criteria for a recommended standard....

OCCUPATIONAL EXPOSURE TO CARBARYL

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

SEPTEMBER 1976

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

DHEW (NIOSH) Publication No. 77-107

CRITERIA DOCUMENT
RECOMMENDATIONS FOR AN OCCUPATIONAL
EXPOSURE STANDARD FOR CARBARYL

Table of Contents

CONTENTS

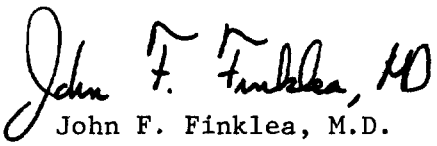
PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. The National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices, to provide relevant data from which valid criteria for effective standards can be derived. Recommended standards for occupational exposure, which are the result of this work, are based on the health effects of exposure. The Secretary of Labor will weigh these recommendations along with other considerations such as feasibility and means of implementation in developing regulatory standards.

It is intended to present successive reports as research and epidemiologic studies are completed and as sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on carbaryl by members of my staff and the valuable constructive comments by the Review Consultants on Carbaryl, by the ad hoc committees of the Society for Occupational and Environmental Health and the American Medical Association, and by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine. The NIOSH recommendations for standards are not

necessarily a consensus of all the consultants and professional societies that reviewed this criteria document on carbaryl. Lists of the NIOSH Review Committee members and of the Review Consultants appear on the following pages.



John F. Finklea, M.D.
Director, National Institute for
Occupational Safety and Health

The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and recommended standard for carbaryl. The Division review staff for this document consisted of Howard L. McMartin, M.D., and Keith H. Jacobson, Ph.D., with Clara H. Williams, Ph.D. (consultant).

Stanford Research Institute developed the basic information for consideration by NIOSH staff and consultants under contract No. CDC-99-74-31. Gamil Debbas, Ph.D. had NIOSH program responsibility and served as criteria manager.

REVIEW COMMITTEE
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

Victor E. Archer, M.D.
Western Area Occupational Health Laboratory

Benjamin H. Bruckner, Ph.D.
Office of Extramural Activities

David Groth, M.D.
Division of Laboratories and Criteria Development

Joseph Mastromauro
Division of Technical Services

Alexander Teass, Ph.D.
Division of Laboratories and Criteria Development

US Department of Labor Liaison:

George Ozga, Ph.D.
Office of Standards Development
Occupational Safety and Health Administration

REVIEW CONSULTANTS ON CARBARYL

John P. Frawley, Ph.D.
Director of Toxicology
Hercules, Incorporated
Wilmington, Delaware 19899

Vernon Jensen
Oil, Chemical, and Atomic
International Workers Union
Washington, DC 20006

Howard I. Maibach, M.D.
Professor of Dermatology
University of California
School of Medicine
San Francisco, California 94143

Stanley Pier, Ph.D.
Associate Professor of Environmental
Health Sciences
University of Texas
School of Public Health
Houston, Texas 77025

Richard J. Sexton, M.D.
Medical Director
Union Carbide Corporation
Chemical and Plastics Division
Charleston, West Virginia 25330

Jack Spence, Ph.D.
Manager
Environmental Health and Toxicology
Standard Oil Company of California
Richmond, California 94104

William W. Steffan
Supervising Industrial Hygiene
Engineer of Occupational Health
Section
State of California Department of Health
San Francisco, California 94101

I. RECOMMENDATIONS FOR A CARBARYL STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to carbaryl in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and safety of employees for up to a 10-hour work shift, 40-hour workweek, over a working lifetime. Compliance with all sections of the standard should therefore prevent adverse effects of carbaryl on the health and safety of employees. The recommended standard is measurable by techniques that are valid, reproducible, and available to industry and government agencies. Sufficient technology exists to permit compliance with the recommended standard. The criteria and standard will be subject to review and revision as necessary.

The criteria and the recommended standard apply to any manufacturing, formulating, or applying operation in which carbaryl is produced, packaged, processed, mixed, blended, handled, or used, or where employees are otherwise potentially exposed. "Carbaryl" is the generic name for the 1-naphthyl ester of N-methylcarbamic acid or 1-naphthyl N-methylcarbamate. "Action level" is defined as one-half the recommended time-weighted average (TWA) environmental exposure limit for carbaryl. "Occupational exposure to carbaryl" is defined as exposure to airborne carbaryl at concentrations greater than the action level. Exposure to carbaryl at concentrations less than or equal to the action level shall not require adherence to the recommended standard, except for Sections 3, 4(a,b), and 7(b). If employees are potentially exposed to other chemicals, such as pesticide vehicles, diluents, or emulsifiers or other pesticides, provisions of any

applicable standards for such chemicals shall also be followed.

Section 1 - Environmental (Workplace Air)

(a) Concentration

Occupational exposure to carbaryl shall be controlled so that no employee is exposed to carbaryl at concentrations greater than 5 mg/cu m in air determined as a TWA concentration for up to a 10-hour work shift, 40-hour workweek.

(b) Sampling and Analysis

Procedures for sampling and analysis of environmental samples shall be as provided in Appendices I and II, or by any methods shown to be at least equivalent in accuracy, precision, and sensitivity to the methods specified.

Section 2 - Medical

Medical surveillance shall be made available as outlined below to workers subject to occupational exposure to carbaryl.

Physicians responsible for workers who may be occupationally exposed to carbaryl shall be familiar with the information contained in Appendix III which describes the suggested treatment of intoxication by this compound.

(a) Medical examinations shall include:

(1) An initial or interim work history.

(2) A comprehensive initial or interim medical history to include at least any history of frequent headaches, dizziness, tightness in

the chest, dimness of vision, and difficulty in focusing eyes.

(3) A physical examination which shall be directed toward at least the cardiorespiratory system, central nervous system (CNS), vision, and kidneys. A complete urinalysis including microscopic examination shall be performed.

(4) Those workers with a history of glaucoma, cardiovascular disease, hepatic disease, renal disease, central nervous system (CNS) abnormalities, and those using anticholinergic drugs shall be counseled about working in jobs involving exposure to carbaryl. Workers shall be advised that a review of the available scientific data warrants consideration of possible effects of carbaryl on the reproductive system. Initial information based on experimental animal studies indicates possible effects on the developing fetus, as well as on other reproductive processes in both men and women. Female workers shall be further informed that the status of present toxicologic information does not necessarily indicate the need for avoiding exposure to carbaryl during pregnancy but suggests that appropriate steps be taken to minimize exposure wherever possible. In addition, nursing mothers who may be exposed to carbaryl shall be informed of the possibility that the baby may ingest the compound from the maternal milk and shall be counseled to minimize exposure in the workplace.

(5) Initial medical examinations shall be made available to all workers within 60 days of the promulgation of a standard based on these recommendations.

(6) Periodic examinations shall be made available on a yearly basis or at some other interval determined by the responsible physician.

(7) At the time of the preplacement examination, it is recommended that a preexposure baseline erythrocyte cholinesterase activity be determined.

(8) A judgment of the worker's physical ability to use negative or positive pressure respirators.

(b) Emergency first-aid services shall be established, under the direction of the responsible physician, to provide care to any worker acutely intoxicated by carbaryl (See Appendix III).

(c) Appropriate medical services and surveillance shall be provided to any worker with adverse health effects from exposure to carbaryl.

(d) Pertinent medical records shall be maintained for all workers occupationally exposed to carbaryl for at least 5 years after termination of employment. These records shall be available to the designated medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employee or former employee, and of the employer.

Section 3 - Labeling and Posting

(a) Labeling

Containers of carbaryl shall bear the following label in addition to, or in combination with, labels required by other statutes, regulations, or ordinances:

CARBARYL

CAUTION!

HARMFUL IF INHALED, SWALLOWED, OR LEFT ON THE SKIN
NO SMOKING

Avoid breathing dust or spray mist.
Avoid contact with eyes, skin, and clothing.
Wash hands and face thoroughly before eating.
Wear long-sleeved work clothes.
Shower or bathe and change into clean clothing after work.

First Aid: On skin contact with carbaryl, wash with soap and water. On eye contact, flush eyes with copious amounts of water. If inhaled or swallowed, consult a physician.

Note to Physician: Carbaryl is a moderate, reversible cholinesterase inhibitor. Atropine sulfate is the antidote. Do not use pralidoxime chloride (2-PAM).

(b) Posting

The following sign shall be posted in a readily visible location at or near entrances to manufacturing and formulating areas containing carbaryl, and at other areas in which there is a risk of exposure:

CARBARYL

CAUTION!

HARMFUL IF INHALED, SWALLOWED, OR LEFT ON THE SKIN
NO SMOKING

Avoid breathing dust or spray mist.
Avoid contact with eyes, skin, and clothing.
Wash hands and face thoroughly before eating.
Wear long-sleeved work clothes.
Shower or bathe and change into clean clothing after work.

First Aid: On skin contact with carbaryl, wash with soap and water. On eye contact, flush eyes with copious amounts of water. If inhaled or swallowed, consult a physician.

Warning signs shall be printed in English and in the predominant language of non-English-reading employees, if any, unless employers use equally effective means to ensure that non-English-reading employees know the hazards associated with carbaryl and the areas in which there is exposure to carbaryl. Employers shall ensure that illiterate employees also know these hazards and the locations of these areas.

Section 4 - Personal Protective Equipment and Clothing

(a) Protective Clothing

Any employee whose work involves likely exposure of the skin to carbaryl or carbaryl formulations, eg, mixing or formulating, shall wear full-body coveralls or the equivalent, impervious gloves, ie, highly resistant to the penetration of carbaryl, impervious footwear, and, when there is danger of carbaryl coming in contact with the eyes, goggles or a face shield. Any employee engaged in field application of carbaryl shall be provided with, and required to wear, the following protective clothing and equipment: goggles, full-body coveralls, impervious footwear, and a protective head covering. Employees working as flaggers in the aerial application of carbaryl shall be provided with, and required to wear, full-body coveralls or waterproof rainsuits, protective head coverings, impervious gloves and impervious footwear.

(b) Eye Protection

Safety goggles and face shields, when required, shall conform to 29 CFR 1910.133.

(c) Respiratory Protection

Engineering controls shall be used when necessary to maintain

airborne carbaryl concentrations below the recommended workplace environmental limit. Compliance with the workplace environmental limit by the use of respirators is allowed only when airborne carbaryl concentrations are in excess of the workplace environmental limit because required engineering controls are being installed or tested, when nonroutine maintenance or repair is being accomplished, or during emergencies. When a respirator is thus permitted, it shall be selected and used in accordance with the following requirements:

(1) To determine the type of respirator to be used, the employer shall measure, when possible, the workplace air concentration of carbaryl initially and thereafter whenever process, worksite, climate, or control changes occur that are likely to increase the carbaryl concentrations. This requirement does not apply when only air-supplied positive pressure respirators are used. The employer shall ensure that no employee is exposed to carbaryl in excess of the recommended TWA environmental limit because of improper respirator selection, fit, use, or maintenance.

(2) Any employee applying carbaryl by aircraft shall be provided with, and required to carry in the aircraft, a respirator as specified in Table I-1.

(3) Employees working as flaggers shall wear appropriate respirators as specified in Table I-1 when exposure to an airborne carbaryl concentration above that specified in Section 1 is likely to occur. Respirators may also be worn during the time necessary to install or test the required engineering controls, for nonroutine operations at concentrations in excess of the recommended TWA environmental limit

resulting from maintenance or repair activities, or during emergencies when air concentrations of carbaryl may exceed the recommended TWA environmental limit.

(4) The employer shall establish and enforce a respiratory protective program meeting the requirements of 29 CFR 1910.134.

(5) The employer shall provide and ensure employee use of respirators approved under the provisions of 30 CFR 11 and in accordance with Table I-1, except during all agricultural applications of carbaryl in which the dust- or spray-applicator nozzle is directed upward when a chin-style respirator equipped with a full-face gas mask pesticide filter and canister shall be provided regardless of the environmental carbaryl concentration.

(6) Respirators specified for use in higher concentrations of carbaryl may be used in atmospheres of lower concentrations.

(7) The employer shall ensure that respirators are clean and adequately maintained and that employees are instructed on the use of respirators assigned to them.

(8) Canisters shall be discarded and replaced with fresh canisters in accord with the manufacturer's recommendations or if the odor of the insecticide breaks through. Unused canisters shall be discarded and replaced when seals are broken, after 3 years if seals are unbroken, or as recommended by the manufacturer.

TABLE I-1

RESPIRATOR SELECTION GUIDE

Concentration	Respirator Type
50 mg/cu m or less	(1) Any supplied-air respirator* (2) Any self-contained breathing apparatus*
250 mg/cu m or less	(1) Any supplied-air respirator with a full facepiece, helmet, or hood (2) Any self-contained breathing apparatus with full facepiece
625 mg/cu m or less	Type C supplied-air respirator operated in pressure-demand or other positive pressure or continuous-flow mode
Greater than 625 mg/cu m, or entry into and exit from unknown concentrations	(1) Self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive pressure mode (2) Combination respirator which includes Type C supplied-air respirator with full facepiece operated in pressure-demand mode and auxiliary self-contained breathing apparatus operated in pressure-demand or other positive pressure mode
Firefighting	Self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive pressure mode
Emergency escape	(1) Any gas mask providing protection against organic vapors and particulates** (2) Any escape self-contained breathing apparatus

*If eye irritation occurs, a full facepiece respirator must be worn.
**Including pesticide respirators meeting the requirements of this class

Section 5 - Informing Employees of Hazards from Carbaryl

At the beginning of their employment in a carbaryl area, workers shall be informed of the hazards, relevant symptoms of overexposure, appropriate emergency procedures, and proper conditions and precautions for safety. The information shall be kept on file and shall be readily accessible to the worker at all places of employment where occupational exposure to carbaryl is likely.

Employers shall institute a continuing educational program to ensure that all workers have current knowledge of job hazards, proper maintenance procedures, and cleanup methods, and that they know how to use respiratory protective equipment and protective clothing correctly. Employees should be informed of the possible additive effects from taking anticholinesterase medication.

Information as required shall be recorded on the "Material Safety Data Sheet" shown in Appendix IV, or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a) Emergency Procedures

Emergency procedures shall be formulated in advance for all work areas where a reasonable potential for emergencies exists, and employees shall be instructed in their implementation.

(1) Procedures shall include prearranged plans for obtaining emergency medical care and for necessary transportation of injured workers.

(2) Approved eye, skin, and respiratory protection as

specified in Section 4 shall be used by personnel essential to emergency operations.

(3) Employees not essential to emergency operations shall be evacuated from exposure areas during emergencies. Perimeters of areas of hazardous exposures shall be delineated, posted, and secured.

(4) Personnel who have to shut off sources of carbaryl, clean up spills, and repair leaks shall be properly trained in such procedures and adequately protected against the attendant hazards.

(b) Engineering Controls

Engineering controls, such as process enclosure or local exhaust ventilation, shall be used when necessary to prevent airborne concentrations of carbaryl from exceeding the recommended TWA environmental limit. Ventilation systems shall be designed to prevent the accumulation or recirculation of carbaryl in the workplace and to remove carbaryl effectively from the breathing zones of exposed employees. Exhaust ventilation systems discharging to outside air must conform with applicable local, state, and federal air pollution regulations. Ventilation systems shall undergo regular preventive maintenance and cleaning to ensure maximum effectiveness, which shall be verified by periodic airflow measurements.

(c) Disposal

(1) Work areas, fixtures, equipment, etc, contaminated by carbaryl spills shall be cleaned promptly. Liquid carbaryl on floors shall be blotted with absorbing clay which, in turn, shall be removed with a sweeping compound. Dry forms of carbaryl shall be removed by vacuum cleaning, followed by thorough scrubbing of the exposed surfaces.

(2) Disposal of waste material shall conform to local, state, and federal regulations to prevent the exposure of humans and animals as well as the pollution of air and water.

(d) Agricultural Practice

(1) In work areas, including those related to agricultural application where dermal or eye contact with carbaryl may occur, the employer shall make readily available to the employees water, soap or detergent, towels, and extra personal protective equipment, including respirators and clothing as specified in Section 4.

(2) During agricultural use of carbaryl sprays or dusts, all individuals involved shall have available for use as necessary protective clothing (gloves, coveralls, head coverings, footwear) and shall use respiratory protective devices, safety goggles, and face shields as stated in Section 4.

Section 7 - Sanitation Practices

(a) Employees working in areas where carbaryl is manufactured, processed, handled, or stored shall wash their hands before eating, drinking, smoking, or using restroom facilities during the work shift.

(b) No food or beverages shall be stored, prepared, or consumed in areas where carbaryl is manufactured, processed, handled, or stored.

(c) Contaminated clothing shall be removed before entering areas where food or beverages are consumed.

(d) Smoking shall be prohibited in areas where carbaryl is manufactured, processed, handled, or stored in unsealed containers.

(e) Employees should shower or bathe and change clothing after the workday.

Section 8 - Monitoring and Recordkeeping Requirements

Workers are not considered to have occupational exposure to carbaryl if airborne concentrations, as determined by an industrial hygiene survey conducted within 6 months of the promulgation of this recommended standard, do not exceed half the recommended TWA environmental limit, ie, action level. Surveys shall be repeated at least once every year and within 30 days after any process change likely to increase the airborne concentration of carbaryl. Records of these surveys, including the basis for concluding that airborne concentrations of carbaryl are at or below the action level, shall be maintained. If the survey indicates that airborne concentrations of carbaryl exceed the action level, then the following requirements apply:

(a) Personal Monitoring

(1) A program of personal monitoring shall be instituted to identify and measure, or permit calculation of, the exposure of all employees who are occupationally exposed to carbaryl. Interim monitoring of employee exposure to airborne concentrations of carbaryl shall be conducted at least every 6 months. If monitoring shows an employee's exposure to be above the recommended TWA environmental limit, the exposure of that employee shall be measured at least once every 30 days, control measures shall be initiated, and the employee shall be notified of the exposure and the control measures being implemented to correct the situation. Such monitoring shall continue until two consecutive samplings, at least a week apart, indicate that employee exposure no longer exceeds

the recommended TWA environmental limit specified in Section 1(a). Semi-annual monitoring may then be resumed.

(2) In all personal monitoring, samples of airborne carbaryl shall be collected which, when analyzed, will provide an accurate representation of the concentration of carbaryl in the air which the worker breathes.

(3) For each TWA determination, a sufficient number of samples shall be taken to characterize each employee's exposure during each work shift. Variations in work and production schedules shall be considered in deciding when samples are to be collected. The number of representative TWA determinations for an operation or process shall be based on the variations in location and jobs of employees in relation to that operation or process.

(b) Recordkeeping Procedures

Records shall be maintained for 5 years and shall include sampling and analytical methods, types of respiratory protective devices used, and TWA concentrations found. All employees shall have access to data on their environmental exposures. These records shall be available to the designated representatives of the Secretary of Labor and of the Secretary of Health, Education, and Welfare. Pertinent records of required medical examinations shall be maintained for at least 5 years after the worker's employment has ended, and shall be available to the designated medical representatives of the Secretary of Labor, of the Secretary of Health, Education, and Welfare, of the employer, and of the employee or former employee.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing occupational diseases arising from exposure to carbaryl. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare, under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe...exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultation with others, formalized a system for the development of criteria upon which standards can be established to protect the health of employees from exposure to hazardous chemical and physical agents. Criteria and this recommended standard should enable management and labor to develop better engineering controls resulting in more healthful work practices and should not be used as a final goal.

These criteria for a standard for carbaryl are part of a continuing series being developed by NIOSH. The proposed standard applies only to the processing, manufacture, or use of carbaryl, or other workplace exposure to carbaryl, as applicable under the Occupational Safety and Health Act of 1970. The standard was not designed for the population-at-large, and any extrapolation beyond occupational exposures is not warranted. It is intended to (1) protect against development of systemic and local effects, (2) be measurable by techniques that are valid, reproducible, and available

to industry and government agencies, and (3) be attainable with existing technology.

Carbaryl is an organic compound used as an insecticide. The principal acute hazards from worker overexposure to carbaryl are the effects of inhibition of the enzyme acetylcholinesterase. This inhibition produces symptoms such as headache, nausea, vomiting, abdominal cramps, and dimness of vision. Effects of prolonged exposure, if any, are not well understood. Research is needed in the following areas: (1) air sampling and analysis for carbaryl; (2) further investigation to clarify possible mutagenic, carcinogenic, and teratogenic effects of carbaryl; and (3) effects of long-term exposure to carbaryl on neuromuscular, CNS, reproductive, and renal functions.

III. BIOLOGIC EFFECTS OF EXPOSURE

The carbamate insecticides, one of which is carbaryl, and the organophosphate insecticides as well, exert their insecticidal action by inhibiting cholinesterase enzymes. [1] This inhibition is the primary mechanism by which these insecticides cause toxicity in mammals. The cholinesterase enzymes hydrolyze acetylcholine and other choline esters; consequently, their inhibition leads to the accumulation of endogenous acetylcholine and other choline esters. Probably, most of the biologic effects of anticholinesterase agents, including carbaryl, are due to the inhibition of acetylcholinesterase which leads to the accumulation of endogenous acetylcholine, the principal choline ester that has demonstrated physiologic significance in humans.

Physiologically, acetylcholine is a chemical mediator of nerve impulses. [2 (pp 404-76)] It transmits nerve impulses to the heart and other parasympathetically innervated structures such as the muscles and glands of the gastrointestinal tract, including the salivary glands, the glands and muscles of the bronchial and urogenital systems, the sphincter muscle of the iris, and the ciliary muscle of the lens of the eye. A few postganglionic sympathetic fibers, such as those to the exocrine sweat glands, also release acetylcholine. In addition, acetylcholine has a neurotransmitter function at the termination of the preganglionic fibers on the neurons of the ganglia of both the sympathetic and parasympathetic parts of the autonomic nervous system and at the neuromuscular junction of

the peripheral nerves and skeletal muscles. Also, a role for acetylcholine as a transmitter in synapses in the CNS has been suggested. The inhibition of cholinesterase allows acetylcholine to accumulate at these sites and thereby leads to overstimulation of these innervated organs.

Based on the ability of horse serum to hydrolyze acetylcholine and butyrylcholine, Stedman et al, [3] in 1932, suggested the term "cholinesterase" to name the enzyme present in serum. Two principal types of enzymes that hydrolyze choline esters have been identified in humans as acetylcholinesterase, or true cholinesterase, and butyrylcholinesterase, variously referred to as pseudo-, serum, or plasma cholinesterase. [2 (pp 404-76)] Acetylcholinesterase catalyzes the breakdown of acetylcholine into acetic acid and choline. Acetylcholinesterase is found at nerve synaptic junctions, at the neuromuscular junction, in erythrocytes, and in other tissues. Plasma cholinesterase is present in various types of glial and satellite cells of the central and peripheral nervous systems, respectively, as well as in plasma, liver, and other organs. Its physiologic function is unknown; inhibition of plasma cholinesterase at most sites produces no apparent functional changes. Lehmann and Liddell [4] speculated that the function of plasma cholinesterase may be to hydrolyze those choline esters that inhibit acetylcholinesteras. These include propionylcholine and butyrylcholine, which can be formed in vitro by enzyme systems responsible for the synthesis of acetylcholine and by bacterial action in the gut. Occasionally, humans have atypical or deficient plasma cholinesterases, discovered through an investigation of abnormal responses to the muscle relaxant succinylcholine, which appear to be genetically controlled variants having differing abilities to hydrolyze

acetylcholine and related compounds. [2 (p 585)]

O'Brien [5] discussed several theories on the mechanism of cholinesterase inhibition by carbamates including carbaryl. One theory which the author proposed after a critical review of the literature on carbamates is briefly described. Carbamates react with cholinesterase in a way similar to the reaction between organophosphates and cholinesterase. An immediate and direct reaction takes place between the carbamate and cholinesterase, resulting in the formation of a reversible enzyme-inhibitor complex. Second, in the case of carbaryl, carbamylation of the enzyme occurs with the release of 1-naphthol. Third, hydrolysis (decarbamylation) of the carbamylated enzyme occurs with regeneration of the original enzyme. The rate at which this step proceeds is a major determinant of the rate at which the inactive enzyme is regenerated or restored to function. With the organophosphate insecticides, the third stage is extremely slow, whereas for the carbamate insecticides, eg, carbaryl, it is relatively rapid with a calculated half-life of 40 minutes for decarbamylation of the enzyme. In addition, if at any stage of the reaction the concentration of the carbamate is reduced, eg, by dilution, the carbamylated enzyme recovers activity by dissociation of the enzyme-inhibitor complex and by hydrolysis of the carbamylated enzyme. Thus, the carbamylated enzyme can be readily and rapidly regenerated and restored to function following inhibition. Therefore, one may assume that inhibition of circulating cholinesterase may not be as readily apparent following exposure to carbaryl as with other cholinesterase inhibitors. This assumption is also supported by the discovery of the ability of a component of human serum albumin to metabolize carbaryl to 1-naphthol, [6] and by the fact that most methods

for determination of cholinesterase activity require dilution of the enzyme-substrate complex, thus accelerating the dissociation. [7] The method most frequently used for the measurement of cholinesterase activity, except in carbamate inhibition, is that of Michel. [8] Using 800 "healthy" blood donors, Rider et al [9] established normal limits of 0.56-0.95 and 0.38-1.39 delta pH/hour for erythrocyte and plasma activities, respectively, by the electrometric method. [8] The donors were men and women between 18 and 60 years of age. Carbaryl differs further from many anticholinesterase agents in that its metabolic changes result in deactivation, [10] while some of the organophosphate insecticides (the thiophosphates) require metabolic activation to produce an effect. [5]

Extent of Exposure

Carbaryl ($C_{12}H_{11}O_2N$) is known chemically as 1-naphthyl N-methyl-carbamate. Table XIII-1 presents the more important physical properties of carbaryl. [11,12,13 (sec 16), HH Moorefield, written communication, February 1976] It is sold in the United States under the trade name Sevin and Table XIII-2 [14] lists its trade names and synonyms.

Carbaryl can be produced by reacting 1-naphthol and methyl isocyanate. [15] Also, phosgene and 1-naphthol can be combined to produce naphthyl chloroformate which reacts with methylamine to produce carbaryl. As the exact sequence of the domestic carbaryl-manufacturing process is not known, it has been suggested that the first production method is probably used. [16]

Total carbaryl production in the United States was estimated to be about 50 million pounds for each of the years 1967 and 1970, [16,17]

45 million pounds in 1971, [18] and 53 million pounds in 1972. [19] Of the total produced in 1972, approximately 28 million pounds were exported. About 25 million pounds were used in the United States, 19 million for agricultural purposes, 3.5 million in homes and gardens, 1.5 million by government, and 1 million for industrial and commercial purposes. Slightly over half the carbaryl used nationwide in 1972 was used in the southeast and the north central states (about 8 million and 5 million pounds, respectively). [19] An estimated 40% of the carbaryl used throughout the world is applied in the production of cotton. [20]

The product of the carbaryl-manufacturing process is a 98% concentrate. [21] Carbaryl is formulated as wettable powders, pellets, granules, dusts, fertilizer mixtures, and liquids. [18]

The people most likely to be occupationally exposed to carbaryl are those engaged in the development, manufacture, and distribution of insecticides, as well as agricultural crop workers, farmers, plant nursery workers, spray pilots, and others engaged in spraying and dusting operations, eg, soil fumigators and exterminators. [22] NIOSH estimates that 100,000 US workers are potentially exposed to carbaryl.

Historical Reports

The cholinesterase-inhibitor physostigmine, an alkaloid extract of the calabar bean, has been used since the mid-19th century for ophthalmologic treatment and diagnostic purposes. [23] Its clinical use predates an understanding of cholinesterase enzyme inhibition.

In 1925, Stedman and Barger [24] elucidated the structure of physostigmine. A year later, Stedman [25] reported on the pharmacologic

action of substituted phenyl carbamates in mammals. He had synthesized a series of compounds and screened them for miotic activity by applying them directly to the eyes of cats.

Research and development on heterocyclic carbamates, initiated in 1947, led to several Swiss patents on dimethylcarbamates having insecticidal activity. [26] Lambrech synthesized carbaryl (Sevin) in the United States in 1953; and in 1956, after preliminary field tests, Sevin was released for testing in agricultural experiment stations. [20] In 1957, Haynes et al [26] described the insecticidal properties and some of the physicochemical characteristics of carbaryl.

Union Carbide Corporation was issued US Patent No. 2,903,478 for carbaryl in 1959, [18] the year after commercial production and sales on an experimental basis were begun. [16,20]

In 1961, Carpenter et al [27] described a series of biologic and toxicologic investigations of carbaryl conducted on experimental animals. In 1962, Best and Murray [28] were the first to report the results of investigations on occupational exposures to carbaryl. These investigations [27,28] are discussed further in this chapter.

Best and Murray [28] described the case of a 19-month-old infant who had miosis, excessive salivation, and incoordination after ingesting an unknown amount of carbaryl. The child responded to gastric lavage and atropine therapy and apparently recovered completely in 12 hours. The authors [28] received a report of this incident in a personal communication, and it probably is the first reported case of symptomatic carbaryl poisoning.

In 1963, Hayes [21] reported that, within 20 minutes after ingesting a 250-mg "carefully measured oral dose" (about 2.8 mg/kg) of carbaryl, a man experienced epigastric pain and sweating. Atropine sulfate was administered, and recovery was complete within 2 hours. Hayes gave no further details on the incident. A later publication [29] indicated that the incident described in 1963 was, in fact, a purposeful ingestion by a scientist.

Effects on Humans

Feldmann and Maibach [30] studied the percutaneous absorption of carbaryl by applying 14C-labeled carbaryl (4 μg/sq cm) dissolved in acetone to the forearm skin of six adult male volunteers. The acetone volatilized in seconds; the skin was not washed for 24 hours. Eight urine specimens were collected from each subject over 5 days as follows: four during the first day, three collections at 4-hour intervals and the fourth 12 hours later; and once daily (total 24-hour specimens) on each of the next 4 days. The amounts of 14C radioactivity in the urine were determined by liquid scintillation counting and were compared with the amount of 14C radioactivity recovered in a similar study involving a single intravenous (iv) injection of one microcurie of carbaryl. After correction with the factor of 7.4% for incomplete urinary excretion obtained in the iv study, the results were expressed in percentages of the dermally applied dose. The results indicated that 73.9% of the 14C-carbaryl applied to the skin was excreted in the urine within 5 days. The absorption of carbaryl was probably increased by the use of acetone in this study.

In a similar study of 14C-carbaryl (4 μg/sq cm) dissolved in acetone,

Maibach et al [31] showed that other parts of human skin were similar to that of the forearm in absorption of carbaryl. Approximately 70% of the 14C-carbaryl was excreted within 5 days after application to the skin over the angle of the jaw. Other pesticides were also studied. Parathion absorption by the skin of the scrotum, axilla, and forehead, for example, was considerably greater than that from the forearm skin.

Wills et al [32] collected urine from two male volunteers who had been administered carbaryl in gelatin capsules at a dose of 2 mg/kg. Total urine samples were collected at 4-hour intervals for the first 16 hours, followed by one 8-hour collection sample. Thereafter, for the next 3 days, total urine was collected and pooled at 24-hour intervals. Urine samples from control subjects had been obtained for the 24-hour period before carbaryl administration. Using these samples, Knaak et al [33] determined the metabolites of carbaryl in the urine of the two volunteers. Portions of all urine samples were subjected to ion-exchange chromatography, and fractions were analyzed by spectrophotofluorometry. Also, composite 4-day samples, one from each subject, were pooled for colorimetric analysis. The metabolites in the 24-hour urine samples, separated by chromatography, were 1-naphthyl glucuronide, unidentified neutrals, 4-(methylcarbamoyloxy)-1-naphthyl glucuronide, and 1-naphthyl sulfate. In addition, another metabolite, 1-naphthyl methylimidocarbonate O-glucuronide, was identified by fluorometry. Moreover, colorimetric analysis revealed an average concentration of 1-naphthol in the urine of 0.81 mg/100 ml. From this, the authors estimated that 37.8% of the orally administered carbaryl would be excreted within 4 days. Of the total determined, fluorometric analysis indicated that only 26-27% was excreted as metabolites during the first 24

hours. These metabolites were identified and quantitated. They were: 1-naphthyl glucuronide 12.9%, 1-naphthyl sulfate 8.5%, and 4-(methylcarbamoyloxy)-1-naphthyl glucuronide 5.1%. Fluorometric analysis revealed small amounts of metabolites in the urine on the second day but none were detected on days 3 and 4. Knaak et al [33] did not explore the possibility that either carbaryl or some of its metabolites may have been excreted in the feces, either directly or indirectly through the enterohepatic circulation, or by other routes.

Using similar techniques in another study, Knaak et al [34] analyzed 24-hour urine specimens from men exposed to carbaryl dust during a packaging operation in a factory (the number of men, exposure periods, and other conditions were unspecified). Twenty-four-hour urine specimens obtained from the same men 72 hours after their last exposure to carbaryl served as controls. The urinary metabolites separated by chromatography were 1-naphthyl glucuronide, 1-naphthyl sulfate, and unidentified neutral metabolites. Concentrations of the glucuronide and sulfate in the urine were estimated to be 25 and 5 μg/ml, respectively.

