolucito JA & Whitcomb E (1971) Mechanical response of skeletal muscle following oral administration of pesticides. Toxicol Appl Pharmacol, **20**: 66-72.

Schafer EA (1972) The acute oral toxicity of 369 pesticidal, pharmaceutical and other chemicals to wild birds. Toxicol Appl Pharmacol, **21**: 315-330.

Schomburg CJ, Glottfeldy DE, & Seiber JN (1991) Pesticide occurrence and distribution in fog collected near Monterey, California. Environ Sci Technol, **25**: 155-160.

Schulze TL, Hauge PN, Mitchell WJ, Remley WJ, Shahied SI, & Marshall FJ (1979) New Jersey Epidemiologic Studies Program-Pesticides - Assessment of human exposure to carbaryl during aerial application for Gypsy moth control in New Jersey. New Jersey State Department of Health.

Seiler JP (1977) Nitrosation *in vivo* and *in vitro* by sodium nitrate and mutagenicity of nitrogenous pesticides. Mutat Res, **48**: 225-236.

Shabanov M, Toshkov A, Georgiev D, & Ibrishimov N (1983) [Effect of carbaryl on experimental *Erysipelothrix rhusiopathiae* infection in rats.] Vet Med Nauk, **20**(5-6): 9-15 (in Russian).

Shafik MT, Sullivan HC, & Enos NF (1971) A method for the determination of 1-naphthol in urine. Bull Environ Contam Toxicol, **6**(1): 34-39.

Shah PV & Guthrie FE (1983) Percutaneous penetration of three insecticides in rats: a comparison of two methods for *in vivo* determination. J Invest Dermatol, **80**(4): 291-293.

Shah PV, Monroe RV, & Guthrie FE (1983) Comparative penetration of insecticides in target and nontarget species. Drug Chem Toxicol, **6**(2): 155-179.

Shah PV, Fisher HL, Sumler MR, Monroe RJ, Chernoff N, & Hall LL (1987) Comparison of the penetration of 14 pesticides through the skin of young and adult rats. J Toxicol Environ Health, **21**(3): 353-366.

Sharma VK & Kaur S (1990) Contact sensitization by pesticides in farmers. Contact Dermatitis, **23**(2): 77-80.

Sharom MS, Miles JRW, Harris CR, & McEwen FL (1980) Behaviour of 12 insecticides in soil and aqueous suspensions of soil and sediment. Water Res, **14**(8): 1095-1100.

Shea TB (1985) Carbaryl inhibition of interferon synthesis in cultured goldfish cells. Bull Environ Contam Toxicol, **34**: 109-113.

Shea TB & Berry ES (1983) Toxicity of carbaryl and 1-naphthol to goldfish (*Carassius auratus*) and Killifish (*Fundulus heteroclitus*). Bull Environ Contam Toxicol, **31**: 526-529.

Shea TB & Berry ES (1984) Suppression of interferon synthesis by the pesticide carbaryl as a mechanism for enhancement of goldfish virus-2 replication. Appl Environ Microbiol, **47**(2): 250-252.

Shehata T, Richardson E, & Cotton E (1984) Assessment of human population exposure to carbaryl from the 1982 Main Spruce budworm spray project. J Environ Health, **46**(6): 293-297.

Shilova SA, Denisova AV, Sedykh EL, & Efron KM (1973) [After effects of insecticide treatment in the subartics.] Zool Zh, **52**(7): 1008-1012 (in Russian).

Shimkin MB, Wieder R, McDonough M, Fishbein L, & Swern D (1969) Lung tumour response in strain A mice as a quantitative bioassay of carcinogenic activity of some carbamates and aziridines. Cancer Res, **29**: 2184-2190.

Shpirt MB (1973) [Toxicological assessment of DDT, HCHC, TMTD, Sevin and Zineb acting on human cell cultures.] Gig Tr Prof Zabol, **14**: 32-35 (in Russian).

Shtenberg AI & Hovaeva LA (1970) [The effect of Sevin on the state of thyroid gland of rats having received artificial full-value ration with different content of iodine.] Gig i Sanit, **8**: 119-122 (in Russian).

Shtenberg AI & Ozhovan MV (1971) [The effect of small doses of Sevin upon the reproduction function of animals in several generations.] Vopr Pitan, **1**: 42-47 (in Russian).

Shtenberg AI & Rybakova MN (1968) Effect of carbaryl on the neuroendocrine system in rats. Food Cosmet Toxicol, **6**: 461-467.

Shtenberg AI, Orlova NV, Pozdnyakov AL, Tropova GP, Zhalbe JP, Khovayeva LA, & Akincheva MJ (1970) [Functional and morphological parallels associated with the state of the sex glands of animals under the influence of Sevin.] In: [Problems of the hygiene and toxicology of pesticides.] Moscow, Meditsina, pp 124-129 (in Russian).

Shtenberg AI, Orlova NV, & Torchinskij AM (1973) [On the effect of pesticides of different chemical structure on gonads and embryogenesis in experimental animals.] Gig i Sanit, **8**: 16-20 (in Russian).

Shukla GS, Omkar & Upadhyay VB (1982) Acute toxicity of few pesticides to an aquatic insect, *Ranatra elongata* (Fabr.) J Adv Zool, **3**(2): 148-150.

Siboulet R, Grinfeld S, Deparis P, & Jaylet A (1984) Micronuclei in red blood cells of the newt *Pleurodeles waltl* Michah: Induction with X rays and chemicals. Mutat Res, **125**(2): 275-281.

Siebert D & Eisenbrand G (1974) Induction of mitotic gene conversions in *Saccharomyces cerevisiae* by *N*-nitrosated pesticides. Mutat Res, **22**: 121-126.

Sikka HC, Miyazaki S, & Rice CP (1973) Metabolism of selected pesticides by marine microorganisms. Springfield, Virginia, National Technical Information Service (Syracuse University Annual Report No. 2 - NTIS AS AD-763 410).

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

Simpson JR (1965) Exposure to orchard pesticides, dermal and inhalation exposures. Arch Environ Health, **10**: 884-885.

Singh JM (1973) Decreased performance behaviour with carbaryl - an indication of clinical toxicity. Clin Toxicol, **6**(1): 97-108.

Singh KP, Pandey SY, Divekar VV, Surana KC, & Paralikar AB (1978) Dissipation of carbaryl residues in and on cauliflower. In: Edwards CA, Veeresh GK, & Krueger HR ed. Proceedings of the Symposium on Pesticide Residues in the Environment in India, 7-10 November 1978. Hebbal, Bangalore, University of Agricultural Sciences, pp 210-214 (UAS Technical Series No. 32).

Singh VP, Gupta S, & Saxena PK (1984) Evaluation of acute toxicity of carbaryl and malathion to freshwater teleosts, *Chauna punctatis* (bloch) and *Heteropneustes fossilis* (bloch). Toxicol Lett, **20**: 271-276.

Sjoblad RD, Minard RD, & Bollag JM (1976) Polymerisation of 1-naphthol and related phenolic compounds by an extracellular fungal enzyme. Pestic Biochem Physiol, **6**: 457-463.

Skraba WJ & Young FG (1959) Radioactive Sevin (1-naphthyl-1-carbon-14 N- methylcarbamate): a convenient synthesis. Agric Food Chem, **7**(9): 612-613.

Smalley HE (1970) Diagnosis and treatment of carbaryl poisoning in swine. J Am Vet Med Assoc, **156**(3): 339-344.

Smalley HE, Curtis JM, & Earl FL (1968) Teratogenic action of carbaryl in beagle dogs. Toxicol Appl Pharmacol, **13**: 392-403.

Smalley HE, O'Hara PJ, Bridges CH, & Radeleef RD (1969) The effect of chronic carbaryl administration on the neuromuscular system of swine. Toxicol Appl Pharmacol, **14**: 409-419.

Snow CD & Stewart NE (1963) Treatment of Tikamook Bay oyster beds with MGS-90 (Sevin) (Unpublished report from the Oregon Fish Commission, submitted to WHO by Rhône-Poulenc Agro, Lyon).

Söderpalm BC & Önfelt A (1988) The action of carbaryl and its metabolite alpha naphthol on mitosis in V79 Chinese hamster fibroblasts. Indications of the involvement of some cholinester in cell division. Mutat Res, **201**(2): 349-363.

Sokur AJ (1971) [Hypokaliaemia in erythrocytes after intoxication of white rats with some pesticides (DDT, Sevin, chlorophos).] Gig Primen Toxicol Pestic Klin Otrav, **1971**: 213-216 (in Russian).

Solomon H & Weis J (1979) Abnormal circulatory development in medaka caused by the insecticides carbaryl, malathion and parathion. Toxicology, **19**: 51-62.

Spain AV (1974) The effects of carbaryl and DDT on the litter fauna of a Corsican pine forest (*Pinus nigra* var. *maritima*): A multivariate comparison. J Appl Ecol, **11**: 467-481.

Springborn Bionomics, Inc. (1988a) Environmental fate of spray applications of the rice insecticide Sevin XLR (a.i. carbaryl): California (Study No. 565- 6118/6112). Wareham, Massachusetts, Springborn Bionomics, Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Springborn Bionomics, Inc. (1988b) Environmental fate of spray applications of the forest insecticide Sevin-4-oil (a.i. carbaryl): Oregon (Study No. 565-6120/6114). Wareham, Massachusetts, Springborn Bionomics, Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Springborn Bionomics, Inc. (1988c) Environmental fate of spray applications of the forest insecticide Sevin-4-oil (a.i. carbaryl): Pennsylvania (Study No. 565-6121/6115). Wareham, Massachusetts, Springborn Bionomics, Inc. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

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

Statham CN & Lech JJ (1975) Potentiation of the acute toxicity of several pesticides and herbicides in trouts by carbaryl. Toxicol Appl Pharmacol, **34**: 83-87.

Stegeman LC (1964) The effects of the carbamate insecticide carbaryl upon forest soil mites and Collembola. J Econ Entomol, **57**(6): 803-808.

Stevenson JH (1978) The acute toxicity of unformulated pesticides to worker honey bees (*Apis Mellifera* L.). Plant Pathol, **27**: 38-40.

