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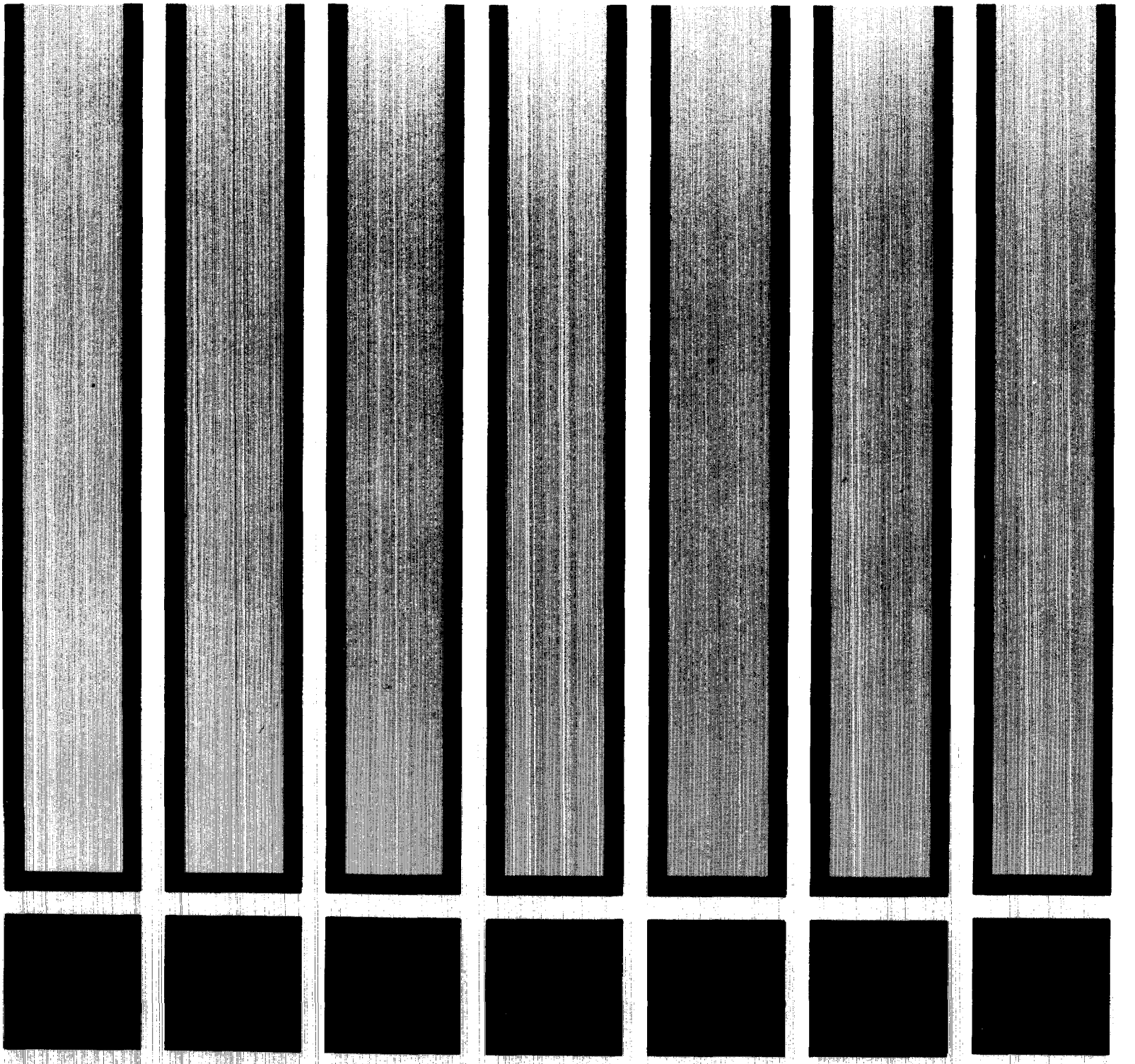
MALATHION



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

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OCCUPATIONAL EXPOSURE TO

MALATHION

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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 malathion by members of my staff and the valuable constructive comments by the Review Consultants on Malathion, by the ad hoc committees of the American Industrial Hygiene Association and the Society of Toxicology, 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 malathion. Lists of the NIOSH Review Committee members and of the Review Consultants appear on the following pages.