Vandekar [35] published the results of a study conducted in 1963 by the WHO Insecticide Testing Unit in three villages of southern Nigeria. The investigators used a water-dispersible carbaryl powder with 85% active ingredient to prepare a spray that contained 5% active ingredient which they expected would deposit 2 g of active ingredient on each square meter of surface. They studied the effects on 10 men who applied the spray as a residual insecticide in 16 houses over a single 6-hour period and on 95 villagers who resided in these houses. The sprayers wore overalls, broad-brimmed oilskin hats, and rubber boots during the entire 6 hours of

spraying, but wore masks for the first hour only. Clinical observations of all 105 individuals involved were recorded throughout the investigation. Plasma cholinesterase activities as well as urinary metabolites were determined before and after spraying. Except for a distinct rash on a single sprayer whose back was splashed while he was filling an applicator with the carbaryl spray, no adverse effects were seen in either the sprayers or the villagers. Plasma cholinesterase activity was determined electrometrically by a micromodification [36] of the method of Michel from blood samples taken by fingerprick and stored at 4 C until analyzed, usually on the same day. This method, like most others, probably underestimates the amount of inhibition of cholinesterase activity caused by carbaryl (see Biologic Evaluation in Chapter IV). A slight reduction in plasma cholinesterase activity was reported [35] for all 10 sprayers the day after the carbaryl application; however, when measured again 5 days after spraying, the enzyme activity was found to be within the preexposure range. A slight but statistically significant reduction in plasma cholinesterase activity was found in the 63 exposed villagers measured 1 week after the spraying. The mean reduction was 8%, ranging from somewhat greater for residents 7- to 14-years-old (10.1%) and those over 30 years of age (10.8%), to less for residents 1- to 6-years-old (5.9%) and for those 15- to 30-years-old (5.3%). The metabolites of carbaryl were estimated [35] according to the colorimetric method of Dawson et al [37] in urine samples usually collected between 8 AM and 10 AM. Excretory levels of naphthol derivatives in the urine of the sprayers were unchanged on the first and second days or thereafter, except for a slight increase on the sixth day after exposure to carbaryl. [35] The urinary excretory levels of

naphthol derivatives for 38 villagers before and for 32 villagers a week after the spraying, however, were significantly different; before exposure, the mean was 30.5 μg/ml, and 50.3 μg/ml afterwards.

In a comprehensive Union Carbide Corporation report submitted to NIOSH, Williams [13 (sec 9,10)] described an inhalation-absorption study of two employees. Employee A, an observer, was located near employee B who was emptying containers of carbaryl in a recovery operation. Employee A had complete body protection, except for the face, but no respiratory protection. Employee B, who made no special effort to avoid body contact, worked with and without gloves, but wore coveralls and an air-supplied respirator. Although observation extended intermittently over 24 days, the carbaryl airborne concentrations were similar on only 2 days. On the first such day, the airborne environmental carbaryl concentrations were 50.9 and 49.3 mg/cu m for employees A and B, respectively. The initial urinary naphthol concentration of employee A obtained before he began work that day was undetectable. After exposure to carbaryl, it rose to a maximum of 3,619 μg/100 ml. For employee B, the initial urinary naphthol concentration of 1,939 μg/100 ml rose to 8,975 μg/100 ml. Both maximum concentrations were from urine samples collected at 6:30 PM, after exposure had ceased. On the second day, similar environmental airborne carbaryl concentrations, 45.2 and 40.6 mg/cu m, were reported for employees A and B, respectively. The initial (second-day) urinary naphthol value for employee A was again undetectable, and the maximum, 2,430 μg/100 ml, was in the sample taken at 5:30 PM. On day 2, corresponding urinary naphthol concentrations for employee B were 1,803 μg/100 ml initially and 2,340 μg/100 ml at 9:30 PM. No noticeable effects on either employee were

observed or expressed; there were no pinpoint pupils, thought to be an early sign of excessive exposure to carbaryl. Methods used for air sampling and analysis were not identified, nor was the method for determining urinary 1-naphthol described.

Long [38] recounted an incident in which a worker, wearing a mask and goggles (skin protection not described) while loading an airplane with a mixture of carbaryl and sulfur, indicated he was weak and dizzy and could not get his breath. He experienced the same symptoms 2 days later, at which time chemical toxemia was the diagnosis. The attending physician noted that, according to the employer, four other employees had been sick or had had similar attacks. Long presented no further details.

Yakim [39] reported in limited detail investigations of the biologic effects of carbaryl in agricultural workers in the USSR. Whole blood cholinesterase activity was determined in men after 4- to 6-hour exposures to airborne concentrations of carbaryl for 3-4 days. The method used to determine blood cholinesterase activity was not specified. Cholinesterase activities decreased 11-22% in men exposed at a mean airborne carbaryl concentration of 2 mg/cu m while working at a loading site. Tractor drivers who disseminated carbaryl and were exposed at an average concentration of 2 mg/cu m of air had a fall of 20-24% in blood cholinesterase activity. Signalers exposed at 4 mg/cu m experienced a 13-30% decrease in cholinesterase activity. Yakim [39] indicated that the blood picture and results of certain tests of physiologic functions (pulse rate, body temperature, Aschner's reflex (oculocardiac), dermographism, and what was described as an orthoclinostatic test) suggested no change in these workers before and after work. Pilots engaged in aerial application

were exposed in the cabin at a mean airborne carbaryl concentration of 7 mg/cu m, but Yakim [39] reported no data on the changes, if any, in their cholinesterase activity or in the blood picture or physiologic functions.

Farago [40] presented the details of a suicide attributed to carbaryl ingestion. The victim, a 39-year-old man described as inebriated, ingested about 0.5 liter of a solution of Sevin 80 (possibly 400 g of carbaryl). He was hospitalized 1.5 hours later, and his stomach was lavaged and circulation-promoting agents were administered. As his condition deteriorated, the patient complained of disturbed vision, and lung edema developed. He received atropine every half hour. One and a half hours after entering the hospital, he also received 250 mg of pralidoxime (PAM). Hayes [21] pointed out that the use of PAM is inappropriate in the treatment of carbaryl intoxication (see Appendix III for medical management). Following the administration of PAM, his condition deteriorated even more rapidly with attendant signs of advancing pulmonary edema. [40] The man died 6 hours after ingesting the carbaryl. Autopsy revealed what was described as dark, livid red spots on the body surface; swollen, edematous brain tissue; severe pulmonary edema; and blood-congested viscera. Farago [40] considered the degree of kidney hyperemia present especially striking. Analysis of the organs showed the following carbaryl concentrations (in mg%): stomach flushing water, 244.6; stomach and contents, 14.8; intestine and contents, 17.6; blood, 1.4; liver, 2.9; kidneys, 2.5; and urine, 3.1. At the time of death, carbaryl had not been completely absorbed from the gastrointestinal tract; that which had been absorbed apparently accumulated in the liver and kidneys. The cholinesterase activity in the blood, determined by an electrometric

method, was strongly inhibited. Thin-layer chromatography revealed one or two (not clear from the paper) metabolites of carbaryl in the stomach, three metabolites in the intestines, four in the liver and kidneys, and five in the urine. None of the metabolites were identified. The presence of a metabolite in the stomach suggests that some metabolism may also occur at that site in human beings.

Of the 25 cases of poisoning from organophosphate and carbamate compounds described by Lopez, [41] only two were attributable to carbaryl alone. The first was a 19-year-old man who ingested watermelon sprayed with 80% carbaryl, and the second was a 33-year-old man who inadvertently drank several milliliters of a solution of 80% carbaryl. Lopez [41] classified the degree of intoxication in both men as light. In addition to nausea, both subjects experienced signs and symptoms including vomiting, hyperreflexia, pallor, intestinal colic, and nasal discharge in the first victim; and salivation, headache, lacrimation, and tremors in the second. The 19-year-old and the 33-year-old patients were treated with 20 mg and 5 mg of deoxycorticosterone and recovered completely in 18 hours and 1.5 hours, respectively. The author hypothesized that either corticoids liberate cholinesterase bound to serum proteins or that further induction of this enzyme had been initiated by deoxycorticosterone.

In a Union Carbide Corporation medical department report dated June 19, 1962 and provided to NIOSH, Sexton [13 (sec 7)] reported an incident at a carbaryl-shipping facility where storage bins had become plugged, necessitating hand-removal of carbaryl dust from hoppers leading to the bins. Fourteen employees were involved, and all of the men were supposedly wearing dust respirators all the time while working. Between early and

late afternoon, 7 of the 14 men reported to the medical department complaining of symptoms they attributed to inhalation of carbaryl dust. It was interpreted that the felt cartridge of the respirators had become clogged with dust, so that not only dust but also the vaporized carbaryl may have passed through the filter cartridge, resulting in exposure. The workers had complaints of nausea, dizziness, or both. In addition, one man complained of headache and another of being "overheated" and perspiring. The seven men had worked 8-16 hours on the day they became ill. The episode occurred on a Saturday afternoon, and company physicians were not notified until the following Monday morning. At that time, all 14 employees were seen at the medical department, where urine and blood specimens were collected. By then, none of the 14 men had any complaints. Blood cholinesterase activities were measured by an electrometric method which probably underestimated the degree of cholinesterase inhibition. Urine was analyzed for conjugated naphthol. The mean conjugated naphthol content of the urine of the seven men who had complained of illness was 1,417 μg (range 200-3,100)/100 cc. The mean conjugated naphthol content of the urine of the seven asymptomatic workers was 2,443 μg (range 1,000-4,200)/100 cc. Mean cholinesterase activities for the ill workers were 1.097 (erythrocyte) and 3.183 (plasma) delta pH units, and for the well employees, 1.258 (erythrocyte) and 3.368 (plasma) delta pH units. No environmental data were reported. Medical personnel concluded that the effects were due to inhalation of carbaryl, related perhaps to respirator malfunction. However, the intoxications reported could have resulted from other than lung absorption.

In a 1970 memorandum by Dernehl [13 (sec 13)] submitted to NIOSH by Union Carbide Corporation, the sequence of events in Union Carbide workers overexposed to carbaryl during its manufacture, formulation, and use was summarized as follows: headache and nausea after 3-4 hours of continuous overexposure to airborne carbaryl dust at unstated concentrations; vomiting, possibly accompanied by mild abdominal cramps, about 30 minutes after the onset of headache and nausea; dimness of vision; and termination of exposure because of the vomiting. Dernehl [13 (sec 13)] added that by the time affected employees were provided medical attention, usually 30-45 minutes after becoming ill, symptoms already had begun to disappear, and only in rare instances did a physician consider atropine sulfate administration necessary. He also pointed out that it was rarely possible to quantitatively determine hazardous exposure levels, but that the employees' verbal descriptions suggested heavy concentrations well above those normally encountered.

Wills et al, [32] in a preliminary study, administered carbaryl in gelatin capsules to male volunteers 25-57 years of age (mean 36). Single oral doses of approximately 0.5, 1.0, and 2.0 mg/kg of carbaryl were given to three pairs of men, who were then observed for signs of intoxication. Blood plasma and whole blood cholinesterase activities were monitored by a pH stat method, and the subjects were questioned about symptomatic effects. Neither objective nor subjective changes were noted in the preliminary study. Wills et al [32] also administered carbaryl to another series of subjects. Two groups of five men each received either placebo capsules or capsules containing 0.06 mg/kg of carbaryl daily for 6 weeks. Two weeks later, two new groups of six men each started ingesting, again for six

weeks, either placebo capsules or doses of carbaryl analyzed at 0.12 mg/kg by one method and by another at 0.13 mg/kg. Blood, urine, and fecal specimens were collected initially and weekly from all subjects throughout each of the 6-week study phases. The authors specifically noted that sulfobromophthalein (BSP) retention in the plasma before and after carbaryl administration did not differ, that cholinesterase activities were not significantly altered, and that no significant effects attributable to carbaryl were present in the hemograms, in the blood chemistry, or in urine or fecal examinations. Blood samples were examined for hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte counts, blood urea nitrogen (BUN), glucose, plasma and whole blood cholinesterase activities, cholesterol, prothrombin time, serum glutamic oxaloacetic transaminase (SGOT), sodium, and potassium. Urinary specimens were examined for turbidity, pH, protein, glucose, erythrocytes, squamous epithelial cells, crystals, and for the ratio of amino acid nitrogen to creatinine. Stool specimens were examined for occult blood. The authors indicated that final EEG recordings for both the treated and the untreated groups were somewhat more synchronized than were the initial ones but showed none of the spiking reportedly found in the EEG of subjects exposed to other (organophosphate) cholinesterase inhibitors. Subjects receiving carbaryl at the higher dose expressed several complaints not reported by the corresponding placebo group. Because most of these occurred the day after ingestion of carbaryl had ended, they were thought to be manifestations of withdrawal. Of the remaining complaints, the authors considered the two instances of difficulty in sleeping and of abdominal cramps to be symptoms of cholinesterase inhibition. Only one subject

reported the third complaint, an eye reaction (pupillary dilation), on one day; since this response usually is not caused by acetylcholinesterase inhibition, the authors attached no particular significance to it.

The only deviations from control levels in all the determinations reported were in the amino acid nitrogen to creatinine ratios, considered an estimate of the reabsorptive capacity of the proximal convoluted tubules of the kidney. [32] Wills et al [32] illustrated in charts the averages and ranges of these ratios for the men on both doses of carbaryl and for their controls, but did not state the actual numerical results. Ratios of the low-dose group (0.06 mg/kg) and their controls were determined initially and at weeks 1, 2, 4, and 6 of the study. Those ratios (low dose) were consistently below the controls except at week 6, when they were equal. Determinations were similarly recorded for the high-dose (0.12 or 0.13 mg/kg) group and their controls. Averages for six control and for six experimental subjects (five at the final determination) were compared. The ratios of the experimental group fell below those of the controls at the end of the first week of carbaryl ingestion, spiked upward at week 2, and fell to a plateau (at about midpoint of the second week's increase), where they remained until the fifth week. The next determinations on four of the subjects, 15 weeks after the last dose, showed that the amino acid to creatinine ratios had returned to the control level. The authors concluded that men who took carbaryl by mouth in daily doses of 0.06 or 0.12 mg/kg for 6 weeks suffered no subjective or objective changes clearly attributable to carbaryl other than a slight, reversible decrease in the ability of the proximal convoluted tubule of the kidney to reabsorb amino acids in the group on the higher dose.

Back, [20] in a 1965 review of product development experiences with carbaryl, referred to "about 50 cases" of intoxication, none fatal, and "less than a dozen" instances of cholinesterase inhibition, apparently due to the carbamate. He noted that, in those instances when exposure had occurred among process workers, formulators, or applicators, the onset of illness consistently resulted in cessation of work and thus of further exposure. The author gave no other details.

Epidemiologic Studies

Best and Murray [28] reported observations made during a 19-month period in a carbaryl-manufacturing plant. Involved in the survey were 59 employees, some of whom were exposed to carbaryl for less than 1 week. A total of 81 samples of airborne particulates (or air samples) were collected on Millipore filters (AA white grid, 47-mm Millipore filter paper). The concentration of carbaryl was determined colorimetrically using the reaction with p-nitrobenzenediazonium fluoroborate. The airborne concentrations of carbaryl under normal and abnormal conditions in the production area, air separator house, stacking and shipping area, and bagging areas are shown in Table III-1. In addition to the work areas listed above, the airborne carbaryl concentrations to which the building services employees were exposed, while not measured, were estimated to be relatively high, because these employees were exposed to dusty jobs in all plant areas. Employees were required to wear respirators only while cleaning the air separator house and at times when high concentrations were anticipated in the bagging areas. The range of concentrations of the 81

TABLE III-1

CARBARYL CONCENTRATIONS IN A MANUFACTURING PLANT

Location	No. of Samples	Concentration in mg/cu m	
		Range	Mean
Production area	49	0.03 - 0.73	0.23
Air separator house	2	19 - 34	31
Stacking and shipping area	6	0.05 - 1.52	0.64
Bagging area (normal)	18	0.20 - 1.60	0.75
Bagging area (abnormal)	6	19 - 40	29

Adapted from Best and Murray [28]

air samples was 0.03-40 mg/cu m. Only eight of the samples equaled or exceeded an airborne concentration of carbaryl of 19 mg/cu m. Of these, two were from the air separator house (29 and 34 mg/cu m), and six were recorded in the bagging area under abnormal conditions, such as when flow system connections or bags broke, or when bags were difficult to fill (range 19-40 mg/cu m). The other 73 samples had carbaryl concentrations equal to or less than 1.6 mg/cu m.

During the first 4.5 months of the Best and Murray [28] study, urine specimens for 1-naphthol determination were taken early in the morning before work on the day after blood samples were drawn for cholinesterase determination. Cholinesterase activity measured by an insensitive method was reported to be only slightly lowered, but since 1-naphthol excretion was significantly high in 10 of 63 urine specimens from employees likely to

have been most heavily exposed, it seems likely that cholinesterase activity might have been affected. For the next 3.5 months, 47 urine samples taken in the evening on days blood was drawn showed an average of 35.4 μg/100 ml which was approximately 9 μg/100 ml more 1-naphthol than that in samples taken the next morning. During the same 3.5-month period, most of the cholinesterase activities fell again from 96-100% of the normal to 70-95% of normal range, measured by an insensitive method. Over the next 3 months, when carbaryl production, bagging, and shipping ceased entirely, the 1-naphthol urinary levels of the above employees decreased to an average of 10.8 μg/100 ml. With resumption of carbaryl-manufacturing operations and of employee blood and urine sampling for the following 8 months, 23% of 138 exposed employee blood samples, but no control blood samples, had some reduction in cholinesterase activity; in this case, the quantitative method of Fleisher and Pope [42] was used but this probably underestimates carbaryl-induced cholinesterase inhibition. In the relatively high exposure groups, blood samples from 5 of 35 workers in the bagging areas, 13 of 67 workers in building services, 6 of 89 workers in production, and 6 of 78 workers in shipping had enzyme activities measured by the method of Fleisher and Pope [42] that were somewhat lower than those from the control group of unexposed workers. With these exceptions, blood cholinesterase activities in the other exposed workers did not vary significantly from those of the controls. The authors did not specify either the basis for selection of the control group or the time when blood samples were taken. The 1-naphthol findings in the same group were much more impressive; 41% (of 138 specimens) had average values of more than 1,000 μg/100 ml, 2.5 times the highest control levels (150-400 μg/100 ml).

In another study by Best and Murray, [28] the 1-naphthol urinary output determined during one workweek was more than doubled in one of two carbaryl baggers. Five other employees regularly assigned to various duties were monitored by 1-naphthol urine determinations twice daily for a single Monday-through-Friday workweek. The 1-naphthol levels in the urine were approximately 150% of their own control levels in two workers and approximately 223, 277, and 285% of their control levels in the three other workers at the end of the workweek. Although all of these employees had been similarly exposed to carbaryl dust in the previous week, they began on Monday of the test week usually with low values of urine 1-naphthol. The 1-naphthol urinary levels were highest on Wednesday to Friday. In the study of two baggers, one, who had been on vacation the previous week, began on Monday with urinary levels in the normal range and never reached the level of the other bagger.

In summarizing their results, Best and Murray [28] stated that relatively large amounts of 1-naphthol were excreted in the urine by employees exposed at air concentrations of carbaryl ranging from 0.23 to 31 mg/cu m but at times reported to be 0.03-40 mg/cu m. Blood cholinesterase activities in exposed employees were either within the normal range or were only slightly inhibited, but, in view of the enzyme assay methods used, these data are of doubtful significance. At no time did any of the employees studied have clinical or subjective evidence of increased acetylcholine activity.

Animal Toxicity

(a) Toxicity Studies

(1) Acute toxicity (other than inhalation) and interactions

Several investigators [27,43,44] have studied the acute oral toxicity of carbaryl in laboratory animals. Carpenter et al [27] calculated the LD50 of carbaryl based on mortality occurring within 14 days after administration by oral gavage of single, graded doses of the test material to groups of five rats weighing 90-120 g. The carbaryl was administered at a concentration of 50 mg/ml in 0.25% agar. The LD50's were 510 mg/kg in rats of unspecified sex and 610 mg/kg in females. Other authors, [43,44] using different strains of rats or different suspending agents, reported slightly different LD50 values. For example, Gaines [43] suspended technical grade carbaryl in peanut oil for oral administration to rats and calculated the LD50 values of carbaryl as 850 and 500 mg/kg for male and female rats, respectively. Gaines [43] also reported that the lowest oral dose which killed a male and a female rat was 600 and 100 mg/kg, respectively. These results suggested that the female rat was more sensitive to carbaryl than was the male. Coulston and Serrone [44] determined the oral LD50 in rats (sex not stated) to be approximately 600 mg/kg. The same authors reported an oral LD50 for mice of 650 mg/kg and an estimated LD50 for dogs and monkeys at less than 500 and greater than 1,000 mg/kg, respectively.

In a series of studies designed to assess the extent of cholinesterase inhibition in animals after administration of carbaryl, Carpenter et al [27] injected carbaryl iv as an 8% solution in 95% ethyl alcohol at doses of 10 and 15 mg/kg of body weight to two groups of three

dogs. Blood samples were taken before, and at intervals of 0.5, 1, 2, 5, and 23 hours after, carbaryl administration. Erythrocyte and plasma cholinesterase activities were determined by an electrometric method which, like many other methods, probably underestimates the degree of inhibition. Ethyl alcohol administered iv at volumes approximating the amount of ethyl alcohol given in the 8% carbaryl solution did not affect either plasma or erythrocyte cholinesterase activity. Recognizing the difficulties in evaluating the rapid reversibility of carbaryl-inhibited cholinesterase activity, the investigators chose to measure the extent of inhibition after equilibrium between substrate and enzyme was attained in the incubation phase of the analysis. They conceded that the values thus attained were not an exact measure of cholinesterase activity, but they believed that the values did represent the relative picture at various time intervals after administration. Results of these determinations revealed no significant changes in either erythrocyte or plasma cholinesterase activities after single iv carbaryl doses of 10 and 15 mg/kg.

Carpenter et al [27] also administered carbaryl in single oral doses by gelatin capsule to six bitches weighing about 8 kg each. One dog received carbaryl at 500 mg/kg, four dogs at 375 mg/kg each, and one dog at 250 mg/kg. The one dog given 250 mg/kg remained normal; the five dogs at the two highest doses showed signs of overstimulation of the parasympathetic nervous system. The signs the authors reported were as follows: the dogs were quiet for 15-30 minutes; then salivation and respiratory rate increased; lacrimation, urination, defecation, and intermittent muscular twitching occurred for 30-90 minutes; and muscle tremors increased (one dog had a minor convulsion). All five dogs had

constriction of pupils, profuse salivation, poor coordination, diarrhea, further increases in respiratory rate, and loss of bladder control after 2.5 hours. Three hours after administration, the animals vomited mucus and thick saliva and had violent intestinal movements, weakness, and considerable muscular spasm. After 5.5 hours, all five animals became quieter, but lacrimation, salivation, slight pupillary constriction, poor coordination, intermittent muscular twitching, and occasional vomiting of mucus persisted. After 7 hours, the pupils were almost normal, salivation decreased, and coordination improved. The authors noted no adverse effects on the following day, except that the dog treated with 500 mg/kg of carbaryl was extremely weak for 24 hours and did not eat for five days. Cholinesterase activities were not determined in the animal receiving 500 mg/kg. Plasma cholinesterase inhibition was found to be "insignificant" in the four dogs given 375 mg/kg, but some erythrocyte cholinesterase inhibition was verified in three of them, the maximum effect occurring within 2-3 hours after carbaryl administration. The maximum inhibition of erythrocyte cholinesterase activity during the first 3 hours for the three dogs was 24-33%. After 7 and 24 hours, these values varied from 12-30% and from 0-14%, respectively.

Carpenter et al [27] studied the effectiveness of atropine sulfate (an agent that blocks the cholinergic receptors, particularly at the parasympathetic neuroeffector junction, to prevent the action of acetylcholine) in combination with pyridine-2-aldoxime methiodide (PAM) (an agent that reactivates the phosphorylated cholinesterase enzymes after poisoning with organophosphate inhibitors) in blocking cholinergic effects produced by a single high dose of carbaryl in the dog. A single dog

weighing 8 kg, which had received carbaryl at a dose of 375 mg/kg in a capsule, was treated with 40 mg of PAM and 10 mg of atropine sulfate after signs of poisoning appeared. This combination failed to control the effects of carbaryl, but subsequent doses of 5 and 10 mg of atropine sulfate without the PAM proved effective. The same investigators administered a lethal oral dose (800 mg/kg) of carbaryl followed by PAM at a dose of 20 mg/kg iv to five female rats with no reduction of the mortality rate. A similar dose of atropine sulfate prevented death in a similarly treated group of five female rats. Similar results were obtained in rabbits. All these studies appear to provide reliable evidence that the administration of large doses of atropine sulfate, but not of PAM, can be effective in treating carbaryl intoxication. The adverse effect of oxime cholinesterase reactivators in animals poisoned with carbaryl was confirmed by Natoff and Reiff [45] in rats and by Akamatsu and Kohgo [46] in mice. Sanderson [47] found oxime treatment ineffective in carbaryl poisoning in rats.

In order to study the interactions between carbaryl and other pesticides, Carpenter et al [27] administered single oral doses of carbaryl in combination with each of 24 other compounds by gavage to rats weighing 90-120 g. The predicted LD50 for each pair of pesticides was calculated from the individual LD50 and proportion of each compound present in the administered dose. The ratio of the predicted toxicity over the observed toxicity was calculated. The authors considered a ratio of two or more indicative of a greater than additive or potentiating effect. They concluded from their data that there was no evidence of carbaryl-caused potentiation or antagonism. However, additive effects were observed with

10 organophosphate pesticides--diazinon, EPN, guthion, malathion, methyl parathion, OMPA, parathion, phosdrin, systox, and trithion. In a similar study in rats, Keplinger and Deichmann [48] obtained values for ratios of predicted over observed toxicity, based on LD50 after oral administration, of 1.30-1.82 for 4 organophosphate pesticides--diazinon, parathion, delnav, and malathion--administered with carbaryl. The authors concluded that these ratios suggested more than an additive effect. However, it is doubtful that this degree of increase in toxicity as evidenced by decreases in LD50's is sufficiently marked to be considered a synergistic or potentiating effect.

(2) Inhalation toxicity

Studies involving the exposure of animals to airborne carbaryl are relatively limited. Carpenter et al [27] exposed six guinea pigs for 4 hours to an airborne carbaryl wettable powder (50%) of 15 μm average particle size at a concentration of 390 (344-722) mg/cu m. The authors noted that at this concentration there was a visible dense cloud of dust. The animals gained weight normally during the subsequent 2-week observation period; however, nasal and local ocular irritation were evident. Autopsy disclosed healed hemorrhagic areas in the lungs. The authors provided no additional information.

Six guinea pigs were exposed for single 4-hour periods at a mean concentration of 230 mg/cu m of a "microfine" (average particle size was 5 μm, ranging from less than 1 to 10 μm) wettable powder containing 85% carbaryl by weight. [27] In the 14-day postexposure observation period, the animals initially showed slight weight losses, but they had returned to their pretreatment weights by the end of the period. Another group of five

guinea pigs survived a 4-hour exposure at a mean concentration of 332 mg/cu m to the same dust. No other information was provided.

An unspecified number of dogs were exposed [27] to microfine wettable powder of carbaryl at concentrations of approximately 75 mg/cu m. Within 5 hours, typical signs of cholinesterase inhibition were seen. Also, repeated exposures to the same formulation did not cause death or other evident injury in rats that inhaled 10 (5-20) mg/cu m for 7 hours/day, 5 days/week, for a total of 90 exposures. In an unpublished report (C Carpenter, written communication, January 6, 1976), the results of the gross and microscopic examinations of tissues taken from rats in the inhalation study were described. No signs of treatment-associated gross or microscopic lesions were present in the rats exposed to carbaryl (Sevin 85S) by repeated inhalation at the concentration used.

Yakim [39] reported the results of exposures of cats to airborne carbaryl. Three groups of four cats each were exposed for one period of 6 hours to carbaryl dust at concentrations of 82 (80.2-83.7), 37 (31.7-42.2), and 20 (18.7-21.2) mg/cu m. Yakim [39] did not specify the particle size, method of sampling, or sex or age of the cats. No deaths occurred, although the highest concentration did cause signs of toxicity which disappeared after exposure ceased. The cholinesterase activities fell immediately after exposure to 39-55% and 53-71% in serum and erythrocytes, respectively, but returned to normal in two of three cats in 72 hours. The third cat showed a partial recovery of cholinesterase activity after 72 hours. Cats exposed to a carbaryl dust at 37 mg/cu m showed 23% serum and 41% inhibition of erythrocyte cholinesterase activity which returned to normal in 48 hours. Carbaryl dust at 20 mg/cu m caused reductions of

11-24% in serum and 15-28% in erythrocyte cholinesterase activities, but recovery was complete in 24 hours. The authors concluded that the single exposure at 20 mg/cu m represented the threshold exposure concentration. Three additional groups of four cats each were exposed repeatedly to carbaryl dust. The first group, at an airborne concentration of 16 (15.3-16.6) mg/cu m, showed no signs of toxicity during the 4-month (6 hours/day) exposure. In the second group, at a concentration of 63 (61.1-64.2) mg/cu m for 6 hours/day for 1 month, periodic salivation was most profuse during the first 2 hours of each exposure. One cat died on the 20th day; the surviving cats showed reductions of 31-40% in serum and 41-58% in erythrocyte cholinesterase activities. The third group was exposed to carbaryl at an average concentration of 40 (37.4-43.3) mg/cu m for 6 hours/day for 2 months. Details were not given, but the author stated that some deterioration occurred in undefined conditioned reflexes of cats at this concentration, mostly after the first exposure; although erythrocyte cholinesterase activity dropped to 50% or less on some days, the conditioned reflexes remained normal. The author concluded that results from inhalation experiments of 1-4 months suggest that 16 mg/cu m constitutes the threshold concentration and 63 mg/cum is the toxic concentration of carbaryl for cats. Based on his studies on cats and humans which were discussed earlier, the author suggested that the maximum permissible concentration in the USSR be set at 1 mg/cu m. The author did not describe the method used to determine cholinesterase activity.

(3) Local (skin and eye) effects

Carpenter et al [27] also reported on studies investigating the possibility of injury to the surface of the eye following contact with

carbaryl. They applied 0.5 ml or more of various concentrations of an undescribed form of carbaryl to one eye of each of five rabbits. The eyes were examined for any immediate local effect; any 24-hour reactions were recorded after application of a 5% aqueous fluorescein stain to reveal the presence of injured tissue. Volumes of 0.5 ml or more as a 10% suspension of technical grade carbaryl caused only mild injury in one of five rabbit eyes at the 24-hour examination. A 25% aqueous suspension of "microfine" carbaryl (a powder containing 85% active agent by weight) with an average particle size of 5 μm caused no injury. Fifty milligrams of carbaryl dust caused only traces of corneal necrosis.

Yakim [39] found that application of a 10% suspension of carbaryl and of 50 mg of powder to the eyes of rabbits caused only transient miosis and hyperemia. Those signs could occur after local absorption of an anticholinesterase agent.

Carpenter et al [27] evaluated the primary skin irritation potential of topically applied carbaryl. A solution of technical grade carbaryl was applied at a concentration of 10% in acetone at a dose of 0.01 ml to the clipped abdominal skin of five rabbits. The authors noted that, whereas most of the carbaryl went into solution, a slight turbidity remained. The rabbits were observed for 24 hours; no signs of irritation were noted.

Gaines [49] investigated the acute dermal toxicity of carbaryl in rats. He applied technical grade carbaryl dissolved in xylene to cleanly clipped areas of skin over the shoulders and forward parts of the backs of 10 male and 10 female rats. The animals were at least 90 days old and ranged in weight from 175 to 200 g. The dermal LD50 values exceeded 4,000 mg/kg in both sexes. Gaines [49] stated that an LD50 by the dermal route

is much more indicative of the possibility of occupational toxicity than the acute oral LD50. Yakim [39] reported that, whereas no deaths occurred in six rabbits when a dose of 500 mg/kg of carbaryl was applied to the skin, serum and erythrocyte cholinesterase activities were inhibited during the first 24 hours after treatment. Yakim [39] also indicated that cholinesterase activity was normal after 72 hours and that the skin was not irritated. The cholinesterase activity was determined colorimetrically by Hestrin's method, [50] but no specific details were given on how the method was carried out. The original method by Hestrin [50] is not a reliable one for measuring cholinesterase activity in blood samples (see Chapter IV, Biologic Monitoring).

Carpenter et al [27] examined the skin sensitization potential of carbaryl. Sixteen male albino guinea pigs were treated with eight intracutaneous injections (3/week on alternate days) of 0.1 ml of a 0.1% carbaryl dispersion in 3.3% propylene glycol made up in 0.75% NaCl. After 3 weeks during which no injections were given, a similar dose was again administered intracutaneously, and all sites of injection were examined 24 and 48 hours after this challenge dose. The authors reported that 4 of the 16 showed evidence of weak sensitization.

(4) Other effects

Carpenter et al [27] fed carbaryl at 1,500 and 2,250 ppm in the diet to two groups of 10 rats each for 96 days. The higher level produced a decrease in the body weights of females, an increase in the liver-to-body-weight ratio in males, and an increase in the kidney weight of females compared with the controls. Food intake was not affected. The only microscopic finding was a minor degree of diffuse, cloudy swelling of

the kidney tubules in 4 of 10 animals fed 2,250 ppm of carbaryl. At the 1,500-ppm dose level, an increase in kidney weights of females was the only deviation from control values; organ damage was not evident upon microscopic examination. The authors speculated that the apparent difference in response between sexes occurred because the dose for females, in mg/kg of body weight, was about 30% greater than that for males at the same dietary intake.