Stevenson JH, Needham PH, & Walker J (1977) Poisoning of honey bees by pesticides: Investigations of the changing pattern in Britain over 20 years. Rothamsted Rep, **2**: 55-66.

Stewart NE, Millemann RE, & Breese WP (1967) Acute toxicity of the insecticide Sevin and its hydrolytic product 1-naphthol to some marine organisms. Trans Am Fish Soc, **96**: 25-30.

Strait JR, Thornwall GC, & Ehrich M (1991) Sensitive high-performance liquid chromatographic analysis for toxicological studies with carbaryl. Washington, DC, American Chemical Society.

Street JC & Sharma RP (1975) Alteration of induced cellular and humoral immune responses by pesticides and chemicals of environmental concern: Quantitative studies on immunosuppression by DDT, Aroclor 1254, carbofuran and methylparathion. Toxicol Appl Pharmacol, **32**(5): 587-602.

Strother A (1970) Comparative metabolism of selected 1-methylcarbamates by human and rat liver fractions. Biochem. Pharmacol, **19**: 2525-2529.

Strother A & Wheeler L (1976) Disposition of ^{14}C-carbaryl in pregnant, nonpregant and fetal tissues of rat. Fed Proc, **35**: 327.

Strother A & Wheeler L (1980) Excretion and disposition of [^{14}C]carbaryl in pregnant, non-pregant and foetal tissues of the rat after acute administration. Xenobiotica, **10**(2): 113-124.

Struble CB, Feil VJ, Pecas JC, & Gerst JW (1983a) Biliary secretion of ^{14}C and identification of 5,6-dihydro-5,6-dihydroxycarbaryl glucoronide as a biliary metabolite of (^{14}C) carbaryl in the rat. Pestic Biochem Physiol, **19**: 85-94.

Struble CB, Pecas JC, & Gerst JW (1983b) Enterohepatic circulation and biliary secretion of 5,6-dihydro-5,6-dihydroxy(^{14}C)carbaryl glucoronide in the rat. Pestic Biochem Physiol, **19**(1): 95-103.

Subbotina SG & Belonozhko GA (1968) [The effect of Sevin on the thermoresistance and fractionary protein content of blood serum.] Gig Primen Toxicol Pestic Klin Otrav, **1968**: 442- 444 (in Russian).

Sud RK, Sud AK, & Gupta KG (1972) Degradation of Sevin (1-naphthyl *N*- methylcarbamate) by *Achromobacter* sp. Arch Microbiol, **87**: 353-358.

Sullivan LJ, Chin BH, & Carpenter CP (1972) *In vitro* vs. *in vivo* chromatographic profiles of carbaryl anionic metabolites in man and lower animals. Toxicol Appl Pharmacol, **22**: 161-174.

Sundaram KMS & Szeto SY (1987) Distribution and persistence of carbaryl in some terrestrial and aquatic components of a forest environment. J Environ Sci Health, **B22**(5): 579-599.

Surprenant DC (1985a) Acute toxicity of carbaryl technical to embryo-larvae of eastern oysters (*Crassostrea virginica*). Wareham, Massachusetts, Springborn Bionomics, Inc. (Report No. BW-85-7-1817) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Surprenant DC (1985b) Acute toxicity of carbaryl technical to mysid shrimp (*Mysidopsis bahia*). Wareham, Massachusetts, Springborn Bionomics, Inc. (Report No. BW-85-6-1790) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Surprenant DC (1985c) The chronic toxicity of carbaryl technical to *Daphnia magna* under flow-through conditions. Wareham, Massachusetts, Springborn Bionomics, Inc. (Report No. BW-85-7-1813) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Sussman HF, Cooke SB, & Bloch V (1969) Human louse infestation; treatment with carbacide. Arch Dermatol, **100**(1): 82-83.

Swartz WJ (1981) Long- and short-term effects of carbaryl exposure in chick embryos. Environ Res, **26**(2): 463-471.

Swartz WJ (1985) Effects of carbaryl on gonadal development in the chick embryo. Bull Environ Contam Toxicol, **34**: 481-485.

Szczepaniak S & Jeleniewicz K (1980) [Alterations of free amino acids concentrations in rat blood erythrocytes following the acute intoxication with carbaryl.] Bromatol Chem Toksykol, **XIII**(2): 159-163 (in Polish with English summary).

Szczepaniak S & Jeleniewicz K (1981) [*In vitro* binding of carbaryl and alpha naphthol with plasma and erythrocytes amino acids.] Bromatol Chem Toksykol, **XIV**(2): 165-168 (in Polish with English summary).

Szczepaniak S & Jeleniewicz K (1986) [Body amino acids balance in acute poisoning with carbaryl.] Farm Pol, **9**: 475-479 (in Polish).

Szczepaniak S, Siemkievicz E, Jeleniewicz K, & Nowinski H (1980) [Effects of carbaryl and chlorfenvinfos on the level of free amino acids in rat blood serum. Part II. Intoxication with a single dose corresponding to 1/5 LD_{50}.] Bromatol Chem Toksykol, **XIII**(4): 351-353 (in Polish with English summary).

Szeto SY, MacCarty HR, Oloffs PC, & Shephard RF (1979) The fate of acephate and carbaryl in water. J Environ Sci Health, **B14**(6): 635-654.

Tagatz ME, Ivey JM, & Lehman HK (1979) Effects of Sevin on development of experimental estuarine communities. J Toxicol Environ Health, **5**: 643-651.

Takahashi RN, Poli A, Morato GS, Lima TCM, & Zanin M (1991) Effects of age on behavioral and physiological responses to carbaryl in rats. Neurotoxicol Teratol, **13**: 21-26.

Tewfik MS & Hamdi YA (1970) Decomposition of Sevin by a soil bacterium. Acta Microbiol Pol Ser B, **19**(2): 133-135.

Thomas A (1981)Introductory remarks: The testes. Environ Health Perspect, **38**: 3-4.

Thomas SJ (1986) Sevin brand carbaryl insecticide: Magnitude of carbaryl residues in sugar beet roots (File No. 34934). Research Triangle Park, North Carolina, Union Carbide Agricultural Products Co., Inc. (Prepared in collaboration with Hazleton Laboratories America, Inc., Chemical and Biomedical Sciences Division, Madison) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon.

Thomas JH, Dieringer CS, & Schein L (1974) Effects of carbaryl on mouse organs of reproduction. Toxicol Appl Pharmacol, **28**: 142-145.

Thomas J, Visalakshi A, & Mohandas N (1982) Contamination of water in rice fields sprayed with carbaryl for insect control. Entomon, **7**(3): 379-380.

Thompson AR (1971) Effects of nine insecticides on the numbers and biomass of earthworms in pasture. Bull Environ Contam Toxicol, **5**(6): 577-586.

Tilak KS, Rao DMR, Devi AP, & Murty AS (1981) Toxicity of carbaryl and 1-naphthol to four species of freshwater fish. J Biosci, **3**(4): 457-462.

Tilden RL & Van Middelem CH (1970) Determination of carbaryl as an amide derivative by electroncapture gas chromatography. J Agric Food Chem, **18**(1): 154-158.

Ting KC, Kho PK, Musselman AS, Root JA, & Tichelaar R (1984) High performance liquid chromatographic method for determination of six N-methylcarbamates in vegetables and fruits. Bull Environ Contam Toxicol, **33**: 538-547.

Tobin JS (1970) Carbofuran. A new carbamate insecticide. J Occup Med, **12**(1): 16-19.

Toor HS & Kaur K (1974) Toxicity of pesticides to the fish *Cyprinus carpio communis* Linn. Indian J Exp Biol, **12**: 334-336.

Tos-Luty S, Puchala-Matysek W, & Latuszynska J (1973) [Carbaryl toxicity in chick embryo.] Bromatol Chem Toksykol, **6**: 409-411 (in Polish with English summary).

Trial JG (1978) The effects of Sevin-4-oil on aquatic insect communities of streams: a continuation of 1976 studies. In: Environmental monitoring of cooperative spruce budworm control projects, Maine 1976 and 1977. Augusta, Maine, Maine Department of Conservation, Forest Service, pp 124-140.

Trial JG (1979) The effects of Sevin-4-oil on aquatic insect communities of stream (1976-1978). In: Environmental moitoring of cooperative spruce budworm control projects, Maine 1978. Augusta, Maine, Maine Department of Conservation, Forest Service, pp 6-22.

Triolo AJ, Lang WR, Coon JM, Lindstrom D, & Herr DL (1982) Effect of the insecticide toxaphene and carbaryl on induction of lung tumors by benzo(a)pyrene in the mouse. J Toxicol Environ Health, **9**(4): 637-649.

Tripathi G & Shukla SP (1988) Toxicity bioassay of technical and commercial formulations of carbaryl to the freshwater catfish, *Clarias batrachus*. Ecotoxicol Environ Saf, **15**(3): 277-281.

Tyburczyk W & Podolak-Majczak M (1984a) [Effect of joint action of sodium nitrite and carbaryl on rats organism.] Bromatol Chem Toksykol, **XVII**(2): 125-129 (in Polish with English summary).

Tyburczyk W & Podolak-Majczak M (1984b) [Effect of joint action of sodium nitrite and carbaryl on rats organism.] Bromatol Chem Toksykol, **XVII**(3): 215-219 (in Polish with English summary).

Tyburczyk W & Podolak-Majczak M (1986) [Effect of joint action of sodium nitrite and carbaryl on rats organism. Part V. The role of glucose-6-phosphate dehydrogenase and haematologic studies.] Bromatol Chem Toksykol, **XIX**(3): 167-173 (in Polish with English summary).

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

US Department of Labour (1978) Occupational health guideline for carbaryl (Sevin/R). Washington, DC, US Department of Labour, pp 1-5.

US EPA (1977) Aspects of pesticidal uses of carbaryl on man and the environment. Washington, DC, US Environmental Protection Agency, Office of Pesticide Programs, 286 pp.

US EPA (1980a) Carbaryl. Decision document. Washington, DC, US Environmental Protection Agency, Office of Pesticides and Toxic Substances, 22 pp.

US EPA (1980b) FIFRA Scientific Advisory Panel. Subcommittee meeting, Arlington, Virginia, 23 July 1980. Washington, DC, US Environmental Protection Agency, 202 pp.