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Director, National Institute for
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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 malathion. The Division review staff for this document consisted of J. Henry Wills, Ph.D., Chairman, Herbert E. Christensen, D.Sc., and Richard A. Rhoden, Ph.D.

Stanford Research Institute developed the basic information for consideration by NIOSH staff and consultants under contract CDC-99-74-31. Jerry LR Chandler, Ph.D., had NIOSH program responsibility and served as criteria manager.

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I. RECOMMENDATIONS FOR A MALATHION STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to malathion in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health of employees for up to a 10-hour work shift and a 40-hour workweek during a working lifetime. Compliance with all sections of the standard should prevent adverse effects by malathion on the health of employees. The 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. Although the workplace environmental limit is considered to be a safe exposure level based on current information, it should be regarded as the upper boundary of exposure and every effort should be made to maintain the exposure as low as is technically feasible. The criteria and standard will be subject to review and revision as necessary.

"Malathion" is defined as 0,0-dimethyl S-(1,2-dicarboethoxyethyl) dithiophosphate, regardless of production process, alone or in combination with other compounds. "Action level" is defined as one-half the recommended time-weighted average (TWA) environmental exposure limit for malathion. "Occupational exposure to malathion" is defined as exposure to airborne malathion at concentrations greater than the action level.

The criteria and recommended standard apply to any area in which malathion or materials containing malathion, alone or in combination with other substances, is produced, packaged, processed, mixed, blended,

handled, stored in large quantities, or applied.

"Overexposure" is defined as either known or suspected exposure above the TWA concentration or any exposure which leads to the development of signs or symptoms of absorption of organophosphorus compounds and cholinesterase (ChE) inhibition. Exposure to malathion at concentrations less than or equal to the action level will not require adherence to the recommended standard except for sections 2, 3(a), 4(a), 5, 6, 7(a-c), and 8(b). If employees are potentially exposed to chemicals such as pesticide vehicles, diluents, emulsifiers, or other pesticides, provisions of any applicable standards for such chemicals shall also be followed.

Section 1 - Environmental (Workplace Air)

(a) Concentration

When skin exposure is prevented, exposure to malathion in the workplace shall be controlled so that employees are not exposed to malathion at a TWA concentration greater than 15 mg/cu m of air for up to a 10-hour work shift, 40-hour workweek.

(b) Sampling and Analysis

Procedures for the collection and analysis of environmental air 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 (medical management and biologic monitoring) shall be made available to workers as outlined below.

Physicians responsible for workers who may be occupationally exposed to organophosphate compounds should be familiar with the information contained in Appendix III which describes the diagnosis and treatment of intoxication by these compounds.

(a) Medical Examinations

(1) Preplacement and periodic medical examinations shall include:

(A) Comprehensive initial or interim medical and work histories.

(B) A physical examination which shall be directed toward, but not limited to, evidence of frequent headache, dizziness, nausea, tightness of the chest, dimness of vision, and difficulty in focusing the eyes.

(C) Determination, at the time of the preplacement examination, of a baseline or working baseline erythrocyte ChE activity (See (b), Biologic Monitoring).

(D) A judgment of the worker's physical ability to use negative or positive pressure regulators as defined in 29 CFR 1910.134.

(2) Periodic examinations shall be made available on an annual basis or at some other interval determined by the responsible physician.

(3) Medical records shall be maintained for all workers engaged in the manufacture or formulation of malathion and such records

shall be kept for at least 1 year after termination of employment.

(4) Pertinent medical information shall be available to authorized 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.