Carpenter et al [27] reported a 2-year study in which rats received carbaryl mixed with feed. Five groups of 40 animals (20 males and 20 females), 60 days old at the beginning of the study, were administered 0, 50, 100, 200, and 400 ppm carbaryl in the diet. Before the start of the study, 10 of the male rats (age 54 days) were selected randomly from each of the 200- and 400-ppm treatment levels and from the control group for hematocrit determinations, which were made initially and at various intervals throughout the study. All surviving animals were killed between days 732 and 736 of the experiment. Gross and microscopic examinations were performed on gastrocnemius muscle, sciatic nerve, lung, kidney, liver, heart, spleen, pancreas, stomach, duodenum, descending colon, testis or ovary, fallopian tube, esophagus, trachea, thyroid, urinary bladder, and adrenal gland tissues. Lung infections, which accounted for 88% of all deaths during the study, appeared to be no more frequent among treated than among control rats. The other causes of death, none of which appeared to be dose related, were peritonitis, 6.5%; neoplasms, 3.3%; anuria, 1.1%; and nephritis, 1.1%. No single type of tumor or site of origin was associated with the inclusion of carbaryl in the diet, nor was the incidence of tumors in the carbaryl-fed groups different from that for control rats. In fact,

mortality in the control group exceeded that in any of the treated groups. No statistically significant difference was found between the rats fed carbaryl and the control group in mean age at death, mean expectation of life at birth, or mean expectation of life after 1 year of administration. The mean age in days at death for both sexes at the 200- and 400-ppm diet levels were 630 and 656 days, respectively, and 585 days for the control rats. Liver and kidney weights which were calculated as percentages of body weights of rats killed periodically during the experiment did not differ from control values. None of the mean hematocrit values for the 400-ppm diet-fed rats differed at any interval from those for the control group, and only a single midexperiment mean for the 200-ppm diet group was different from the controls. No significance was attached to this isolated deviation. Microscopic examination of tissues from randomly selected animals fed carbaryl in the diet for 180 and 270 days revealed no significant difference from the controls. Kidney changes of a mild, transitory nature observed in female rats fed 400-ppm carbaryl diet for 365 days were characterized as a cloudy swelling of the proximal convoluted tubules. After 2 years of receiving 400-ppm of carbaryl in the diet, some rats developed renal changes consisting of cloudy swelling of the proximal convoluted and loop tubules of the kidney, but the incidence was not significant. The authors considered the cloudy swelling of the hepatic cords, principally located around the central veins, to be more noteworthy. This was a finding of statistical significance in the group of animals on the 400-ppm diet for 2 years. Microscopic examination of rats at the lower doses, ie, 50, 100, and 200 ppm, revealed no differences between the treated and control animals. The authors concluded that after two years

none of the tissues examined from the rats on the 400-ppm diet showed permanent degenerative changes which could be attributed to toxicity of the insecticide.

Aspects of the comparative toxicology of carbaryl in rats and monkeys were presented in an abstract by Serrone et al. [51] The authors concluded that monkeys tolerated much larger single oral doses of carbaryl (up to 1,000 mg/kg) than did rats or dogs. Although monkey plasma cholinesterase was inhibited at a dose of 600 mg/kg in a 6-month study (number of doses and frequency not stated), little inhibition occurred at lower doses. The authors also noted that electron microscopic studies of the kidneys of rats and monkeys treated with carbaryl disclosed a marked vacuolation of the epithelium in the proximal renal tubules. In a review article which discusses the same or similar studies, Coulston and Serrone [44] presented an electron photomicrograph of renal tissue from a monkey treated with carbaryl at 600 mg/kg (length and frequency of treatment not stated) that also demonstrated this lesion. In the abstract, [51] the authors also reported having observed no disturbances in urinary function other than a discoloration of the urine (this was also reported in swine [52]), which the authors thought might be caused by the presence of a metabolite of carbaryl. It is difficult to draw any conclusions from these studies, [44,51] since the length and frequency of treatment was not specified and only a single electron photomicrograph was presented.

Carpenter et al [27] administered carbaryl in gelatin capsules to Basenji-Cocker dogs for 1 year. A control group received no carbaryl. Fourteen dogs were randomly distributed by sex and litter among the treated and control groups. Carbaryl was administered 5 days/week at doses of

approximately 0.45, 1.8, and 7.2 mg/kg. Hematocrit, hemoglobin, erthyrocyte fragility, and differential leukocyte evaluations were made prior to the initial dose and after 3, 6, 7.5, 9, and 12 months of administration. Except at 7.5 months, determination of BSP retention and serum alkaline phosphatase, urea nitrogen, and bilirubin concentrations were made at the same intervals. Plasma and erythrocyte cholinesterase determinations were also made five times during the 3-week pretreatment period, as controls. Twenty additional cholinesterase assays were performed electrometrically weekly for 9 weeks, twice during the next month, and about monthly thereafter. After a year of treatment, the dogs were anesthetized and exsanguinated. Brain, spinal cord, thorax, abdomen, gastrocnemius muscle, and sciatic nerve were examined. One of two bitches that received carbaryl at 0.45 mg/kg had shown transient hind leg weakness after the 189th day of administration. Carbaryl treatment was continued without pause and, within 21 days, the dog appeared to be normal. There was no statistically significant difference between treated and control animals with respect to mean body weight, mean blood values (hematocrit, hemoglobin, and differential leukocyte count), BSP retention, serum urea nitrogen, total serum bilirubin, and serum alkaline phosphatase values. Cholinesterase activity was not significantly different in the treated and in the control dogs; however, the method used to determine cholinesterase activity probably underestimated the degree of inhibition. The weights of livers and kidneys of the carbaryl-treated and control animals also did not differ. Microscopic examination revealed diffuse, cloudy swelling of the proximal convoluted and loop tubules of the kidney and focal sudanophilic "dust" in the glomeruli of dogs given carbaryl at 7.2 mg/kg. The authors

judged these to be transient conditions rather than the early stages of toxic degeneration, because the microscopic findings were also present in the control dogs, but to a lesser extent. Although considerable intracellular fat was observed in the proximal kidney tubules of the females, the authors did not regard this as indicative of toxicity, but rather as a variability within the normal range. Carpenter et al [27] concluded that tissues from the dogs killed after 1 year of carbaryl administered orally in doses of 7.2 mg/kg or less showed no permanent degenerative changes.

(b) Paralytic Effects

Grob, [53] in a review of neuromuscular pharmacology, indicated that the only residual effects after exposure to some organophosphate cholinesterase inhibitors were a few instances of paralysis. These disorders resembled the peripheral neuritis and demyelination (Ginger Jake paralysis) which occur at 14 days or more after exposure to triorthocresylphosphate (TOCP). Consequently, cholinesterase-inhibiting compounds are frequently tested for nerve-demyelination potential early in their development.

Carpenter et al [27] studied in chickens (Rhode Island Red hens) the potential of carbaryl to cause the type of paralysis referred to as Ginger Jake paralysis seen with TOCP. The chemicals (carbaryl and TOCP) were suspended in lard and single doses administered subcutaneously to chickens (13 carbaryl- and 10 TOCP- treated) at doses of 0.25, 0.5, 1.0, 2.0, and 3.0 g/kg (number of hens at each dose level unspecified). Five control hens were untreated, two hens were vehicle-treated (lard), and one additional hen was given undiluted TOCP at 1.0 mg/kg. Chickens that

received 1.0 g/kg or less of carbaryl did not develop signs of leg weakness. At 2.0 g/kg, leg weakness was observed on the first or second day following administration; in one case, the chicken was unable to walk for 3 days, but none developed late paralysis (after 14 days) typical of TOCP-demyelinating injury. All chickens given TOCP at 3.0 g/kg showed leg weakness at 14 days which persisted until they died. Microscopic examination of tissue sections of brain, sciatic nerve, and spinal cord revealed no evidence of demyelination at any carbaryl dose level; however, demyelination was present in some TOCP-treated chickens. The authors concluded that leg weakness was evidence of a transient cholinergic effect caused by the slow absorption of carbaryl from the subcutaneous depot. Evidence of slight degeneration (focal loss of striations and fatty infiltration of gastrocnemius muscle fibers) was present at the 3.0 g/kg dose of carbaryl and at all doses of TOCP. These authors concluded that the role of carbaryl in the production of leg weakness in chickens may be described as cholinergic rather than demyelinating.

Gaines' study [43] in chickens supports the studies of Carpenter et al. [27] Gaines pretreated an unspecified number of chickens with 15 mg/kg of atropine orally to protect against the acute effects of the subcutaneous administration of 800 or 1,600 mg/kg of carbaryl. The animals were then observed for 21 days. The higher dose of carbaryl caused leg weakness within 24 hours; all chickens recovered by day 24. As stated above, in TOCP poisoning paralysis develops after 14 days and continues until death.

Smalley et al [52] fed a ration containing carbaryl to 13-week-old Yorkshire pigs. One male and one female pig received 150 mg of carbaryl/kg/day for 72 and 83 days, respectively; one female and two male

pigs received 150 mg/kg/day for 28 days followed by 300 mg/kg/day for either 18 (both males) or 57 (one female) additional days. Two pigs from the same litter served as controls. During the first 4 weeks of treatment, signs of carbaryl effect were limited to brown discoloration of the urine upon exposure to light and air. The first group (one sow and one boar) that received 150 mg/kg/day showed signs of toxicity on days 45 and 62 respectively. The second group (2 boars and 1 sow), whose dose was increased from 150 to 300 mg/kg/day on day 29, exhibited signs of toxicity on days 37, 39, and 41. Animals in both groups were reluctant to stand, remaining recumbent for long periods; later, they were ataxic, incoordinated, and had tremors. In the first group, the boar became prostrate and died on day 72; the sow became prostrate on day 80 and died on day 83. In the second group, both males were prostrate by days 43-44 and died on day 46, while the female became prostrate on day 71 and died on day 85. Microscopic examination of skeletal muscle revealed three distinctive types of myodegeneration, one type related to trauma or ischemia, another characterized as hyaline and vacuolar degeneration, and a third type associated with dystrophic calcification of mitochondria and the sarcotubular system. In the myelinated tracts of the cerebellum, brain stem, and upper spinal cord, the moderate-to-severe edema was considered by the authors to be caused by vascular changes characterized by endothelial hypertrophy, hyalinization of vessel walls, and widespread hemorrhages; however, no demyelination of nerve tissue was observed. In another publication, Smalley [54] indicated that administration of hydrochlorothiazide, a diuretic, reversed the signs of toxicity of carbaryl in chronically treated pigs. He suggested that the mechanism of this

reversal was related to increased excretion of carbaryl in the urine. In the same study, two 5-mg doses of atropine given intramuscularly, 2 hours apart, proved effective in controlling signs of acute carbaryl intoxication in pigs administered single oral doses of carbaryl at 2 g/kg. One sow which received carbaryl in the diet at a dose of 150 mg/kg/day developed paresis on day 93. Atropine therapy, 5 mg (im) repeated at 8-hour intervals for a total of 40 mg over a 3-day period was not effective in controlling signs resulting from repeated administration of carbaryl. The author stated that the only unusual gross or microscopic lesions were in the striated muscle, and that these lesions resembled myopathies of toxic or nutritional origin. The author suggested that brown urine might be evidence of carbaryl poisoning, but it may have actually indicated only carbaryl absorption.

The sensitivity of the pig to carbaryl was compared with that of the dog in a study by Miller et al. [55] A single 20-mg/kg dose of carbaryl was injected iv into eight male miniature pigs. Four control pigs received the vehicle only, which consisted of peanut oil, saline, and lecithin. Both control and experimental pigs were killed 20 minutes after injection. Five male pigs had been fed carbaryl at 125 mg/kg in the diet for 6-8 weeks and were then killed, and five served as controls. Five male dogs received carbaryl at 30 mg/kg by single iv injection. Five additional dogs received the same vehicle as the pigs and served as controls. Both control and experimental dogs were killed 20 minutes after injection. Six male dogs received carbaryl at 125 mg/kg in the diet for 2 months, and five additional dogs were used as controls. All eleven were killed at the end of the study. The signs of carbaryl toxicity following iv injection were

more marked in the pigs than in the dogs. Tremor, ataxia, incoordination, and paraplegia were observed in the pigs, but only lacrimation, salivation, and occasional tremors occurred in the dogs. Dietary administration failed to produce any overt signs of toxicity in the dog, whereas a spastic paresis of the posterior extremities developed in the pigs after 6-8 weeks on the carbaryl diet. There was a significant depression of brain cholinesterase of a similar degree in each species, but the method may not have adequately detected cholinesterase inhibition.

(c) Behavioral Effects

Santolucito and Morrison [56] examined the effect of carbaryl on the EEG of the rhesus monkey. Daily oral carbaryl doses of 0.01 and 1.0 mg/kg were given to four and three rhesus monkeys, respectively, for 18 months; seven monkeys served as controls. During that period, the experimental animals showed no obvious changes in behavior. After 18 months, a single 15-minute EEG recording was made from each monkey while they were immobilized and anesthesized. There were no significant quantitative EEG changes, but whether this was due to anesthetic suppression is not known.

Sideroff and Santolucito [57] conducted a series of investigations on the effects of carbaryl on rat behavior. Two techniques, liquid reinforcement and electroshock avoidance, were combined and used in this study. Each of four groups of male rats weighing 200-250 g was composed of 5-9 controls and an equal number of treated animals which were injected subcutaneously with carbaryl at 10 mg/kg, once weekly, for 2-5 weeks. The results of the experiments showed a statistically significant difference between the control and the treated animals. This led the authors to conclude that the carbaryl-treated rats were less motivated (fewer lever

pressings for water) and less inhibited by aversive (electroshock) situations than were the control rats.

Singh [58] found that a decrease in physical activity of rats, as measured in an activity-wheel cage, occurred following single ip injections of carbaryl at 0.56 and 2.24 mg/kg. Atropine at 2 mg/kg ip did not alter the carbaryl effect in female rats. In male rats, the effects of the 2.24 mg/kg dose were reversed.

(d) Reproduction Studies, Including Teratogenesis and Mutagenesis

Epstein et al [59] included carbaryl in a series of agents screened for dominant lethal-mutations in mice. Carbaryl was administered orally in daily doses of 50 and 1,000 mg/kg to 10 male mice each for 5 days. One mouse in the 1,000 mg/kg group died. Each of the 19 surviving males was then caged for mating with three untreated virgins each week for 8 consecutive weeks. The females were killed on about the 13th day of gestation. At autopsy, each female was scored for pregnancy and for number of total implants, including live implants and early fetal deaths. The authors assessed the reduction in total implants by comparing the number of total implants in females mated with treated and control males. While these specific data for carbaryl were not discussed further in the paper, the authors included carbaryl in a class of agents which did not meet "any screening criteria for mutagenic effects."

In addition to the dominant-lethal test, the results of several other studies of the mutagenic potential of carbaryl have been reported. In a plant study undertaken by Amer, [60] 0.5 and 0.25% saturated solutions of carbaryl (pure and formulated), prepared at 22 and 60 C, were applied to Allium cepa germinating roots for 4 and 24 hours. The pure and formulated

solutions prepared at the higher temperature (60 C) caused abnormal forms of mitotic figures and a complete arrest of the process. Solutions prepared at the lower temperature caused fewer abnormal forms of mitotic figures and partial arrest of the mitotic process. The formulation caused more severe arrest than did the pure solutions. The relevance of these data to humans is not clear at this time.

In another plant study, Wuu and Grant [61] using barley (Hordeum vulgare L) seeds and seedlings found that carbaryl at 1,000 ppm for 12 hours on the sprouted seeds induced meiotic changes, namely, chromosomal aberrations of 0.55% in the C-1 generation and 2.9% in the C-2 generation. The positive controls, treated with ethylmethanesulfonate at 1,000 ppm and X-rays at 5,500 R, and the untreated control sprouted seeds showed chromosomal abnormalities of 1.57%, 3.91%, and 0.22%, respectively, in the C-1 generation and 0.38%, 1.26%, and 0.49%, respectively, in the C-2 generation. The seedlings sprayed once with carbaryl at a concentration of 500 ppm which showed 1.21% chromosomal abnormalities contrasted with the untreated control rate of 0.66%.

Brzeskij and Vaskov [62] examined the effects of carbaryl on mutations and fertility in Drosophila melanogaster using criteria of (1) deletions in X-chromosomes, (2) recessive sex-linked lethal and sublethal mutations caught in F2 by Moeller-5 method, and (3) male fertility by examining sex cells in different stages. They found no effects on fertility of males at any stage of spermatogenesis but found a low rate of recessive sex-linked lethal and sublethal mutations. Therefore, they concluded that carbaryl was a weak mutagen. Elespuru et al [63] found that carbaryl was not mutagenic in Hemophilus influenzae. Siebert and

Eisenbrand [64] examined carbaryl for genetic activity in a diploid strain of Saccharomyces cerevisiae, heteroallelic at the gene loci ade-2 and trp-5. Even at a concentration of 4.97 millimolar, carbaryl did not change the frequency of mitotic gene conversion compared with control solvents and was judged genetically inactive. Uchiyama et al [65] assayed carbaryl for mutagenic activity by using (1) the back-mutation method with an auxotrophic mutant of E coli B/r WP-2 try and (2) recombination assay with B subtilis Marburg 17a, of recombination-capable strain, and Marburg 45T of recombination-lacking strain. Carbaryl did not result in mutagenic changes, even at the highest concentration of 10 mg/plate, with either method.

The preceding mutagenic studies on a mammal (mice), [59] on bacteria (H influenzae, [63] and E coli and B subtilis [65]), and on yeast (S cervisiae) [64] indicate that carbaryl is not a mutagen under these experimental conditions, although experiments on an insect (Drosophila) indicate weak mutagenicity. [62] However, nitrosocarbaryl (N-nitroso-N-methyl-1 naphthylcarbamate) was a strong mutagen in H influenzae, [63] S cerevisiae, [64] and E coli and B subtilis. [65] Uchiyama et al [65] also pointed out that the N-methyl carbamates, including carbaryl, might be convertible to nitroso compounds. They speculated that since carbamates are widely used and since nitrite is a common constituent of human saliva, the stomach would then provide the acid medium necessary for nitrosation. Nevertheless, the significance of the formation of nitrosocarbaryl in relation to any effect of carbaryl on humans remains to be determined.

Smalley et al [66] investigated the teratogenic potential of carbaryl incorporated into the diet of pregnant beagles throughout gestation

(averaging 62 days). Fifty-five bitches were treated with carbaryl as follows: 10 at 3.125 mg/kg, 10 at 6.25 mg/kg, 18 at 12.5 mg/kg, 9 at 25 mg/kg, and 8 at 50 mg/kg. Sixteen animals used as controls were maintained under similar conditions but received no carbaryl. After parturition, the bitches and pups were carefully examined. Radiographs were taken of the pups if skeletal abnormalities were observed or suspected. Defective pups were killed and necropsied after birth, the rest at weaning; abnormalities were characterized and recorded. At all levels of treatment, the percentage of pups born alive was lower than in the controls. At the highest carbaryl dose (50 mg/kg/day), eight animals were bred, three conceived, but no pups were born alive. Dystocia was present in about one out of three of the treated bitches; none of the control bitches had dystocia. The authors did not state whether the dystocia was maternal or fetal but, from the information given on the appearance of the reproductive organs, it is inferred that the dystocia was maternal. The average numbers of pups/litter at the two highest dose levels were 3.5 and 3.8; the control average was 5.4. Of the total number of pregnant beagles at all carbaryl doses, 21% produced pups showing evidence of embryotoxicity. At the lowest dose (3.125 mg/kg) and in the control group, there were no abnormal pups. Excluding fetal deaths and resorptions, 21 pups (11.6%) were abnormal; all were from dams that received the four higher doses. Teratogenic effects included abdominal-thoracic fissures with varying degrees of intestinal organ agenesis, extra phalanges, brachygnathia (shortened lower jaw), and failure of skeletal formation. This study [66] was listed in the Registry of Toxic Effects of Chemical Substances [14] as showing teratogenic effects and will be discussed and evaluated further (see Absorption and Metabolism

under Animal Toxicity, Correlation of Exposure and Effect, and Chapter V, Basis for the Recommended Standard).

In studies [67] designed to evaluate the effects of carbaryl on reproduction in primates, carbaryl was administered in 1% aqueous gum traqacanth by stomach tube to mature female rhesus monkeys throughout the gestation period, as follows: 2.0 mg/kg to 4 monkeys and 20.0 mg/kg to 10 animals. Seven control monkeys received the vehicle. Monkeys at all treatment levels, including controls, were mated and confirmatory pregnancy tests performed. Two of four monkeys given carbaryl at 2.0 mg/kg were pregnant but both aborted. Six of 10 monkeys on the 20 mg/kg dose were pregnant; 3 aborted and 3 delivered normal babies. Five of seven control monkeys were pregnant; one aborted, and four delivered normal babies. Although not directly dose related, abortion rates for the treated groups--100% (two of two) at 2 mg/kg, 50% (three of six) at 20 mg/kg--exceeded the 20% rate (one of five) for the control group. It is difficult to make conclusions on the basis of this report since the number of monkeys used was too small. Abortions were reported but no terata were found; this agrees with Wilson [68] who has indicated that with several suspected or proved teratogens, the range of doses causing terata in the primate is small; moreover, unlike rodents, primates are more likely to respond to potential teratogens by aborting.

Dougherty and Coulston [69] extended the previous study [67] using 79 female rhesus monkeys; 78 finished the study. The animals were divided into 4 groups of 16 each and 1 group of 15 (vehicle control). Each monkey of three groups was given carbaryl in a gelatin capsule at 0.2, 2.0, or 20 mg/kg/day from day 20 through day 38 of gestation; the fourth group was

given empty capsules; the fifth group was not treated. All monkeys were mated and delivered naturally with the following results: the 0.2 mg/kg group had 14 live births and 2 abortions; the 2.0 mg/kg group had 15 live births and 1 abortion; the 20.0 mg/kg group had 12 live births, 3 abortions, and 1 was not pregnant; the vehicle control group had 13 live births, and 2 abortions; the untreated control group had 13 live births, 2 abortions, and 1 stillborn. No terata were found. The authors concluded that carbaryl was not teratogenic, that it was not associated either with a high incidence of abortion or stillbirth or with abnormal gestation length or mean body weight, and that it did not have any adverse effect on adult females or surviving infants. Microscopic examination of the tissues of the young monkeys which died was not performed.

Weil et al [70] reported a study of the teratogenic potential of dietary carbaryl in rats. After mating, pregnant rats were assigned at random to one of three treatment schedules: (1) carbaryl in the diet throughout pregnancy or until weaning of the pups; (2) carbaryl in the diet from days 1 to 7 of pregnancy; and (3) carbaryl in the diet from days 5 to 15 of pregnancy. Females for each of the three treatment schedules were randomly assigned to three groups of six rats each and administered 20, 100, or 500 mg/kg of carbaryl. Six rats were assigned to the control group. Neither fertility nor gestation was affected by carbaryl in the diet. However, at the dose of 500 mg/kg until weaning, 2/3 of the pups died within 4 days after birth. The viability of pups in the other treated groups was not significantly affected. The mean body weights of the pups from control and treated dams were similar, although the adult female rats and their pups that received 500 mg/kg of carbaryl during pregnancy and

nursing weighed less than did the control dams and pups at time of birth. No gross or teratogenic anomalies associated with carbaryl treatment were found in the pups weaned at 21 days of age. Six adult rats of each of the nine treatment groups and one control group were killed on days 19-21 of their pregnancies. The uteri were examined for resorption sites and for dead and living pups. Gross and microscopic examination revealed no significant abnormalities attributable to carbaryl in the 709 fetuses examined. The poor survival of the rat pups allowed to nurse may have been related to the excretion of carbaryl or its metabolites in the milk and to the greater sensitivity of young rats to carbaryl, or it may have been related to the inability of the dams treated with carbaryl at 500 mg/kg to successfully nurse and rear their young, as indicated by their limited body weight gains.

The teratogenic potential of carbaryl has also been investigated in various other species of animals. Robens [71] administered carbaryl to guinea pigs daily in gelatin capsules on days 11-20 of gestation at a dose of 300 mg/kg. This resulted in 38% mortality in 26 pregnant dams, as compared with no deaths in control guinea pigs given empty gelatin capsules. Fetal mortality was 17.5% in the litters of surviving treated dams and 9.5% in control litters. There were 11 terata among the fetuses of these treated dams. The changes included skeletal defects, most of which involved the cervical vertebrae. Carbaryl was also administered as a single-dose treatment of 300 mg/kg to another group of 40 guinea pigs, some (number not specified) of which received their single doses between days 11 and 20 of gestation. Maternal mortality for this group was 12.5%; and fetal mortality was 6.5%, which was below that for the control group

(9.5%). All nine malformed fetuses were produced in the litters of dams treated on days 12, 13, 14, 15, and 16. Eight of the nine had vertebral malformations, and two revealed organ agenesis. One of the two malformations in control fetuses was dental, the other vertebral. The mortality of the adult females in all groups which produced terata, was greater than in the controls. Robens [71] stated that the doses required to produce terata in guinea pigs were at least 1,000 times the level of carbaryl allowed in human food. This study [71] was one of those listed in the Registry of Toxic Effects of Chemical Substances [14] as showing teratogenic effects, and will be further discussed later.

Oral administration [71] of carbaryl in gelatin capsules at doses of 50, 100, and 200 mg/kg to four, four, and nine pregnant rabbits, respectively, on days 5-15 of gestation produced neither terata nor dose-related fetal mortality, as compared to the results from 21 pregnant control does. The author indicated that signs of cholinesterase inhibition did not occur following any dose of carbaryl used in this study.

Carbaryl was administered by stomach tube to pregnant hamsters [71] on days 6, 7, and 8 of gestation at a dose of 125 mg/kg, or on day 7 or 8 at 250 mg/kg. Two of six hamsters treated with one dose of 250 mg/kg of carbaryl died, none of the eight hamsters given 125 mg/kg died, and none of the controls. Signs of cholinesterase inhibition (salivation, diarrhea, and incoordination) were observed in all treated hamsters. Fetal mortality was 30.3% at the high dose (250 mg/kg), 10.0% at the low dose (125 mg/kg), and 5.5% in the controls. No anomalies were found in any of four fetuses examined from each litter. The results show that, among the species studied, [71] terata were produced only in guinea pigs and by doses which

also caused mortality and morbidity in some of the dams. Also, since only one level was used in the single- and multiple-dose guinea pig studies, no conclusions of dose-related significance can be made.

In another study by Weil et al, [72] 300 pregnant guinea pigs in groups of 5 or 10 were administered doses of 100, 200, or 300 mg/kg of carbaryl by dietary inclusion, or 50, 100, or 200 mg/kg by gastric intubation, for 1-, 2-, 3-, 5-, or 15-day intervals during days 10-24 of gestation and were killed prior to parturition on day 34 or 35. Two control groups of 10 and 30 guinea pigs were treated in the same manner as the dietary- and gavage-treated guinea pigs, respectively. Body-weight gains for all guinea pig dams treated on days 12, 13, 14, 15, and 16 were less than those of the control animals, and this effect was more marked in intubated than in diet-treated guinea pigs at the same dose. Fewer carbaryl-gavaged than control-gavaged pregnant guinea pigs died. Dietary carbaryl produced no dose-related incidence or significant numbers of terata, as compared with controls. Oral intubation of carbaryl at 50 mg/kg to pregnant guinea pigs on days 10-24 of gestation produced 15.7% fetal skeletal anomalies compared with 9.1% for control pups, while doses of 100 and 200 mg/kg resulted in 5.4 and 8.3%, respectively. The authors [72] contrasted their results with those of Robens [71] and Shtenberg and Ozhovan [73] (discussed later in this section) who used gastric intubation as the route of administration, thereby causing greater toxicity than when compounds are incorporated in food. Weil et al [72] concluded that a carbaryl dose of 300 mg/kg in the diet or 200 mg/kg by intubation did not result in teratogenic effects in guinea pigs. They questioned whether the material used in the USSR study [73] was sufficiently pure. Argauer and

Warthen [74] have subsequently shown contamination of samples of carbaryl manufactured outside the United States (see later discussion in review of Carcinogenesis).

Benson et al [75] investigated the teratogenic potential of carbaryl in mice. Carbaryl was administered in the diet at levels of 10 or 30 mg/kg to groups of 20 pregnant mice from day 6 of gestation until birth of the pups. Twenty untreated females served as controls. The treated and control adults did not differ in mortality, behavior, physical condition, resorptions, or fetal deaths. The fetuses from treated dams did not differ from control fetuses in mortality and weight, but nine so-called minor fetal abnormalities in two litters occurred at the high dose (30 mg/kg), compared with two for the controls. The authors concluded that, because of the small incidence of abnormalities (6% at 30 mg/kg vs 2.1% in controls) and the lack of a consistent pattern in those found, the abnormalities were not related to administration of carbaryl. Lack of sufficient detail in their report makes an analysis for an independent evaluation impractical. However, lack of graded response in various abnormalities reported, at doses of 0, 10, or 30 mg/kg, supports their conclusion.

Vashakidze [76] carried out a 3-month study on rats at oral doses of 50, 100, and 300 mg/kg to measure the reproductive effects of what was described as Sevin powder. At doses of 100 and 300 mg/kg administered to female rats, there was a disruption in the sexual cycle reported as a decreased frequency or absence of estrus, proestrus and diestrus as well as elongation of the latter two phases. At the same doses, treated females impregnated by untreated males were reported to have reduction in litter size and prolonged pregnancy with what was described as deformation of the

womb. Autopsy showed embryos either dead or at various stages of development. The author reported that 50 mg/kg of the compound administered during organ differentiation, which was reported to be on the 9th or 10th day of development, caused developmental disorders. These disorders were explained in the study as either the death or cessation of development of the embryo. At unspecified doses, males were reported to show decreased sperm motility and deformed spermatozoa. At 300 mg/kg, treated males were unable to impregnate untreated females. It is not possible from the study described by Vashakidze [76] to determine either the purity or chemical composition of the material administered to rats that was described by the author as Sevin powder or the method of oral administration. Since the study was purely descriptive with no data presented, the results cannot be adequately evaluated. This study, unevaluated, was one of those listed in the Registry of Toxic Effects of Chemical Substances [14] as showing teratogenic effects.

Shtenberg and Rybakova [77] administered carbaryl described as 100% active material orally at doses of 7, 14, and 70 mg/kg to groups of 24 rats of each sex for periods of up to 12 months. A group of equal size received no carbaryl. The method of administration, whether by dietary inclusion or by stomach tube, is not clear from the text description. When compared with control rats, growth was inhibited in those receiving 14 and 70 mg/kg of carbaryl, but not in those receiving 7 mg/kg. Cholinesterase activity in blood as measured by acetylcholine-hydrolysis time was decreased in the 14 mg/kg and 70 mg/kg groups from the third month (first determination) until the end of the study. After 12 months of treatment, there was a dose-related decrease in spermatozoal motility at all doses. Microscopic

examination of the testes showed edema of interstitial tissue, destruction of germinal epithelium, and reduction in spermatocytes and spermatids. In females, the estrus cycle was prolonged by an increase in length of the diestrus phase at the 14 mg/kg and 70 mg/kg doses. All groups of carbaryl-treated rats showed an increase in gonadotropic hormone production in the hypophysis as determined by tests on immature mice. Decreased thyroid activity was indicated by a reduction in the absorption and excretion of 131-I. When examined microscopically, the cortex of the adrenal glands also showed evidence of increased activity in the zona glomerulosa and zona fasciculata. The authors suggested that the primary site of action was probably the anterior pituitary which caused secondary changes in the reproductive glands; however, a direct effect of carbaryl on the reproductive glands was not ruled out.

Collins et al [78] studied the effects of carbaryl on the reproductive cycle in a three-generation reproduction study in rats. Carbaryl (technical grade, 99% purity) was administered by incorporation into the diet at levels of 0, 2,000, 5,000, and 10,000 ppm and was continued throughout the study. Groups of 20 pairs of weanling rats at each dose plus the same number of untreated controls were mated at 100 days of age. Two litters (F1a and F1b) were produced from each pair. Animals from the first litter (F1a) were reared to weaning and then killed. Those from the second litter (F1b) were raised to weaning and 20 littermate pairs were selected to produce the next generation. The same procedure was followed until two litters had been produced for each of three generations (F1a, F1b, F2a, F2b, F3a, and F3b). All the rats of the third generation (first and second litters) were killed at weaning. The authors stated that

microscopic studies of the rat tissues were not performed. The ability of the female rats to produce young (fertility) was decreased only at the 10,000-ppm level. No litters resulted from the second mating of the second generation at this dose; therefore, no third generation was produced. The viability of the pups from dams treated at 5,000 and 10,000 ppm was significantly decreased. The average litter size and survival of offspring until 4 and 21 days of age were significantly decreased in a dose-related manner at both the 5,000-ppm and 10,000-ppm dietary levels. Mean weanling body weights at all carbaryl dose levels were significantly lower than those of control young and showed a dose-related suppression. The decreased fertility in rats on the highest dose was suggested by the authors as possibly due to an effect of carbaryl on sperm motility and the enzymatic activity of testes and ova, and mediated indirectly through effects on the hypothalamohypophyseal complex. The authors also suggested that the decreased survival rate of the 1- to 4-day-old pups, especially at the two higher doses, appeared to result from an increased susceptibility of the pups to metabolic damage from carbaryl treatment. Collins et al [78] concluded that the no-effect level for carbaryl was below 2,000 ppm.

A three-generation study of similar design was conducted in rats by Weil et al. [72] This study design differed from that of Collins et al [78] in that offspring of the first mating of the third generation (F3a), when killed at 21 or 90 days of age, were examined for tissue changes. The female rats used to produce the second litter of the third generation (F3b) were killed at day 18 or 19 of the second gestation period; examination of the uterine contents for viable or dead fetuses, resorption sites, fetal weight, and skeletal or soft tissue anomalies of the fetuses was performed

as in teratogenic studies. Some males of the second generation (F2a) were removed from treatment at 224 days of age and mated for 10 consecutive weeks to virgin females that had never received carbaryl, to test for dominant-lethal mutagenicity. The possible differences between gastric intubation versus dietary inclusion were also compared in this study. The dose levels for those rats treated by intubation were 0, 3, 7, 25, and 100 mg/kg, while the doses given in the diet were 0, 7, 25, 100 (also 100 in corn oil), and 200 mg/kg. Carbaryl at a level of 100 mg/kg by oral intubation produced signs of cholinesterase inhibition and increased mortality of parents at all breeding periods; it decreased the number of pups born alive (F1a, F2a, F3a) and the percentage of females that produced litters (F1b only); it decreased the number of fetuses and of live fetuses; it increased the frequency of fetal resorption; it lengthened the gestation period of female rats yielding first generation, second litter (F1b); and it decreased the body weights of the original parents before the first mating. The lower doses (3, 7, and 25 mg/kg) of carbaryl by oral intubation were without effect. The effects of 200 mg/kg of carbaryl administered by inclusion in the diet were limited to an initial decrease in body weight gain in the original rats and lengthened gestation periods of the first and second generations as compared with the controls. No signs of cholinesterase inhibition were observed at this dose level. The authors reported that the teratogenic and dominant-lethal portions of the study did not indicate any carbaryl-related effects. The results of this study, and of the previously discussed guinea pig teratogenic study included in this paper, [72] suggested that, at equal doses, carbaryl administered by stomach tube can produce a more pronounced toxic effect

than by dietary inclusion. This is probably due to the higher blood levels from the rapid absorption which can occur from gastric intubation.