US EPA (1981) Environmental fates and impacts of major forest use of pesticides. Washington, DC, US Environmental Protection Agency, Office of Pesticides and Toxic Substances.

US EPA (1984) Health and environmental profile for carbaryl. Cincinnati. Ohio, US Environmental Protection Agency.

Usha Rani MV, Reddi OS, & Reddy PP (1980) Mutagenicity studies involving aldrin, endosulfan, demethoate, phosphamidon, carbaryl and ceresan. Bull Environ Contam Toxicol, **25**(2): 277-282.

Vandekar M (1965) Observations of the toxicity of carbaryl, folithion and 3- isopropylphenyl *N*-methylcarbamate in a village scale trail in Southern Nigeria. Bull World Health Organ, **33**: 107-115.

Vandekar M, Plestina R, & Wilhelm M (1971) Toxicity of carbamates for mammals. Bull World Health Organ, **44**: 241-249.

Varshney TN & Gaur AC (1972) Effect of DDT and Sevin on soil fungi. Acta Microbiol Acad Sci Hung, **19**: 97-102.

Vashakidze VI (1966) [On the question of the embryotropic, gonadotropic and mutagenic effect of some pesticides.] Gig Primen Toxicol Pestic Klin Otrav, **1966**: 80-83 (in Russian).

Vashakidze VI (1975) [Effect of small doses of Sevin on gonad function following its repeated effect on white rats SbTr NII.] Gig Tr Prof Zabol, **14**: 235-266 (in Russian).

Vasilos AF, Dmitrienko VD, & Shroyt IG (1975) [Disruption of the mitotic system following acute Sevin poisoning.] Izv Akad Nauk Moldavskoj SSR Ser Khim Nauk, **3**: 64-67 (in Russian).

Venkateswarlu K, Chendrayan K, & Sethunathan N (1980) Persistence and biodegradation of carbaryl in soils. J Environ Sci Health, **B15**(4): 421-429.

Venkat Reddy P, Prem Veer Reddy G, & Subramanyams S (1974) Cytological effects of the insecticide Sevin on the mitotic cells of *Poecilocerus pictus*. Curr Sci, **43**(6): 187-189.

Verma SR, Tonk IF, Gupta AK, & Saxena M (1984) Evaluation of an application factor for determining the safe concentration of agricultural and industrial chemicals. Water Res, **18**(1): 111-115.

Viter VF (1978) [Monotonous and intermittent inhalatory effect of Sevin upon some behavioural reactions of experimental animals.] Gig i Sanit, **11**: 33-34 (in Russian).

Vyatchanikov KA & Alexachina ZA (1968) [Experimental investigations for procuring therapeutic and protective means at intoxications by Sevin.] Gig Primen Toxicol Pestic Klin Otrav, **1968**: 442-444 (in Russian).

Wagner R (1973) [Identification and estimation of organophosphate insecticides and carbaryl on ready made thin-layer plates.] Z Gesamte Hyg Grenzgeb, **19**(7): 504-510 (in German).

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

Walker N, Janes NF, Spokes JR, & Van Berkum P (1975a) Degradation of 1-naphthol by a soil pseudomonad. J Appl Bacteriol, **39**: 281-286.

Walker M, Gale GR, Atkins LM, & Gadse-Den RH (1975b) Some effects of carbaryl on Ehrlich ascites tumor cells *in vitro* and *in vivo*. Bull Environ Contam Toxicol, **14**(4): 441-448.

Waller GD (1969) Susceptibility of an alfalfa leaf-cutting bee to residues of insecticides on foliage. J Econ Entomol, **62**(1): 189-192.

Ward SA, May DG, Heath AJ, & Branch RA (1988) Carbaryl metabolism is inhibited by Cimetidine in the isolated perfused rat liver and in man. J Toxicol Clin Toxicol, **26**(5/6): 269-281.

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

Weber FJ, Shea TB, & Berry SE (1982) Toxicity of certain insecticides to protozoa. Bull Environ Contam Toxicol, **28**: 618-631.

Weil CS & Carpenter CP (1962) Studies on carcinogenesis completed in 1962. Pittsburgh, Pennsylvania, Carnegie-Mellon Research Institute (Special Report 25-122) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Weil CS & Carpenter CP (1965) Results of a three generations reproductive study on rats fed Sevin in their diet. Pittsburgh, Pennsylvania, Carnegie-Mellon Research Institute, 18 pp (Report No. 28-53) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Weil CS & Carpenter CP (1974) Sevin: range finding toxicity studies. Pittsburgh, Pennsylvania, Carnegie Mellon (Report No. 37-53) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Weil CS, Woodside MD, Carpenter CP, & Smyth HF Jr (1972) Current studies of tests of carbaryl for reproductive and teratogenic effect. Toxicol Appl Pharmacol, **21**: 390-404.

Weil CS, Woodside MD, Bernard JB, Condra NI, King JM, & Carpenter CP (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**: 621-638.

Weston RF, Inc. (1982) Carbaryl: A profile on its characteristics as pesticide. Rockville, Maryland, Roy F. Weston, Inc., Environmental Health Sciences Centre.

Whitehurst WE, Bishop ET, Critchfield FE, Gyrisco GG, Huddleston EW, Arnold H, & Lisk OJ (1963) The metabolism of Sevin in dairy cows. J Agric Food Chem, **11**: 167-169.

WHO (1982) Recommended health-based limits in occupational exposure to pesticides. Report of a WHO study group. Geneva, World Health Organization, 110 pp (WHO Technical Report Series 677).

WHO (1986) IPCS Environmental Health Criteria 64: Carbamate pesticides - A general introduction. Geneva, World Health Organization, 136 pp.

WHO (1992) The WHO recommended classification of pesticides by hazard and guidelines to classification 1992-1993. Geneva, World Health Organization, 66 pp (Unpublished document WHO/PCS/92.14).

WHO/FAO (1975) Data sheets on pesticides No. 3: Carbaryl. Geneva, World Health Organization, 8 pp (Unpublished document VBC/DS/75.3, Rev. 1).

Whorton MD, Milby TH, Stubbs HA, Avasha BH, & Hull EG (1979) Testicular function among carbaryl exposed employees. J Toxicol Environ Health, **5**: 925-941.

Wiggins OG & Weiden MHJ (1969) Fate of Sevin applied to the surface of bean fruit and bean plants under field conditions. Clayton, North Carolina, Union Carbide Corporation (Report No. 11377) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Wilkes L, Mulkey N, & Wargo J (1977) Research report laboratory soil metabolism study of carbaryl (Project No. 285). Monument, Colorado, Analytical Development Corp. (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Wills JH, Jameson E, & Coulston F (1968) Effects of oral doses of carbaryl on man. Clin Toxicol, **1**:(3) 265-271.

Wiltrout RW, Ercegovich CD, & Ceglowski WS (1978) Humoral immunity in mice following oral administration of selected pesticides. Bull Environ Contam Toxicol, **20**(3): 423-431.

Winterlin W & Walker G (1973) Carbaryl residues in bees, honey, and bee bread following exposure to carbaryl via the food supply. Arch Environ Contam Toxicol, **1**(4): 362-374.

Wojciechowski JP, Kaur P, & Sabharual PS (1982) Induction of ouabain resistance in V-79 cells by four carbamate pesticides. Environ Res, **29**: 48-53.

Wolfe HP, Durham W, & Armstrong J (1967) Exposure of workers to pesticides. Arch Environ Health, **14**: 622-633.

Wolfe NL, Zepp RG, & Paris DF (1978) Carbaryl, propham and chlorpropham: A comparison of the rates of hydrolysis and photolysis with the rate of biolysis. Water Res, **12**(8): 565-571.

Woodruff RC, Phillips JP, & Irwin D (1983) Pesticide-induced complete and partial chromosome loss in screens with repair-defective females of *Drosophila melanogaster*. Environ Mutagen, **5**: 835-846.

Woodward DF & Mauck WL (1980) Toxicity of five forest insecticides to cutthroat trout and two species of aquatic invertebrates. Bull Environ Contam Toxicol, **25**: 846-853.

Wright CG, Leidy RB, & Dupress HE (1981) Insecticides in the ambient air of rooms following their application for control of pests. Bull Environ Contam Toxicol, **26**(4): 548-553.

Wuu K & Grant W (1966) Morphological and somatic chromosomal aberrations induced by pesticides in barley (*Hordeum vulgare*). Can J Genet Cytol, **8**: 481-501.

Wyrobek AJ, Watchmaker G, Gordon L, Wong K, Moore D, & Whorton D (1981) Sperm shape abnormalities in carbaryl-exposed employees. Environ Health Perspect, **40**: 225-265.

Yadav PR & Jaglan RS (1982) Persistence of carbaryl residues in and on unprocessed and processed cauliflower curds. Beitr Trop Landwirtsch Veterinärmed, **20**(1): 89-95.

Yadav GS, Kathpal TS, & Singh H (1985) Efficacy of monocrotophos, carbaryl, and endosulfan against *Antigastra catalaunalis* Dup. and their persistence in soil and sesamum seeds. Indian J Agric Sci, **55**(6): 438-442.

Yakim VS (1965) [Toxicological hygienic characteristics of Sevin.] Gig Primen Toxicol Pestic Klin Otrav, **1965**: 423-431 (in Russian).

Yakim VS (1967) [Data for substantiating the MAC values for Sevin in the air of the working zone.] Gig i Sanit, **4**: 23-33 (in Russian).

Yakim VS (1968) [The toxicity of Sevin at inhalatory intake.] Gig Primen Toxicol Pestic Klin Otrav, **1968**: 115-117 (in Russian).

Yakim VS (1970) [Content and distribution of Sevin in warm-blooded animals organism and its effect on ChE activity.] Gig Primen Toxicol Pestic Klin Otrav, **1970**: 214-218 (in Russian).

Yess NJ, Houston MG, & Gunderson EL (1991a) Food and Drug Administration pesticide residue monitoring of foods: 1978-1982. J Assoc Off Anal Chem, **75**(2): 265-272.

Yess NJ, Houston MG, & Gunderson EL (1991b) Food and Drug Administration pesticide residue monitoring of foods: 1983-1986. J Assoc Off Anal Chem, **74**(2): 273-280.