(b) Biologic Monitoring

(1) Definitions

(A) "Preexposure baseline" for erythrocyte ChE is defined as the mean of two ChE activity determinations, each of which is derived from a separate sample of blood taken at least 1 day apart after a period of at least 60 days without known exposure to any ChE-inhibiting compounds. If the determinations produce values differing by more than 15%, additional determinations on new samples must be performed until successive tests do not differ by more than 15%.

(B) "Working baseline" for erythrocyte ChE is defined as the mean of two ChE activity determinations, each of which is derived from a separate sample of blood taken at least 1 day apart and differing by no more than 15%, or the arithmetic mean of normal values for an appropriate control population of adults for that laboratory, whichever is higher. A "working baseline" need be determined only for an individual whose work history does not permit a preexposure baseline to be determined as specified in paragraph (b)(1)(A) of this section.

(C) "Mean of normal values" is defined as the arithmetic mean of erythrocyte ChE activities for healthy adults as determined by the laboratory's experience with repeated analyses, but which

is not inconsistent with the mean baseline activities presented in Appendix IV.

(2) Routine Monitoring

(A) All employees who are to be engaged in the manufacture or formulation of malathion shall have preexposure erythrocyte ChE baselines determined whenever their work histories allow an accurate preexposure determination, as specified in paragraph (b)(1)(A) of this section. Those new employees with work histories precluding preexposure baseline ChE determinations shall have working baseline determinations performed.

(B) Within 60 days after the effective date of a standard, all present employees potentially exposed to malathion shall have working baseline erythrocyte ChE activities determined.

(C) An employee who has been removed from malathion exposure shall not be allowed to return to work involving occupational malathion exposure until said employee's erythrocyte ChE activity has returned to at least 75% of the working or preexposure baseline value, or unless the responsible physician has approved said employee's return.

(D) All employees shall be provided a copy of their initial, periodic, and any special ChE test results as soon as possible after the test, plus an interpretation.

Section 3 - Labeling and Posting

(a) Labeling

Containers of malathion shall be labeled as follows:

MALATHION

CAUTION! HARMFUL IF INHALED OR SWALLOWED
HARMFUL IF LEFT ON SKIN

Do not breathe spray, vapor, or mist.
Do not take internally.

Avoid contact with eyes, skin, and clothing.
Wash hands before eating.
Take shower or bath after work.
Wear long-sleeved work clothing.
Change to clean clothing daily.

NOTE TO PHYSICIAN: Malathion is a cholinesterase inhibitor. Atropine sulfate is antidotal.

(b) Posting

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

TOXIC CHEMICAL

MALATHION IN USE

DO NOT BREATHE DUST OR MIST

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

Section 4 - Personal Protective Equipment and Clothing

(a) Protective Clothing

Any employee whose work involves likely exposure of the skin to malathion or malathion formulations, eg, mixing or formulating, shall wear full-body coveralls or the equivalent, impervious gloves, and impervious footwear and, when there is danger of malathion coming in contact with the eyes, safety goggles shall be provided and worn. Any employee who applies malathion shall be provided with and required to wear the following protective clothing and equipment: goggles, whole-body coveralls, and impervious footwear.

(b) Respiratory Protection

Engineering controls shall be used wherever feasible to maintain airborne malathion concentrations below the recommended workplace environmental limit. Compliance with the workplace environmental limit by the use of respirators is allowed only when airborne malathion 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) For the purpose of determining the type of respirator to be used, the employer shall measure, when possible, the atmospheric concentration of malathion in the workplace initially and thereafter whenever process, worksite, climate, or control changes occur which are likely to increase the airborne malathion concentrations; this requirement does not apply when only atmosphere-supplying positive pressure respirators

are used. The employer shall ensure that no employee is exposed to malathion at or above the workplace environmental limit because of improper respirator selection, fit, use, or maintenance.

(2) A respiratory protective program meeting the requirements of 29 CFR 1910.134 and 30 CFR 11 shall be established and carried out by the employer.

(3) The employer shall provide respirators in accordance with Table I-1 and shall ensure that the appropriate respirator is worn.