Shtenberg and Ozhovan [73] gave carbaryl dissolved in sunflower oil perorally to rats (second (F2) through fifth (F5) generation) at doses of 2 and 5 mg/kg. According to their written communication to Weil and coworkers, [72] this was administered by gastric intubation. A control group was maintained under similar conditions. The test material was administered to both sexes of each generation for 6 months, but the rats were paired for breeding after 4 months of treatment. Sperm motility and resistance (not defined), spermatogenesis, and duration of sperm survival (in a nutrient medium) were significantly reduced in male rats of both treated groups from the second to the fourth generation when compared with the controls. Microscopic examination of testicular tissue revealed what was described as dystrophic-atrophic changes in the nature of the spermiogenic epithelium. In both the third and fourth generations, the duration of estrus was decreased and the interestral period lengthened in rats after 3 months of 5 mg/kg carbaryl treatment; at 6 months, rats receiving 2 mg/kg carbaryl were similarly affected. Microscopic examination of ovarian tissue revealed what was called an atrophically sclerotic process in the follicles of carbaryl-treated females. The authors stated that the effect was seen to increase from generation to generation. The dose of carbaryl at which these tissue changes were seen was not specified. Fertility of the females (litter size) decreased progressively from the second through the fourth generations, the effect being dose related. Survival of the pups during the first month of life decreased as the dose of carbaryl was increased. The adverse effect on

survival was seen to increase progressively from the third through the fifth generations. From the results of these studies, the authors concluded that carbaryl has a direct and negative influence on the reproductive glands.

Collins et al [78] conducted a three-generation study in Mongolian gerbils (Meriones unguiculatus). Carbaryl was administered in the diet at levels of 0, 2,000, 4,000, 6,000, and 10,000 ppm. No litters were produced from the second mating of the third generation (F3b) at the 10,000-ppm level. Adverse effects on fertility, litter size, pup viability, and survival to day 21 appeared sporadically in the second and third generations at carbaryl treatment levels of 2,000, 4,000, and 6,000 ppm, and in all generations at 10,000 ppm. Survival from day 4 to weaning was significantly decreased in all generations at doses of 4,000 ppm and above, while effects were seen in the second and third generations at 2,000 ppm. No grossly visible abnormalities were observed in any of the offspring. Microscopic examination (tissues not specified) revealed no changes. Mean weanling weights were variably lower in gerbils treated with 4,000 ppm or more of carbaryl.

(e) Carcinogenesis

Carpenter et al [27] investigated the lung cancer potential of carbaryl which was injected subcutaneously once a week into 60 male mice (tumor-susceptible A/Jax and C3H strains) during their third to eighth months of age, after which a gross examination only was made for lung tumors. Technical carbaryl was suspended in 0.25% agar at a concentration of 5.0%, and 0.2 ml was injected into each mouse, delivering a carbaryl dose of 10 mg/week to each mouse (or a dose of about 400 mg/kg/week in a 25

g mouse). One control group received injections of 0.25% agar only, and another was untreated. The authors stated that males of the A/Jax strain have a high rate of spontaneous lung tumor. Under the conditions of the experiment, subcutaneous administration of carbaryl did not significantly increase the incidence of tumors, lung infection, or death in tumor-susceptible mice over that in the controls.

Innes et al, [79] in a study of 120 compounds performed in conjunction with the National Cancer Institute, administered carbaryl to neonatal mice daily for about 18 months. The mice received the test material (4.64 mg/kg) by stomach tube on days 7-28 of age and thereafter in the diet at a level stated to be equivalent to the amount ingested. A total of 72 mice, 36 of each sex, composed the treatment group. Eleven of the compounds studied caused a significant elevation of tumors; 89 more compounds, including carbaryl, gave no significant evidence of tumorigenicity; the remaining 20 warranted, it was concluded, further evaluation. Further data on carbaryl-treated mice were not supplied. The authors pointed out that there was no way to predict whether humans are more or less susceptible than mice to the induction of tumors by the compounds tested in this study. In addition, they indicated that the dose received by the mice was far in excess of that likely to be consumed by humans.

Andrianova and Alekseyev [80] administered carbaryl orally to 60 male mongrel rats at 30 mg/kg twice weekly for periods of up to 22 months (whether by incorporation into their diet or by intubation is not clear). Another 48 mongrel rats were treated by subcutaneous implantation of a paraffin capsule containing 20 mg of Sevin (carbaryl) 97.65% pure obtained

from the Shchelkov Chemical Plant. The control group consisted of 48 male rats, but it was not stated whether they were sham-treated orally or had empty capsules implanted subcutaneously. Of the 12 surviving rats in the orally treated carbaryl group, 4 had tumors; there were 2 subcutaneous fibrosarcomas, 1 polymorphous cell sarcoma (the tumor grew into the stomach wall but did not affect the organs of the abdominal cavity), and 1 osteosarcoma. Of the 10 surviving rats in the subcutaneously treated group, 2 had subdermal tumors, both of them said to be fibrosarcomas, but not at the implantation site. In the control group, 46 of 48 rats survived, and only 1 had a tumor at 11 months, a fibrosarcoma at an unspecified location. Although the authors concluded that carbaryl could produce tumors in rats, the results of this study are not conclusive because of the high mortality in the experimental group and the absence of information on how the controls were treated. This study [80] was listed, unevaluated, in the Registry of Toxic Effects of Chemical Substances [14] as showing carcinogenic effects. It will be further discussed and evaluated (see Correlation of Exposure and Effect and Chapter V, Basis for the Recommended Standard). As previously mentioned in the discussion of reproduction studies, Weil et al [72] have questioned the chemical purity of the carbaryl produced outside the United States. The following paper may partially answer the question. Argauer and Warthen [74] analyzed various samples of carbaryl (1-naphthyl methylcarbamate) for the presence of the contaminant 2-naphthyl methylcarbamate by using liquid and thin-layer chromatography with confirmation by spectrofluorometry. Contamination of carbaryl with the 2-naphthyl methylcarbamate can occur if the precursor 1-naphthol, used to synthesize the carbaryl, is not pure.

The presence of the 2-naphthyl isomer is undesirable since the compound has been reported to have caused cancerous tumors in rats and in mice when given orally or intravenously. [74] Of the four samples of carbaryl produced in the United States which were analyzed in this study, none contained a detectable amount of the 2-naphthyl contaminant. Each of the four samples produced in foreign countries contained measurable amounts (2.3 and 14 mg in the 250-mg technical samples; 1.3 and 12.4 mg in the 500-mg samples of 50% wettable powder) of the 2-naphthyl isomer measured as 2-naphthol in a previously hydrolyzed sample. In the previously cited paper by Carpenter et al, [27] there was no dose-related incidence of tumors or increase in tumors over the controls in rats given US-manufactured carbaryl in the diet at levels of 50, 100, 200, and 400 ppm for 2 years.

Shimkin et al [81] synthesized N-methyl naphthyl carbamate and compared it to 21 other carbamates, one of which was ethyl carbamate, a known carcinogen, by a sensitive, pulmonary-tumor-induction bioassay method in Strain A/He mice from the National Cancer Institute. The compound was administered ip to 16 mice at 0.5 mg 3 times weekly for 4 weeks; the total dose to each mouse was 6.0 mg (1,190 μmoles/kg). Three control groups of mice (32 in each group) were injected with water or the vehicle tricaprylin or were untreated. The experiments were terminated 20 weeks after the last injection by killing the animals. The lungs were examined microscopically for tumors. While several of the carbamates were actively tumorigenic (ethyl carbamate, most active; methyl carbamate, inactive), the synthesized N-methyl naphthyl carbamate was classed as marginal. Two important points need to be emphasized concerning the compound described in the study of Shimkin et al [81] as N-methyl naphthyl carbamate. First, there is a lack

of information on the purity of this specially synthesized compound, and, secondly and more importantly, it is not clear from the structural formula presented whether the compound was 2-naphthyl N-methylcarbamate or 1-naphthyl N-methylcarbamate (carbaryl). Therefore, it is difficult to draw any conclusion as to the potential for carcinogenicity of carbaryl from this study. In a study using Ehrlich ascites tumor cells, injected intraperitoneally, Walker et al [82] determined that carbaryl, also injected ip, produced a moderate but significant inhibition of tumor growth in vivo in mice. The authors also found that carbaryl "reduced appreciably" the rates of incorporation of the isotopically labeled precursors, uridine-5-3H, thymidine-methyl-3H and L-leucine-14C into ribonucleic acid, desoxyribonucleic acid, and protein, respectively, in Ehrlich ascites tumor cells, in vitro.

(f) Absorption and Metabolism

Hwang and Schanker [83] studied the absorption of 14C-labeled carbaryl by the intestine and the lung in rats. They instilled 0.1 ml of a (0.025-0.05 mM 14C-labeled carbaryl) test solution into a tightly secured tracheal cannula (at the tracheal bifurcation) in 12 anesthetized rats. At the end of 2, 4, and 6 minutes, the lungs were removed, processed, and analyzed by liquid scintillation for the recoverable 14C-labeled material. The entire small intestine was isolated in 15 rats and 1 ml of a 0.005-0.1 millimolar 14C-labeled carbaryl aqueous solution was injected into the lumen of the small intestine. At 2, 4, 6, 8, and 10 minutes, the intestines were removed and the unabsorbed 14C label was recovered and measured by liquid scintillation. By plotting the measured amounts recovered at the various times, it was determined that the absorption half-

time for the lungs of rats was 2.6 minutes and for the intestine 6.4 minutes. By varying the known concentration of the carbaryl solution, the investigators determined that 14C-labeled carbaryl crosses the wall of the rat intestine by simple diffusion. The authors indicated that absorption through the lung was much more rapid than through the intestine and also appeared to occur by a process of simple diffusion.

Casper et al [84] examined the gastric absorption of 14C-labeled carbaryl in the isolated (empty) stomachs (with portal circulation intact) of an unspecified number of rats and found about 53% and 82% of the 14C label in the portal blood in 22 and 67 minutes, respectively. The authors verified the identity of the 14C material in the portal blood using several analytical techniques (chromatography and infrared spectroscopy) and concluded that approximately 90% of the labeled material found in the portal blood was 14C-labeled carbaryl. They concluded that carbaryl could be rapidly absorbed from the stomach in the fasting rat, but that absorption would be expected to be retarded by the presence of additional gastric contents.

In a percutaneous absorption study, Hurwood [85] studied the carbaryl residues in selected tissues (liver, kidney, muscle, and omental and perirenal fat) of steers and in the milk of cows. Fourteen steers were used in the study. Six steers were sprayed once and six were sprayed three times, at 2-day intervals, with 2 gallons of 0.3% carbaryl as a colloidal dispersion in water. Two untreated steers served as controls. Two animals from each group were killed at 1, 3, and 7 days after application of the spray for tissue analysis to detect any carbaryl residue. Perirenal fat from the steers was found to have the highest concentration in the tissues

examined 1 day after treatment. All tissue examined had some carbaryl residue 3 days after treatment. However, no detectable tissue residue was present in the steers' tissues after 7 days. Each of three dairy cows was sprayed once with 2 gallons of the 0.3% carbaryl spray, and milk samples were analyzed from both daily milkings for the next 5 days. Carbaryl was found in the greatest concentration at the first milking, 5 hours after spraying. It was excreted in the milk for at least 69 hours but was not found in milk taken 77 hours after spraying the cows.

Bukin and Filatov [86] studied the tissue distribution of carbaryl and its metabolites in rabbits. Carbaryl was administered in single oral doses ranging from 100 to 700 mg/kg. No clinical signs were observed and no carbaryl was found in the organs or tissues at autopsy, 24-80 hours after carbaryl treatment at 100, 200, or 300 mg/kg . After single doses of 400 mg/kg, an unspecified number of rabbits were killed at various intervals, and tissues, bile, and urine were analyzed for carbaryl. Residual amounts of carbaryl determined by paper chromatography are listed in Table XIII-3. At doses of 600 and 700 mg/kg, residual carbaryl ranged from 0.075 to 1.2 mg/kg in all organs and tissues examined; the time of examination was not reported however. The high dose (700 mg/kg) was fatal to all rabbits. These results suggest rapid excretion and little long-term retention of carbaryl in rabbits.

Carpenter et al, [27] in their 1961 report on the effects of carbaryl in mammals, established that approximately 31.3 ± 1.6% of the 1-naphthol portion of an orally administered dose of 0.015 g of carbaryl to each of 18 rats was recovered from their urine in 48 hours as a conjugated form, probably as the glucuronide.

In a study by Knaak et al, [34] carbaryl labeled with carbon-14 at various moieties, including the naphthyl (naphthyl-labeled), methyl (methyl-labeled) and carbonyl (carbonyl-labeled) moieties, was administered by gavage to three groups of four rats each. One group received 20.0 mg/kg each of methyl-labeled carbaryl; another group of four received 20.0 mg/kg each of naphthyl-labeled carbaryl; and the third group received 9.0 mg/kg of carbonyl-labeled carbaryl. The average total amount of labeled carbaryl which was detected and measured by a scintillation spectrometer from all sources--urine, feces, expired air (carbon dioxide), and carcasses--was 94% over a 7-day period. However, the authors stated that the excretion of carbaryl was essentially complete by the end of 3 days. Ninety-five percent of the naphthyl-labeled compound was detected in urine and feces; 99% of the carbonyl-labeled compound was found in urine, feces, and respiratory carbon dioxide; and approximately 91% of the methyl-labeled carbaryl was detected in urine, feces, carbon dioxide, and carcasses of the rats.

In the same publication, [34] the authors reported on administration of carbaryl ip to three groups of three 150-g male rats as naphthyl-labeled, methyl-labeled, or carbonyl-labeled carbaryl. Each rat was administered 3.0 mg of the appropriate labeled material in 300 mg of polyethylene glycol 400. The naphthyl- and methyl-labeled carbaryl were also administered ip at the same doses to three 200-g guinea pigs of unstated sex. From 24-hour pooled specimens of rat urine, 73, 47, and 48% of the naphthyl-, methyl- and carbonyl-labeled compounds, respectively, were recovered as carbaryl equivalents. Guinea pig urine, also 24-hour pooled specimens, yielded 85% of the total amount of naphthyl- and methyl-

labeled carbaryl administered. The urinary metabolites of the rat and guinea pig were identified from chromatographs. From those determinations, the authors showed that carbaryl, in the rat and guinea pig, is transformed into a series of eight or more metabolites. The major metabolites in this series were two glucuronides, the 4(methyl carbamoyloxy)-1-naphthyl glucuronide also known as 4-hydroxycarbaryl glucuronide and the 1-naphthyl methylimidocarbonate-O-glucuronide. Hydrolyzed products were also present; the glucuronide and the sulfate of 1-naphthol were detected in both rat and guinea pig urine after administration of the naphthyl-labeled carbaryl. The 1-naphthyl methylcarbamate N-glucuronide was present in guinea pig urine only after administration of either naphthyl- or methyl-labeled carbaryl. Table XIII-4 lists the metabolites found in rat and guinea pig urine with those of other mammals for comparison. Unidentified neutrals and other unidentified metabolites were found in excretions of both rats (one group, A) and guinea pigs (two groups, A and B). The investigators also found evidence that carbaryl could have been conjugated directly with glucuronic acid to form 1-naphthyl methylcarbamate N-glucuronide and 1-naphthyl methylimidocarbonate-O-glucuronide.

The in vitro metabolism of carbaryl by rat and guinea pig liver preparations was investigated in the same study. [34] Naphthyl-labeled carbaryl was incubated with fortified liver homogenates or microsomal preparations obtained by differential centrifugation. Metabolites formed by both rat and guinea pig liver preparations included 1-naphthyl glucuronide, 4-hydroxycarbaryl, 4-hydroxycarbaryl glucuronide, and unidentified water-soluble neutrals. The formation from carbaryl of 1-naphthyl, 1-naphthyl methylimidocarbonate-O-glucuronide, and 4-hydroxy-1-

naphthyl methylcarbamate was observed with rat, but not with guinea pig, liver preparations. These studies indicate a metabolic profile similar to that seen in the urinary excretion studies with carbaryl.

The metabolism of carbaryl in the dog was reported by Knaak and Sullivan. [87] Two forms of carbaryl, labeled with carbon-14 at either the naphthyl or methyl moiety, were separately and sequentially administered 7 days apart, in gelatin capsules to three female beagles weighing 9 kg each in doses of 25 mg/kg. Urine and feces were collected daily for 7 days and analyzed for 14C by liquid scintillation counting techniques. Although similar techniques for detection were used, those metabolites found in rats and in most other mammals were not present in dog urine (Table XIII-4). The beagles did not seem to be able to excrete unconjugated 1-naphthol or hydroxylate carbaryl. However, it probably can form naphthyl glucuronide and sulfate, and it does seem to be able to conjugate carbaryl directly. The only other metabolite found in dog urine was 1-naphthyl methylimidocarbonate-o-glucuronide. The dog also differs from the rat in the route and quantity of excretion. Almost half the total carbaryl equivalents excreted by the dog were found in the feces and were accounted for by the naphthyl label, whereas only about 10% were found in the rat feces. [34] Rat urine yielded about 68% [34] and dog urine about 23% [87] of the dose as the methyl label.

Knaak et al, [33] using techniques similar to those they used in studies of other mammals, [34,87] examined fecal and urinary metabolites in two young female swine weighing 14.5 and 18 kg. [33] One animal was given methyl-labeled carbaryl and the other naphthyl-labeled carbaryl at doses of 25 mg/kg in gelatin capsules. Urine and feces were collected over a 5-day

period. The pigs excreted 83.4 and 1.6% of the naphthyl label in urine and feces, respectively, and 70 and 1.0% of the methyl label in urine and feces, respectively. Two major metabolites, 1-naphthyl methylimidocarbonate-o-glucuronide and 4(methylcarbamoyloxy)-1-naphthyl glucuronide, were identified. In addition, several unidentified metabolites and 1-naphthyl glucuronide from the naphthyl label were obtained. Swine metabolites are listed with others in Table XIII-4. In the same report, [33] the metabolism of carbaryl in sheep was described. One 42-kg ewe was given a dose of 25 mg/kg of naphthyl-labeled carbaryl orally in gelatin capsules; 2 weeks later a similar procedure was used to administer methyl-labeled carbaryl. Three major metabolites excreted were 1-naphthyl methylimidocarbonate-o-glucuronide, 4(methylcarbamoyloxy)-1-naphthyl glucuronide, and 1-naphthyl sulfate. The two metabolites having only the naphthyl label were 1-naphthyl glucuronide and the sulfate. The sheep metabolites are listed with others in Table XIII-4.

One female rhesus monkey weighing 4.6 kg was orally administered labeled carbaryl at a dose of 300 mg/kg, in two phases. [33] In the first phase, the naphthyl-labeled form was ingested, and, in the second phase 4 days later, the methyl-labeled form of carbaryl was administered. The monkey excreted in the urine two major metabolites: 1-naphthyl methylimidocarbonate-o-glucuronide and 4(methylcarbamoyloxy)-1-naphthyl glucuronide. Small quantities of the sulfate-conjugated naphthyl and 4-hydroxycarbaryl were excreted in monkey urine. The monkey metabolites are listed in Table XIII-4.

In Effects on Humans, the results of studies by Knaak et al [33] on the urinary metabolites of carbaryl in two men were discussed. The men,

weighing approximately 81 and 86 kg, ingested carbaryl in gelatin capsules at doses of 2 mg/kg. Urine was collected before administration, for control determinations, and for 4 days after administration. Only 26-27% of the dose was accounted for in the composite 4-day urine collected from the two men. The following were identified from the urine specimens: 1-naphthyl glucuronide and sulfate, and conjugates of glucuronic and sulfuric acids, 4-(methylcarbamoyloxy)-1-naphthyl glucuronide. The human metabolites are presented in Table XIII-4 for comparison with six other mammals.

In view of the possible relevance of the metabolism of carbaryl with respect to its teratogenic potential in various mammalian species, it is important to identify those species that metabolize the compound similarly or dissimilarly to humans. The results of the preceding studies on the metabolism of carbaryl in human beings, rats, guinea pigs, sheep, monkeys, swine, and dogs [33,34,87] show that the similarity of metabolic products allows these species, with the exception of the dog, to be divided into two groups: in the first, humans, rats, guinea pigs, and sheep, and in the second, monkeys and swine. Low doses of carbaryl were reported [66] to cause teratogenic effects in the beagle dog. (See previous discussion of reproduction studies.) However, unlike humans, the beagle does not excrete 1-naphthol nor does it hydroxylate carbaryl. Carbaryl was not found to be a teratogen in monkeys [67,69] and rats, [70] but in one study carbaryl produced terata in guinea pigs at very high doses, [71] while in another study of the same species using moderately high doses carbaryl was not found to be teratogenic. [72] Present studies show that the metabolism of carbaryl in the dog differs from that in humans, monkeys, rats, and guinea

pigs, so it is unwarranted now to extrapolate from dogs to humans regarding the teratogenic potential of carbaryl.

The excreted metabolites identified in rats, humans, and guinea pigs [34]; in monkeys, swine, sheep, and humans [33]; and in the dog [87] have been summarized in Table XIII-4 so that the metabolic pathways of carbaryl in several species may be compared.

Correlation of Exposure and Effect

Carbaryl, a methyl carbamate compound, has anticholinesterase properties. [5] Therefore, regardless of its route of entry, once absorbed, it can induce signs and symptoms of toxicity by causing an increase of acetylcholine at its sites of action in the central, autonomic, and peripheral nervous systems. This increase in acetylcholine is a consequence of the inhibition of acetylcholinesterase, the enzyme which hydrolyzes acetylcholine. [2,5] The relationship of the inhibition of cholinesterase in plasma and erythrocytes to the inhibition of acetylcholine in the nervous system and at other sites of action has not been clearly established.

Evaluation of the available information suggests that carbaryl may be absorbed after oral ingestion, [40,41] during exposure to airborne concentrations, [28] or upon direct dermal contact. [30,31] The signs and symptoms observed as a consequence of exposure to carbaryl in the workplace are clearly manifestations of excessive cholinergic stimulation, and thus inhalation or dermal exposure resulted in the following signs and symptoms: nausea and dizziness, headache, perspiration [13 (sec 7)]; headache, nausea, vomiting, mild abdominal cramping, dimness of vision [13 (sec 13)];

skin rash [35]; and weakness, dizziness, and difficulty in breathing. [38] Oral ingestion, usually unrelated to occupational exposure, has resulted in the following signs and symptoms, most of which are also due to excessive cholinergic stimulation: miosis, excessive salivation, and incoordination [28]; epigastric pain, sweating [21]; disturbed vision, and pulmonary edema [40]; nausea, vomiting, hyperreflexia, pallor, intestinal colic, nasal discharge, salivation, headache, lacrimation, and tremors [41]; difficulty in sleeping, and abdominal cramping. [32] Overexposure to carbaryl in the workplace environment apparently results in a rapid onset of symptoms which causes voluntary cessation of work and termination of exposure. [13 (sec 13),20] In addition, employees who have been overexposed to carbaryl in the workplace apparently recover rapidly. [13 (sec 7,13)]

Animal studies have indicated that absorption of carbaryl by the lungs, [83] intestine, [83] and stomach [84] is fairly rapid. The characteristics of the urinary metabolites encountered in both humans [33,34] and animal species [33,34,87] would indicate that the liver is the primary site for metabolizing carbaryl after its absorption by various routes. Support for this hypothesis is found from in vitro studies [34] using carbaryl incubated with rat and guinea pig liver preparations which resulted in the formation of metabolites almost identical to those observed in the urine of animals treated with carbaryl.

Several studies by Knaak and coworkers [33,34,87] compared metabolic processes of carbaryl in seven mammals, namely rat, guinea pig, dog, swine, sheep, monkey, and human. Table XIII-4 lists the various metabolites and the means by which they were detected. It was concluded [87] that the dog (beagle) probably conjugates carbaryl and excretes much of the degradation

products in the feces, unlike most of the other species, in which the urine is the major excretory route. Most of the other mammals hydrolyze and hydroxylate, as well as conjugate, carbaryl before excretion. From the studies of Knaak and coworkers, [33,34,87] humans, rats, guinea pigs, and sheep metabolize carbaryl in one manner, monkeys and swine in another, and dogs in a third. One metabolite which appeared in the urine of all species, except the dog, was conjugated 1-naphthol [33,34,87] which might be useful in assessing carbaryl exposure. [13 (sec 7,9,10),28,32-35]

Best and Murray [28] observed 59 employees during a 19-month period in a carbaryl-manufacturing plant where airborne concentrations of carbaryl ranged from 0.03 to 40 mg/cu m. Their report indicated that relatively large quantities of 1-naphthol were excreted in urine, that blood cholinesterase activity was either within the normal range or slightly inhibited, and that at no time did any of the employees studied have clinical or subjective evidence of increased acetylcholine activity. However, the methods used to determine cholinesterase activity in this study probably underestimated the degree of cholinesterase inhibition.

Williams [13 (sec 10)] reported only limited data suggesting that airborne concentrations of carbaryl around 50 mg/cu m during an approximate 8-hour workday did not produce symptoms of toxicity if the workers were provided either respiratory or dermal protective equipment. The report of Yakim [39] indicated that reductions in blood cholinesterase activity occurred following 4- to 6-hour exposures of workers for 3-4 days to an average airborne carbaryl concentration of 2 or 4 mg/cu m. He did not adequately describe how he measured the airborne concentrations or the method used to determine cholinesterase activity. At these concentrations

and durations of exposure, no symptomatic changes due to anticholinesterase activity were reported by the author. It is apparent from the literature reviewed that the airborne carbaryl concentration at which significant signs and symptoms may first appear in humans has yet to be determined. Vandekar [35] observed no adverse effects when sprayers and 95 villagers in Nigeria were exposed to carbaryl from an application of a 5% solution in their dwellings.

Several inhalation studies [27,39] on animals exposed to airborne carbaryl have been conducted. Carbaryl at a concentration of 390 mg/cu m has been shown to produce nasal and ocular irritation in guinea pigs upon 4-hour exposure. [27] Exposure concentrations of 63 mg/cu m in cats [39] and 75 mg/cu m in dogs [27] produced signs of cholinesterase inhibition within 2-5 hours of exposure. Rats exposed to carbaryl dust in air at an average concentration of 10 mg/cu m (5-20 mg/cu m) for 7 hours/day, 5 days/week, for 90 days did not show any grossly visible changes, and all the animals survived. [27] Microscopic examination of several tissues including lung taken from these animals revealed no carbaryl-associated lesions. Yakim [39] exposed four cats at an airborne carbaryl concentration of 63 mg/cu m for 6 hours/day for a month. Cholinergic stimulation, indicated by periodic salivation, was observed during the first 2 hours of exposure each day. Exposure at an average concentration of 40 mg/cu m for 6 hours/day for 2 months produced some deterioration in conditioned reflexes of the cats. No further information was given. No signs of toxicity were observed upon exposure of cats for 4 months (6 hours/day) at a concentration of 16 mg/cu m, while at 40 mg/cu m erythrocyte cholinesterase activity dropped to 50% or less. The method for

determining cholinesterase activity was not disclosed. [39] The above studies [27,39] indicate that typical signs of cholinergic stimulation are evident at airborne concentrations of 63 and 75 mg/cu m in the cat and dog, respectively, while exposure at 16 mg/cu m appears to constitute a no-effect level with respect to toxic manifestations of cholinesterase inhibition in the cat. [39]

Dermal absorption of carbaryl has been investigated in both humans and experimental animals. In two dermal absorption studies on humans, [30,31] approximately 74 and 70% of 14C-labeled carbaryl were recovered from urine within 5 days after application of carbaryl in acetone to the skin of the forearm and of the face near the angle of the jaw, respectively. In another study [13 (sec 9,10)] comparing absorption after inhalation and dermal exposure in humans, two employees in a plant manufacturing carbaryl were exposed at approximately the same airborne concentrations on each of 2 days. Employee A was protected from skin contact but not from inhalation of carbaryl; employee B was protected from airborne carbaryl but not from carbaryl contact on his arms and hands. Measurement of 1-naphthol (a carbaryl metabolite) in control and postexposure urine revealed that the concentration of urinary 1-naphthol excreted by employee A was over 3,600 and 2,400 μg/100 ml and by employee B over 7,000 and more than 500 μg/100 ml, on days 1 and 2, respectively, thus indicating that, under similar exposures, lungs and skin readily absorb carbaryl. No topical reactions have been reported in humans except for a single case [35] of a rash of uncertain cause associated with carbaryl exposure, and no dermal irritation has been reported in carbaryl-treated experimental animals when carbaryl was directly applied. [27,39] A slight

degree of local eye injury and necrosis has been found in rabbits when carbaryl was applied directly to the eye, and guinea pigs were weakly sensitized in a skin-sensitivity test. [27] In addition, miosis and conjunctival hyperemia, which are signs of anticholinesterase activity, also have been observed in rabbits' eyes treated locally. [39] In cattle sprayed with carbaryl, the compound was present in all body tissues examined 1 and 3 days, but not 7 days, after exposure. [85] The concentration of carbaryl in the milk of cows was highest 5 hours after skin exposure but fell to an undetectable level 77 hours after spray application. No detectable carbaryl residue was found in meat of steers 7 days after spraying.

A few studies on the effects of carbaryl administered orally to humans have been reported. A report [40] of one case of suicide attributed to carbaryl has been found. This incident is clouded by the fact that the subject was treated with an oxime (PAM), which is usually recommended for treatment of poisonings due to excessive absorption of organophosphate anticholinesterase agents, but which has had an adverse effect on animals poisoned with carbaryl. [45,46]

A single oral dose of 250 mg of carbaryl (approximately 2.8 mg/kg) produced early symptoms including sweating and epigastric pain in an adult male [21] who intentionally swallowed the chemical. [29] A rapid recovery followed treatment with atropine. [21] Best and Murray [28] described a case in which an unknown amount of carbaryl was ingested by a 19-month-old infant who then had typical signs of anticholinesterase intoxication including miosis, excessive salivation, and incoordination. Recovery was complete after atropine treatment. Lopez [41] described light intoxication

in a young man who ate watermelon which had been sprayed with 80% carbaryl, and in another person who drank several milliliters of a solution of 80% carbaryl. Symptoms reported by the author in the men were nausea, vomiting, hyperreflexia, pallor, intestinal colic, nasal discharge, salivation, headache, lacrimation, and tremors.

Daily oral carbaryl doses of 0.12 mg/kg in gelatin capsules administered to 6 volunteers for 6 weeks caused no changes except an apparently slight decrease in the ability of the proximal convoluted tubules of the kidney to reabsorb amino acids as assessed by the urinary amino acid nitrogen to creatinine ratio. [32] This functional, but reversible, alteration was reported to be present only in the group of volunteers who ingested 0.12 mg/kg/day, and not in the group receiving 0.06 mg/kg/day, in which the urinary amino acid nitrogen to creatine ratios were lower than the controls. Repeated oral administration of carbaryl produced mild renal changes in rhesus monkeys, [44,51] rats, and dogs. [27] The oral doses administered to experimental animals were considerably higher, viz, 600 mg/kg in the monkey at an unstated length and frequency, 7.2 mg/kg in the dog for 1 year, and 400 ppm in the diet of rats for 2 years, than the dose required to produce the changes in human renal function reported by Wills et al. [32] Furthermore, the renal changes in rats were not significant after 2 years of administration; in the dogs, the same cloudy swelling of the renal tubules was found in the experimental and, to a lesser extent, in the control groups. [27] Doses of 0.12 mg/kg of carbaryl administered to man were reported by the authors to be responsible for reversible renal tubular dysfunction. [32] Since calculation of the ratios was carried out on only 5 subjects and that differences apparent from the

graphic illustration of the data are not striking, the results presented in this study are difficult to interpret. As discussed earlier, it is difficult to draw conclusions from the vacuoles seen in a single electron photomicrograph of the monkey kidney tissue studies. [44,51] The long-term administration of carbaryl to rats and dogs [27] resulted in some cases in an incidence of renal damage only slightly greater in test animals than in the controls. Considering all the present data, the evidence for renal dysfunction is at best suggestive but not conclusive.

In order to study the paralytic effects of carbaryl, Carpenter et al [27] administered the compound at very high doses to chickens (0.25-3 g/kg). There was leg weakness at doses greater than 1 g/kg, attributed by the authors to transient cholinergic effects, but no microscopic evidence of demyelination. Another study in chickens by Gaines [43] lends support to the conclusion of Carpenter et al. [27] Smalley et al [52] showed that repeated administration of large doses of carbaryl to swine (150-300 mg/kg) produced ataxia and prostration without demyelination, and, in another study [55] at a dose of 125 mg/kg, the compound failed to produce paralysis in dogs but did produce paraplegia and spastic paresis in miniature pigs. [55] Carbaryl did not cause any demyelination in the chicken, the animal of choice for detecting this form of paralysis, and, since no data have been found concerning demyelinating paralytic effects of carbaryl in humans, it is concluded that, based on available evidence, carbaryl is not likely to cause chronic neurotoxicity, ie, Ginger Jake paralysis.

The effects of carbaryl on the developing fetus have been investigated in several studies. [66,67,69-71] Smalley et al [66] described reduced viability of pups and dystocia, probably maternal, in

beagle dams given oral doses of carbaryl ranging from 3.25 to 50 mg/kg throughout gestation. Litter size was reduced as compared to controls in the 25 and 50 mg/kg dose groups. Teratogenic effects were seen at doses ranging from 6.25 to 50 mg/kg. In a study [67] on primates, the abortion rate was increased at carbaryl doses as low as 2 mg/kg given orally. This effect was not dose related, since a dose of 20 mg/kg produced only half as many abortions (3 out of 6) as the 2 mg/kg dose (2 of 2). In addition, the small number of pregnant animals in each group (2 and 6, respectively) and in the control group (5 animals) prevents reliable conclusions based on a statistical evaluation. [67] A later report by Dougherty and Coulston [69] describes another monkey study using 79 animals. These investigators observed no signs of toxicity in adult females, no increase in abortions over controls, and no fetal abnormalities in monkeys given carbaryl (range 0.2-20 mg/kg/day) during days 20-38 of gestation.