Young RR (1990) Mutagenicity test on carbaryl (technical) in the CHO/HGPRT forward mutation assay. Kensington, Maryland, Hazleton Laboratories America, Inc. (Study No. 10862-0-435) (Unpublished proprietary information submitted to WHO by Rhône-Poulenc Agro, Lyon).

Zabezhinski MA (1970) [Possible carcinogenic effect of β-Sevin.] Vopr Onkol, **16**: 106-107 (in Russian).

Zapko WG (1970) [Effect on some liver functions of acute intoxication of experimental animals with cuprosin, Sevin, Eptam and TMTD.] Gig Primen Toxicol Pestic Klin Otrav, **1970**: 237-240 (in Russian).

Zeakes SJ, Hansen MF, & Robel RJ (1981) Increased susceptibility of Bobwhites (*Colinus virginianus*) to *Histomonas meleagridis* after exposure to Sevin insecticide. Avian Dis, **25**(4): 981-987.

Zepp RG & Cline DM (1977) Rates of direct photolysis in the aquatic environment. Environ Sci Technol, **11**: 359-366.

Zepp RG, Wolfe N, Gordon L, & Fincher RC (1976) Light-induced transformations of methoxychlor in aquatic systems. J Agric Food Chem, **24**: 727-733.

Zinkl JG, Hennys ChJ, & Dewelse LR (1977) Brain cholinesterase activity in birds from forest sprayed trichlorfon (Dylox) and carbaryl (Sevin-4- oil). Bull Environ Contam Toxicol, **17**(4): 379-386.

Zuberli R & Zubairi MY (1971) Carbaryl degradation by *Pseudomonas phaseolicola* and *Aspergillus niger*. Pak J Sci Ind Res, **14**(4-5): 383-384.

Zweig G, Gao R-Y, Witt JM, Propendorf W, & Bogen K (1984) Dermal exposure to carbaryl by strawberry harvesters. J Agric Food Chem, **32**(6): 1232-1236.

Zweig G, Leffingwell JT, & Propendorf W (1985) The relationship between dermal pesticide exposure to fruit harvesters and dislodgeable foliar residues. J Environ Sci Health, **B20**(1): 27-59.

ANNEX I. TREATMENT OF CARBAMATE PESTICIDE POISONING IN MAN

(From EHC 64: Carbamate Pesticides - A General Introduction)

All cases of carbamate poisoning should be dealt with as an emergency and the patient should be hospitalized as quickly as possible.

Extensive descriptions of the treatment of poisoning by anticholinesterase agents are given in several major references (Kagan, 1977;Taylor, 1980; Plestina, 1984).

The treatment is based on:

(*a*) minimizing the absorption;
(*b*) general supportive treatment; and
(*c*) specific pharmacological treatment.

I.1 Minimizing the absorption

When dermal exposure occurs, decontamination procedures include removal of contaminated clothes and washing of the skin with alkaline soap or with a sodium bicarbonate solution. Particular care should be taken in the cleaning of the skin area where venupuncture is performed. Blood might be contaminated with carbamates and therefore inaccurate measures of ChE inhibition might result. Extensive eye irrigation with water or saline should also be performed. In the case of ingestion, vomiting can be induced, if the patient is conscious, by the administration of ipecacuanha syrup (10-30 ml) followed by 200 ml of water. However, this treatment is contraindicated in the case of pesticides dissolved in hydrocarbon solvents. Gastric lavage (with the addition of bicarbonate solution or activated charcoal) can also be performed, particularly in unconscious patients, taking care to prevent aspiration of fluids into the lungs (i.e., only after a tracheal tube has been put in place).

The volumes of the fluids introduced in the stomach should be recorded and samples of gastric lavage frozen and stored for subsequent chemical analysis. If the formulation of the pesticide involved is available, it should also be stored for further analysis (i.e., detection of toxicologically relevant impurities). A purge to remove the ingested compound can be administered.

I.2 General supportive treatment

Artificial respiration (via a tracheal tube) should be started at the first sign of respiratory failure and maintained for as long as necessary.

Cautious administration of fluids is advised as well as general supportive and symptomatic pharmacological treatment and absolute rest.

I.3 Specific pharmacological treatment

I.3.1 Atropine

Atropine should be given, beginning with 2 mg iv repeated at 15 to 30-min intervals. The dose and the frequency of atropine treatment varies from case to case, but should maintain the patient fully atropinized (dilated pupils, dry mouth, skin flushing, etc.).

I.3.2 Oxime reactivations

Although it might be suspected that oxime cholinesterase reactivators would be as helpful in carbamate poisoning as they are in organophosphorous poisoning, this is not the case. There is experimental evidence that the pyridinium oxime 2-PAM is not effective in carbamate poisoning and there is some evidence that it makes poisoning by certain carbamates, including carbaryl, worse.

I.3.3 Diazepam

Diazepam should be included in the therapy of all but the mildest cases. Besides relieving anxiety it appears to counteract some aspects of CNS-derived symptoms that are not affected by atropine. Doses of 10 mg sc or iv are appropriate and may be repeated as required.

Other centrally acting drugs and drugs that may depress respiration are not usually recommended in the absence of artificial respiration procedures.

References to Annex I

KAGAN, J.S. (1977) [The toxicity of organophosphorus pesticides.] Moscow (in Russian).

PLESTINA, R. (1984) Prevention, diagnosis, and treatment of insecticide poisoning. Geneva, World Health Organization. (Unpublished WHO document VBC/84.889).

TAYLOR, P. (1980) Anticholinesterase agents. In: Goodman, L.S. & Gilman, A., ed. The pharmacological basis of therapeutics. 6th ed., New York, Macmillan Publishing Co., pp. 100-119.

RESUME ET EVALUATION, CONCLUSIONS ET RECOMMANDATIONS

1. Résumé et évaluation

1.1 Identité, propriétés et méthodes d'analyse

Carbaryl est la dénomination commune d'un dérivé de l'acide carbamique, le *N*-méthylcarbamate de 1-naphtyle. Le produit technique consiste en un solide cristallin blanc, peut volatil et peu soluble dans l'eau, qui est stable à la lumière et à la chaleur mais qui s'hydrolyse facilement en milieu alcalin. Il existe une norme FAO pour le carbaryl qui stipule un degré de pureté de 98%, avec une limite pour les impuretés (*N*-méthylcarmate de β-naphtyle) de 0,05%.

Pour les analyses portant sur le carbaryl et ses métabolites, il existe de nombreuses méthodes: chromatographie sur couche mince, spectrophotométrie, chromatographie en phase gazeuse, chromatographie en phase liquide à haute pression et spectrométrie de masse à ionisation chimique. La limite de détection peut descendre en-dessous du nanogramme et le taux de récupération dépasse généralement 80%.

1.2 Production et usages

On utilise le carbaryl depuis une trentaine d'années comme insecticide agissant par contact et par ingestion avec certaines propriétés endothérapiques; il permet de lutter contre de nombreux vecteurs et ravageurs. La principale unité de production se trouve aux Etats-Unis d'Amérique. Plus de 290 fabricants proposent une gamme de formulations de carbaryl qui dépasse les 1500 produits.

1.3 Transport, distribution et transformation dans l'environnement

Dans la plupart des conditions, le carbaryl ne persiste pas dans l'environnement. Dans l'eau, son temps de demi-hydrolyse dépend de la température, du pH et de la concentration initiale; il varie de quelques minutes à plusieurs semaines. Le principal produit de décomposition est le 1-naphtol.

L'accumulation du carbaryl, exprimée sous la forme d'un facteur de bioconcentration dans l'environnement aquatique, et plus précisément chez les poissons d'eau douce, varie de 14 à 75. Le carbaryl s'adsorbe plus facilement sur les sols à forte teneur organique que sur les sols sableux. Aux doses d'emploi usuelles, et lorsqu'il est appliqué conformément "aux bonnes pratiques agricoles", il se dissipe rapidement, avec une demi-vie de 8 jours à un mois dans les conditions normales. Il arrive que le carbaryl soit entraîné par les pluies ou par les travaux agricoles de la surface vers les couches sous-jacentes (à un mètre de profondeur).

Le carbaryl peut contaminer la végétation, soit au cours de l'épandage soit par migration à partir d'un sol contaminé.

La décomposition du carbaryl dans l'environnement dépend de son degré de volatilisation, de photodécomposition et de dégradation chimique ou microbienne dans le sol, l'eau et les végétaux. la vitesse de décomposition est plus rapide en climat chaud.

1.4 Concentrations dans l'environnement et exposition humaine

Dans la population générale, le carbaryl est principalement absorbé par la voie alimentaire.

Les résidus présents dans des échantillons de rations totales sont relativement faibles, et ils vont de traces à 0,05 mg/kg. Aux Etats-Unis d'Amérique, on estime que pendant les premières années d'utilisation du carbaryl, l'ingestion journalière de carbaryl était de 0,15 mg/personne/jour (dans 7,4% des composites); cette dose est tombée à 0,003 mg/personne/jour en 1969 (dans seulement 0,8% des composites). Pendant la période d'épandage, on peut retrouver parfois du carbaryl dans les eaux de surface et les retenues d'eau.

La population peut être exposée au carbaryl lors d'opérations de lutte de contre les ravageurs ou les vecteurs tant au domicile que sur les aires de loisir.

Les travailleurs peuvent être exposés au carbaryl lors de la fabrication, de la formulation, de l'emballage, du transport et du stockage du produit ainsi que pendant son épandage. Les concentrations dans l'atmosphère des lieux de travail au cours de la

production varient de < 1 mg/m³ à 30 mg/m³. Il peut y avoir une importante exposition cutanée chez les travailleurs de l'industrie et les ouvriers agricoles en cas de mesures de protection insuffisantes.

1.5 Cinétique et métabolisme

Le carbaryl est rapidement absorbé au niveau des poumons et des voies digestives. Une dose de carbaryl dans l'acétone appliquée sur la peau de volontaires humains a été absorbée par voie percutanée à raison de 45% en 8 heures. Toutefois, les données obtenues *in vitro* concernant la pénétration cutanée ainsi que les données toxicologiques indiquent que l'absorption percutanée s'effectue généralement à un rythme beaucoup plus lent.