(4) Respiratory protective devices described in Table I-1 shall be of the type approved under the provisions of 29 CFR 1910.134 and 30 CFR 11.

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

(6) The employer shall ensure that respirators are adequately cleaned, and that employees are instructed on the use of respirators assigned to them and on how to test for leakage.

(7) Canisters shall be discarded and replaced with fresh canisters in accord with the manufacturer's recommendation or if the odor of malathion breaks through. Unused canisters shall be discarded and replaced when seals are broken or on expiration of the manufacturer's recommended storage life if the seals are unbroken.

TABLE I-1

RESPIRATOR SELECTION GUIDE

Concentration of Malathion	Respirator Type
150 mg/cu m or less (dust)	Dust respirator
150 mg/cu m or less (aerosol or vapor)	(1) Chemical cartridge respirator with replaceable pesticide cartridge and half-mask facepiece (2) Type C supplied-air respirator, demand type (negative pressure), with half-mask facepiece
300 mg/cu m or less	Full-face gas mask, chin-style with pesticide canister
750 mg/cu m or less	(1) Full-face gas mask, chest- or back-mounted type (2) Type C supplied-air respirator, demand type (negative pressure), with full facepiece, hood, or shroud
Emergency (no concentration limit)	(1) Self-contained breathing apparatus (positive pressure) with full facepiece (2) Combination supplied-air respirator, pressure-demand type, with auxiliary self-contained air supply

Section 5 - Informing Employees of Hazards from Malathion

(a) Before work involving potential exposure to malathion begins, all new or reassigned employees shall be informed of the hazards of malathion, relevant symptoms of overexposure to malathion, appropriate emergency procedures, and of the conditions and precautions required for

safe handling of malathion.

(b) The information shall be posted in the work area, shall be kept on file, and shall be readily accessible to the worker at all places of employment where occupational exposure to malathion may occur.

(c) A program of employee education shall be instituted within 30 days after the promulgation of the standard. The program shall be designed to ensure that all employees occupationally exposed to malathion understand and remain aware of job hazards as well as emergency, maintenance, and cleanup procedures, and that they know how to correctly use and maintain respiratory protective equipment and protective clothing. The training shall be repeated at least annually after the employee's initial training required under this paragraph.

(d) In addition to the requirements of paragraph (c) above, employees occupationally exposed to malathion shall be kept currently informed through posting as specified in Section 3(b), and shall be instructed as to the availability of biologic monitoring information. The information specified in Section 2(b)(2) shall be kept on file and shall be readily accessible to each employee at or near each workplace where exposure to malathion may occur. In addition, all employees shall be informed of their biologic monitoring results as specified in Section 2(b)(2)(D).

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

Section 6 - Work Practices

(a) Each employer shall contact and advise a physician or other nearby medical service that an emergency arising from exposure to malathion may occur.

(b) All malathion spills shall be cleaned up as soon as possible. Continuous surveillance of spills shall be provided until decontamination is completed. Contaminated areas shall be roped off or access to them otherwise prevented. They shall also be posted.

(c) Spills of malathion on floors shall be absorbed with absorbing clay. Sweeping compound shall be utilized to facilitate the removal of all visible traces of malathion-contaminated clay.

(d) Equipment and fixtures contaminated with malathion shall be decontaminated with an alkaline solution (5% NaOH) or with an equivalent or superior decontaminating solution.

(e) If empty metal containers contaminated with malathion are to be disposed of in a sanitary landfill, they shall be decontaminated with strong alkaline solution (10% NaOH), or with an equivalent or superior decontaminating solution, and punctured before disposal.

(f) If empty malathion-contaminated metal drums or containers are to be reclaimed, they shall be decontaminated or sealed tightly, and the reclaimer informed of the prior malathion contamination.

(g) The employer shall provide for cleaning and laundering of work clothing and personal protective equipment, and for their decontamination as needed.

(h) Whenever malathion significantly contaminates clothing or the insides of personal protective equipment, the contaminated articles shall

be removed immediately, and the employee shall be required to wash with soap and water.