Robens [71] found that fetal deaths and terata occurred in guinea pigs administered carbaryl at a dose of 300 mg/kg during various intervals of gestation. This dose was also lethal to some dams, and the author indicated that this dose, which produced terata and maternal deaths in guinea pigs, was at least 1,000 times the level of carbaryl allowed in human food. The high mortality rate in the pregnant dams at this high dosage makes a conclusion of teratogenicity in this study difficult since another study by Weil et al [72] in the same species reported no carbaryl-related teratogenicity at dietary and intubation levels of 300 and 200 mg/kg, respectively. Doses of 50, 100, and 200 mg/kg of carbaryl given to pregnant rabbits [71] produced no adverse effects on dams or offspring. In hamsters [71] given carbaryl at doses of 125 and 250 mg/kg during

gestation, fetal mortality was higher than in controls, but no terata were found. Rats were administered carbaryl in the diet at doses of 20, 100, and 500 mg/kg at various intervals throughout pregnancy or until weaning of the pups. [70] No teratogenic effects that could be attributed to carbaryl were observed at any dose level. As discussed earlier, the dog differs markedly from several other species, including humans, in its metabolism of carbaryl. This difference could account for the teratogenic effects observed in the study by Smalley et al. [66] The lack of carbaryl-related teratogenicity in other species does not now warrant the conclusion that carbaryl should be classified as a teratogen in humans.

Effects of carbaryl on various aspects of the reproductive cycle of rodents have been observed at doses given either in the diet or by oral intubation, ranging from 2 to 20 mg/kg and from 2,000 to 10,000 ppm. [72,73,78] Effects seen in rats with doses as low as 2 and 5 mg/kg included decreased spermatogenesis, sperm motility, and duration of estrus. [73] Decreased litter size and reduced survival of the pups have been observed with varying frequencies in rats and gerbils at all doses studied [73,78] except in a three-generation reproduction study of rats conducted by Weil et al [72] in which adverse effects on viability of pups and litter size, as well as decreased fertility and lengthened gestation period, were seen only at doses of 100 mg/kg given by oral intubation, and not at lower doses. In the same study, [72] lengthened gestation periods in rats administered carbaryl in the diet were seen only at a dose of 200 mg/kg. Collins et al [78] studied rat parents and offspring in a three-generation reproduction study. Doses of 2,000, 5,000, and 10,000 ppm carbaryl in the diet showed that, at the highest dose and to a lesser extent at the next

lower dose, the viability of the pups, survival of offspring, and litter size decreased from the first generation on. The lowest dose (2,000 ppm) affected only body weight gain of the parents and weanlings. In a similar three-generation reproduction study on gerbils given carbaryl in the diet (2,000, 4,000, 6,000, and 10,000 ppm), Collins et al [78] reported that no litters were produced in the F3b generation at 10,000 ppm, and that there was a decrease in fertility, pup viability, litter size, and survival of pups from day 4 to weaning which appeared sporadically at all doses. Collins et al [78] suggested that the effect of carbaryl on reproduction was due to an indirect effect on the testes and ova mediated through the hypothalamohypophyseal complex. Carbaryl given to rats by gastric intubation at doses of 2 and 5 mg/kg produced adverse effects on fertility and survival of the pups during the first month of life. [73] The same doses produced a decrease in spermatogenesis and a decreased duration of estrus. In addition, microscopic changes of an adverse nature were noted in ovarian follicles and spermiogenic epithelium of the testes after carbaryl treatment.

In another study, Shtenberg and Rybakova [77] administered carbaryl orally to rats of both sexes at doses of 7, 14, and 70 mg/kg for up to 12 months. Growth of rats was inhibited at 14 and 70 mg/kg, and sperm motility in males also decreased in a dose-related manner after 12 months of treatment. Degenerative changes in the testes, including edema of interstitial tissue and destruction of germinal epithelium, were noted in carbaryl-treated male rats. In females, the estrus cycle was prolonged at the 14 and 70 mg/kg doses. From the above studies, [72,73,77,78] it may be concluded that oral administration of carbaryl to rodents has an effect on

several aspects of their reproduction. However, it is difficult to relate these effects from oral administration at high doses to rodents to those encountered by inhalation and dermal absorption in humans, at lower doses in the workplace environment.

From the results of a screening experiment for dominant-lethal mutagenic effects, [59] in which mice received carbaryl at doses up to 1,000 mg/kg for 5 days, there is no evidence that carbaryl is a dominant-lethal mutagen in mice. More recent studies on bacteria [63,65] and on yeast [64] indicate that carbaryl is not a mutagen; however, experiments on an insect indicates that it is a weak mutagen. [62] Nitrosocarbaryl in several microbiologic studies [63-65] proved to be a strong mutagen. The significance of this finding in terms of its relevance to humans exposed to carbaryl remains to be determined.

Shimkin et al [81] synthesized N-methyl naphthylcarbamate and compared it in mice to 21 other carbamates using a pulmonary tumor bioassay. While some of the carbamates were positive, the synthesized compound was classed as marginal. Shimkin et al [81] classified the synthesized N-methyl naphthylcarbamate as a marginal tumorigen in mice; however, the lack of information on the purity of the compound and the structural formula written in the study leave doubt as to whether 2-naphthyl or 1-naphthyl N-methyl carbamate (carbaryl) was tested and make the results of the study difficult, if not impossible, to interpret.

Oral administration of carbaryl to mice (4.6 mg/kg/day for 18 months) revealed no significant evidence of tumorigenicity. [79] Subcutaneous injection of carbaryl, approximately 400 mg/kg/week, into tumor-susceptible mice for 5 months did not increase the incidence of tumors over that in the

control animals. [27] No dose-related incidence of tumors or increase in tumors over the controls was established by Carpenter et al [27] in rats given carbaryl in the diet at levels of 50, 100, 200, and 400 ppm for a period of 2 years. Andrianova and Alekseyev [80] found tumors in mongrel rats given carbaryl orally (30 mg/kg twice weekly) or by subcutaneous implantation (paraffin capsules containing 20 mg of carbaryl) for 22 months. The results of this study are not conclusive because of the high mortality in the experimental group, the absence of sufficient control and other background data, and the fact that the carbaryl used in these experiments was probably contaminated. An evaluation of the carcinogenic studies [27,79-81] does not now warrant a conclusion that carbaryl is a carcinogen.

IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION

Environmental Data

Airborne concentrations of carbaryl and the potential for respiratory and dermal exposures have been examined in the workplace. The three major types of possible occupational exposure--the manufacture of technical carbaryl, the production of formulations of carbaryl, and the use of carbaryl for application purposes--have been considered.

Best and Murray [28] reported air concentrations at various sites in a carbaryl-manufacturing plant. The air samples were collected on membrane filters and analyzed by a colorimetric method for determining the airborne concentration of carbaryl. The mean carbaryl concentration of 49 air samples in the production area was 0.23 (range 0.03-0.73) mg/cu m of air. In the bagging area, 18 air samples with a mean of 0.75 (range 0.20-1.60) mg/cu m were collected under "normal conditions." Under abnormal conditions (described in Chapter III), the carbaryl concentration ranged from 19.0 to 40.0 mg/cu m, with an average of 29 mg/cu m for six samples. "Stackers" (handlers of bags for shipment) were exposed at a mean air concentration of 0.64 (range 0.05-1.52) mg/cu m based on six samples collected. In the air separator house, only two airborne concentrations of carbaryl were measured, and these were in the range of 29.0-34.0 mg/cu m with an average of 31.0 mg/cu m. Union Carbide Corporation [13 (sec 9,10)] also supplied information on individual air concentration samples from the shipping department of the same plant. These air samples, collected and analyzed in the same manner as that used by Best and Murray, [28] were obtained sporadically over a 2.5-year period. Mean values, presented

below, are calculations from the original data. A total of 96 air samples from the bagging operation had a mean carbaryl airborne concentration of 2.96 mg/cu m, with a range of 0.32-13.33 mg/cu m. Near an instrument panel, the mean airborne concentration was 2.76 (range 0.12-10.51) mg/cu m based on 44 samples. In the shipping department office, the mean carbaryl airborne concentration was 0.33 (range 0.04-0.83) mg/cu m from 43 samples, which was comparable to the mean airborne concentration in the outside loading area of 0.37 (range 0.04-0.74, 8 samples) mg/cu m. Mean airborne carbaryl concentrations in railroad cars and trailer trucks, presumably loaded with bags of carbaryl, were 0.54 (range 0.10-1.22, 24 samples) and 0.64 (range 0.26-1.62, 9 samples) mg/cu m, respectively.

Comer et al [88] investigated potential dermal and respiratory exposures to carbaryl in formulating-plant workers and orchard spray workers. The subjects included baggers and mixers at three plants formulating 4 and 5% carbaryl dust and spray workers operating tractor-drawn airblast equipment for applying 0.045-0.06% carbaryl spray, apparently from a wettable powder, to fruit trees. Dermal contamination by carbaryl sprays and dusts was determined by attaching absorbent cellulose pads and layered gauze pads, respectively, to various areas of the workers' bodies and clothing. Respiratory exposures were estimated from the contamination on special filter pads inserted in the filter cartridges of respirators worn by the subjects. The filter pads were shielded to prevent direct impingement of droplets or particles onto the pads except for those carried by respiratory action. A total of 480 dermal and 73 respirator-pad samples were analyzed spectrofluorometrically for carbaryl during different exposure situations including 48 for formulating-plant workers and 32 for

orchard spray workers. In addition, the authors measured the urinary excretion of 1-naphthol in 102 urine samples from the formulating-plant workers, using a spectrofluorometric method. Mean values for potential carbaryl exposure among the formulating-plant workers were calculated to be 73.9 (range 0.80-1,209) mg/hour of work activity by the dermal route and 1.1 (range 0.03-4.1) mg/hour by the respiratory route. For the orchard workers, the mean values were 59.0 (range 1.7-212) and 0.09 (range 0.01-1.08) mg/hour by the dermal and respiratory routes, respectively. The authors found that, in the bagging and mixing sections of formulating plants, the areas with greatest potential of dermal exposure were the front of the chest and neck, the forearms and hands, and the face. Among spray applicators, the areas of greatest potential exposure were the shoulders and the back of the neck. The authors further calculated that the mean potential for both dermal and respiratory exposures of formulating workers would be 75 mg/hour, or 600 mg over an 8-hour workday. The authors did not report the airborne concentrations of carbaryl dust to which the workers in the formulating plants or orchards were exposed. In the 102 urinary specimens analyzed during and after exposure, 1-naphthol concentrations were 0.2-65.0 ppm (20-6,500 μg/100 ml), with a mean value of 8.9 ppm (890 μg/100 ml). The authors stated that carbaryl exposure at the beginning of the workday was followed by peak excretory levels of 1-naphthol by late afternoon and evening, followed by a drop to lower levels at the start of the next workday. The rate of excretion of 1-naphthol varied from 0.004 to 3.4 mg/hour, with a mean value of 0.5 mg/hour. The authors indicated that this was equivalent to the excretion of approximately 0.7 mg/hour of carbaryl, or an absorption of 5.6 mg of carbaryl during an 8-hour period.

When this absorption value of carbaryl (5.6 mg/8 hours) was compared to the total potential dermal and respiratory exposure value (600 mg/8 hours) for the formulating-plant workers, it was suggested that absorption from dermal contact with carbaryl dust was probably not very complete. The authors concluded that dermal absorption of carbaryl from dry formulations in formulating plants may be only a small fraction of the total potential calculated exposure.

Jegier [89] measured respiratory and dermal exposures to carbaryl (Sevin 50 WP, 0.5-8.0 lb/100 gal water) for tractor operators engaged in orchard-spraying operations. Air samples were collected from the tractor operators' breathing zones, and results of the analyses for carbaryl were used to calculate respiratory exposures which were determined by a filter-pad method. Filter pads were attached to double-unit respirators and absorbent materials were strapped to the forehead and wrists of observers riding beside the tractor drivers to estimate respiratory and dermal exposures, respectively. The airborne concentrations of carbaryl in seven breathing-zone samples ranged from 0.18 to 0.81 mg/cu m, with a mean of 0.60 mg/cu m. Calculated mean respiratory exposure based on the measured air concentrations and an assumed lung ventilation rate of 444 liters/hour was in close agreement with the mean respiratory exposure of 0.29 (range 0.24-0.53) mg/hour as determined by the filter-pad technique. The mean dermal exposure was estimated at 25.3 (range 18.5-30.3) mg/hour.

Simpson [90] measured dermal and respiratory exposure of workers spraying carbaryl in an orchard. Filter papers were pinned to the operators' clothing and cotton absorbent pads were inserted into the cartridges of respirators. These were analyzed for carbaryl to determine

dermal and respiratory exposures. Simpson [90] estimated the mean respiratory exposure rate to carbaryl at 482 (range 10-1,080) μg/hour. The mean dermal exposure rates, in μg/100 sq cm/hour, were: hat (or head), 1,150; arm, 1,134; chest, 1,122; shoulder, 957; back, 774; wrist, 734; and thigh, 587.

Kale and Dangwal [91] investigated the air concentrations of carbaryl and other pesticides in several agricultural settings. Air samples were collected with a midget impinger containing either distilled water or alcohol. The authors stated that the samples were collected as close as possible to a worker's breathing level and in a manner to avoid interfering with his work. In the first instance, a 50% wettable powder of carbaryl was applied to mango trees with a hand pump sprayer under medium air-movement conditions; only traces of carbaryl were detected. In the second agricultural application, 10% carbaryl dust was applied to cotton with a rotary hand duster in medium wind conditions; again, only traces of carbaryl were present. In a third farming operation, similar to the second but with high air movement, carbaryl concentrations were 0.1-0.8 mg/cu m of air. During the application in medium wind of 10% carbaryl dust by rotary hand duster to wheat approximately 30 cm high, airborne concentrations of carbaryl were 0.8-1.6 mg/cu m. Neither the collecting medium nor the analytical procedure for determining carbaryl was identified by the authors, nor did they mention any biologic evaluation of the workers.

Control of Exposure

Engineering design and work practices for carbaryl should have, as their main objectives, controlling airborne concentrations and minimizing

skin and eye contact. The environmental data previously presented suggest that concentrations of airborne carbaryl are significantly lower, and therefore there is potentially less absorption in agricultural occupations than in manufacturing and formulating operations.

In manufacturing and formulating plants and in other locations where suitable and practical, closed systems, properly operated and maintained, should be used to achieve reduced airborne concentration and to minimize skin contact. Where closed systems are not feasible, well-designed local exhaust ventilation should be provided. Guidance for design can be found in Industrial Ventilation--A Manual of Recommended Practice, [92] or more recent revisions, and in Fundamentals Governing the Design and Operation of Local Exhaust Systems, Z9.2-1971. [93] Exhaust air should not be recirculated and should be filtered to prevent pollution of the outdoor air. Neither respiratory protective equipment nor personal protective clothing is an acceptable substitute for proper engineering controls, but both should be available for emergency purposes and for nonroutine maintenance and repair situations.

Tests performed by Union Carbide Corporation [13 (sec 16)] have shown that dust clouds of technical carbaryl and formulations of carbaryl can be ignited in closed spaces, and that explosions could occur. According to this manufacturer, carbaryl also may have an electrostatic potential that could produce a spark. Thus, it is recommended that equipment in confined spaces always be adequately grounded. Union Carbide Corporation reported that the minimum concentration of technical grade carbaryl dust to produce explosive mixtures is 20.3 g/cu m.

Sampling and Analysis

In 1962, Best and Murray [28] reported measurements of airborne concentrations of carbaryl dust in a manufacturing plant, based on a sampling method using cellulose ester membrane filters (AA white grid). During subsequent determinations of airborne carbaryl dust concentrations in this plant, 0.8-μm membrane filters composed of a copolymer of acrylonitrile and polyvinyl chloride were used for carbaryl collection. [13 (sec 11)]

Popendorf et al [94] used membrane-filter air samplers (with a sampling rate of 3 ± 0.25 liters/minute) in the measurement of concentrations of foliar pesticide residues likely to become airborne in work situations. Although the use of carbaryl was not included in this report, it appears that this sampling procedure, when coupled with an appropriate analytical procedure, may be useful for evaluating airborne carbaryl concentrations.

Air sampling specific for carbaryl was reported in a study by Klisenko [95] in 1965. He used FPP-KhA filters (no other identification of material) to collect carbaryl in air for a period of 4-5 minutes at a sampling rate of 5 liters/minute. The reagent diazobenzenesulfonic acid was used to develop color with carbaryl in the methanol extract for subsequent colorimetric determination. The sensitivity was 1 mg carbaryl in 4 ml of final solution. The author did not report the efficiency of the sampling method.

In the same study, Klisenko [95] investigated carbaryl analysis by ultraviolet spectrophotometry, still using diazobenzenesulfonic acid as the coupling reagent. He found appreciable interference at 281 nm from

methanolic extracts of the FPP-KhA filters. To avoid such interference in the ultraviolet range, carbaryl in the air was absorbed at a sampling rate of 0.5 liter/minute in 5 ml of methanol in a scrubber with a porous disc. No information regarding carbaryl collection efficiency was given. The sensitivity was reported to be 0.1 μg of carbaryl in 2.5 ml of solution.

In 1971, Kale and Dangwal [91] used midget impingers (with a collecting medium such as distilled water or alcohol) for air sampling of several different types of pesticides, including carbaryl, at spraying or dusting sites. The absorbing solution selected for carbaryl collection was not identified, and no information was presented on collection efficiency or sampling details such as flowrate and sampling time. Also, the authors did not mention the analytical procedure used for the carbaryl determinations.

Reports of the filter collection methods, [13 (sec 11),28,95] as well as the scrubber methods, including midget impingers, [91,95] did not specify carbaryl collection efficiencies. Since carbaryl formulations include wettable powders, dusts, and granules, [13 (sec 18)] the membrane filter collection technique would be expected to provide an effective collection method for airborne particulate carbaryl.

Most reported environmental exposure data for airborne carbaryl dust levels have been based on the membrane-filter collection method. [13 (sec 11),28] Membrane filters which have been used for particulate collection are polymeric (plastic) [96] or glass-fiber filters. [97] Because they are highly efficient, involve no fragile glassware such as impingers, and require no liquids, membrane filters are better suited to personal monitoring than are sampling techniques utilizing glassware and liquids.

The membrane filter method is recommended as the air sampling method of choice.

The sampling method recommended in Appendix I involves the use of a glass-fiber membrane filter (Type A), 37 mm in diameter, mounted in a two-piece cassette filter holder and held in place by a backup pad. [97] Details of membrane filter sampling and airflow calibration procedures are given in Appendix I.

The analytical procedures usually employed for determining carbaryl concentrations are based on quantifying 1-naphthol [13 (sec 11),28,98-101] derived from the alkaline hydrolysis of carbaryl. In 1962, Best and Murray [28] presented a colorimetric method to quantitatively determine 1-naphthol. This method involved measurement of the intensity of a blue dye formed by the reaction between p-nitrobenzenediazonium fluoroborate and 1-naphthol. This method may be used to determine either the free urinary 1-naphthol concentration or the total urinary 1-naphthol concentration. In the former case, the metabolite is extracted from the urine, and in the latter case, the naphthol conjugates are first hydrolyzed to 1-naphthol. This method was modified by Johnson [98] in 1964 with regard to sample preparation of food products and was adopted the same year by the Association of Official Analytical Chemists (AOAC) [99] as the recommended method for the quantitative determination of carbaryl. Except for the incorporation of a further optional modification in sample preparation by Benson and Finocchiaro [100] in 1965, this method remains the official AOAC analytical method. [101]

Another analytical approach was investigated by Frei et al. [102] When carbaryl was hydrolyzed to 1-naphthol and the latter determined

fluorometrically on thin-layer chromatograms, a visual detection limit of 0.006 μg/spot and an instrumental detection limit of 0.001 μg/spot were reported. This procedure was developed for carbaryl residue analysis but was not applied to air-sample analysis.

Early attempts to use gas-liquid chromatography for the quantitative determination of carbaryl indicated that, under the conditions commonly used for such analyses, carbaryl underwent thermal decomposition to 1-naphthol. [103,104] Such analytical techniques, therefore, were not applicable to the analysis of samples which might contain 1-naphthol or carbaryl analogs that in turn might generate 1-naphthol upon thermal decomposition. Two approaches to overcoming the problem of thermal decomposition of carbaryl have been investigated.

The first approach was to prepare thermally stable derivatives of carbaryl. Fishbein and Zielinski [103] prepared trimethylsilyl carbaryl by the reaction of carbaryl with excess hexamethyldisilazane and trimethylchlorosilane in pyridine. The reaction mixture was analyzed for the trimethylsilyl derivative of carbaryl using 6-ft x 6-mm ID glass columns containing various solid supports and stationary liquid phases in a gas chromatograph equipped with a flame ionization detector. The authors did not specify the sensitivity of the method. Khalifa and Mumma [105] prepared trifluoroacetyl and heptafluorobutyryl derivatives of carbaryl, which were thermally stable under the conditions selected, for analysis by a gas chromatograph equipped with a 63Ni electron capture detector. The authors did not report the specific conditions used for derivatization, nor did they present evidence that derivative formation was quantitative. Tilden and Van Middelem [106] described a gas-liquid chromatographic method

in which the carbaryl was quantitatively hydrolyzed to yield methylamine through acid hydrolysis. The resulting methylamine was quantitatively converted to 4-bromo-N-methylbenzamide by reaction with 4-bromobenzoyl chloride. Analysis of the 4-bromo-N-methylbenzamide was performed using a gas chromatograph equipped with a 63Ni electron capture detector and a 6-ft x 4-mm glass column containing 3% Carbowax 20M on Chromosorb W. The lower limit of detection of pure carbaryl was 20 pg by this method. The use of derivatization for carbaryl analysis has been applied primarily to residue analysis, where the carbaryl is usually extracted in an organic solvent and high sensitivity is required because of the small sample sizes. Reports in which such methods have been applied to air samples have not been found, but the time-consuming stepwise handling of samples required by these methods is a distinct disadvantage.

A second approach to overcoming the problem of thermal decomposition of carbaryl during analysis by gas-liquid chromatography was to design the system so that decomposition is minimized or eliminated. Thus, Riva and Carisano [107] indicated that the recovery of undecomposed carbaryl was better than 90% for a 300-ng sample if the 0.5% SE-30 on 100-120 mesh Gas-Chrom P column was silanized by repeated injections of hexamethyldisilazane before sample injection. Presumably the silane treatment prevents the adsorption of carbaryl on active sites of the solid support and glass column where decomposition occurs. Lewis and Paris [108] indicated that by using a short column (0.3 m) and low column temperatures, thermal decomposition could be prevented. Using a gas chromatograph equipped with such a column containing 3% SE-30 on Gas-Chrom Q and a 63Ni electron capture detector, they were able to analyze for carbaryl in quantities as

small as 0.2-0.5 ng/injection volume. Again, both these methods were devised for residue analysis, and no information on their application to air sampling and analysis has been found. As a result of the lack of quantitative information on the sensitivity, accuracy, and precision of gas chromatographic methods as applied to analysis of air samples for carbaryl, such methods are not now recommended.

The p-nitrobenzenediazonium fluoroborate colorimetric method has been selected as the analytical method. This method has been used for many years by Union Carbide Corporation [13 (sec 11)] and others, [28,98-101] and has shown the required sensitivity for evaluation of personal exposures to carbaryl in accordance with the TWA environmental limit [97] discussed in Chapter V of this document. The principle of the method is that alcoholic potassium hydroxide is used to hydrolyze the carbaryl to 1-naphthol, which is determined colorimetrically after reaction with p-nitrobenzenediazonium fluoroborate. The presence of 1-naphthol in the air sample leads to erroneously high values for determination of the airborne concentrations of carbaryl. In addition, other substances such as phenols and aromatic amines that form derivatives with p-nitrobenzenediazonium fluoroborate or that absorb around 475 nm, will interfere if present in the air sample. Details of this method are presented in Appendix II.

When both 1-naphthol and carbaryl are in the air sample, gas chromatographic methods will probably allow separation of the two compounds, however, details for such methods are not worked out. When they are developed, our recommendations will be reconsidered. Since carbaryl is metabolized by humans to 1-naphthol, the recommended analytical method may be superior in detecting toxicity because of its lack of specificity.

Biologic Evaluation

Evaluation of the available literature cited in Chapter III would indicate that there are two possible means of determination of carbaryl exposure in the workplace environment. These are the measurement of 1-naphthol in the urine and determination of cholinesterase activity in the blood. The urinary concentration of 1-naphthol, one of the principal metabolites of carbaryl, which is excreted in the urine as the sulfate or glucuronide, [33,34] has been used as an indication of exposure to carbaryl in the workplace. [28] Comer et al [88] reported that the highest concentrations of urinary naphthol occurred usually after the daily exposure had ended. Because of the possible occurrence of carbaryl in food [109] and because 1-naphthol itself may be encountered during the manufacturing process, [15,16] many individuals exposed to carbaryl in the workplace might normally have small amounts of 1-napthol in the urine from sources other than airborne carbaryl. Although there is evidence that urinary 1-naphthol levels increase on exposure of humans to airborne carbaryl, [13 (sec 9,10),28,88] no definite quantitative relationship has been established between exposure to airborne carbaryl and total urinary 1-naphthol excretion. Therefore, measurement of urinary 1-naphthol as an indicator of carbaryl exposure is not now recommended.

Since the basis for the acute toxicity of anticholinesterase agents is the inhibition of the enzyme acetylcholinesterase, [7] the measurement of this enzyme activity would appear to be a useful biologic monitoring technique. The rapid regeneration of the carbamylated enzyme [5,110] probably makes the degree of inhibition by carbaryl at any given time elusive. The enzyme activity when analyzed in the sample tends to be higher

than was the actual case when the blood sample was obtained, and thus the degree of inhibition may be interpreted as less than actually occurred. [110] The California Department of Health [111] has recommended that, because of the reversibility of the complex of enzyme and carbamate, blood samples should be drawn and analyzed within 4 hours after exposure when carbamate poisoning is suspected.

Biologic monitoring of cholinesterase activity in blood, plasma, serum, or erythrocytes is not recommended as a means of assessing occupational exposure to carbaryl because (1) the rapid reversibility of carbaryl-induced cholinesterase inhibition makes cholinesterase determination impractical in occupational situations where blood samples cannot be analyzed immediately, and (2) occupational exposure to carbaryl results in a rapid onset of symptoms, self-termination from further exposure, and rapid recovery.

Although monitoring of cholinesterase activity is not specifically proposed as a requirement for carbaryl exposure, it can, properly performed, give useful information in exposures to carbaryl as well as to other cholinesterase-inhibiting compounds such as the organophosphate pesticides. For those who plan to carry out these measurements, it should be pointed out that individual variation due to disease states and genetic makeup may influence the results. A decrease in the activity of serum cholinesterase has been found in liver disease, [112] pregnancy, [113] and malignant neoplasms. [114] In patients suffering from pulmonary tuberculosis, plasma cholinesterase activity was also decreased. [115] Familial reduction in pseudocholinesterase levels was reported by Lehmann and Ryan [116] and by Kalow, [117] and later was found to be related to the

presence of an atypical gene. [118] Between 1 in 3,370 and 1 in 10,500 individuals tested in a healthy Canadian population was found to be homozygotic for this atypical gene [117] and thus could be expected to have a genetically determined deficiency in plasma cholinesterase. Erythrocyte cholinesterase activity was inhibited in certain pulmonary and extrapulmonary cancers [115] and in paroxysmal nocturnal hemoglobinuria. [119] Familial symptomatic reduction in erythrocyte cholinesterase activities also has been reported. [120] For those situations where measurements of cholinesterase activity is applicable, an assessment of cholinesterase methodology is presented below.

Measurement of cholinesterase (true or pseudo-) activity depends basically on two principles. The first involves measurement of the product formed as a result of hydrolysis of the substrate by the enzyme; this product can be estimated directly or indirectly by various techniques. The second principle involves measurement of the disappearance of the substrate, which also can be measured directly or indirectly by various techniques.

In early assays for cholinesterase, acetylcholine was usually used as a substrate and changes were measured as the ester was hydrolyzed. This change has been determined manometrically, [121,122] by changes in color of acid-base indicators, [123] and by pH measurement. [8]

Manometric methods for the analysis of cholinesterase are precise, but they are inherently tedious and time-consuming. These methods are based on the measurement of the amount of carbon dioxide released when acetic acid is allowed to react with bicarbonate ion. Both erythrocyte and plasma cholinesterase activities have been assayed manometrically. [7,124]

However, Winteringham and Disney [125] believed that since dilution of the enzyme was necessary to achieve sensitivity when using conventional manometric methods, these methods were inappropriate for measurements in cases of carbamate exposure. Such dilution decreased the percentage of enzyme bound to the carbamate substrate by enhancing the dissociation of the complex. [125]

A photometric method based on the change in color of an acid-base indicator has been adapted to measure cholinesterase activity in the presence of a large amount of serum by using a calibration based on the ratio of final to initial absorbance, [123] thereby eliminating the errors from the effects of dye binding with protein in the serum. This method is not applicable to hemolytic serum. Turbidity and extraneous colors interfere with the method. An automated method used by Winter [126] has not proved adequate for the assay of erythrocyte cholinesterase [127]; the automated micro determination of cholinesterase, as described by Levine et al, [127] involved a 1:4 dilution of plasma and serum and a 1:10 dilution of erythrocytes. Thus, these automated methods [126,127] have limitations resulting from dilution in determining carbaryl-induced cholinesterase inhibition. The principle of colorimetric or electrometric measurement of the acetic acid liberated from the hydrolysis of acetylcholine by cholinesterase has led to several useful field screening procedures for cholinesterase activity. Such field methods have poor precision (± 25%) and are adequate only for screening purposes. [128-131]

The electrometric method of Michel, [8] developed primarily to shorten the time required for analysis, was well suited to determinations of both erythrocyte and plasma cholinesterase activities. This method has

been used to measure erythrocyte and plasma cholinesterase activities in humans exposed to organophosphate cholinesterase inhibitors. [132] This method makes use of electrodes to measure changes in pH (expressed as delta pH/unit time) resulting from the production of acetic acid when cholinesterase hydrolyzes acetylcholine. However, when this method, [8] or modifications thereof, [132] are applied to the evaluation of carbamate exposures, problems are anticipated as a result of diluting the samples during the assay process.

More recently, Winteringham and Disney [133] devised a radiometric assay of acetylcholinesterase. In this method, a drop of 14C-labeled acetylcholine, used as the substrate, was mixed with the diluted blood sample on a slide. The enzymatic hydrolysis was stopped by adding a drop of acid inhibitor after a measured time period. The amount of unhydrolyzed 14C-labeled substrate was then measured with a Geiger-Muller tube after removal of volatile 14C-acetate by drying in hot air. This activity was then compared to that contained in a previously inactivated sample containing a measured amount of 14C-labeled substrate. By this method, the enzyme activity can be determined at low substrate concentrations and with minimal dilution.

Potter [134] modified the radiometric method to use both 14C- and tritium-labeled acetylcholine; the reaction product (labeled acetate) was quantified by liquid scintillation spectrometry after separation from the labeled acetylcholine by an extraction procedure. The advantage of the radiometric method is that the biologic fluids require no dilution, thereby preventing greater dissociation of the enzyme-carbamate complex. In a critical review of the measurement of cholinesterase activity, Wills [7]

suggested that the radiometric modification described by Potter [134] might be particularly appropriate for reversible inhibitors such as the carbamates. However, the WHO Expert Committee on Insecticides [29] did not recommend the radiometric method for general use. The expense, the necessity for complicated apparatus, and the difficulty in calculating the results were cited as disadvantages.

The basic principle of titrimetric techniques involves titration with standard alkali of the acid released during hydrolysis of the choline ester at a constant pH and use of either an indicator or a potentiometer. [110] According to Witter, [110] acetylcholine, acetyl-beta-methylcholine, or butyrylcholine can be used as the substrate in this method. Noting that the continually changing color in the reaction mixture was often difficult to match with the indicator standard, Witter [110] suggested that this difficulty was due to the color of the blood or the plasma, or to other factors such as the presence of activators or inhibitors. However, the author indicated that this difficulty was obviated if a potentiometer was used to measure the pH. Jensen-Holm et al [135] used an automatic titrator for measuring the cholinesterase activity in blood and other biologic material. The authors claimed that the method had the advantage of following the course of acid liberation (and therefore of cholinesterase activity) during the whole period of the determination. However, the method was subject to serious error due to nonspecific acid liberation in the organ homogenates before addition of substrate; but this error very rarely occurred in fresh blood. Another automatic titrimetric technique, [13 (sec 12)] in which cholinesterase activity of erythrocytes or plasma was determined in refrigerated equipment, was developed to retard the rapid

reversibility of the inhibition of cholinesterase activity by carbaryl. However, no data were reported on the samples analyzed.

Measurements of the production of acid by the addition of base to maintain a constant pH as hydrolysis of substrate occurs are referred to as pH-stat methods [7,136] and are automated versions of the method of Hall and Lucas. [137] Such methods have been used less frequently than the delta-pH methods in determining cholinesterase activity in plasma and erythrocytes. According to Crane et al, [138] they are slightly less precise than the delta-pH methods. Since these methods involve the addition of a base to neutralize the acid, they effectively increase the dilution of the sample and may therefore cause dissociation of the carbamate-enzyme complex. Therefore, pH-stat methods are of limited use in measuring carbaryl-induced cholinesterase inhibition.

Hestrin [50] reported on the stoichiometric reaction of acetylcholine with alkaline hydroxylamine to form acetohydroxamic acid which forms a red-purple complex with ferric chloride. Hestrin's work led to the development of other methods using the same principle for measuring serum cholinesterase activity by determining the amount of unhydrolyzed acetylcholine. [139,140] However, Hestrin's method [50] is not specific for acetylcholine; esters of other short-chain carboxylic acids, lactones, and anhydrides also react with hydroxylamine with resultant formation of hydroxamic acid.