Les principales voies métaboliques du carbaryl consistent en une hydroxylation du cycle et une hydrolyse. Il en résulte la formation de nombreux métabolites qui subissent ensuite une conjugaison avec formation de sulfates, de glucuronides et de mercapturates hydrosolubles qui sont excrétés dans l'urine. L'hydrolyse conduit à la formation de 1-naphtol, de dioxyde de carbone et de méthylamine. L'hydroxylation produit du 4-hydroxycarbaryl, du 5-hydroxycarbaryl, du *N*-hydroxyméthylcarbaryl, du 5,6-dihydro-5,6-dihydroxycarbaryl et du 1,4-naphtalènediol. Le principal métabolite chez l'homme est le 1-naphtol.

Dans les conditions normales d'exposition, il est improbable que le carbaryl s'accumule chez les animaux. Il est excrété principalement par la voie urinaire étant donné que la détoxification de son produit d'hydrolyse, le 1-naphtol, s'effectue essentiellement par la formation de conjugués hydrosolubles. Dans le cas des métabolites du carbaryl, le cycle entérohépatique joue également un rôle considérable, en particulier après administration par voie orale.

Le produit d'hydrolyse, l'acide *N*-naphtolcarbamique, se décompose spontanément en méthylamine et dioxyde de carbone. La méthylamine subit ensuite une déméthylation en dioxyde de carbone et formiate, ce dernier étant ultérieurement excrété, en majeure partie dans l'urine.

Des métabolites du carbaryl sont également présents en faible proportion de la dose absorbée dans la salive et le lait.

1.6 Effets sur les êtres vivants dans leur milieu naturel

Les valeurs de la CL_{50} pour les crustacés varient de 5 à 9 µg/litre (puces d'eau et mysidés), 8 à 25 µg/litre (orchesties) et 500 à 2500 µg/litre (écrevisses). Chez les insectes aquatiques, les limites de sensibilité sont du même ordre. Les plécoptères et éphémèroptères (perles et éphémères) en constituent les groupes les plus sensibles. Les mollusques sont moins sensibles avec des valeurs de la CE_{50} de l'ordre de quelques mg/litre. Dans le cas des poissons, la plupart des valeurs de la CL_{50} se situent entre 1 et 30 mg/litre. Les salmonidés constituent le groupe le plus sensible.

La toxicité aiguë est faible pour les oiseaux. La DL_{50} pour la sauvagine et le gibier à plumes en général est > 1000 mg/kg. D'après les tests, l'oiseau le plus sensible est un francolin (*Francolinus levaillanti*) (DL_{50} = 56 mg/kg). Rien n'indique que les oiseaux aient eu à souffrir de l'effet des épandages effectués sur les zones forestières à la dose de 1,1 kg de carbaryl/ha.

Le carbaryl est très toxique pour les abeilles et les lombrics. Dans le cas des abeilles, la DL_{50} par voie orale est de 0,16 µg/insecte (soit 1-2 mg/kg).

On est fondé à penser que le carbaryl puisse avoir une influence temporaire sur la composition en espèces des écosystèmes terrestres et aquatiques. Par exemple, une étude a montré que les effets exercés sur certaines communautés d'invertébrés terrestres pourraient persister au moins 10 mois après un seul épandage.

1.7 Effets sur les animaux d'expérience et les systèmes d'épreuve in vitro

La toxicité aiguë, exprimée sous la forme de la DL_{50}, varie considérablement selon l'espèce, la formulation et le véhicule du produit. La DL_{50} estimative par voie orale pour le rat varie de 200 à 850 mg(kg. Les chats sont plus sensibles, avec une DL_{50} de 150 mg/kg. Les porcs et les singes le sont moins, avec une DL_{50} > 1000 mg/kg.

Une concentration de 792 mg de matière active par m^3, qui constitue la valeur maximale qu'on puisse obtenir pour un aérosol, a produit, au cours d'une exposition de 4 heures, une mortalité de

20% (1/5) chez des rattes. A des concentrations de 20 mg/m^3, des aérosols de carbaryl ont provoqué une réduction de l'activité cholinestérasique chez des chats lors d'une exposition de 4 heures, mais cette concentration n'a eu aucun effet observable chez des rats.

Le carbaryl est légèrement irritant pour l'oeil et n'a que peu ou pas de pouvoir sensibilisateur. Lors d'études à long terme, la concentration sans effet nocif observable a été évaluée à 10 mg/kg de poids corporel (200 mg/kg de nourriture) pour le rat et à 1,8 mg/kg de poids corporel (100 mg/kg de nourriture) pour le chien. Chez le chat, soumis à une exposition de longue durée par inhalation, la concentration sans effet nocif observable est de 0,16 mg/m^3. Le carbaryl a un faible potentiel d'accumulation.

1.7.1 Reproduction

On a montré que le carbaryl avait des effets indésirables sur la reproduction des mammifères et le développement périnatal chez un certain nombre d'espèces. Ces effets sur la reproduction consistent en une réduction de la fécondité, une diminution de l'effectif des portées et une réduction de la viabilité postnatale. Les effets toxiques du carbaryl sur le développement se traduisent pas un certain nombre de morts foetales, une réduction du poids foetal et la présence de malformations. A l'exception d'un petit nombre d'études, les effets nocifs sur la reproduction et le développement n'ont été constatés en totalité qu'à des doses manifestement toxiques pour la mère, et dans un certain nombre de cas, la mère était plus sensible au carbaryl que l'embryon ou le foetus. Ces effets toxiques sur la femelle gestante consistaient en une mortalité accrue, une réduction de la croissance et des dystocies. Les données indiquent que, par rapport à l'organisme adulte, la fonction de reproduction et le processus de développement des mammifères n'est pas particulièrement sensible au carbaryl.

1.7.2 Mutagénicité

Un certain nombre de tests *in vitro* et *in vivo* ont été effectués sur la carbaryl afin d'en évaluer le pouvoir mutagène; divers points d'aboutissement de ces effets ont été étudiés sur divers systèmes (bactéries, levures, végétaux, insectes et mammifères).

Les données disponibles montrent que le carbaryl n'a aucune tendance à endommager l'ADN. On ne dispose d'aucun rapport confirmant les caractères mutagènes suivants: induction de recombinaisons mitotiques, conversion génique, et synthèse non programmée de l'ADN chez les procaryotes (*H. influenzae, B. subtilis*) ni chez les eucaryotes (*S. cerevisiae, A. nidulans*, lymphocytes humains en culture et hépatocytes de rat) *in vitro*.

La recherche de mutations géniques, qui a donné lieu à un grand nombre d'épreuves sur systèmes bactériens, a toujours donné des résultats négatifs, sauf dans deux cas. Lors de plusieurs études portant sur les mutations géniques et effectuées sur des cellules mammaliennes *in vitro*, le carbaryl n'a donné qu'un seul résultat positif équivoque dans une de ces études. Toutefois, cette étude présentait un certain nombre de défauts et ce résultat n'a pas été confirmé par ceux d'autres études comparables.

Des lésions chromosomiques ont été observées *in vitro* sur des cellules humaines, des cellules de rat et de hamster ainsi que des cellules végétales exposées à des fortes doses de carbaryl. Aucun effet de ce genre n'a été observé lors d'épreuves *in vivo* sur des systèmes mammaliens, même à des doses atteignant 1000 mg/kg.

On a montré que le carbaryl perturbe le mécanisme d'élongation des fibres du fuseau chez les cellules végétales et mammaliennes *in vitro*. On ne sait pas encore très bien si les résultats des épreuves effectuées sur des végétaux sont extrapolables à l'homme.

Compte tenu de la base de données sont on dispose actuellement, on peut conclure que rien n'autorise à soupçonner le carbaryl de présenter un risque d'effets mutagènes pour les cellules somatiques ou germinales de l'homme.

Un dérivé nitrosé du carbaryl, le *N*-nitrosocarbaryl, peut provoquer des recombinaisons mitotiques et des conversions géniques chez les procaryotes (*H. influenzae, B. subtilis*) et les eucaryotes (*S. cerevisiae*) *in vitro*, et il donne des résultats positifs lors de "spot tests" effectués sur *E. coli*.

En outre, les résultats expérimentaux indiquent que le *N*-nitroso-carbaryl se lie à l'ADN provoquant la formation de liaisons alcalino-sensibles et des cassures monocaténaires.

Il n'est pas établi que le nitrosocarbaryl soit un agent clastogène *in vivo* (cellules de la moelle osseuse et cellules germinales) même à doses toxiques élevées.

1.7.3 Cancérogénicité

De nombreuses études ont été consacrées au pouvoir cancérogène du carbaryl chez le rat et la souris. La plupart de ces études ont donné des résultats négatifs mais il s'agit de travaux anciens qui ne satisfont pas aux normes actuelles. Quoiqu'il en soit, de nouvelles études portant sur ces mêmes animaux et qui, elles, satisfont aux exigences modernes, sont actuellement en cours[a]. La dernière évaluation du CIRC (CIRC, 1987) a conclu que l'existence de cancers imputables au carbaryl n'était pas documentée chez l'homme et qu'on ne possédait pas de preuves suffisantes d'un pouvoir cancérogène de cette substance chez les animaux de laboratoire. Il n'a donc pas été possible de classer le carbaryl en fonction de son pouvoir cancérogène pour l'homme (Groupe 3).

On a montré que le *N*-nitrosocarbaryl induisait des tumeurs locales chez les rats (sarcomes au point d'injection ou carcinomes spinocellulaires au niveau de la portion cardiaque de l'estomac, lorsque la substance est administrée par voie orale). Etant donné la biochimie du carbaryl chez l'homme, on peut considérer comme négligeable le risque de cancérisation par le *N*-nitrosocarbaryl résultant d'une exposition humaine au carbaryl.

1.7.4 Effets sur les différents organes et systèmes

a) Système nerveux

Les effets du carbaryl sur le système nerveux tiennent essentiellement à l'inhibition de la cholinestérase qui est généralement passagère. Ces effets ont été étudiés sur des rats et des singes. Des doses de 10 à 20 mg de carbaryl par kg, administrées pendant 50 jours par voie orale, ont provoqué des perturbations dans

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[a] Ces études n'ont pas encore fait l'objet d'un examen par le PISC. La société qui effectue ces travaux indique qu'aux doses les plus fortes étudiées, on note une augmentation significative de la fréquence des tumeurs chez les deux espèces.

l'apprentissage et l'exécution de certaines épreuves par les rats traités.