(i) Extra clothes shall be available for use when employees' personal clothing becomes contaminated with malathion.

(j) Employees potentially exposed to malathion while spraying shall remain upwind from the spray whenever possible.

(k) Employers shall ensure that persons who launder clothes contaminated with malathion understand the hazards associated with malathion's use.

Section 7 - Sanitation Practices

(a) Malathion-manufacturing and malathion-formulating facilities shall have eyewash fountains and showers as specified in 29 CFR 1910.151(c).

(b) The employer shall provide access to a free-flowing water source at fixed facilities, with soap and towels for all employees to use in emergencies.

(c) Employees shall be required to shower at the end of each work shift.

(d) Employees shall be prohibited from eating, drinking, or smoking in malathion-contaminated areas.

(e) Employees occupationally exposed to malathion shall be required to wash hands and face before eating, drinking, smoking, or applying cosmetics or dermal preparations.

Section 8 - Monitoring and Recordkeeping Requirements

Workers are not considered to have occupational exposure to malathion if environmental 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 result in increased airborne concentrations of malathion. Records of these surveys, including the basis for concluding that airborne concentrations of malathion are at or below the action level, shall be maintained. If the survey indicates that airborne concentrations of malathion 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 malathion. Interim monitoring of employee exposure to airborne concentrations of malathion shall be conducted at least every 6 months. If monitoring of an employee's exposure to malathion reveals that the employee is exposed at concentrations in excess of 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 of 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 TWA environmental limit specified in Section 1(a). Semiannual monitoring may

then be resumed.

(2) In all personal monitoring, samples of airborne malathion shall be collected which, when analyzed, will provide an accurate representation of the concentration of malathion 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 job functions of employees in relation to that operation or process.

(b) Recordkeeping Procedures

Records shall be maintained for at least 5 years and shall include sampling and analytical methods, types of respiratory protective devices used, and TWA concentrations found. Each employee shall have access to data on the employee's own environmental exposures and records. These records shall be made available to the designated representatives of the Secretary of Health, Education, and Welfare. Pertinent records of required medical examinations shall be maintained for 1 year 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 malathion. 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 for a 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 malathion are part of a continuing series of criteria developed by NIOSH. The proposed standard applies only to the manufacture, formulation, application, or other vocational exposure to malathion 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 vocational exposures is not warranted. It is intended to (1) protect against development of acute and chronic systemic and local effects on the skin and eyes, (2) be measurable by techniques that are

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

No attempt has been made in this document to cope with all the literature on malathion, such as that concerning insect data. Currently available scientific evidence indicates that, compared with other organophosphates, malathion is of low toxicity in humans.

NIOSH believes that future research on malathion should be directed toward the effects on enzymes, particularly aliesterase, of chronic exposure to malathion and the physiologic significance of these effects. Additional data should be obtained on its potential mutagenic or carcinogenic effects. There should be research directed toward the development of an accurate field test for ChE monitoring, and toward simpler and more efficacious methods of collecting malathion aerosols and vapors. Also, NIOSH recommends that the rates and mechanisms of skin absorption of various malathion formulations be determined and that certain biochemical constants and rates be determined. These recommendations are discussed further in Chapter VII.

III. BIOLOGIC EFFECTS OF EXPOSURE

The normal function of the central nervous system (CNS) can be significantly altered by malathion intoxication. Acetylcholine (ACh), a choline ester, normally mediates neurotransmission in preganglionic autonomic fibers, postganglionic parasympathetic fibers, and in some postganglionic sympathetic fibers. [1] These fibers innervate the heart, iris, salivary glands, stomach, small intestine, urinary bladder, bronchial glands, eccrine sweat glands, and other structures. There is also evidence that ACh functions as a transmitter at neuromuscular junctions (motor endplates) and at certain synapses within the CNS. [1]

Two types of enzymes normally hydrolyze choline esters in humans: acetylcholinesterase (AChE) or true ChE (Enzyme Commission (EC) 3.1.1.7), and butyrylcholinesterase (BuChE) (EC 3.1.1.8), otherwise known as plasma ChE, serum ChE, or pseudocholinesterase. [1] AChE is found in neurons, at the neuromuscular junction, in erythrocytes, and in certain other tissues.