Meyer and Wilbrandt [141] adapted a histochemical principle to the measurement of plasma and erythrocyte cholinesterase in blood based on the measurement of free SH-groups produced by the hydrolysis of esters of thiocholine by the active enzyme. Techniques using thiocholine esters have

been used to measure cholinesterase activity in plasma, serum, and erythrocytes, and have been adapted to automatic analytical equipment. [7] This measurement can be accomplished iodometrically, [141] colorimetrically, [142] or spectrophotometrically. [143] Ellman et al [143] were able to determine cholinesterase activity in blood, erythrocytes, and tissue homogenates, using the spectrophotometric method. The authors claimed several advantages for this method: it operates in the visible region of the spectrum, thus permitting spurious changes to be observed directly; it is extremely sensitive; and it requires no special handling of tissue homogenates. The colorimetric method of Gary and Routh [142] is a very rapid micro method, with only a 3-minute incubation period necessary, and has been used to determine serum and plasma cholinesterase activities. However, the application of these methods [141-143] to measuring carbaryl-induced cholinesterase inhibition is limited by the dilution required in the sample preparation.

Cranmer and Peoples [144] described a method for the determination of cholinesterase activity that involved the incubation of erythrocytes or plasma with 3,3'-dimethylbutyl acetate as a substrate. The reaction product, 3,3'-dimethylbutanol, was extracted into carbon disulfide and determined by gas-liquid chromatography. According to the authors, their method has been applied only to strong inhibitors of cholinesterase and not to reversible inhibitors. Therefore, its validity for assaying carbamate inhibition estimation has not been demonstrated.

Baum [145] described a method of measuring cholinesterase activity using a liquid membrane electrode having a high selectivity for acetylcholine. This method permitted a continuous determination of the

rate of change of substrate concentration in the presence of active enzyme. When the acetylcholine concentration fell below 0.1 μM, interference from sodium in the saline buffer solutions used became serious. No information was given on the applicability of this method for determining cholinesterase activity in whole blood or erythrocyte samples.

V. DEVELOPMENT OF A STANDARD

Basis for Previous Standards

In 1964, the American Conference of Governmental Industrial Hygienists (ACGIH) [146] proposed a tentative threshold limit value (TLV) for carbaryl of 5 mg/cu m of air. This was adopted as a recommended TLV by the ACGIH in 1966 [147] and has not been changed since then. The ACGIH limit for carbaryl continues to be 5 mg/cu m of air. [148]

According to the most recent (1971) ACGIH Documentation, [149] the TLV of 5 mg/cu m for carbaryl was recommended to provide a safety factor for protection against systemic effects. Cholinesterase inhibition was considered by the Threshold Limits Committee to be the basis of the toxic action of carbaryl; no other types of toxicity were mentioned. The TLV was based on the work of Best and Murray, [28] who indicated that 31 mg/cu m of carbaryl could be tolerated. However, the 31 mg/cu m was an average of only two air samples. Neither the duration of exposure nor the number of workers exposed at that concentration was specified by Best and Murray. [28] This exposure (31 mg/cu m) was calculated by the ACGIH to be equivalent to inhalation of 310 mg/man/day.

The documentation referred to the work of Carpenter et al, [27] who reported that airborne concentrations of 10 (5-20) mg/cu m of Sevin 85S produced neither mortality nor grossly visible injury in rats exposed 7 hours/day, 5 days/week, for 90 exposures. The ACGIH calculated that man in such an atmosphere would inhale about 100 mg of carbaryl a day.

Standards for carbaryl in foreign countries are those of the Federal Republic of Germany (5 mg/cu m as an 8-hour TWA) [150] and of the USSR (1

mg/cu m as a ceiling). [151] The basis of the USSR standard is inferred to represent a tenfold margin of safety derived from a threshold concentration obtained in long-term animal studies. [39] In addition, this concentration (1 mg/cu m) was stated as being somewhat below the concentration which caused a slight fall in cholinesterase activities of workers. [39]

The present United States federal standard for occupational exposure to carbaryl is an 8-hour TWA limit of 5 mg/cu m of air (29 CFR 1910.1000, published in the Federal Register 40:23072, May 28, 1975). This standard is based on the ACGIH TLV recommendation.

Basis for the Recommended Standard

The absorption of airborne carbaryl during workplace exposure is considered to be primarily through the routes of inhalation and dermal contact and, to a lesser extent, by ingestion. The airborne concentration at which carbaryl will induce some or no signs or symptoms of poisoning in humans has not been reported. The airborne concentrations of carbaryl present when 7 of 14 men engaged in hand-removal of carbaryl from a plugged storage bin became ill were not determined. [13 (sec 7)] Although these workers were supposedly wearing respirators, the protective devices were ineffective against inhalation of carbaryl dust. The complete recovery of the workers in less than 36 hours without medical intervention suggests a rapid reversibility of carbaryl intoxication once exposure is halted.

Best and Murray [28] reported that signs and symptoms of carbaryl intoxication were not detected among 59 workers exposed to airborne concentrations ranging from 0.03 to 40 mg/cu m. Workers exposed at high concentrations of carbaryl usually wore respirators, and those exposed at

lower concentrations did not routinely wear respirators. Significant inhibition of cholinesterase activity was not reported; however, the methods used were not adequately sensitive.

In a short-term inhalation-absorption study, [13 (sec 9,10)] two workers who wore either a respirator or skin protection equipment, but not both, were exposed to airborne carbaryl at a concentration of approximately 50 mg/cu m during 2 workdays. No apparent adverse effects were observed.

A report from Russia [39] involving agricultural workers' exposure to carbaryl indicated that exposure at 2 mg carbaryl/ cu m in the air, 4-6 hours/day, for 3-4 days produced some inhibition of cholinesterase activity (11-24%). However, clinical assessment showed no additional evidence of changes induced by cholinesterase inhibition. The method used for determining cholinesterase activity was not specified.

Several species of animals have been experimentally exposed to airborne carbaryl. [27,39] There were no deaths reported in guinea pigs exposed to carbaryl for 4 hours at concentrations of 230, 322, and 390 mg/cu m, but nasal and local ocular irritation were noted in those animals exposed at the highest concentration. [27] Signs of cholinesterase inhibition were noted in dogs within 5 hours of exposure to carbaryl at 75 mg/cu m. [27] Neither deaths nor carbaryl-associated lesions (C Carpenter, written communication, January 1976) were reported in rats exposed to carbaryl at an average concentration of 10 mg/cu m (5-20 mg/cu m) for 7 hours/day, 5 days/week, for 90 days. [27] Three groups of four cats each were exposed to carbaryl at 16, 40, and 63 mg/cu m, 6 hours/day, for varying periods up to 4 months. [39] At 16 mg/cu m, there were no signs of toxicity after 4 months' exposure; at 40 mg/cu m, there was a loss of

unspecified conditioned reflexes and a 50% decrease in erythrocyte cholinesterase activity during 2 months' exposure; at 63 mg/cu m, the cats exposed to carbaryl for one month showed periodic salivation, with 31-40% and 41-58% decreases in serum and erythrocyte cholinesterase activities, respectively. The author concluded that 16 mg/cu m was the threshold concentration for carbaryl in cats. If humans and lower animals do not differ signifcantly in their susceptibility to inhaled carbaryl, the results of inhalation studies in several animal species [27,39] would indicate that 16 mg/cu m can be considered the no-adverse-effect level with respect to toxic manifestations of cholinesterase inhibition in humans. This assumption is supported by the work of Best and Murray, [28] who noted no symptoms of carbaryl intoxication in humans exposed to the insecticide at airborne concentrations ranging from 0.03 to 40 mg/cu m. It is also not in conflict with the results of Yakim [39] who reported reductions in blood cholinesterase activity (measured by an unspecified method) following 4- to 6-hour exposures of workers to carbaryl at average airborne concentrations of 2-4 mg/cu m, since no clinical evidence of anticholinesterase activity was observed at these concentrations.

Few oral ingestion studies on the effects of carbaryl in humans have been found. A suicide attributed to the ingestion of an apparently large dose (possibly 400 g) of carbaryl was reported. [40] The significance of this report cannot be determined since the patient was treated with an oxime, a useful antidote for cholinesterase inhibition caused by organophosphates, but not useful in cases of carbaryl poisoning. [21]

Single oral doses of up to 2 mg/kg of carbaryl taken by male volunteers produced no signs or symptoms of intoxication. [32] A higher

single oral dose of 250 mg of carbaryl (approximately 2.8 mg/kg) caused immediate symptoms including epigastric pain and sweating in an adult male who intentionally swallowed the chemical. [21] Recovery, after atropine sulfate administration, was complete within a few hours. Male volunteers receiving daily oral doses of 0.12 mg/kg for 6 weeks reportedly exhibited a slight decrease in the ability of the proximal convoluted tubules of the kidney to reabsorb amino acids as indicated by an increase in the urinary amino acid nitrogen to creatinine ratios. [32] The increase in urinary amino acid nitrogen to creatinine ratio is at best a rough measure of the reabsorptive capacity of the proximal renal tubule.

Increased amino acid nitrogen to creatinine ratios seen in humans administered 0.12 mg/kg carbaryl orally, once daily for 6 weeks, were reversible and no increase in the ratios was seen in subjects administered carbaryl at 0.06 mg/kg for the same period of time. [32] These results are difficult to interpret because they were derived from only five subjects given the higher dose. Moreover, determination of ratios was absent and any graphically illustrated data were unimpressive.

Dietary administration of carbaryl to rats for 2 years at 400 ppm and to dogs for 1 year at 7.2 mg/kg resulted in a transient cloudy swelling of the proximal renal tubules in both species. [27] The incidence of renal changes seen in the rats was not significant, and similar changes were noted in treated as well as in control dogs. Marked vacuolization of the proximal tubular epithelium of the kidney in a monkey administered 600 mg/kg of carbaryl for an unspecified period of time was reported. [44,51] It is difficult to draw any conclusion from these studies, [44,51] since only a single electron photomicrograph was presented and the length and

frequency of treatment was not specified. Without other confirming renal tubular function tests in significant numbers of occupationally exposed subjects or animals exposed at various concentrations of airborne carbaryl, the results of the studies previously discussed [27,32,44,51] do not confirm carbaryl-related renal dysfunction in humans. However, sufficient suspicion of carbaryl-related renal effects is established by these studies to warrant a recommendation for surveillance of kidney function in workers. The possibility of effects of carbaryl on the kidney needs further investigation.

No data were found which concerns the effect of carbaryl on any phase of human reproduction. It was reported that carbaryl was not teratogenic in the monkey, [67,69] mouse, [75] rat, [70] rabbit, [71] hamster, [71] or guinea pig, [72] but was teratogenic in the beagle dog [66] and in the guinea pig. [71] Two studies on rhesus monkeys, performed in the same laboratory, were available. The first study [67] made use of 21 mated females, 7 of which were controls. The monkeys were administered carbaryl at oral doses of 2.0 mg/kg (4 animals) and 20.0 mg/kg (10 animals) throughout gestation. No fetal abnormalities were found; however, the abortion rate was high but not dose related. There was a 50% abortion rate (three of six pregnant animals) at the high dose, 100% (two of two pregnant animals) at the low dose, and 20% (one of five) in the controls. The small number of animals used in this study precludes any reliable evaluation of these results. The second study [69] involved 79 monkeys, 48 test and 31 controls. The doses of carbaryl were 0.2, 2.0, and 20.0 mg/kg administered orally from days 20 to 38 of gestation. Abortions occurred in 2 of 16 at the lowest dose, in 1 of 16 at the mid-dose, in 3 of 15 at the highest

dose, in 2 of 15 in vehicle-treated controls, and in 2 of 15 in the untreated controls. It was concluded that carbaryl was not associated with the producing of terata, abortion, stillbirths, or of any other adverse reproductive effects.

Beagle dogs, [66] unlike monkeys, did show reproductive and teratologic abnormalities when administered carbaryl. Oral doses were 3.125, 6.25, 12.5, 25, and 50 mg/kg throughout gestation. Dystocia occurred in 1/3 of treated animals, while decreased numbers of live births occurred at all dose levels, as compared to control dams. There were abnormalities in pups at all dose levels except at 3.125 mg/kg. The litters were smaller than those of the controls in the 25 mg/kg and 50 mg/kg dose groups.

The teratogenic potential of carbaryl was investigated in several other species. Weil et al [70] administered carbaryl in the diet to rats at doses of 20, 100, and 500 mg/kg at various intervals throughout pregnancy or until weaning of the pups. No teratogenic effects attributable to carbaryl were observed at any dose. Carbaryl was administered in gelatin capsules to guinea pigs and rabbits. [71] A dose of 300 mg/kg given either once or daily during days 11-20 of gestation produced a higher incidence of terata in treated guinea pigs than in controls. This dose also induced a high mortality rate in the dams. There was no evidence from rabbits receiving carbaryl at 50, 100, or 200 mg/kg during days 5-15 of gestation of terata when compared to results from pregnant controls. Robens [71] also administered carbaryl by gastric intubation to hamsters at doses of 125 and 250 mg/kg during days 6-8 of gestation. No teratogenic effects were observed at either dose; however,

30% fetal mortality was observed at the high dose, 10% at the low dose, and 5.5% in the control group. Dietary or gastric administration to guinea pigs of carbaryl doses ranging from 50 to 300 mg/kg on days 10-24 of gestation produced no significant increase in the incidence of terata as compared to controls. [72] Mice receiving carbaryl in the diet at 10 or 30 mg/kg from day 6 of gestation to delivery showed no evidence of carbaryl-related terata. [75]

It may be concluded from the above studies [66,67,69-72,75] that carbaryl in doses as low as 6.25 mg/kg is teratogenic in only one species, ie, the beagle dog. [66] The positive findings in the beagle dog and in the guinea pig are not persuasive. In the one study using guinea pigs, [71] terata were produced only at doses which resulted in mortality and morbidity in some of the dams. In another study in the same species, [72] carbaryl administered by gastric intubation or dietary inclusion was found not to be teratogenic. Although carbaryl was found to be teratogenic in the beagle dog at relatively low doses, [66] the dog metabolizes carbaryl differently than the rat, guinea pig, monkey, and, more importantly, humans. [33,34,87] The dog, unlike humans, neither excretes 1-naphthol nor hydroxylates carbaryl. In view of the apparent differences between dog and humans with respect to the metabolism of carbaryl, and the fact that carbaryl was reported not to be teratogenic in the rat [70] and guinea pig, [72] animals that metabolize carbaryl similarly to humans, a standard based on teratogenic effects is not recommended. This recommendation will be reconsidered if results from future research warrant a change.

Reproductive effects of carbaryl in rats have been reported by Shtenberg and Ozhovan [73] in a five-generation reproduction study. Doses

as low as 2 and 5 mg/kg, administered by gastric intubation, produced adverse effects including a decrease in spermatogenesis, a decrease in sperm motility, an increase in the duration of the estrus, a decrease in fertility of females, and a decrease in the survival of pups during the first month of life. In addition, degenerative changes of ovarian and testicular tissue were observed in the rats receiving carbaryl.

Shtenberg and Rybakova [77] administered carbaryl orally to rats of both sexes at doses of 7, 14, and 70 mg/kg for up to 12 months. Growth of the rats was inhibited at 14 and 70 mg/kg, while sperm motility in males also decreased in a dose-related manner after 12 months of treatment. Degenerative changes in the testes, including edema of interstitial tissue and destruction of germinal epithelium, were noted in carbaryl-treated male rats. In females, the estrus cycle was prolonged at the 14 and 70 mg/kg doses. In a three-generation reproduction study on gerbils given carbaryl in the diet (2,000, 4,000, 6,000, and 10,000 ppm), Collins et al [78] reported that no litters were produced at 10,000 ppm in the F3b generation, and that there was a decrease in fertility, pup viability, litter size, and survival of pups (to day 4 and to weaning) which appeared sporadically at all dose levels.

In a similar three-generation reproduction study, Collins et al [78] reported that doses of 5,000 and 10,000 ppm carbaryl in the diet reduced survival of offspring, viability of the pups, and litter size in rats from the first generation on. At 2,000 ppm, only body weight gain of the parents and weanling weight were affected. In contrast, Weil et al [72] did not see any effect when carbaryl was administered by dietary inclusion to rats in a dose range of 7-100 mg/kg. An increased duration of the

gestation period was the only effect seen at 200 mg/kg in the diet. Administration of carbaryl by gastric intubation to rats in a dose range of 3-100 mg/kg showed effects only at the highest dose which included decreased pup viability and litter size, as well as decreased fertility and lengthened gestation period in the females.

The above studies [72,73,77,78] indicate that carbaryl has an effect on several aspects of reproduction in rodents administered carbaryl. Because of the uncertainty in extrapolating reproductive effects seen in animals administered carbaryl orally to those that may be encountered from pulmonary and dermal absorption during occupational exposure, a standard based on these effects is not now recommended. The effects of airborne carbaryl on reproduction is clearly an area for future research.

Mutagenic studies have been carried out in mammalian (mouse) [59] and bacterial systems (E coli, H influenzae, and B subtilis) [63,65] and on yeast (S cervisiae). [64] These studies indicate that, under the experimental conditions used, carbaryl did not demonstrate any mutagenic effects. Experiments on an insect (Drosophila) [62] showed only weak mutagenicity. These studies do not warrant a conclusion that carbaryl is a mutagen. Microbiologic studies on bacterial systems [63,65] and yeast cells [64] indicated that nitrosocarbaryl is a strong mutagen. However, there are no available data indicating that carbaryl is converted by the human body to nitrosocarbaryl. In addition, the reaction would most likely occur at low pH, ie, in the stomach, so it would be applicable to ingested, but perhaps not to inhaled, carbaryl. Thus, from present evidence, it does not seem likely that carbaryl will cause mutations in exposed workers.

The carcinogenic potential of carbaryl has been investigated in mice. [27] Male mice received 10 mg carbaryl subcutaneously once weekly during their 3rd to 8th months of life. There was no increased incidence of tumors over that observed in controls. Innes et al [79] administered carbaryl to mice (4.64 mg/kg) by stomach tube on days 7-28 of age and then in the diet, at a level stated to be equivalent to the amount ingested, for the duration of the experiment, which lasted approximately 18 months. Carbaryl gave no significant evidence of tumorigenicity in this experiment.

Rats were administered carbaryl (50-400 ppm) in the diet for a period of 2 years [27]; there was no dose-related increase in the incidence of tumors over that in controls. In a USSR study, [80] rats received carbaryl at 30 mg/kg twice weekly by the oral route for up to 22 months. A second group of rats were treated with carbaryl (20 mg) by subcutaneous implantation in a paraffin capsule for the same duration. Only 12 of 60 animals receiving carbaryl by the oral route survived, and 4 had cancerous tumors. Only 10 of 48 rats survived treatment with carbaryl subcutaneously and 2 had subdermal fibrosarcomas, neither being at the implantation site. Only one tumor was observed in the control group, in 46 of 48 rats which survived. The high and unexplained death rates in test animals, though the authors suggested little carbaryl toxicity, and the unusual incidence of fibrosarcomas in test and control rats in the absence of a local cause such as implantation, makes this study difficult or impossible to interpret. In addition, there is reason to suspect that the sample used was contaminated by the 2-naphthyl derivative.

Shimkin et al [81] administered N-methyl naphthyl carbamate of their own formulation ip to mice, 0.5 mg 3 times/week for a total dose of 6

mg/mouse over a 12-week period and observed the animals for the development of pulmonary tumors. When compared to other carbamates which were actively tumorigenic in this study, the synthesized compound was classed as giving a marginal response. No information was given as to the purity of the compound synthesized and, more importantly, it is not clear from the structural formula shown in the publication [81] whether 2-naphthyl-N-methylcarbamate or 1-naphthyl-N-methylcarbamate (carbaryl) was synthesized. Consequently, the tumorigenic results reported in the study are impossible to interpret as being carbaryl related. The studies described previously [27,79-81] do not warrant a conclusion that carbaryl is a carcinogen. Future research may clarify the apparent discrepancies in the USSR study [80] and thereby support or refute the implications of the study by Innes et al. [79]

The neuromuscular degenerative potential of carbaryl was investigated in pigs by Smalley et al. [52] Microscopic examination showed skeletal myodegeneration and vasogenic edema of the CNS but not demyelination after 1-3 months of large oral doses (150-300 mg/kg daily) of carbaryl. The toxic effects noted at these doses included tremors, ataxia, incoordination, prostration, and eventual death. [52] Reports of neuromuscular changes such as these have not been found for other species of experimental animals. Carpenter et al [27] administered carbaryl to chickens at very high single subcutaneous doses, 0.25-3 g/kg, and found that leg weakness occurred in 1-2 days at doses higher than 1 g/kg. There was no microscopic evidence of demyelination in tissue sections of the sciatic nerve, spinal cord, and brain. The authors concluded that leg weakness was the only evidence of a transient cholinergic effect in the

chicken. The results of another study in chickens by Gaines [43] lends support to the conclusions of Carpenter et al [27] that carbaryl does not cause demyelination. Male dogs treated with 30 mg/kg of carbaryl iv were found to have less marked signs of intoxication including leg weakness than male pigs treated iv with 20 mg/kg carbaryl. [55] Dietary administration of 125 mg/kg of carbaryl failed to produce overt signs of toxicity in dogs, but did produce spastic paresis of the posterior extremities in pigs. [55] The results obtained with chickens [43,116] and dogs [55] show that apparently only very high doses of carbaryl will produce neuromuscular effects, eg, leg weakness, in these species, probably as a consequence of cholinesterase inhibition. Since no demyelination occurred in the swine [52] nor in the chicken, [27] which is the animal of choice for demonstrating demyelinating effects, it may be concluded that carbaryl is unlikely to produce demyelinating paralytic effects in humans.

The potential for dermal penetration by carbaryl in humans has been established experimentally by Feldmann and Maibach [30,31] and suggested indirectly by Union Carbide Corporation. [13 (sec 9,10)] In addition, absorption of carbaryl occurs through the skin of animals as indicated by death in rats [49] and inhibition of cholinesterase activity in rabbits [39] after dermal application of carbaryl at high doses to these species. However, the quantitative dermal absorption of carbaryl by humans during occupational exposure has not been accurately determined. Adverse local ocular effects have not been reported in humans, but minor eye irritation has been demonstrated in animals after local application of carbaryl. [39] It is therefore concluded that dermal and eye exposure are factors to be considered in the workplace environment. Appropriate work practices to

prevent or limit such contact are thus recommended.

Overexposure to carbaryl in the workplace environment apparently results in a rapid onset of symptoms which leads to voluntary cessation of work and termination of exposure. [13 (sec 13),20] Moreover, employees who have been overexposed to carbaryl in the workplace apparently recover rapidly. [13 (sec 7,13)] Because of a possible additive effect on the inhibition of the enzyme cholinesterase, workers occupationally exposed to both carbaryl and other anticholinesterase agents probably are at a greater risk than those exposed only to carbaryl. Those workers who have a congenital deficiency in cholinesterase enzymes or who routinely take anticholinesterase drugs should be cautioned that they are at a greater risk of intoxication by carbaryl.

The current ACGIH [149] recommended standard of 5.0 mg/cu m was based on the study by Best and Murray, [28] which suggested that over a period of 19 months, workers could tolerate airborne carbaryl concentrations up to 31 mg/cu m. At no time were there any signs or symptoms indicative of anticholinesterase activity, although absorption of carbaryl was verified by measurement of urinary 1-naphthol levels. To provide a safety factor for protection against systemic effects, a Threshold Limit Value of 5.0 mg/cu m was recommended. While available data to derive a safe limit are insufficient, there is no significant evidence indicating that the limit should be changed. In the absence of these needed data, it is proposed that the present workplace environmental limit of 5.0 mg carbaryl/cu m as a TWA concentration be continued.

Available data do not indicate that exposure of workers at this concentration will result in intoxication, and some data suggest that this

limit offers a good margin of safety. However, pertinent investigations, including epidemiologic studies of workers exposed to carbaryl, are needed to validate this recommended limit or, if appropriate, to provide a basis for a better limit.

Sampling and analysis methods were reviewed in Chapter IV. Airborne particulate carbaryl should be collected on a glass-fiber membrane filter mounted with a backup pad in a two-piece closed-face cassette. This sampling method, chosen because it is the best now available, has been shown to provide the required degree of collection efficiency for airborne particulate carbaryl. A colorimetric method was selected for analysis of carbaryl because it is reliable, sensitive, and simple to carry out. The selected method is not entirely specific for carbaryl analysis and several compounds including 1-naphthol can interfere with the precision of the method if they are present in the air sample to be analyzed.

Work practices are discussed in Chapter VI. In operations involving the handling or use of carbaryl formulations, the potential for skin and eye contamination with subsequent absorption is great, and therefore protective clothing and equipment should be worn whenever required to prevent absorption through the skin or contamination of the eye. To minimize percutaneous absorption, employees exposed to carbaryl should wear freshly laundered work clothes before the work shift. They should also shower or bathe and change clothing after the workday. Storage, handling, and eating of food in carbaryl exposure areas should be prohibited to prevent food contamination, and therefore ingestion of carbaryl by employees.

The neurotransmitter function of acetylcholine in the nervous system and the inactivation of acetylcholine by cholinesterase has been discussed in Chapter III. The inhibition of cholinesterase by carbaryl in the nervous system warrants a requirement for preplacement physical examinations directed towards the cardiorespiratory system, the CNS, and the eyes. In addition, such examinations must be made on a yearly basis or at some other interval determined by the responsible physician for employees subject to occupational exposure to carbaryl. It is recommended that preplacement erythrocyte cholinesterase determinations be performed if one of the methods described as suitable in Chapter IV can be used. Such a preplacement determination can serve as a useful comparison in the event of overexposure. Since the kidney is the primary organ for excretion of carbaryl and its metabolites, it is proposed that medical surveillance include a complete urinalysis including microscopic examination.

No information has been found regarding the passage of carbaryl into human milk. As discussed in Chapter III, carbaryl has been found in the milk of dairy animals after their exposure to the insecticide. It seems reasonable to assume that carbaryl may be excreted in human milk, and therefore nursing mothers must be counseled to minimize exposure to carbaryl wherever possible. Research to confirm or refute this assumption should be performed.

It is recognized that many workers are exposed to small amounts of carbaryl or are working in situations where, regardless of amounts used, there is only negligible contact with the material. Under these conditions, it should not be necessary to comply with many of the provisions of this recommended standard, which has been prepared primarily

to protect workers' health under more hazardous circumstances. Concern for workers' health requires that protective measures be instituted below the enforceable limit to ensure that exposures stay below that limit. For these reasons, an action level of carbaryl has been defined as occupational exposure above half the recommended TWA environmental limit, thereby delineating those work situations which do not require the expenditure of health resources for environmental and medical monitoring and associated recordkeeping. This level has been chosen on the basis of professional judgment rather than on quantitative data that delineate nonhazardous areas from areas in which a hazard may exist. However, because of nonrespiratory hazards such as those resulting from skin or eye contact, it is recommended that appropriate work practices and protective measures be required regardless of the TWA concentrations. Similarly, food storage, handling, and eating should be prohibited in carbaryl work areas regardless of TWA concentrations.

VI. WORK PRACTICES

Occupational exposures to carbaryl may occur among people engaged in the manufacture, formulation, or application of the insecticide. Potentially exposed applicators include agricultural workers, spray pilots, and exterminators. [22] Even though absorption of pesticides by the oral and respiratory routes may be more rapid and more complete than by the percutaneous route, the amount of absorption by ingestion and inhalation is probably too small a fraction of the total potential exposure to be considered the main factor in most cases of intoxication of workers in the field. [152] Studies also showed that considerably more insecticide was deposited on exposed skin surfaces than that reaching the respiratory tract. [89,90] The average potential respiratory exposure tended to be higher in agricultural dusting operations than in agricultural spraying operations, while the potential dermal exposure was about the same in both spray and dust applications. [153] Absorption of carbaryl into the body has occurred by three routes of entry: dermal, [30,31] respiratory, [13 (sec 7,9,10)] and oral. [32-34,40] Simpson [90] summarized the relative importance of the dermal and respiratory routes of absorption of carbaryl by orchard spray applicators by stating that, although inhalation exposure is considerably less than dermal exposure, it has an additive effect. Inhalation would be an important factor only if the worker already had experienced sufficient percutaneous absorption approaching a level of absorption at which symptoms occur. [90] Employees occupationally exposed simultaneously to carbaryl and other anticholinesterase agents are at a greater risk because of a possible additive effect on the inhibition of the

enzyme cholinesterase. However, available evidence indicates that the effect would not be potentiated. [48,116] Those employees who have a congenital deficiency in cholinesterase enzymes or who routinely take anticholinesterase drugs should likewise be cautioned against additive effects.

Because the potential for skin contamination, with subsequent absorption of carbaryl through the skin, is great during many handling operations involving carbaryl formulations, [88] use of appropriate personal protective equipment is necessary during such operations to minimize skin exposure. The specific protective equipment required depends on the degree of potential exposure and the body areas that may be exposed. Workers should use all personal protective equipment and exercise all precautions specified on the label of the carbaryl formulation being used.

Protective clothing should be worn wherever required to prevent skin contact with carbaryl. In agricultural situations, personal protective clothing and respiratiors may be the only practical ways to minimize worker exposure. The areas of highest potential exposure for formulating-plant workers have been found to be the hands, forearms, and front of the body; [88] for spray operators, the areas of highest potential exposure have been reported to be the shoulders and back of the neck, [88] the head, arm, chest, shoulders, and back. [90] Hats and other special clothing covering these areas should be used. Long-sleeved coveralls and gloves are recommended for all exposure situations. Fresh clothing should be worn daily. In addition, workers should be advised to shower or bathe after the workday.

In agricultural situations, because of possible bodily contamination by contact with sprayed foliage, as established for other insecticides, [154] immediate entry into sprayed areas should be avoided if possible. Johnson and Stansbury [155] established the half-life of carbaryl on various growing crops to be 2-4 days, and the half-life in soil to be approximately 8 days.

All personnel exposed to carbaryl should wear freshly laundered coveralls or work uniforms (long pants and long-sleeved shirts). [156] Work clothes should be laundered separately from household laundry. If the coveralls or uniform might become wet by mist or spray, use of a waterproof raincoat will provide the best protection for the upper back, shoulders, and forearms, [152] but this may cause discomfort or even heat stress in a hot environment. [157] Under such conditions, wearing long-sleeved clothing such as water-repellant or waterproof clothing that will not be easily penetrated by the insecticide should provide a significant measure of protection. [152]

Protection of the lower trunk and legs from contamination is important where the potential exists for liquid spillage, soaking by continued contact with sprays or sprayed foliage, or penetration of clothing through excessive contact with carbaryl. Waterproof trousers will provide the best protection for the lower trunk and leg areas. [152] Even though the coveralls or uniform is covered by waterproof protective clothing, daily bathing after work [152] and daily changes to freshly laundered clothing [152,157,158] are important for minimizing percutaneous absorption.

The head and neck should be protected from contact with carbaryl. [156] Therefore, some type of protective headgear, such as waterproof rainhats and washable safety hardhats and caps, should be worn. Waterproof or water-repellant parkas also may be used to protect the head and neck at the same time. [156] Personnel potentially exposed to downward drifts of carbaryl [152] should wear wide-brimmed, water-repellant, or waterproof hats to obtain additional protection for the head and neck areas. [152]

Workers handling concentrated wettable powders, concentrated liquids, or finely divided dust formulations should wear protective gloves of natural rubber [156,158] or of neoprene, [159] although the permeability of natural rubber or neoprene to carbaryl remains to be determined. Contact of wet skin with carbaryl should be avoided to minimize absorption.

If an employee might come in contact with concentrated formulations, his hands often will be the body area receiving the highest exposure. Unlined rubber gauntlet gloves, which cover the wrist area not normally protected by the sleeve, provide the best protection. [152] These gloves can be turned wrong side out for proper cleansing of the inside surface.

Use of waterproof footwear is necessary to minimize exposure when the carbaryl formulation may wet the feet. [152] Footwear should be washed and dried thoroughly, inside and out, as frequently as necessary to remove carbaryl contamination. [156]

Safety goggles should be used to minimize eye exposure when spray or dust drift may be encountered, [156] but a face shield is superior to goggles when liquid pesticide is handled. [157] Use of eye protection by pilots applying carbaryl by aircraft is particularly important. Although reports of miosis following eye exposure to carbaryl were not found, Upholt

et al [160] showed that eye exposure of pilots to the cholinesterase inhibitor tetraethylpyrophosphate (TEPP) induced miosis. Infrequent unilateral eye contamination of pilots applying TEPP was found to result in incoordination and reduced ability to judge distance. [160] Although TEPP is a highly toxic organophosphate insecticide and carbaryl is a considerably less toxic carbamate insecticide, carbaryl is also a cholinesterase inhibitor. Therefore, the possibility of the development of these effects after unilateral eye contamination should be considered. The accompanying incoordination could present a significant safety hazard to pilots. [160] It is therefore recommended that pilots engaged in aerial spraying of carbaryl wear goggles.

Respiratory protection as specified in Chapter I must be used whenever airborne concentrations of carbaryl cannot be controlled by either engineering or administrative controls to the workplace environmental limit recommended in this standard. High levels of airborne carbaryl in industry may be present in uncontrolled atmospheres. [13 (sec 10),28]

To minimize absorption of carbaryl through ingestion, employees must not store and use food, beverages, tobacco, or other materials that may be placed in the mouth in the exposure areas. Washing of hands before eating and smoking to further minimize the potential for ingestion is a good practice and should be required.

The employer is responsible for proper disposal of surplus pesticides and pesticide containers. [161,162] Disposal activities should be directed toward minimizing the potential for exposure of personnel to carbaryl and toward minimizing adverse environmental effects. Spills of carbaryl, generally in dry, solid forms, should be vacuumed or shoveled into suitable

containers for subsequent reuse or for transfer to a waste disposal facility. [13 (sec 16)] Liquid spills should be covered with large amounts of absorbent clay and shoveled into disposable containers and the process repeated until the contaminated area is dry. The area is then scoured with hydrated lime and water and the slurry is then blotted with absorbent. [159] The Environmental Protection Agency has established regulations defining prohibited procedures pertinent to the disposal of surplus pesticides and containers (40 CFR 165, published in the Federal Register 39:36867-70, October 15, 1974). Specifically, open dumping is prohibited, and water dumping is generally prohibited. Open burning is also prohibited, except for small quantities of combustible containers, not to exceed 50 pounds or the quantity emptied in a single workday, whichever is less. Such open burning may be performed only where it is consistent with federal, state, or local ordinances. "Open burning" means the combustion of a pesticide, pesticide container, or pesticide-related waste in any fashion other than by incineration in a pesticide incinerator (40 CFR 165, published in the Federal Register 39:36867-70, October 15, 1974). Applicable local, state, and federal regulations should be consulted; if such regulations do not exist, suggested precautions include incineration and burial. Incineration or burial should be performed in a manner not contributing to air or water pollution.