Lors d'une petite étude portant sur des porcs, du carbaryl administré pendant 72 à 82 jours en mélange avec la nourriture à raison de 150 mg/kg de poids corporel, a produit un certain nombre d'effets neuromusculaires. On a observé en outre chez des poulets ayant reçu de fortes doses de carbaryl, une faiblesse réversible des pattes. Aucun signe de démyélinisation n'a été observé dans le cerveau, le nerf sciatique ou les coupes de moelle épinière examinées au microscope. On n'a pas observé d'effets de ce genre à l'issue d'études à long terme sur des rongeurs.

b) Système immunitaire

Administré *in vivo* à des doses provoquant des signes cliniques manifestes, le carbaryl exerce divers effets sur le système immunitaire. Nombre de ces effets ont été observés à des doses voisines de la DL_{50}. Dans la plupart des études où les doses utilisées permettaient la survie des lapins et des souris examinés, on n'a pas observé d'effets significatifs sur le système immunitaire. Plusieurs de ces travaux présentaient des défauts, par exemple un manque de cohérence et parfois des contradictions manifestes dans les résultats, défauts qui ne permettent pas de dégager des résultats obtenus un mécanisme immunotoxique bien défini.

c) Sang

Le carbaryl affecterait l'hémostase mais les résultats concernant le sens de cet effet sont contradictoires. On a observé que le carbaryl produisait une augmentation de la formation de méthémoglobine liée à la dose dans des érythrocytes de moutons présentant un déficit en glucose-6-phosphate-déshydrogénase. La sérum-albumine humaine réagit *in vitro* sur le groupement ester du carbaryl. Le carbaryl se lie aux acides aminés libres.

d) Foie

On a fait état de troubles affectant le métabolisme des glucides et la synthèse des protéines au niveau du foie ainsi que d'une perturbation de la fonction détoxifiante de cet organe chez les mammifères. Le carbaryl induit faiblement l'activité pharmaco-

métabolisante des microsomes hépatiques. Il y a raccourcissement de la durée du sommeil induit par le phénobarbital. Les taux hépatiques de cytochrome P-450 et b_5 sont augmentés. Ces modifications du métabolisme hépatique pourraient expliquer en partie le triplement de la DL_{50} pour le carbaryl observé chez des rats préalablement traités par cette substance.

e) Fonction gonadotrope

Il a été signalé que le carbaryl augmentait la fonction gonadotrope de l'hypophyse chez le rat.

1.7.5 Mécanisme fondamental de la toxicité

Le carbaryl est un inhibiteur de l'activité cholinestérasique. Cet effet est lié à la dose et rapidement réversible. On n'a pas observé de vieillissement de la cholinestérase carbamylée. Tous les métabolites reconnus du carbaryl ont une activité anticholinestérasique sensiblement plus faible que le carbaryl lui-même.

1.8 Effets sur l'homme

Le carbaryl est facilement absorbé par inhalation et après administration par voie orale mais moins facilement pas la voie percutanée. Etant donné que l'inhibition de la cholinestérase est le principal mécanisme de l'action du carbaryl, le tableau clinique d'une intoxication par cette substance est dominé par les symptômes correspondants, à savoir: augmentation de la sécrétion bronchique, sueurs profuses, salivation et larmoiement; myosis, bronchoconstriction, crampes abdominales (vomissements et diarrhée); bradycardie; fasciculation des petits muscles (dans les cas graves le diaphragme et les muscles respiratoires sont également atteints); tachycardie, céphalées, vertiges, angoisses, confusion mentale, coma et dépression des centres respiratoires. Ces signes d'intoxication se manifestent rapidement après l'absorption et disparaissent aussi vite une fois que l'exposition a cessé.

Des études contrôlées sur des volontaires humains ont montré que des doses uniques inférieures à 2 mg/kg étaient bien tolérées. Une dose unique de 250 mg (2,8 mg/kg) a suscité des symptômes modérés d'inhibition cholinestérasique (douleurs épigastriques et

sueurs) en l'espace de 20 minutes. Les sujets ont complètement récupéré dans les 2 heures suivant un traitement par le sulfate d'atropine.

En cas d'exposition excessive d'origine professionnelle au carbaryl, on observe des symptômes légers bien avant qu'une dose dangereuse ne soit absorbée, ce qui explique que les cas graves d'intoxication professionnelle par le carbaryl soient rares. Lors des épandages agricoles, l'exposition percutanée peut être importante. Cependant on n'observe en général aucun effet irritant local, encore que l'on ait décrit des éruptions cutanées à la suite l'éclaboussures accidentelles de carbaryl en formulation liquide.

Les données concernant les effets du carbaryl sur le nombre de spermatozoïdes et la modification de leur morphologie chez les travailleurs de l'industrie sont contradictoires. Aucun effet indésirable sur la reproduction n'a été signalé.

L'indicateur biologique le plus sensible de l'exposition au carbaryl est l'apparition de 1-naphtol dans les urines et la diminution de l'activité cholinestérasique du sang. On peut donc utiliser la concentration urinaire du 1-naphtol comme indicateur biologique à condition qu'il n'y ait pas de 1-naphtol sur le lieu de travail. Lors de certains cas d'exposition professionnelle, on a constaté que 40% des échantillons d'urine contenaient plus de 10 mg de 1-naphtol total par litre. Dans un cas d'intoxication aiguë, on en a trouvé 31 mg/litre d'urine. On considère qu'il y a danger à partir de 10 mg/litre et que les symptômes apparaissent à partir de 30 mg de 1-naphtol par litre d'urine (Fiche d'information sur le carbaryl, OMS, 1973, VBC/DS/75.3).

La mesure de l'activité cholinestérasique peut constituer un test très sensible pour la surveillance médical des travailleurs, à condition que le dosage soit effectué peu après l'exposition.

2. *Conclusions*

On estime que le carbaryl est peu dangereux pour l'homme en raison de sa faible tension de vapeur, de sa décomposition rapide, de la désinhibition spontanée également rapide de la cholinestérase et en raison du fait que les symptômes d'intoxication apparaissent bien

avant qu'une dose dangereuse ne se soit accumulée dans l'organisme. On ne dispose pas encore de bonnes études de cancérogénicité qui satisfassent aux normes actuelles en la matière.

2.1 Exposition de la population générale

Les quantités résiduelles de carbaryl qui demeurent dans les denrées alimentaires et l'eau de boisson après l'utilisation normale de cet insecticide en agriculture, sont très inférieures à la dose journalière acceptable (DJA) (0,01 mg/kg de poids corporel/jour) et il est improbable qu'elles puissent constituer un risque pour la santé de la population dans son ensemble.

2.2 Sous-groupes de population exposés à un risque élevé

Lorsqu'on utilise du carbaryl à des fins de santé publique, soit au domicile soit sur des aires de loisir, il y a un risque d'exposition excessive si l'on ne suit pas les règles concernant son emploi.

2.3 Exposition professionnelle

En faisant respecter des méthodes de travail raisonnables et notamment un certain nombre de précautions de sécurité et des mesures de protection individuelle, avec une surveillance convenable, il n'existe aucun risque qui puisse résulter d'une exposition professionnelle au cours de la fabrication, de la formulation et de l'épandage du carbaryl. Les produits non dilués doivent être manipulés avec de grandes précautions car toute faute de manipulation peut entraîner une contamination cutanée. Sur le lieu de travail, la concentration atmosphérique ne doit pas dépasser 5 mg/m^3.

2.4 Effets sur l'environnement

Le carbaryl est toxique pour les abeilles et les lombrics. On ne doit pas procéder à son épandage pendant la floraison.

En utilisation normale, le carbaryl ne devrait pas poser des problème écologique. Il est adsorbé en grande partie sur les particules de sol et il ne passe pas facilement par lessivage dans les eaux souterraines. Il subit une décomposition rapide dans l'environnement et n'est donc pas persistant. L'emploi de carbaryl

ne devrait pas entraîner d'effets nocifs à court terme sur l'écosystème.

3. Recommandations

- La manipulation et l'épandage du carbaryl doivent s'effectuer en observant les précautions qui s'imposent pour tous les pesticides. On suivra rigoureusement les instructions d'utilisation qui figurent sur l'emballage.

- La fabrication, la formulation, l'emploi et l'élimination du carbaryl doivent se faire avec toutes les précautions voulues pour réduire au minimum la contamination de l'environnement.

- Les travailleurs qui sont soumis à une exposition régulière doivent faire l'objet d'un contrôle médical périodique.

- La chronologie des épandages de carbaryl doit être réglée de manière à éviter tout effet sur les espèces non visées.

- Il importe d'effectuer des études de cancérogénicité satisfaisant aux normes modernes.

RESUMEN Y EVALUACION, CONCLUSIONES Y RECOMENDACIONES

1. Resumen y evaluación

1.1 Identidad, propiedades y métodos analíticos

El 1-naftil *N*-metil carbamato, derivado del ácido carbámico, se conoce por el nombre común de carbarilo. El producto de calidad técnica es un sólido cristalino blanco, de baja volatilidad y escasa hidrosolubilidad, y estable a la luz y al calor, pero fácilmente hidrolizable en medio alcalino. La FAO ha establecido una especificación mínima de pureza del 98%, con un límite de impureza del 0,05% para el β-naftil N-metil carbamato.

Para analizar el carbarilo y sus metabolitos, se pueden utilizar numerosas técnicas, como la cromatografía de capa fina, la espectrofotometría, la cromatografía de gases, la cromatografía líquida de alta presión y la espectrometría de masas con ionización química. Pueden alcanzarse límites de detección inferiores a un nanogramo, y la recuperación supera por lo general el 80%.

1.2 Producción y usos

El carbarilo se viene utilizando desde hace unos 30 años como insecticida de contacto y de ingestión, posee algunas propiedades sistémicas y permite combatir una amplia serie de plagas. La planta de fabricación más importante está en los Estados Unidos. Más de 290 fabricantes transforman el carbarilo para integrarlo en más de 1500 productos diferentes.