Inhibition of AChE leads to the accumulation of endogenous ACh [1] and, consequently, to the poisoning of the exposed individual.

BuChE is present in various types of glial or satellite cells of the central and peripheral nervous systems as well as in plasma, in the liver, and in other organs. [1] Its physiologic function is unknown; inhibition of the plasma enzyme at most sites produces no apparent functional derangement. [1] A diagram of the metabolism of malathion is presented in Figure XV-1.

Malathion itself has only a slight direct inhibitory action on erythrocyte ChE and nonspecific esterases but one of its metabolites,

malaoxon, is an active inhibitor. Malaoxon reacts with AChE to form the dimethylphosphoryl derivative, which is incapable of hydrolyzing ACh. [2-5] The resulting enzyme-inhibitor complex either may be slowly reactivated by dephosphorylation or permanently inactivated by aging via demethylation to the monomethylphosphoryl enzyme. The aging reaction is believed to play a critical role in the toxic actions of many organophosphates containing secondary or tertiary alkyl groups. [6]

Reactivation of the erythrocyte enzyme-inhibitor complex is accelerated by nucleophilic reactivators such as choline, pyridine, hydroxylamine, hydroxamic acids, and oximes. [7] Childs et al [8] found that the oximes were generally superior to the hydroxamic acids in reactivating organophosphate-inhibited ChE's. Subsequent studies have shown that pyridine-2-aldoxime methachloride (pralidoxime chloride) is highly effective in the reactivation of inhibited erythrocyte and neuroeffector ChE's if aging has not occurred. Wilson and Ginsburg [9] reported that pyridine-2-aldoxime is capable of reducing the toxicity of parathion in rats.

Extent of Exposure

Malathion (0,0-dimethyl S-(1,2-dicarboethoxyethyl) dithiophosphate), formerly known as malathon, [10] belongs to the family of organophosphorus pesticides. Pertinent physical properties of malathion are presented in Table XV-1, [11] and common trade names and synonyms for malathion are in Table XV-2. [12] Malathion is a colorless to light-amber liquid, with a solubility of 145 ppm in water at 25 C. While of limited solubility in

petroleum oils, it is miscible with most organic solvents. [13]

Malathion is produced by the reaction of 0,0-dimethyl dithiophosphoric acid and diethyl maleate dissolved in an alcohol or a ketone in the presence of a tertiary amine. An antipolymerization agent, such as hydroquinone, is usually used to inhibit polymerization of diethyl maleate. [13] Commercial malathion was introduced in 1950 as an experimental insecticide bv the American Cyanamid Company [11] and patented by the same company in 1951 (US Patent 2,578,652). By 1971, the annual production of malathion in the US totaled about 35 million pounds. [14,15]

Malathion is marketed as 99.6% technical grade liquid. Available formulations include wettable powders (25% and 50%), emulsifiable concentrates, dusts, and aerosols. [13,16]

Malathion is used in the control of certain insect pests on fruits, vegetables, and ornamental plants. It has been used in the control of houseflies, mosquitoes, and lice, [16] and on various farm and livestock animals. [17]

NIOSH estimates that approximately 75,000 workers in the US are occupationally exposed to malathion.

Historical Reports

The first indications that some organophosphorus compounds might be highly toxic appeared during the early 1930's when symptoms of ACh poisoning were experienced by the synthesizers of dimethyl and diethyl phosphorofluoridate. [18] In 1936, during an investigation of svnthetic insecticides, Schrader studied the phosphorus compounds, and in 1937 he

formula for organophosphate contact insecticides. [18]

Effects on Humans

Malathion absorption through the gastrointestinal tract, [19-26] the skin, [27-32] and the respiratory tract has been examined. [33,34] In vocational exposures, the skin is an impo rtant route of entry to the body, [35-37] and a case of intoxication following extensive skin exposure has been reported. [38] All but two reports of fatalities from malathion poisoning reviewed to date have involved ingestion [22,23,40]; two people may have died from contamination of the skin with malathion, but the attribution of the deaths to malathion remains somewhat uncertain.