VII. RESEARCH NEEDS

Further research is required to assess the effects of long-term occupational exposure to carbaryl, primarily as airborne dust. There is a need for epidemiologic studies of populations exposed to carbaryl, alone and in combination with other materials, in industry and in agriculture.

Animal studies which focus directly on exposures simulating those of industrial and agricultural workers, including qualitative studies of the effects of exposure to known airborne concentrations, are also important to clarify mechanisms.

The toxicity of carbaryl by various routes of exposure should be correlated with possible variations in absorption, metabolism, and products excreted. Investigation into the validity of urinary 1-naphthol as an indicator of carbaryl exposure is particularly important, since cholinesterase inhibition by carbaryl is readily reversible, and hence of less value in detecting exposure than would otherwise be the case. The suggestion that carbaryl can cause tubular or other renal dysfunction suggested by the amino acid nitrogen to creatinine ratio reported by Wills et al [32] should be studied further to determine whether carbaryl is directly responsible for this effect and the mechanism involved. Since carbaryl is metabolized to 1-naphthol in humans and is excreted in the urine, more information is needed on the toxicity of 1-naphthol and its effect on renal function.

The excretion of carbaryl and its metabolites in milk and its effects on the nursing young should be evaluated in various species. Information

is needed to clarify if carbaryl is excreted in human milk and its effect on the infant.

Further research is needed to support or refute conclusions arrived at in this document about the lack of applicability of available data obtained from experimental animals, on fetal deformities from carbaryl. The mechanism of development of such effects in animals in which fetal abnormalities have been observed, eg, whether they are a sequel of an anti-cholinesterase action or whether they result from toxic action of carbaryl metabolites in such species, should be elucidated. But of even more importance is the development of a national surveillance system that can relate incidences and nature of spontaneous abortions, fetal abnormalities, or developmental defects in children to the occupations and therefore to the exposures of the parents to chemical and physical agents. This would have applicability not only to carbaryl but also to many other occupational hazards.

Research is also needed for clarifying present conflicts in data on mutagenic or carcinogenic effects of carbaryl on mammals. Since nitrosocarbaryl has been shown to be mutagenic in yeast [64] and bacteria, [63,65] the possibility that this compound may be formed in the mammalian body if carbaryl is present should be investigated.

Improved sampling and analytical methods for carbaryl are needed. Materials impervious to all carbaryl formulations should be identified for use in protective clothing.

VIII. REFERENCES

1. O'Brien RD: Organophosphates and carbamates, in Hochster RM, Quastel JH (eds): Metabolic Inhibitors--A Comprehensive Treatise. New York, Academic Press, 1963, vol 2, chap 25

2. Koelle GB: Drugs acting at synaptic and neuroeffector junctional sites, in Goodman LS, Gilman A (eds): The Pharmacological Basis of Therapeutics, ed 5. New York, Macmillan Publishing Co Inc, 1975, chaps 21-23

3. Stedman E, Stedman E, Easson LH: CCXLV. Choline-esterase--An enzyme present in the blood-serum of the horse. Biochem J 26:2056-66, 1932

4. Lehmann H, Liddell J: Human cholinesterase (pseudocholinesterase)--Genetic variants and their recognition. Br J Anaesth 41:235-44, 1969

5. O'Brien RD: Insecticides--Action and Metabolism. New York, Academic Press Inc, 1967, chaps 3-5

6. Casida JE, Augustinsson KB: Reaction of plasma albumin with 1-naphthyl N-methylcarbamate and certain other esters. Biochim Biophys Acta 36:411-26, 1959

7. Wills JH: The measurement and significance of changes in the cholinesterase activities of erythrocytes and plasma in man and animals. CRC Crit Rev Toxicol 1:153-202, 1972

8. Michel HO: An electrometric method for the determination of red blood cell and plasma cholinesterase activity. J Lab Clin Med 34:1564-68, 1949

9. Rider JA, Hodges JL Jr, Swader J, Wiggins AD: Plasma and red cell cholinesterase in 800 "healthy" blood donors. J Lab Clin Med 50:376-83, 1957

10. Dorough HW, Casida JE: Nature of certain carbamate metabolites of the insecticide Sevin. J Agric Food Chem 12:294-304, 1964

11. Metcalf RL: Insecticides, in Kirk-Othmer Encyclopedia of Chemical Technology, ed 2 rev. New York, Interscience Publishers, 1966, vol 11, p 711

12. Arylam, in Stecher PG (ed): The Merck Index--An Encyclopedia of Chemicals and Drugs, ed 8. Rahway, NJ, Merck and Co Inc, 1968, p 104

13. Information Concerning the Development of the Criteria Document and Recommended Health Standard for Carbaryl. Unpublished report submitted to NIOSH by Union Carbide Corp, South Charleston, W Va, March 25, 1975, Parts 1 (sec 1-14) and 2 (sec 15-21)

14. Christensen HE, Luginbyhl TT (eds): Registry of Toxic Effects of Chemical Substances--1975 Edition. Rockville, Md, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 1975, p 285

15. Kundiev JI, Vojtenko GA: Carbamates, thiocarbamates--Esters of carbamic acid--Carbaryl, in Encyclopaedia of Occupational Health and Safety. Geneva, International Labour Office, 1972, vol 1, p 248

16. Naphthalene, in Chemical Economics Handbook. Menlo Park, Calif, Stanford Research Institute, 1970, pp 677.5021A-677.5021B

17. Isocyanates, in Chemical Economics Handbook. Menlo Park, Calif, Stanford Research Institute, 1971, pp 666.5022X-666.5022Y

18. Johnson O: Pesticides '72--Part 1. Chem Week 110:33-66, 1972

19. Von Rumker R, Lawless EW, Meiners AF: Production, Distribution, Use and Environmental Impact Potential of Selected Pesticides. Environmental Protection Agency, Office of Pesticide Programs, 1974, pp 7, 133-40

20. Back, RC: Carbamate insecticides--Significant developments in eight years with Sevin insecticide. J Agric Food Chem 13:198-99, 1965

21. Carbamate insecticides--Carbaryl, in Hayes WJ Jr: Clinical Handbook on Economic Poisons--Emergency Information for Treating Poisoning, PHS bulletin No. 476. Atlanta, US Dept of Health, Education, and Welfare, Public Health Service, 1963, pp 44-46

22. Gafafer WM (ed): Occupational Diseases--A Guide to Their Recognition, PHS publication No. 1097. US Dept of Health, Education, and Welfare, Public Health Service, 1966, pp 243-44

23. Laqueur: [On a new therapeutic application of physostigmine.] Zentralbl Med Wiss 14:421-22, 1876 (Ger)

24. Stedman E, Barger G: XLII. Physostigmine (eserine)--Part III. J Chem Soc 127:247-58, 1925

25. Stedman E: XCIV. Studies on the relationship between chemical constitution and physiological action--Part I. Position isomerism in relation to the miotic activity of some synthetic urethanes. Biochem J 20:719-34, 1926

26. Haynes HL, Lambrech JA, Moorefield HH: Insecticidal properties and characteristics of 1-naphthyl N-methylcarbamate. Contrib Boyce Thompson Inst 18:507-13, 1957

27. Carpenter CP, Weil CS, Palm PE, Woodside MW, Nair JH III, Smyth HF Jr: Mammalian toxicity of 1-naphthyl-N-methylcarbamate (Sevin insecticide). J Agric Food Chem 9:30-39, 1961

28. Best EM Jr, Murray BL: Observations on workers exposed to Sevin insecticide--A preliminary report. J Occup Med 4:507-17, 1962

29. OMS-29 (carbaryl)--Chemical name--1-naphthyl methylcarbamate, in Safe Use of Pesticides in Public Health--Sixteenth Report of the WHO Expert Committee on Insecticides, WHO technical report series No. 356. Geneva, World Health Organization, 1967, pp 45-46

30. Feldmann RJ, Maibach HI: Percutaneous penetration of some pesticides and herbicides in man. Toxicol Appl Pharmacol 28:126-32, 1974

31. Maibach HI, Feldmann RJ, Milby TH, Serat WF: Regional variation in percutaneous penetration in man--Pesticides. Arch Environ Health 23:208-11, 1971

32. Wills JH, Jameson E, Coulston F: Effects of oral doses of carbaryl on man. Clin Toxicol 1:265-71, 1968

33. Knaak JB, Tallant MJ, Kozbelt SJ, Sullivan LJ: The metabolism of carbaryl in man, monkey, pig, and sheep. J Agric Food Chem 16:465-70, 1968

34. Knaak JB, Tallant MJ, Bartley WJ, Sullivan LJ: The metabolism of carbaryl in the rat, guinea pig, and man. J Agric Food Chem 13:537-43, 1965

35. Vandekar M: Observations on the toxicity of carbaryl, Folithion and 3-isopropylphenyl N-methylcarbamate in a village-scale trial in southern Nigeria. Bull WHO 33:107-15, 1965

36. Stubbs JL, Fales JT: A capillary sampling technique for the determination of cholinesterase activity in red cells and plasma. Am J Med Technol 26:25-32, 1960

37. Dawson JA, Heath DF, Rose JA, Thain EM, Ward JB: The excretion by humans of the phenol derived in vivo from 2-isopropoxyphenyl N-methylcarbamate. Bull WHO 30:127-34, 1964

38. Long KR: Pesticides--An occupational hazard on farms. Am J Nurs 71:740-43, 1971

39. Yakim VS: [The maximum permissible concentration of Sevin in the air of the work zone.] Gig Sanit 32:29-32, 1967 (Rus)

40. Farago A: [Fatal suicidal case of Sevin (1-naphthyl-N-methyl-carbamate) poisoning.] Arch Toxicol (Berl) 24:309-15, 1969 (Ger)

41. Lopez C: [Therapy with corticosteroid compounds in acute poisoning with carbaryl and organophosphate pesticides.] Int Arch Arbeitsmed 26:50-62, 1970 (Ger)

42. Fleisher JH, Pope EJ: Colorimetric method for determination of red blood cell cholinesterase activity in whole blood. Arch Ind Hyg Occup Med 10:323-34, 1954

43. Gaines TB: Acute toxicity of pesticides. Toxicol Appl Pharmacol 14:515-34, 1969

44. Coulston F, Serrone DM: The comparative approach to the role of nonhuman primates in evaluation of drug toxicity in man--A review. Ann NY Acad Sci 162:681-704, 1969

45. Natoff IL, Reiff B: Effect of oximes on the acute toxicity of anticholinesterase carbamates. Toxicol Appl Pharmacol 25:569-75, 1973

46. Akamatsu K, Kohgo K: [Antidotal effect of bis (4-hydroxyiminomethyl-pyridiniomethyl) ether dichloride (toxogonin) on acute toxicity caused by several insecticides, particularly in comparison with 2-pyridine aldoxine methiodide (PAM).] Showa Yakka Daigaku Kiyo 4:15-34, 1966 (Jap)

47. Sanderson DM: Treatment of poisoning by anticholinesterase insecticides in the rat. J Pharm Pharmacol 13:435-42, 1961

48. Keplinger ML, Deichmann WB: Acute toxicity of combinations of pesticides. Toxicol Appl Pharmacol 10:586-95, 1967

49. Gaines TB: The acute toxicity of pesticides to rats. Toxicol Appl Pharmacol 2:88-99, 1960

50. Hestrin S: The reaction of acetylcholine and other carboxylic acid derivatives with hydroxylamine, and its analytical application. J Biol Chem 180:249-61, 1949

51. Serrone DM, Stein AA, Coulston F: Biochemical and electron microscopic changes observed in rats and monkeys medicated orally with carbaryl. Toxicol Appl Pharmacol 8:353, 1966

52. Smalley HE, O'Hara PJ, Bridges CH, Radeleff RD: The effects of chronic carbaryl administration on the neuromuscular system of swine. Toxicol Appl Pharmacol 14:409-19, 1969

53. Grob D: Neuromuscular pharmacology. Annu Rev Pharmacol 1:239-60, 1961

54. Smalley HE: Diagnosis and treatment of carbaryl poisoning in swine. J Am Vet Med Assoc 156:339-44, 1970

55. Miller E, Earl FL, Michel TC, Van Loon EJ: Comparative response of dog and pig to neurotoxic agents, in Proceedings of the Fifth International Committee on Laboratory Animals Symposium. Stuttgart, Germany, Gustav Fischer Verlag, 1973, pp 45-49

56. Santolucito JA, Morrison G: EEG of rhesus monkeys following prolonged low-level feeding of pesticides. Toxicol Appl Pharmacol 19:147-54, 1971

57. Sideroff SI, Santolucito JA: Behavioral and physiological effects of the cholinesterase inhibitor carbaryl (1-naphthyl methyl carbamate). Physiol Behav 9:459-62, 1972

58. Singh JM: Decreased performance behavior with carbaryl--An indication of clinical toxicity. Clin Toxicol 6:97-108, 1973

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

60. Amer S: Cytological effects of pesticides--I. Mitotic effects of N-methyl-1-naphthyl carbamate--"Sevin." Cytologia 30:175-81, 1965

61. Wuu KD, Grant WF: Chromosomal aberrations induced by pesticides in meiotic cells of barley. Cytologia 32:31-41, 1967

62. Brzeskij VV, Vaskov VI: [Studies on mutation and calculation of fertility in Drosophila melanogaster under the effect of carbaryl.] Angew Parasitol 13:23-28, 1971 (Ger)

63. Elespuru R, Lijinsky W, Setlow JK: Nitrosocarbaryl as a potent mutagen of environmental significance. Nature 247:386-87, 1974

64. Siebert D, Eisenbrand G: Induction of mitotic gene conversion in Saccharomyces cerevisiae by N-nitrosated pesticides. Mutat Res 22:121-26, 1974

65. Uchiyama M, Takeda M, Suzuki T, Yoshikawa K: Mutagenecity of nitroso derivatives of N-methylcarbamate insecticides in microbiological method. Bull Environ Contam Toxicol 14:389-94, 1975

66. Smalley HE, Curtis JM, Earl FL: Teratogenic action of carbaryl in beagle dogs. Toxicol Appl Pharmacol 13:392-403, 1968

67. Coulston F: The Effect of Carbaryl on Reproduction in the Rhesus Monkey. Albany, NY, Albany Medical College, Institute of Experimental Pathology and Toxicology, 1971, 18 pp

68. Wilson JG: Use of rhesus monkeys in teratological studies. Fed Proc 30:104-09, 1971

69. Dougherty WJ, Coulston F: Teratogenic evaluation of carbaryl in the rhesus monkey (Macaca mulatta). Unpublished report submitted to Union Carbide Corp, June 6, 1975

70. Weil CS, Woodside MD, Carpenter CP, Smyth HF Jr: Current status of tests of carbaryl for reproductive and teratogenic effect. Toxicol Appl Pharmacol 21:390-404, 1972

71. Robens JF: Teratologic studies of carbaryl, Diazinon, Norea, Disulfram, and Thiram in small laboratory animals. Toxicol Appl Pharmacol 15:152-63, 1969

72. Weil CS, Woodside MD, Bernard JB, Condra NI, King JM, Carpenter CP: Comparative effect of carbaryl on rat reproduction and guinea pig teratology when fed either in the diet or by stomach intubation. Toxicol Appl Pharmacol 26:621-38, 1973

73. Shtenberg AI, Ozhovan MV: [The effect of low Sevin doses on the reproductive function of animals in a number of generations.] Vopr Pitan 30:42-49, 1971 (Rus)

74. Argauer RJ, Warthen JD Jr: Separation of 1- and 2-naphthols and determination of trace amounts of 2-naphthyl methylcarbamate in carbaryl formulations by high pressure liquid chromatography with confirmation by spectrofluorometry. Anal Chem 47:2472-74, 1975

75. Benson BW, Scott WJ, Beliles RP: Sevin--Safety evaluation by teratological study in the mouse. Unpublished report submitted to Union Carbide Corp, 1967, 19 pp

76. Vashakidze VI: [Some questions on the harmful influence of Sevin on the sexual fuction of experimental animals.] Soobshch Akad Nauk Gruz SSR 39:471-74, 1965 (Rus)

77. Shtenberg AI, Rybakova MN: Effect of carbaryl on the neuroendocrine system of rats. Food Cosmet Toxicol 6:461-67, 1968

78. Collins TFX, Hansen WH, Keeler HV: The effect of carbaryl (Sevin) on reproduction of the rat and the gerbil. Toxicol Appl Pharmacol 19:202-16, 1971

79. Innes JRM, Ulland BM, Valerio MG, Petrucelli L, Fishbein L, Hart ER, Pallotta AJ, Bates RR, Falk HL, Gart JJ, Klein M, Mitchell I, Peters J: Bioassay of pesticides and industrial chemicals for tumorigenicity in mice--A preliminary note. J Nat Cancer Inst 42:1101-14, 1969

80. Andrianova MM, Alekseyev IV: [Carcinogenic properties of the pesticides Sevin, Maneb, Ciram and Cineb.] Vopr Pitan 29:71-74, 1970 (Rus)

81. Shimkin MB, Wieder R, McDonough M, Fishbein L, Swern D: Lung tumor response in strain A mice as a quantitative bioassay of carcinogenic activity of some carbamates and aziridines. Cancer Res 29:2184-90, 1969

82. Walker EM Jr, Gale GR, Atkins LM, Gadsden RH: Some effects of carbaryl on Ehrlich ascites tumor cells in vitro and in vivo. Bull Environ Contam Toxicol 14:441-48, 1975

83. Hwang SW, Schanker LS: Absorption of carbaryl from the lung and small intestine of the rat. Environ Res 7:206-11, 1974

84. Casper HH, Pekas JC, Dinusson WE: Gastric absorption of a pesticide (1-naphthyl N-methylcarbamate) in the fasted rat. Pestic Biochem Physiol 2:391-96, 1973

85. Hurwood IS: Studies on pesticide residues--2. Carbaryl residues in the body tissues and milk of cattle following dermal application. Queens J Agric Anim Sci 24:69-74, 1967

86. Bukin AL, Filatov GV: [Sevin toxicity for mammals and birds.] Veterinariya Moscow 42:93-95, 1965 (Rus)

87. Knaak JB, Sullivan LJ: Metabolism of carbaryl in the dog. J Agric Food Chem 15:1125-26, 1967

88. Comer SW, Staiff DC, Armstrong JF, Wolfe HR: Exposure of workers to carbaryl. Bull Environ Contam Toxicol 13:385-91, 1975

89. Jegier Z: Health hazards in insecticide spraying of crops. Arch Environ Health 8:670-74, 1964

90. Simpson GR: Exposure to orchard pesticides--Dermal and inhalation exposures. Arch Environ Health 10:884-85, 1965

91. Kale SC, Dangwal SK: Hazards during the use of pesticides/insecticides in agricultural farms, in Proceedings of the 1970 Seminar on Pollution and Human Environment, Bombay, India, August 26-27, 1971, pp 192-204

92. American Conference of Governmental Industrial Hygienists, Committee on Industrial Ventilation: Industrial Ventilation--A Manual of Recommended Practice, ed 13. Lansing, Mich, ACGIH, 1974

93. American National Standards Institute Inc: Fundamentals Governing the Design and Operation of Local Exhaust Systems, ANSI Z9.2-1971. New York, ANSI, 1971, 63 pp

94. Popendorf WJ, Spear RC, Selvin S: Collecting foliar pesticide residues related to potential airborne exposure of workers. Environ Sci Technol 9:583-85, 1975

95. Klisenko MA: [Determination of Sevin in air and biological materials.] Zh Anal Khim 20:634-36, 1965 (Rus)

96. I--Choosing a filter system, in Gelman Membrane Filtration Products--New Dimensions, 1975-1976 ed. Ann Arbor, Mich, Gelman Instrument Co, 1975, pp 4-5

97. Carbaryl (Sevin), method No. S273, in Documentation of NIOSH Validation Tests, NIOSH Contract No. CDC-99-74-45. US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 1976, 15 pp

98. Johnson DP: Determination of Sevin insecticide residues in fruits and vegetables. J Assoc Off Anal Chem 47:283-86, 1964

99. Changes in official methods of analysis made at the seventy-seventh annual meeting, October 14, 15, 16, and 17, 1963--24. Metals, other elements, and residues in foods. J Assoc Off Anal Chem 47:190-91, 1964

100. Benson WR, Finocchiaro JM: Rapid procedure for carbaryl residues--Modification of the official colorimetric method. J Assoc Off Anal Chem 48:676-79, 1965

101. Carbaryl (1-naphthyl N-methylcarbamate) (Sevin) (14)--Official final action, in Horwitz W (ed): Official Methods of Analysis of the Association of Official Analytical Chemists, ed 12. Washington, DC, Association of Official Analytical Chemists, 1975, pp 537-38

102. Frei RW, Lawrence JF, Belliveau PE: An in situ fluorimetric method for the determination of Sevin and alpha-naphthol on thin layer chromatograms. Z Anal Chem 254:271-74, 1971

103. Fishbein L, Zielinski WL Jr: Gas chromatography of trimethylsilyl derivatives--I. Pesticidal carbamates and ureas. J Chromatogr 20:9-14, 1965

104. Wheeler L, Strother A: Chromatography of N-methylcarbamates in the gaseous phase. J Chromatogr 45:362-70, 1969

105. Khalifa S, Mumma RO: Gas chromatographic separation of the aglycone metabolites of carbaryl. J Agric Food Chem 20:632-34, 1972

106. Tilden RL, Van Middelem CH: Determination of carbaryl as an amide derivative by electron-capture gas chromatography. J Agric Food Chem 18:154-58, 1970

107. Riva M, Carisano A: Direct gas chromatographic determination of carbaryl. J Chromatogr 42:464-69, 1969

108. Lewis DL, Paris DF: Direct determination of carbaryl by gas-liquid chromatography using electron capture detection. J Agric Food Chem 22:148-49, 1974

109. Duggan RE, Lipscomb GQ, Cox EL, Heatwole RE, Kling RC: Pesticide residue levels in foods in the United States from July 1, 1963 to June 30, 1969. Pestic Monit J 5:73-212, 1971

110. Witter RF: Measurement of blood cholinesterase--A critical account of methods estimating cholinesterase with reference to their usefulness and limitations under different conditions. Arch Environ Health 6:99-125, 1963

111. Cholinesterase Testing Information, pesticide safety information series No. 7. Sacramento, California Dept of Food and Agriculture and California Dept of Health, 1974, 2 pp

112. Fremont-Smith K, Volwiler W, Wood PA: Serum acetylcholinesterase--Its close correlation with serum albumin, and its limited usefulness as a test of liver functions. J Lab Clin Med 40:692-702, 1952

113. Wetstone HJ, LaMotta RV, Middlebrook L, Tennant R, White BV: Studies of cholinesterase activity--IV. Liver function in pregnancy--Values of certain standard liver function tests in normal pregnancy. Am J Obstet Gynecol 76:480-90, 1958

114. White BV, Wetstone H, LaMotta R: Serum cholinesterase activity in malignant neoplasms. Trans Am Clin Climatol Assoc 69:176-81, 1957

115. Vaccarezza JR, Willson JA, Bochi AA: A new test for the presumptive diagnosis of neoplastic disease--Further investigations of cholinesterase in plasma, whole blood and blood cells on cancer of the lung, extrapulmonary tumors and tuberculosis. Dis Chest 49:449-58, 1966

116. Lehmann H, Ryan E: The familial incidence of low pseudocholinesterase level. Lancet 2:124, 1956

117. Kalow W: Familial incidence of low pseudocholinesterase level. Lancet 2:576-77, 1956

118. Kalow W, Genest K: A method for the detection of atypical forms of human serum cholinesterase--Determination of dibucaine numbers. Can J Biochem Physiol 35:339-46, 1957

119. Auditore JV, Hartmann RC: Paroxysmal nocturnal hemoglobinuria--II. Erythrocyte acetycholineesterase defect. Am J Med 27:401-10, 1959

120. Johns RJ: Familial reduction in red-cell cholinesterase. N Engl J Med 267:1344-48, 1962

121. Ammon R: [The enzymatic cleavage of acetylcholine.] Arch Gesamte Physiol 233:486-91, 1933 (Ger)

122. Kalow W, Lindsay HA: A comparison of optical and manometric methods for the assay of human serum cholinesterase. Can J Biochem Physiol 33:568-74, 1955

123. Caraway WT: Photometric determination of serum cholinesterase activity. Am J Clin Pathol 26:945-55, 1956

124. Callaway S, Davies DR, Rutland JP: Blood cholinesterase levels and range of personal variation in a healthy adult population. Br Med J 376:812-16, 1951

125. Winteringham FPW, Disney RW: A radiometric method for estimating blood cholinesterase in the field. Bull WHO 30:119-25, 1964

126. Winter GD: Cholinesterase activity determination in an automated analysis system. Ann NY Acad Sci 87:629-35, 1960

127. Levine JB, Scheidt RA, Nelson VA: An automated micro determination of serum cholinesterase. Ardsley, NY, Technicon Instruments Corp, 1966, pp 582-85

128. Gerarde HW, Hutchison EB, Locher KA, Golz HH: An ultramicro screening method for the determination of blood cholinesterase. J Occup Med 7:303-13, 1965

129. Davies DR, Nicholls JD: A field test for the assay of human whole-blood cholinesterase. Br Med J 390:1373-75, 1955

130. Fleisher JH, Woodson GS, Simet L: A visual method for estimating blood cholinesterase activity. Arch Ind Health 1:510-20, 1956

131. Edson EF, Fenwick ML: Measurement of cholinesterase activity of whole blood. Br Med J 1:1218, 1955

132. Witter RF, Grubbs LM, Farrior WL: A simplified version of the Michel method for plasma or red cell cholinesterase. Clin Chim Acta 13:76-78, 1966

133. Winteringham FPW, Disney RW: A simple method for estimating blood cholinesterase. Lab Pract 13:739-40, 745, 1964

134. Potter LT: A radiometric microassay of acetylcholinesterase. J Pharmacol Exp Ther 156:500-06, 1967

135. Jensen-Holm J, Lausen HH, Milthers K, Moller KO: Determination of the cholinesterase activity in blood and organs by automatic titration--With some observations on serious errors of the method and remarks of the photometric determination. Acta Pharmacol Toxicol 15:384-94, 1959

136. Nabb DP, Whitfield F: Determination of cholinesterase by an automated pH stat method. Arch Environ Health 15:147-54, 1967

137. Hall GE, Lucas CC: Choline-esterase activity of normal and pathological human sera. J Pharmacol Exp Ther 59:34-42, 1937

138. Crane CR, Sanders DC, Abbott JK: A Comparison of Serum Cholinesterase Methods: II, FAA-AM-72-12. US Dept of Transportation, Federal Aviation Administration, Office of Aviation Medicine, 1972, pp 1-6

139. De la Huerga J, Yesinick C, Popper H: Colorimetric method for the determination of serum cholinesterase. Am J Clin Pathol 22:1126-33, 1952

140. Wetstone HJ, LaMotta RV: The clinical stability of serum cholinesterase activity. Clin Chem 11:653-63, 1965

141. Meyer A, Wilbrandt W: [On the determination of the activity of the cholinesterase in human blood.] Helv Physiol Pharmacol Acta 12:206-16, 1954 (Ger)

142. Garry PJ, Routh JI: A micro method for serum cholinesterase. Clin Chem 11:91-96, 1965

143. Ellman GL, Courtney KD, Andres V Jr, Featherstone RM: A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem Pharmacol 7:88-95, 1961

144. Cranmer MF, Peoples A: A sensitive gas chromatographic method for human cholinesterase determination. J Chromatogr 57:365-71, 1971

145. Baum G: Determination of acetylcholinesterase by an organic substrate selective electrode. Anal Biochem 39:65-72, 1971

146. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for 1964. Cincinnati, ACGIH, 1964, p 15

147. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for 1966. Cincinnati, ACGIH, 1966, p 7

148. American Conference of Governmental Industrial Hygienists: TLVs--Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1974. Cincinnati, ACGIH, 1975, p 13

149. American Conference of Governmental Industrial Hygienists, Committee on Threshold Limit Values: Documentation of the Threshold Limit Values for Substances in Workroom Air, ed 3. Cincinnati, ACGIH, 1971, pp 37-38

150. Committee for the Study of Substances Harmful to Health: Maximum Workplace Concentrations, communication No. XI. Berlin, Federal Republic of Germany, German Research Association, 1975

151. Winell M: An international comparison of hygienic standards for chemicals in the work environment. Ambio 4:34-35, 1975

152. Wolfe HR: Protection of individuals who mix or apply pesticides in the field, in Proceedings of the National Conference on Protective Clothing and Safety Equipment for Pesticide Workers. Atlanta, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, 1972, pp 35-39

153. Wolfe HR, Durham WF, Armstrong JF: Exposure of workers to pesticides. Arch Environ Health 14:622-33, 1967

154. Ware GW, Morgan DP, Estesen BJ, Cahill WP, Whitacre DM: Establishment of reentry intervals for organophosphate-treated cotton fields based on human data--I. Ethyl- and methyl parathion. Arch Environ Contam Toxicol 1:48-59, 1973

155. Johnson DP, Stansbury HA: Adaptation of Sevin insecticide (carbaryl) residue method to various crops. J Agric Food Chem 13:235-38, 1965

156. Bailey JB, Swift JE: Pesticide Information and Safety Manual. Berkeley, Calif, University of California Cooperative Extension, 1968, 147 pp

157. Interpreting the Safety Procedures on the Pesticide Label, pesticide safety information series No. 1. Sacramento, California Dept of Food and Agriculture, Agricultural Chemicals and Feed, 1974, 4 pp

158. Shriver D: Respirators and other protective devices, in Pesticide Information Manual. College Park, University of Maryland, Cooperative Extension Service, 1972, pp C-29 to C-30

159. Environmental Health and Toxicology--Sevin 99% Concentrate--C12H11NO2, material information bulletin No. 565-1975. San Francisco, Chevron Environmental Health Center, 1975, 4 pp

160. Upholt WM, Quinby GE, Batchelor GS, Thompson JP: Visual effects accompanying TEPP-induced miosis. Arch Ophthalmol 56:128-34, 1956

161. Working Group on Pesticides: Summary of interim guidelines for disposal of surplus or waste pesticides and pesticide containers, in Pesticide Information Manual. College Park, University of Maryland, Cooperative Extension Service, 1972, pp I-5 to I-14

162. Safe Disposal of Empty Pesticide Containers, technical release No. 23-65. Elizabeth, NJ, National Pest Control Assoc, 1965, 8 pp

IX. APPENDIX I

AIR SAMPLING METHOD

The sampling method for airborne carbaryl presented in Appendix I is adapted from a validated NIOSH method. [97]

General Requirements

To evaluate conformance with the standard, collect breathing-zone samples representative of the individual worker's exposure. Record the following on all sampling data sheets:

(a) The date and time of sample collection.

(b) Sampling duration.

(c) Volumetric flowrate of sampling.

(d) Worker's name and job title and description of work station.

(e) Temperature and atmospheric pressure.

(f) Other pertinent information.

Air Sampling

(a) Collect breathing-zone samples as close as practicable to the employee's face, without interfering with the employee's freedom of movement, to characterize the exposure from each job or specific operation dealing with manufacture, formulation, or application of carbaryl.

Collect eight 1-hour breathing-zone samples representative of worker exposure in each operation. Sampling flowrates should be checked frequently. When filters become clogged so that airflow is too restricted, change the filters and initiate the collection of new samples.

(b) Collect samples using a portable sampling pump whose flow can be determined to an accuracy of ± 5% at 1.5 liters/minute. Connect the pump to the filter unit, which consists of a glass-fiber filter (Type A, 37 mm in diameter) mounted in a polystyrene 37-mm, two-piece cassette holder and supported by a backup pad. Use only membrane filters which are free of organic binders. Do not use Tenite filter holders.

(c) Operate the sampler at a known flowrate of 1.5 liters/minute, and record the total sampling time. A sample size of 90 liters is recommended.

(d) Remove the glass-fiber filter from the cassette filter holder within 1 hour of sampling and place it in a clean screwcap bottle. Handle the filter only with clean tweezers. The bottle caps should be lined with Teflon for proper seal. These bottles (a 45-mm tissue-sample holder is satisfactory for shipping) are also used to contain the solution during analysis.

(e) With each batch of 10 samples, submit 1 filter from the same lot used for sample collection, subjecting it to exactly the same handling as the samples except that no air is drawn through it. Label this as a blank.

(f) Take the screwcap bottles which contain the samples and ship them in suitable containers designed to prevent damage while in transit.

Calibration of Sampling Trains

The accurate calibration of a sampling pump is essential for the correct interpretation of the volume indicated. The frequency of calibration is dependent on the use, care, and handling to which the pump is subjected. In addition, pumps should be recalibrated if they have been subjected to misuse or if they have just been repaired or received from a manufacturer. If the pump receives hard usage, more frequent calibration may be necessary. Regardless of use, maintenance and calibration should be performed on a regular schedule and records of these kept.

Ordinarily, pumps should be calibrated in the laboratory both before they are used in the field and after they have been used to collect a large number of field samples. The accuracy of calibration is dependent on the type of instrument used as a reference. The choice of calibration instrument will depend largely upon where the calibration is to be performed. For laboratory testing, a 1- or 2-liter buret or wet-test meter is recommended, although other standard calibrating instruments, such as spirometer, Marriott's bottle, or dry-gas meter, can be used.

Instructions for calibration with the soapbubble meter follow. If another calibration device is selected, equivalent procedures should be used. The calibration setup for personal sampling pumps with a glass-fiber membrane filter is shown in Figure XIII-1. Since the flowrate given by a pump is dependent on the pressure drop of the sampling device, in this case a membrane filter, the pump must be calibrated while operating with a representative filter and backup pad in line.

(a) While the pump is running, check the voltage of the pump battery with a voltmeter to assure adequate voltage for calibration.

Charge the battery if necessary.

(b) Place the glass-fiber membrane filter with backup pad in the filter cassette.