1.3 Transporte, distribución y transformación en el medio ambiente

En la mayoría de las situaciones, el carbarilo no persiste en el entorno. En el agua, su semivida por hidrólisis depende de la temperatura, del pH y de la concentración inicial, y varía entre varios minutos y varias semanas. El principal producto de degradación es el 1-naftol.

Se ha estudiado la acumulación de carbarilo en peces de agua dulce, y expresada como factor de bioconcentración en el medio acuático se ha cifrado en valores comprendidos entre 14 y 75. El carbarilo es adsorbido más fácilmente en los suelos que poseen un alto contenido orgánico que en los suelos arenosos. A un ritmo habitual de aplicación conforme con unas «prácticas agrícolas adecuadas», la disipación es rápida, con una semivida de entre 8 días y un mes en condiciones normales. Ocasionalmente, por efecto de la lluvia y del cultivo agrícola, el carbarilo es transportado de la superficie al subsuelo (a un metro de la superficie).

El carbarilo contamina la vegetación durante el rociamiento o por desplazamiento hasta las plantas a través del suelo contaminado.

La degradación del carbarilo en el entorno depende del grado de volatilización, fotodescomposición y degradación química y microbiana que se produzca en el suelo, el agua y las plantas. La descomposición es más rápida cuando el clima es cálido.

1.4 Niveles ambientales y exposición humana

La principal fuente de ingestión de carbarilo entre la población general son los alimentos.

Los residuos hallados en muestras de la ingesta alimentaria total son relativamente escasos, pues oscilan entre cantidades ínfimas y 0,05 mg/kg. En los Estados Unidos, la ingesta diaria durante los primeros años de aplicación de carbarilo fue de 0,15 mg/día por persona (lo contenían el 7,4% de los compuestos); la cifra se redujo a 0,003 mg/día por persona en 1969 (sólo lo contenían un 0,8% de los compuestos). Durante el periodo de aplicación se encuentra carbarilo ocasionalmente en las aguas superficiales y los embalses.

La población general puede estar expuesta al carbarilo durante las operaciones de lucha contra las plagas, en su vivienda o en zonas recreativas.

Los trabajadores pueden estar expuestos al carbarilo durante su fabricación, formulación, envasado, transporte y almacenamiento, así como durante y después de su aplicación. Las concentraciones halladas en la atmósfera del lugar de trabajo durante su producción

oscilaron entre < 1 mg/m^3 y 30 mg/m^3. Si las medidas de protección son inadecuadas, los trabajadores industriales y agrícolas pueden sufrir exposiciones cutáneas importantes.

1.5 Cinética y metabolismo

El carbarilo es absorbido rápidamente por los pulmones y el tracto digestivo. En voluntarios se observó una absorción cutánea del 45% a las 8 horas de aplicar una dosis del producto diluida en acetona. Sin embargo, los datos referentes a la penetración cutánea *in vitro* y a la toxicidad indican que la absorción cutánea se produce por lo general a una velocidad mucho menor.

Las principales vías metabólicas del carbarilo son la hidroxilación del anillo y la hidrólisis. El resultado son numerosos metabolitos que experimentan conjugación, con formación de sulfatos, glucurónidos y mercapturatos hidrosolubles, que se excretan por la orina. Como resultado de la hidrólisis se forman 1-naftol, dióxido de carbono y metilamina. La hidroxilación da lugar a 4-hidroxicarbarilo, 5-hidroxicarbarilo, *N*-hidroximetilcarbarilo, 5-6-dihidro-5-6-dihidroxicarbarilo y 1,4-naftalendiol. El metabolito principal en el hombre es el 1-naftol.

En condiciones normales de exposición, el carbarilo rara vez se acumula en los animales. El producto se excreta principalmente por la orina, debido a que la detoxificación del producto de su hidrólisis, el 1-naftol, se produce principalmente por transformación en conjugados hidrosolubles. La circulación enterohepática de los metabolitos del carbarilo es también considerable, sobre todo tras su administración oral.

El producto de la hidrólisis, el ácido carbámico *N*-naftol, se descompone espontáneamente en metilamina y dióxido de carbono. La posterior desmetilación de la metilamina da lugar a dióxido de carbono y formato, siendo este último excretado principalmente por la orina.

Un pequeño porcentaje de las dosis de carbarilo absorbidas aparecen como metabolitos en la saliva y la leche.

1.6 Efectos en otros organismos en el medio ambiente

En los crustáceos, las CL_{50} oscilan entre 5 y 9 µg/litro (pulgas de agua, mísidos), 8 y 25 µg/litro (anfípodos), y 500 y 2500 µg/litro (cangrejos de río). El margen de sensibilidad es parecido en los insectos acuáticos; Plecoptera y Ephemeroptera (gusarapa y cachipollas) son los grupos más sensibles. Los moluscos son menos sensibles, situándose su CE_{50} en niveles de unos pocos mg/litro. En cuanto a los peces, la mayoría de las CL_{50} están comprendidas entre 1 y 30 mg/litro; el grupo más sensible son los salmónidos.

En el caso de las aves la toxicidad aguda es baja. La DL_{50} para las aves de caza, sean acuáticas o terrestres, es > 1000 mg/kg. El ave más sensible analizada es el mirlo de alas rojas (DL_{50} = 56 mg/kg). En zonas forestales rociadas con 1,1 kg de carbarilo por hectárea no se observó ningún efecto en las aves locales.

El carbarilo es muy tóxico para las abejas y las lombrices de tierra. La DL_{50} oral para las primeras es de 0,18 µg/abeja (aproximadamente 1-2 mg/kg).

Hay indicios de que el carbarilo puede alterar temporalmente la composición de especies en los ecosistemas tanto terrestres como acuáticos. Por ejemplo, un estudio reveló que en determinadas colonias de invertebrados terrestres sus efectos pueden persistir durante por lo menos 10 meses tras una sola aplicación.

1.7 Efectos en animales de experimentación y en sistemas de prueba in vitro

La toxicidad aguda, expresada como DL_{50}, varía considerablemente según las especies, fórmulas y vehículos. Las estimaciones de la DL_{50} oral en la rata oscilan entre 200 y 850 mg/kg. Los gatos son más sensibles, pues presentan una DL_{50} de 150 mg/kg. Los cerdos y los monos son menos sensibles, pues su DL_{50} es > 1000 mg/kg.

La exposición a 792 mg de ingrediente activo de carbarilo nebulizado, que es la máxima concentración a la que se llegó durante 4 horas, provocó la muerte de una de cinco ratas hembra. Aerosoles de carbarilo a concentraciones de 20 mg/m^3 dieron lugar a una disminución de la actividad colinesterasa (ChEA) en gatos durante exposiciones únicas de 4 horas, pero esa misma concentración no tuvo efectos observables en ratas.

El carbarilo produce leves irritaciones oculares y tiene un potencial de sensibilización escaso o nulo. Estudios prolongados revelaron un NOEL de 10 mg/kg de peso corporal (200 mg/kg ingesta alimentaria) en las ratas, y de 1,8 mg/kg de peso corporal (100 mg/kg dieta) en los perros. El NOEL por inhalación prolongada es de 0,16 mg/m^3 en los gatos. El potencial de acumulación de carbarilo es bajo.

1.7.1 Reproducción

Se ha demostrado que el carbarilo tiene efectos adversos sobre la reproducción y el desarrollo perinatal en diversas especies de mamíferos. Los efectos sobre la reproducción comprenden problemas de infertilidad, una disminución del tamaño de las camadas y una reducción de la viabilidad postnatal. Los efectos tóxicos sobre el desarrollo observados son un aumento de la mortalidad *in utero*, una disminución del peso del feto y la aparición de malformaciones. Salvo en un reducido número de estudios, todos los efectos adversos sobre la reproducción y el desarrollo se observaron sólo a dosis manifiestamente tóxicas para la madre, y en varios casos ésta resultó ser más sensible al carbarilo que su prole. Entre los efectos tóxicos para la madre cabe citar la letalidad, una disminución del crecimiento y la distocia. Los datos disponibles indican que los procesos de reproducción y desarrollo de los mamíferos no son especialmente sensibles al carbarilo en comparación con la susceptibilidad del organismo adulto.

1.7.2 Mutagenicidad

Se ha evaluado la posible mutagenicidad del carbarilo mediante diversas pruebas *in vitro* e *in vivo*, empleando para ello bacterias, levadura, plantas, insectos y mamíferos, y analizando diversos puntos finales.

Según los datos disponibles, el carbarilo no es lesivo para el ADN. No se ha notificado ningún dato que confirme que ha habido inducción de la recombinación mitótica, conversión génica o síntesis imprevista de ADN en procariotas (*H. influenzae, B. subtilis*) y eucariotas (*S. cerevisiae, A. nidulans*, linfocitos humanos en cultivo, y hepatocitos de rata) *in vitro*.

Se obtuvieron resultados negativos en las pruebas de detección de mutaciones génicas en un gran número de ensayos realizados con bacterias, salvo en dos casos. En varios estudios de mutagenicidad del carbarilo llevados a cabo con células de mamífero *in vitro*, se obtuvo sólo un resultado positivo equívoco en un estudio de células en cultivo. Ese estudio, sin embargo, presentaba varias deficiencias y sus resultados no han sido confirmados en estudios comparables.

Se han notificado lesiones cromosómicas a altas dosis de carbarilo en células humanas y de rata y hámster *in vitro*, así como en plantas. No se han observado efectos de ese tipo en pruebas *in vivo* con mamíferos, ni siquiera a dosis de hasta 1000 mg/kg.

Se ha mostrado que el carbarilo altera el mecanismo de las fibras del huso en células de plantas y mamíferos *in vitro*. Es dudoso el interés de realizar ensayos con plantas para extrapolar sus resultados al hombre.

Cabe concluir que los datos disponibles no corroboran la suposición de que el carbarilo plantea un riesgo de inducción de cambios génicos en las células somáticas o germinales del hombre.

El producto nitrosado del carbarilo, el *N*-nitrosocarbarilo, puede inducir fenómenos de recombinación mitótica y conversión génica en los procariotas (*H. influenzae, B. subtilis*) y eucariotas (*S. cerevisiae*) *in vitro*, y arroja resultados positivos en las pruebas *in situ* con *E. coli*.