Clyne and Shaffer [17] reported the experiences of three men who sprayed a liquid malathion formulation in grain-filled ship holds. Ceilings and inner walls of 34 ships' holds were sprayed intermittently during 4.5 months with either 5 or 10 quarts/ship of 57% emulsifiable liquid. The sprayers worked while lying on their backs on top of the grain and did not wear protective equipment. They did, however, wear coveralls which were changed daily; they showered after completing spraying for the day and washed their hands and faces after spraying each hold. The total duration of exposure was estimated to have been 35-40 hours. Erythrocyte and plasma ChE activities were monitored before, during, and after the project and were reported to have remained normal throughout. No symptoms of illness were detected in the men, despite what must have been very heavy dermal and respiratory exposure and probable oral exposure by swallowing airborne material.

The Expert Committee on Insecticides of the World Health Organization [41] briefly described its summary conclusions from reports on a large-scale field trial of malathion in Uganda in 1963-1965, and on routine spraying of malathion in 29,000 Central American houses from 1963 to 1967. The one safety precaution observed was to keep the compound away from foodstuffs, yet the only report of illness was in three sprayers whose uniforms were described as continually wet with malathion in kerosene for 3 days. Two of the sprayers were moderately ill for 3 days, and the third for 1 day, with symptoms of anticholinesterase poisoning. No further data were supplied in this report. Another case of symptomatic malathion poisoning directly attributable to workplace exposure involved a 16-year-old man who for 10 days was heavily exposed in Florida to malathion dust being applied to control the Mediterranean fruitfly (RM Clyne, written communication, February 1975). The young man used no protective measures to prevent exposure and, although his skin was visibly contaminated with dust, he reportedly did not bathe during the entire 10 days. He presumably inhaled a great deal of the dust and, in addition, frequently drank water directly from his cupped hands. After 10 days of exposure, he became ill with obvious manifestations of organophosphorus pesticide intoxication. He was admitted to a hospital, treated for 24 hours, and released as clinically well within 48 hours.

The State of California Department of Public Health publishes annual reports entitled Occupational Disease in California Attributed to Pesticides and Other Agricultural Chemicals--Some Current Problems. [42] The values contained in these reports are derived from data submitted by California physicians in accordance with the state's "Doctor's First Report

of Work Injury" reporting law. [43] The report required by this law is a brief summary of initial diagnostic impression and is accepted for statistical purposes by the state with little or no further communication. The data in Table III-1 were taken from the respective California Department of Health reports. In 1970, 33,085 occupational disease reports were included in the annual summary. Of these, 1,493, or 4.5%, were attributed to agricultural chemicals, but only 9, or 0.6%, of these reports involved malathion.

TABLE III-1

REPORTS OF OCCUPATIONAL DISEASE ATTRIBUTED TO MALATHION BY INDUSTRY AND YEAR, CALIFORNIA

Year	Industry Group		
	Agriculture	Manufacturing	All Other
1969	4 (162)	1 (40)	3 (29)
1970	5 (244)	0 (47)	4 (41)
1971	1 (197)	5 (31)	4 (41)

Numbers in parentheses refer to the total number of organophosphate poisonings.