(c) Assemble the sampling train as shown in Figure XIII-1.

(d) Turn the pump on and moisten the inside of the soapbubble meter by immersing the buret in the soap solution and drawing bubbles up the inside until they are able to travel the entire buret length without bursting.

(e) Adjust the pump rotameter to provide a flowrate of 1.5 liters/minute.

(f) Start a soapbubble up the buret and measure with a stopwatch the time it takes the bubble to pass through a minimum of 1.0 liter.

(g) Repeat the procedure in (f) above at least three times, average the results, and calculate the flowrate by dividing the volume between the preselected marks by the time required for the soapbubble to traverse the distance.

(h) Record the following calibration data: volume measured, elapsed time, air temperature, atmospheric pressure, serial number of the pump, date, and name of the person performing the calibration.

(i) Corrections to the flowrate may be necessary if the atmospheric pressure or temperature at the time of sample collection differs significantly from those conditions under which calibration was performed. Corrected flowrates may be calibrated using the following formula:

$$q\ (\text{sampling}) = q\ (\text{indicated}) \times \sqrt{\frac{P\ (\text{sampling})}{P\ (\text{calibration})} \times \frac{T\ (\text{calibration})}{T\ (\text{sampling})}}$$

where:

q = volumetric flow rate (liters/minute)
P = atmospheric pressure (torr or pounds/square inch)
T = temperature (degrees Kelvin or Rankine)

X. APPENDIX II

ANALYTICAL METHOD FOR CARBARYL

The analytical method for carbaryl presented in Appendix II is a validated NIOSH method. [97]

Principle of the Method

A known volume of air is drawn through a glass-fiber membrane filter to trap the carbaryl particles present. Alcoholic potassium hydroxide is used to extract and hydrolyze the carbaryl trapped in the filter. An aliquot is then reacted with p-nitrobenzenediazonium fluoroborate to form a colored complex. The amount of complex formed is determined with a spectrophotometer to give a quantitative measurement of carbaryl. [97]

Range and Sensitivity

This method has been validated over the range of 1.96-13.43 mg/cu m, at 24 C and 763 mmHg. The probable range of the method is 0.1-18 mg/cu m, based on the range of standards used to prepare the standard curve. For samples of higher concentration where the absorbance is greater than the limits of the standard curve, the samples may be diluted with methanolic potassium hydroxide (prior to removal of an aliquot to use for color development) to extend the upper limit of the range. A concentration of 0.5 mg/cu m of carbaryl in a 90-liter air sample gives a 0.05 absorbance in a 1-cm cell.

Interferences

The presence of any background 1-naphthol will exaggerate the analytical reading. Other substances such as phenols and aromatic amines which form derivatives with p-nitrobenzenediazonium fluoroborate or those which have significant absorbance around 475 nm will interfere if present in the air sample.

Precision and Accuracy

The coefficient of variation (Cv) for the total analytical and sampling method in the range of 1.96-13.43 mg/cu m was 0.057. This value corresponds to a 0.28 mg/cu m standard deviation at the recommended environmental limit of 5 mg/cu m.

A collection efficiency of 1.00 was determined for the collection medium. Thus, no correction for collection efficiency is necessary, and it is assumed that no bias is introduced in the sample collection step. There is also no apparent bias in the sampling and analytical method. Thus, Cv is a satisfactory measure of both accuracy and precision of the sampling and analytical method.

Apparatus

(a) 25-ml volumetric flasks.

(b) Screwcap bottles (45-mm tissue-sample holders with Teflon-lined caps).

(c) Assorted micropipets to deliver between 3 and 35 microliters.

(d) 10-ml glass syringe attached to a stainless steel Luer-Lok fitted filter folder for 13-mm Teflon filters.

(e) 10- and 25-ml glass-stoppered graduated cylinders.

(f) Mechanical wrist-action shaker.

(g) Spectrophotometer cell with 1-cm path length.

(h) Spectrophotometer.

Reagents

(a) Carbaryl, analytical grade.

(b) Potassium hydroxide, 0.1 M in absolute methanol.

(c) p-Nitrobenzenediazonium fluoroborate: Dissolve 25 mg in 5 ml of absolute methanol. Add 20 ml of glacial acetic acid to this solution. Prepare fresh daily.

(d) Glacial acetic acid.

(e) Carbaryl Standard Solution: Dissolve 460 mg of carbaryl in 10 ml of methylene chloride.

Analysis of Samples

(a) Analyze each filter separately.

(b) Add 20 ml of 0.1 M methanolic potassium hydroxide to the screwcap bottle containing the filter.

(c) Place the bottle on a mechanical wrist-action shaker for 5 minutes.

(d) Transfer 2 ml of the solution to a clean screwcap bottle.

(e) Add 17 ml of glacial acetic acid and immediately cover the bottle with a Teflon-lined screwcap. Mix by swirling.

(f) Add 1 ml of p-nitrobenzenediazonium fluoroborate solution. The color will develop in 3-5 minutes. The sample should be analyzed within 20 minutes.

(g) The solution will contain glass fibers from the filter. Use the 10-ml syringe fitted with a filter holder containing a Teflon filter to transfer the solution from the bottle to the 1-cm cell. The solution is poured into the barrel of the syringe and forced through the filter into the cell by moving the plunger down the barrel.

(h) Adjust the baseline of the spectrophotometer to zero with distilled water in both cells.

(i) Read the absorbance of the sample at 475 nm against a blank prepared in the same fashion as the samples.

Calibration and Standards

(a) Pipet 20 ml of 0.1 M methanolic potassium hydroxide into each of six 25-ml volumetric flasks.

(b) Carefully pipet 3, 8, 15, 25, and 35 microliters of the standard solution into the flasks. Process one flask as a blank.

(c) After 5 minutes, pipet 2 ml of each solution into a clean 25-ml volumetric flask.

(d) Add 17 ml of glacial acetic acid and mix.

(e) Add 1 ml of p-nitrobenzenediazonium fluoroborate solution and mix.

(f) Allow the solution to react for 20 minutes.

(g) Adjust the baseline of the spectrophotometer to zero by reading distilled water in both cells.

(h) With the wavelength set at 475 nm, read the absorbance of the sample against the absorbance of the blank.

(i) Construct a calibration curve by plotting absorbance against micrograms of carbaryl in the standard.

Calculations

(a) Determine from the calibration curve the micrograms of carbaryl present in each sample.

(b) The concentration of carbaryl in the air sampled can be expressed in mg/cu m (mg/cu m = μg/liter):

$$\text{Carbaryl, mg/cu m} = \frac{\mu\text{g in sample}}{\text{air volume sampled (liters)}}$$

XI. APPENDIX III

SUGGESTED MEDICAL MANAGEMENT OF SYMPTOMATIC CARBARYL INTOXICATION

Carbaryl intoxication can generally be treated successfully with measures directed toward alleviation of symptoms.

If more aggressive treatment should be considered necessary, atropine sulfate can be administered. Pralidoxime chloride (PAM) and other oximes should not be used in carbaryl poisoning. In his Clinical Handbook on Economic Poisons, [21] Hayes pointed out that, depending on the severity of the case, all methods used for treating organophosphorus compounds may be useful in the management of carbaryl intoxication, with the specific exception of pralidoxime (PAM) which should not be used.

XII. APPENDIX IV

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, An Identification System for Occupationally Hazardous Materials. The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or

competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, eg, "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute Inc. Flashpoint, shock sensitivity

or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 degrees Fahrenheit (21.1 degrees Celsius); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a TWA concentration, as a permissible exposure, or by some other indication of an acceptable standard. Other data are acceptable, such as lowest LD50 if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments might be:

> Skin Contact--single short contact, no adverse effects likely; prolonged or repeated contact, possibly mild irritation.
>
> Eye Contact--some pain and mild transient irritation; no corneal scarring.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first-aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed employees.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances, such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect employees assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill" or "incineration." Warnings such as "comply with local, state, and federal antipollution ordinances" are proper but not sufficient. Specific procedures shall be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be specified as to type and NIOSH or US Bureau of Mines approval class, ie, "Supplied air," "Organic vapor canister," etc. Protective equipment must be specified as to type and materials of construction.

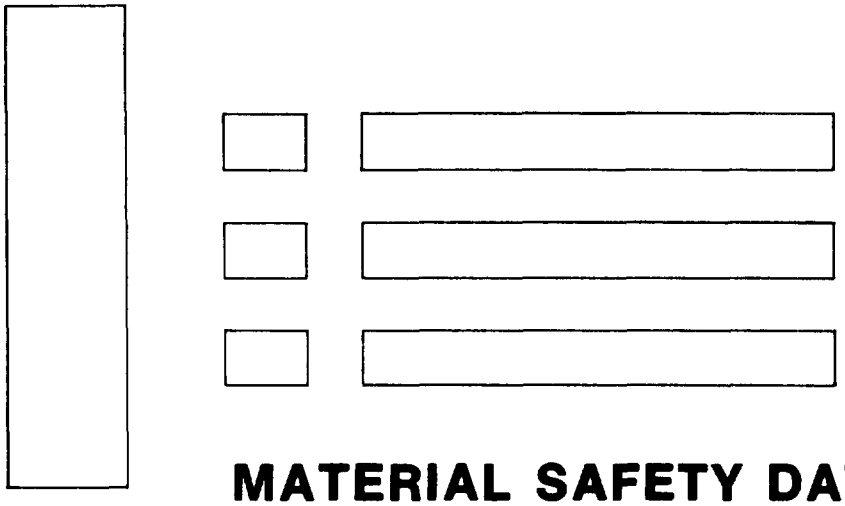
(i) Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to employees exposed to the hazardous material. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.



MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION	
MANUFACTURER'S NAME	REGULAR TELEPHONE NO. EMERGENCY TELEPHONE NO.
ADDRESS	
TRADE NAME	
SYNONYMS	

II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA			
BOILING POINT, 760 MM HG		MELTING POINT	
SPECIFIC GRAVITY (H_2O=1)		VAPOR PRESSURE	
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H_2O, % BY WT	
% VOLATILES BY VOL		EVAPORATION RATE (BUTYL ACETATE=1)	
APPEARANCE AND ODOR			

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	
FLAMMABLE LIMITS IN AIR, % BY VOL.	LOWER		UPPER
EXTINGUISHING MEDIA			
SPECIAL FIRE FIGHTING PROCEDURES			
UNUSUAL FIRE AND EXPLOSION HAZARD			

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN

INHALATION:

INGESTION

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY STATEMENTS

OTHER HANDLING AND STORAGE REQUIREMENTS

PREPARED BY _____

ADDRESS: _____

DATE _____

XIII. TABLES AND FIGURE

TABLE XIII-1

PHYSICAL PROPERTIES OF CARBARYL

Appearance	White, crystalline solid
Empirical formula	C12H1102N
Formula weight	201.22
Flashpoint, open cup (Cleveland)	193 C
Melting point	142 C
Specific gravity	1.232 at 20 C
Vapor pressure	0.000041 mmHg at 25 C, 0.00015 mmHg at 40 C
Explosibility (minimum concentration of technical grade dust)	0.02 oz/cu ft (20.3 g/cu m)
Solubility in water	40 ppm at 30 C
Solubility in organic solvents	Moderately soluble in acetone, N,N-dimethyl formamide, isophorone and cyclohexanone
Stability	Stable to light, heat, and acids; hydrolyzed in alkalies

Adapted from Kirk-Othmer, [11] Merck Index, [12] Union Carbide Corporation, [13 (sec 16)] and HH Moorefield (written communication, February 1976)

TABLE XIII-2

SYNONYMS AND TRADE NAMES FOR CARBARYL

Atoxan
Caprolin
Carpolin
Compound 7744
Crag Sevin
Experimental insecticide 7744
Gamonil
N-methyl-alpha-naphthylcarbamate
N-methyl-alpha-naphthylurethan
N-methyl-1-napthyl carbamate
1-Naphthol N-methylcarbamate
Alpha-naftyl-N-methylkarbamat (Czech)
Alpha-naphthyl N-methylcarbamate
1-Naphthyl N-methylcarbamate
Panam
Sevidol
Sevin
Union Carbide 7,744

Compiled from the Registry of Toxic Effects of Chemical Substances, 1975 edition [14]

TABLE XIII-3

CONCENTRATIONS (MG/KG) OF CARBARYL
IN RABBIT TISSUES AND EXCRETORY FLUIDS AFTER
SINGLE ORAL DOSES OF 400 MG/KG OF CARBARYL

Sample	Hours after Administration						
	0.5	1	2.5	4	18	24	48
Brain	0.0075	0	0.03	0.054	0	0.215	0.03
Medulla oblongata	0.015	-	0.03	0.09	-	-	0
Cerebellum	0.021	-	0.03	-	-	-	0
Kidneys	0.03	0.75	0.75	0.18	1.125	0	0
Spleen	0.075	0.075	-	0.036	0	0	0
Liver	0.225	0.975	0.15	0.036	0.15	0	0.075
Heart	0.3	0	0.03	0.018	0	0	0
Lungs	0.003	0	0	0.015	0	0	0
Lumbar muscles	0.03	0.03	0	0.012	0	0	0
Femoral muscles	0.03	0	0	0	0	0	0
Bile	3.75	0.075	4.5	0.18	1.5	1.5	1.5
Urine	1.5	1.125	11.25	1.8	0	0.75	0
Testes	0.075	0	0	0.09	-	0	0
Kidney fat	1.25	-	0.6	0.036	-	0	0.03

Adapted from Bukin and Filatov [86]

TABLE XIII-4

CARBARYL METABOLITES FROM MAMMALIAN* URINE

Metabolites	Labeled Forms of Carbaryl**			Unlabeled Carbaryl***
	14C-Naphthyl	14C-Methyl	14C-Carbonyl	
Unidentified neutrals	R G M P S D	R G M P S D	R	R Ho Hi
1-Naphthyl methylcarbamate N-glucuronide	G	G		R
Unidentified metabolite (A)	R G D	R G M D	R	R Ho
1-Naphthyl methylimido-carbonate-o-glucuronide	R G M P S D	R G M P S D	R	R Ho
Unidentified metabolite (B)	G D	G D		
4-(Methylcarbamoyloxy)-1-naphthyl glucuronide	R G M P S	R G M P S	R	R Ho
1-Naphthyl glucuronide	R G P S			R Ho Hi
4-(Methylcarbamoyloxy)-1-naphthyl sulfate	R G M S	R G M S	R	R
1-Naphthyl sulfate	R G M S			R Ho Hi
Unidentified metabolite (C)		S		
Unidentified metabolite (D)	S	S		

*Rat (R), guinea pig (G), monkey (M), swine (P), sheep (S), dog (D), and human (H)
**Analysis by radiometric techniques; rats and guinea pigs treated ip, all others orally
***Analysis by fluorometric techniques; rats treated orally, humans orally (o) and by inhalation (i)

\dapted from Knaak et al [33,34] and Knaak and Sullivan [87]

TABLE XIII-5

EFFECTS OF CARBARYL EXPOSURE ON HUMANS

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	Reference
Respiratory and possibly dermal	59 workers	0.03 - 40 mg/cu m 16 mo (hourly exposure not stated) 8 mo (hourly exposure not stated)	Whole blood ChE* activities inhibited but within normal range; urinary 1-naphthol 1,000 μg/100 ml** or higher in 41% of samples (conc low on Mon, rising during workweek, in substudy of 7 workers)	28
"	Agricultural workers (number unknown)	2 - 4 mg/cu m 4 - 6 hr/d, 3 - 4 d	Whole blood ChE activities inhibited 11-30%; other clinical tests negative	39
"	10 sprayers	Insecticide (unknown conc) single application	Rash in 1 splashed worker; plasma ChE slightly inhibited on d 1, normal on d 5 after application in all 10	35
"	95 exposed villagers	Insecticide (unknown conc) 1 wk	Plasma ChE activity still inhibited 1 wk after spraying	35
"	1 man (with respirator)	40.6 - 49.3 mg/cu m for 2 d	Urinary 1-naphthol 2,340 and 8,975 μg/100 ml	13 (sec 9, 10)
"	1 man (no respirator)	45.2 - 50.9 mg/cu m for 2 d	Urinary 1-naphthol 2,340 and 3,619 μg/100 ml	13 (sec 9, 10)
"	1 man	Carbaryl-sulfur mixture (unknown conc and duration)	Weakness, dizziness, shortness of breath on day of exposure and 2 d later	38

TABLE XIII-5 (CONTINUED)

EFFECTS OF CARBARYL EXPOSURE ON HUMANS

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	Reference
Respiratory and possibly dermal	14 exposed male workers	Dust (unknown conc) 8 - 16 hr	Urinary 1-naphthol 2,443 µg/100 ml for 7 asymptomatic workers; 1,417 for 7 symptomatic workers, all with dizziness, nausea, 1 with headache, 1 with overheating, perspiration	13 (sec 7)
"	Workers (number unknown)	Dust (unknown conc)	Urinary 1-naphthyl glucuronide and 1-naphthyl sulfate higher during exposure than 72 hr after exposure	34
Dermal	6 men	4 µg/sq cm 14C-carbaryl in acetone to forearm	Recovery in urine, 73.9% of dose over 5 d	30
"	6 men	4 µg/sq cm 14C-carbaryl in acetone to angle of jaw	Recovery in urine, 70% of dose over 5 d	31
Oral	2 men	2 mg/kg	Recovery in urine, 26-27% of dose in 24 hr as metabolites, 1-naphthyl sulfate, 1-naphthyl glucuronide, 4-(methylcarbamoyloxy) -1 naphthyl glucuronide	33 32
"	2 men 2 men 2 men	0.5 mg/kg 1.0 mg/kg 2.0 mg/kg (single doses)	No change in plasma or whole blood ChE; no toxic symptoms	32

TABLE XIII-5 (CONTINUED)

EFFECTS OF CARBARYL EXPOSURE ON HUMANS

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	Reference
Oral	5 men	0.06 mg/kg/d 6 wk	Urinary rise of aa/cr***	32
"	5 men	0.12 mg/kg/d 6 wk	Urinary rise of aa/cr***	32
"	1 man	2.8 mg/kg (form unstated)	Epigastric pain, sweating; recovery in 2 hr with atropine therapy	21
"	1 child (19 mo old)	Solution (unknown conc)	Miosis, salivation, incoordination; recovery in 12 hr with atropine therapy	28
"	1 man	Solution (unknown conc; ate watermelon sprayed with 80% carbaryl)	Nausea, vomiting hyperreflexia, pallor, intestinal colic, nasal discharge; recovery in 18 hr with deoxycorticosterone	41
"	1 man	80% solution (several ml)	Nausea, salivation, headache, tremors, lacrimation; recovery in 1.5 hr with deoxycorticosterone	41
"	1 man	80% solution 0.5 liter	Whole blood ChE strongly inhibited; death in 6 hr; carbaryl present in gastrointestinal tract, blood, liver, kidneys, and urine	40

*Cholinesterase
**Normal range, 150-400 μg/100 ml urine
***Amino acid nitrogen to creatinine ratio

TABLE XIII-6

EFFECTS OF CARBARYL EXPOSURE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration*	Effects	Reference
Respiratory	Guinea pigs	6	390 mg/cu m (dust) 4 hr	Nasal and eye irritation; hemorrhagic areas in lungs	27
"	"	6	230 mg/cu m (dust) 4 hr	Slight initial weight loss; recovery by d 14	27
"	Rats	-	10 mg/cu m (dust) 7 hr/d 5 d/wk for 90 d	No effects	27
"	Dogs	-	75 mg/cu m (dust) (duration unknown)	Typical signs of ChE** inhibition within 5 hr	27
"	Cats	4	82 mg/cu m (dust) 6 hr	Signs of toxicity observed; ChE inhibited, normal after 72 hr	39
"	"	4	37 mg/cu m (dust) 6 hr	ChE inhibited, normal after 48 hr	39
"	"	4	20 mg/cu m (dust) 6 hr	ChE inhibited, normal after 24 hr	39
"	"	4	63 mg/cu m (dust) 6 hr/d for 1 mo	Salivation; ChE inhibited 31-40% (serum), 41-58% (erythrocyte); 1 death at d 20	39
"	"	4	40 mg/cu m (dust) 6 hr/d for 2 mo	Up to 50% erythrocyte ChE inhibition; deterioration of conditioned reflexes (undefined)	39
"	"	4	16 mg/cu m (dust) 6 hr/d for 4 mo	No effects	39

TABLE XIII-6 (CONTINUED)

EFFECTS OF CARBARYL EXPOSURE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration*	Effects	Reference
Ocular	Rabbits	5	0.5 ml of 10% suspension applied to 1 eye of each animal	Mild irritation in 1 eye after 24 hr	27
"	"	5	50 mg dust	Traces of corneal necrosis	27
"	"	5	25% suspension in water	No injury	27
"	"	-	10% suspension in water, or 50 mg powder	Transient miosis, hyperemia	39
Dermal	"	5	0.01 ml of 10% soln in acetone	No irritation	27
"	"	6	500 mg/kg (form unspecified)	Inhibition of serum and erythrocyte ChE in 1st 24 hr	39
"	Rats	10 M 10 F	Various doses in xylene	LD50 greater than 4,000 mg/kg in both sexes	49
Intracutaneous	Guinea pigs	16	0.1 ml (0.1% in propylene glycol) 8 alternate days (3 wk after last dose, another challenge dose injected)	Weak sensitization in 4 animals	27
Subcutaneous	Rats	5-9 per group	10 mg/kg/wk 2 - 5 wk	Behavioral changes; decreased motivation and response to electroshock	57

TABLE XIII-6 (CONTINUED)

EFFECTS OF CARBARYL EXPOSURE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration*	Effects	Reference
Subcutaneous	Mice	60 M	10 mg/mouse/wk in 0.25% agar 5 mo	No increases in tumors, infections, or mortality compared to control animals	27
"	Chickens	13	0.25 - 3 g/kg (suspended in lard)	Leg weakness observed at 2 g/kg; no effects at doses of 1 g/kg or less	27
"	Chickens (atropinized)	-	0.8 - 1.6 g/kg	Leg weakness; recovery by d 24	43
ip	Rats	-	0.56 mg/kg and 2.24 mg/kg	Decreased physical activity; reversed with atropine therapy	58
iv	Dogs	6	10 and 15 mg/kg in ethyl alcohol	No change in erythrocyte or plasma ChE activity	27
"	"	5	30 mg/kg	Lacrimation, salivation, tremors	55
"	Miniature pigs	8 M	20 mg/kg	Tremors, ataxia, incoordination, paraplegia	55
Oral	Guinea pigs (pregnant)	26 F	300 mg/kg/d in gelatin capsule d 11 - 20 of gestation	Maternal mortality 38%; fetal mortality 17.5% in survivors' litters (9.5% in controls); 11 terata in fetuses of treated	71

TABLE XIII-6 (CONTINUED)

EFFECTS OF CARBARYL EXPOSURE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration*	Effects	Reference
Oral	Guinea pigs (pregnant)	40 F	300 mg/kg in capsule single dose d 11 - 20 of gestation	Maternal mortality 12.5%; fetal mortality 6.5% (controls 9.5%); 9 malformed fetuses in litters of treated	71
"	"	150 F	100, 200, 300 mg/kg in diet 1- to 15-d intervals during d 10 - 24 of gestation	Weight gains less than controls; no significant increase in terata compared to controls	72
"	"	150 F	50, 100, 200 mg/kg by intubation 1- to 15-d intervals during d 10 - 24 of gestation	Increased fetal anomalies at 50 mg/kg only (15.7% vs 9.1% in controls)	72
"	Rabbits (pregnant)	17 F	50, 100, 200 mg/kg in capsules on d 5 - 15 of gestation	No terata or dose-related mortality compared to controls	71
"	Rats (pregnant)	18 F	500 mg/kg/d in diet during various intervals of gestation or until weaning of pups	Weight gain of offspring reduced; 2/3 mortality of pups within 4 d after birth	70
"	"	36 F	20 and 100 mg/kg/d in diet during various intervals of gestation or until weaning of pups	No effect on viability of pups compared to controls	70

TABLE XIII-6 (CONTINUED)

EFFECTS OF CARBARYL EXPOSURE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration*	Effects	Reference
Oral	Rats	- F	610 mg/kg (gavage)	LD50	27
"	"	-	510 mg/kg (gavage)	LD50	27
"	"	- M	850 mg/kg (gavage)	LD50	43
"	"	- M	600 mg/kg (gavage)	Lowest lethal dose	43
"	"	- F	500 mg/kg (gavage)	LD50	43
"	"	- F	100 mg/kg (gavage)	Lowest lethal dose	43
"	"	10 M,F	2,250 ppm in diet 96 d	Cloudy swelling of kidney tubules in 4	27
"	"	20 F	400 ppm in diet 2 yr	Cloudy swelling of hepatic cords; cloudy swelling of kidney tubules present after 1 yr; incidence not significant compared to controls after 2 yr	27
"	"	60 F 80 M	50, 100, 200 ppm in diet, 2 yr	Effects seen similar to controls	27
"	"	48 M 48 F	14 and 70 mg/kg/d 12 mo	Increased gonadotropic hormone, adrenal cortex activity; growth inhibition; blood ChE inhibited after 3 mo; testicular changes; estrus cycle prolonged	77

TABLE XIII-6 (CONTINUED)

EFFECTS OF CARBARYL EXPOSURE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration*	Effects	Reference
Oral	Rats	24 M 24 F	7 mg/kg/d 12 mo	Increased gonadotropic hormone, adrenal cortex activity	77
"	Mice	20 M	50 - 1,000 mg/kg/d 5 d (gavage)	Death in 1 of 10 at 1,000 mg/kg; no evidence for dominant lethal mutagenicity after mating	59
"	Rats	60 (F0)	2,000, 5,000, 10,000 ppm in diet 3 generations	Weight below controls for all treated weanlings; average litter size and survival of offspring decreased at 5,000- and 10,000-ppm levels	78
"	"	16 (F0)	200 mg/kg/d in diet 3 generations	Initial decrease in weight gain in F0; lengthened gestation period in F1 and F2 compared to controls	72
"	"	48 (F0)	7, 25, 100 mg/kg/d in diet 3 generations	No effects compared to controls in all generations	72
"	"	16 (F0)	100 mg/kg/d by gavage 3 generations	Increased fetal mortality; sporadic adverse effects on litter size, adult survival time, fetal resorption in all generations	72
"	"	32 (F0)	3, 7, 25 mg/kg/d by gavage 3 generations	No effects compared to controls in all generations	72

TABLE XIII-6 (CONTINUED)

EFFECTS OF CARBARYL EXPOSURE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration*	Effects	Reference
Oral	Rats	- F	2 and 5 mg/kg/d in sunflower oil 4 generations (F2 to F5) 6 mo each	Fertility decreasing progressively, dose-related (F2 to F4); reduced estrus time in F3 and F4	73
"	"	- M	2 and 5 mg/kg/d in sunflower oil 3 generations (F2 to F4) 6 mo each	Sperm motility, spermatogenesis, duration of sperm survival reduced compared to controls	73
"	Gerbils	108 (F0)	2,000 - 10,000 ppm in diet 3 generations	Decreased fertility, litter size, pup viability in all generations; at and above 4,000 ppm, weanling weights less than controls	78
"	Hamsters (pregnant)	6 F	250 mg/kg/d (gavage) d 7 - 8 of gestation	Signs of ChE inhibition; salivation, diarrhea, incoordination; 2 deaths; fetal mortality 30.3% (control 5.5%), no teratologic defects in fetuses	71
"	"	8 F	125 mg/kg/d (gavage) d 6 - 8 of gestation	Fetal mortality 10% (control 5.5%), no teratologic defects in fetuses	71

TABLE XIII-6 (CONTINUED)

EFFECTS OF CARBARYL EXPOSURE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration*	Effects	Reference
Oral	Mice (pregnant)	20 F	30 mg/kg/d in diet from d 6 of gestation to delivery	Minor abnormalities in 9 fetuses (controls, 2)	75
"	"	20 F	10 mg/kg/d in diet from d 6 of gestation to delivery	No effects compared to controls	75
"	"	36 M 36 F	4.64 mg/kg/d 18 mo (from d 7 of age)	No significant increase in tumors compared to controls	79
"	Dogs (pregnant)	55 F	3.125 - 50 mg/kg/d (diet) throughout gestation	Dystocia in 1/3 of dams, none in controls; 11.6% terata at doses of 6.25 mg/kg or more	66
"	Rhesus monkeys	10 F	20.0 mg/kg/d by gavage throughout gestation	Abortions 3 in 6 pregnancies (1 abortion in 5 pregnancies for 7 controls)	67
"	"	4 F	2.0 mg/kg/d by gavage throughout gestation	Abortions 2 in 2 pregnancies	67
"	"	16	20 mg/kg/d in capsules d 20 - 38 of gestation	Abortions 3 in 15 pregnancies, no terata	69
"	"	16	2 mg/kg/d in capsules d 20 - 38 of gestation	Abortions 1 in 16 pregnancies, no terata	69

TABLE XIII-6 (CONTINUED)

EFFECTS OF CARBARYL EXPOSURE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration*	Effects	Reference
Oral	Rhesus monkeys	16	0.2 mg/kg/d in capsules d 20 - 38 of gestation	Abortions 2 in 16 pregnancies, no terata (4 abortions, 1 stillborn in 31 pregnancies for 31 controls; no terata)	69
"	Pigs	1 M 1 F	150 mg/kg/d in diet until death	First signs of toxicity at d 45 and 62; ataxia, incoordination, tremors, vascular degeneration, myopathy, cerebral edema; death on d 72 (M) and 83 (F)	52
"	"	2 M 1 F	150 mg/kg/d in diet for 28 d, 300 mg/kg/d until death	First signs of toxicity at d 37, 39, 42; ataxia, incoordination, tremors; vascular degeneration, myopathy, cerebral edema; death on d 46 (2 M) and 85 (F)	52
"	Miniature pigs	5 M	125 mg/kg/d in diet 6 - 8 wk	Spastic paresis of posterior extremities	55

*Single dose unless duration is specified
**Cholinesterase

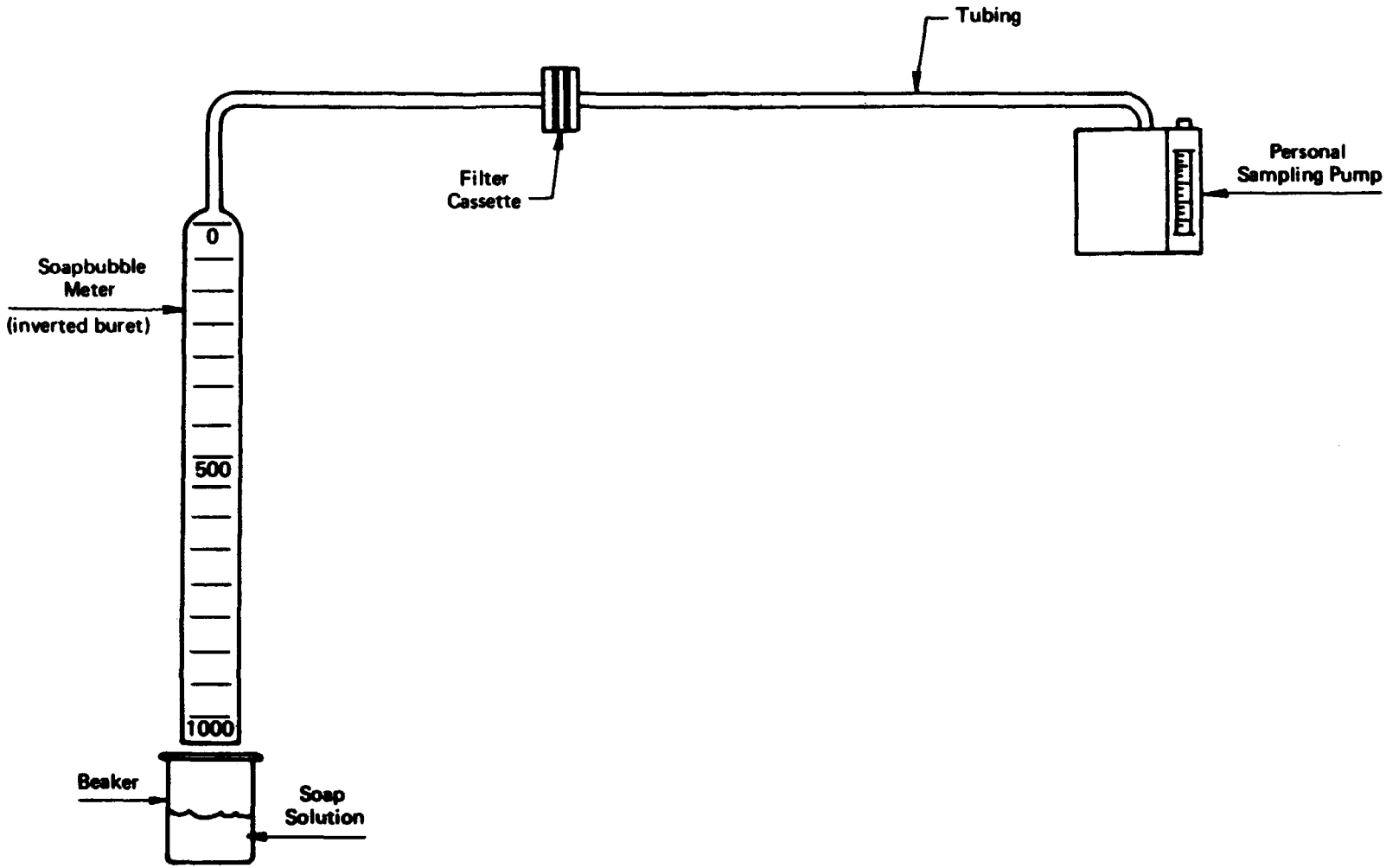


FIGURE XIII-1 CALIBRATION SETUP FOR PERSONAL SAMPLING PUMP WITH FILTER CASSETTE

☆U.S. GOVERNMENT PRINTING OFFICE: 1977 - 757-057/5743

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH
ROBERT A. TAFT LABORATORIES
4676 COLUMBIA PARKWAY, CINCINNATI, OHIO 45226

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE, $300

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF H.E.W.
HEW 399

DHEW (NIOSH) Publication No. 77-107