Además, resultados experimentales indican que el *N*-nitroso-carbarilo se une al ADN, causando la ruptura de los enlaces alcalisensibles y de las cadenas simples.

No se ha demostrado que el nitrosocarbarilo sea clastógeno *in vivo* (médula ósea y células germinales), ni siquiera a dosis tóxicas elevadas.

1.7.3 Carcinogenicidad

Se han realizado numerosos estudios en la rata y el ratón para determinar los posibles efectos carcinógenos del carbarilo. Los resultados de la mayoría de esos estudios fueron negativos, pero se

trata de trabajos realizados hace muchos años y que no satisfacían los criterios actuales. Se están realizando nuevos estudios conformes con los actuales criterios en ratones y ratas.[a] En la más reciente evaluación del CIIC (CIIC, 1987) se llegaba a la conclusión de que no había información sobre el cáncer en el hombre y de que los indicios de carcinogenicidad en animales de experimentación eran insuficientes. No se podía clasificar el carbarilo en lo que se refiere a su carcinogenicidad para la especie humana (Grupo 3).

Se ha mostrado que el *N*-nitrosocarbarilo induce la aparición de tumores localmente en la rata (sarcoma en el lugar de la inyección o carcinoma de células escamosas del antro cardiaco al administrarlo por vía oral). Teniendo en cuenta las transformaciones químicas que sufre el carbarilo en el hombre, el riesgo de carcinogenicidad por *N*-nitrosocarbarilo como consecuencia de la exposición a esta sustancia puede considerarse insignificante.

1.7.4 Efectos en distintos órganos y sistemas

a) Sistema nervioso

Los efectos del carbarilo sobre el sistema nervioso se deben principalmente a la inhibición de la colinesterasa y son por lo general temporales. En unos estudios sobre los efectos en el sistema nervioso central de ratas y monos se observó que la administración oral de 10-20 mg/kg durante 50 días provocaba trastornos del aprendizaje y del comportamiento en las ratas.

En un pequeño estudio realizado con cerdos, el carbarilo (150 mg/kg de peso corporal en la alimentación durante 72-82 días) tuvo diversos efectos neuromusculares. Se observó una debilidad reversible de las patas en pollos sometidos a altas dosis de carbarilo. No se observaron signos de desmielinización en los cortes de cerebro, nervio ciático o médula espinal examinados al microscopio. Tampoco se notaron efectos de esa índole en estudios prolongados realizados con roedores.

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[a] El IPCS aún no ha examinado esos estudios. La sociedad encargada de realizarlos ha indicado que se observa un aumento significativo de tumores a la dosis más elevada en las dos especies.

b) Sistema inmunitario

Se ha notificado que el carbarilo administrado *in vivo* a dosis que producen claros signos clínicos tiene diversos efectos en el sistema inmunitario. Muchos de los efectos descritos se detectaron a dosis cercanas a la DL_{50}. La mayoría de los estudios llevados a cabo con conejos y ratones a dosis compatibles con la supervivencia no han revelado efectos de importancia en el sistema inmunitario. Sin embargo, varios de esos estudios adolecían de incoherencia y a veces de contradicción patente entre los resultados, lo cual no permite describir un mecanismo inmunotóxico bien definido.

c) Sangre

Se ha señalado que el carbarilo afecta a la coagulación, pero existe cierta controversia en cuanto al tipo de efecto. En eritrocitos de oveja con déficit de glucosa-6-fosfato deshidrogenasa, el carbarilo provocó un aumento dosis-dependiente de la formación de metahemoglobina (Met-Hb). La albúmina sérica humana reaccionó *in vitro* con el grupo éster del carbarilo. El carbarilo se une a los aminoácidos libres de la sangre.

d) Hígado

Se han señalado trastornos del metabolismo de los carbohidratos y de la síntesis de proteínas, así como de la función de detoxificación en el hígado de ciertos mamíferos. El carbarilo es un inductor ligero de la actividad de metabolización de medicamentos que reside en los microsomas hepáticos. Se observa un acortamiento del periodo de sueño inducido por el fenobarbital. Los niveles hepáticos de citocromo P-450 y b_5 aumentan. Los cambios del metabolismo hepático son tal vez parcialmente responsables de la triplicación de la DL_{50} por carbarilo en ratas tratadas previamente con dicho compuesto.

e) Función gonadotrópica

Se ha señalado que el carbarilo estimula la función gonadotrópica de la hipófisis de la rata.

1.7.5 Mecanismo principal de toxicidad

El carbarilo inhibe la acción de la colinesterasa, efecto que depende de la dosis y es fácilmente reversible. No se observó ningún fenómeno de «maduración» de la colinesterasa carbamilada. Todos los metabolitos identificados del carbarilo son considerablemente menos activos que éste como inhibidores de la colinesterasa.

1.8 Efectos en el hombre

El carbarilo es fácilmente absorbido por inhalación y por vía oral, y menos fácilmente por vía cutánea. Como su principal mecanismo de acción es la inhibición de la colinesterasa (ChE), en el cuadro clínico de la intoxicación predominan los síntomas de esa inhibición, tales como: hipersecreción bronquial, aumento de la sudación, de la salivación y del lagrimeo; pupilas puntiformes, broncoconstricción, espasmos abdominales (vómitos y diarrea); bradicardia; fasciculación de los músculos finos (que también afecta en los casos graves al diafragma y a los músculos respiratorios); taquicardia; cefalea, vértigo, ansiedad, confusión mental, convulsiones y coma; y depresión del centro respiratorio. Los signos de intoxicación aparecen rápidamente tras la absorción y desaparecen pronto al cesar la exposición.

En estudios controlados realizados con voluntarios se observó una buena tolerancia a dosis únicas inferiores a 2 mg/kg. Una dosis única de 250 mg (2,8 mg/kg) provocó síntomas moderados de inhibición de la ChE (dolor epigástrico y sudación) al cabo de 20 minutos. La recuperación completa se produjo tras dos horas de tratamiento con sulfato de atropina.

En los casos de sobreexposición ocupacional al carbarilo, se observan síntomas leves mucho antes de que llegue a absorberse una dosis peligrosa; de ahí que raras veces se produzcan casos graves de intoxicación ocupacional por este compuesto. Durante las aplicaciones agrícolas, la exposición cutánea puede desempeñar un papel importante. No suelen observarse efectos irritantes locales, pero se ha descrito la aparición de exantema cutáneo tras la salpicadura accidental con formulaciones de carbarilo.

Los datos acerca de los efectos del carbarilo sobre el número y la morfología de los espermatozoides en trabajadores industriales son discordantes. No se han notificado efectos adversos sobre la reproducción.

El indicador biológico más sensible de la exposición al carbarilo es la aparición de 1-naftol en la orina y una disminución de la actividad ChE de la sangre. Si no hay 1-naftol en el entorno de trabajo, los niveles urinarios de este producto se pueden emplear como indicador biológico. Durante la exposición ocupacional, el 40% de las muestras de orina contenían más de 10 mg de 1-naftol/litro. En un caso de intoxicación aguda se hallaron 31 mg/litro en la orina. El nivel de riesgo es > 10 mg/litro, y el nivel de aparición de síntomas, 30 mg 1-naftol/litro de orina (hoja de datos sobre el carbarilo, OMS, 1973, VBC/DS/75.3).

El análisis de la actividad ChE puede ser una prueba de gran sensibilidad a efectos de vigilancia, siempre que se realice poco después de la exposición.

2. Conclusiones

Se considera que los riesgos que plantea el carbarilo para el ser humano son escasos, debido a su baja presión de vapor, a su rápida degradación y a la recuperación espontánea y rápida de la colinesterasa inhibida, así como al hecho de que los síntomas aparecen normalmente mucho antes de que pueda haberse acumulado en el organismo una dosis peligrosa. Aún no se dispone de estudios satisfactorios sobre la carcinogenicidad conformes con los criterios actuales.

2.1 Exposición de la población general

Los niveles de residuos de carbarilo presentes en los alimentos y el agua de bebida, resultantes de su uso normal en la agricultura, son muy inferiores a la ingesta diaria admisible (IDA) (0,01 mg/kg de peso corporal al día), y difícilmente pueden representar un riesgo para la salud de la población general.

2.2 Subpoblaciones de alto riesgo

El uso del carbarilo con fines de salud pública en la vivienda o en zonas recreativas puede ser causa de sobreexposición si se descuidan las normas aconsejadas para su aplicación.

2.3 Exposición ocupacional

Si se vela por el cumplimiento de unas prácticas laborales razonables, en particular las medidas de seguridad, la protección del personal y una supervisión adecuada, la exposición ocupacional durante la fabricación, formulación y aplicación de carbarilo no planteará riesgos. Las concentraciones no diluidas se deben manejar con sumo cuidado, dado que unas prácticas laborales incorrectas pueden ser causa de contaminación cutánea. Las concentraciones en el aire del lugar de trabajo no deberían superar los 5 mg/m^3.

2.4 Efectos en el medio ambiente

El carbarilo es tóxico para las abejas y las lombrices. No debería aplicarse a los cultivos durante la floración.

Si se emplea normalmente, el carbarilo no debería suscitar preocupación desde el punto de vista del medio ambiente. El carbarilo se adsorbe en buena parte en el suelo y no se lixivia fácilmente hacia las aguas subterráneas. Se degrada rápidamente en el entorno, por lo que no tiende a persistir. El uso de carbarilo no debería tener efectos nocivos a corto plazo en el ecosistema.

3. Recomendaciones

- La manipulación y la aplicación del carbarilo se deberían realizar adoptando las precauciones previstas para todo plaguicida y siguiendo minuciosamente las instrucciones suministradas en el envase para emplear correctamente el producto.

- Deberían controlarse cuidadosamente la fabricación, la formulación, el uso y la eliminación del carbarilo, con objeto de reducir al mínimo la contaminación del medio ambiente.

- Los trabajadores expuestos regularmente al producto deberían someterse a chequeos periódicos.

- Debería determinarse la época de aplicación del carbarilo de manera que no afecte a las especies que no se desee combatir.

- Deberían realizarse estudios de carcinogenicidad que satisfagan los criterios actuales.

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