Adapted from Occupational Disease in California Attributed to Pesticides and Other Agricultural Chemicals 1969--Some Current Problems [42]

A number of published case reports have been found which describe the toxic effects of acute exposure to malathion. Goldin et al, [39] in 1964, described the case of a 42-year-old woman who ingested a minimum of 120 ml of 50% malathion garden spray. She was admitted to a hospital 30 minutes

later, at which time she was comatose, markedly cyanotic, flaccid, devoid of tendon reflexes, and markedly miotic. Immediate treatment was begun with 1 mg of atropine im and 500 mg of 2-PAM iv. The history obtained from her family revealed that she had suddenly become unconscious with a major convulsion lasting for several minutes, and that excessive salivation and bronchial hypersecretion had developed rapidly thereafter. Approximately 1 hour after ingestion of the malathion, she received an additional 2,000 mg 2-PAM iv (total dose 40 mg/kg). At this stage, profuse diarrhea and massive bronchial hypersecretion which necessitated frequent tracheal-bronchial suction developed. Subcutaneous atropine therapy, 1-3 mg/hour, was begun. After 24 hours, the patient was able to move her arms and legs sluggishly on command. While pronounced tongue tremor and brisk jaw jerk were present, areflexia and pinpoint pupils persisted, as did the bronchial hypersecretion and cyanosis. Strength of muscles, other than those of respiration, returned to normal on about the 10th day after ingestion. After approximately 15 days, diaphragmatic and intercostal strength had recovered sufficiently to maintain spontaneous breathing. Neurologic recovery was gradual, with the tongue tremor and brisk jaw jerk disappearing, and the tendon reflexes returning, within about 1 week. The patient was discharged 5 weeks after admission. Laboratory investigations during the patient's hospital course included determinations of plasma and erythrocyte ChE activities. Serum ChE activity was less than 22% of laboratory normal for the first 9 days. Thereafter, the level gradually rose to 100% by the 31st day. The erythrocyte ChE activity was first measured on the 12th day, when it was found to be 10% of normal. It remained between 10 and 25% of normal until the 45th day after hospital

admission and then gradually rose to 100% by 130 days after admission. By this time the patient had been discharged. Hematocrit measurement showed a small drop after admission, from 43 to 37%, and the reticulocyte count never rose above 2%. Sternal bone marrow examination on the 25th day was essentially normal. Blood urea levels rose to 77 mg/100 ml of blood during the first 5 days, thereafter returning to normal as the nonrenal uremia due to diarrhea and hypersecretion was controlled. Electrocardiograms (ECG'S) taken immediately after admission and daily thereafter showed a prolongation of the P-R interval that persisted for 5 days, as well as changes in the S-T segment which the authors [39] reported as consistent with panmyocardial ischemia. These latter changes disappeared gradually as the patient's respiratory function improved.

Crowley and Johns [19] in 1966 described the case of a 45-year-old maintenance worker who ingested between 50 and 90 cc of commercial insecticide containing 50% malathion in a petroleum hydrocarbon base. Within an hour, he developed nausea, vomiting, and profuse diarrhea; shortly after, he also developed generalized sweating, increased salivation, lacrimation, and visual blurring. He began to have wheezing, giddiness, a feeling of generalized numbness, loss of coordination, urinary and fecal incontinence, and violent shaking and tremors, but he did not lose consciousness. Two hours after ingestion, he was brought to the hospital emergency room where he was found to be hyperactive, irritable but alert, and in mild respiratory distress. His skin was slightly dusky, his pupils were pinpoint, and excessive amounts of secretions were present in his mouth, pharynx, and respiratory passages. Scattered moist rales and expiratory wheezes were heard throughout his lung fields, but chest

expansion during respiration appeared adequate. Bowel sounds were active. Neurologic examination revealed normal sensory function with respect to superficial pain, touch, vibration, and proprioception. He had generalized skeletal muscle fasciculations and mild generalized weakness. Coordination was normal. Deep tendon reflexes were absent and his plantar responses were flexor. The patient was admitted to the hospital and immediately given 2 mg atropine iv, and this was continued as necessary until 18 days after admission. During the first 24 hours after malathion ingestion, his respiration became increasingly labored, apparently because of the increasing volume and tenacity of respiratory tract secretions together with pulmonary congestion and weakness of respiratory muscle contractions. The level of consciousness exhibited by the patient fluctuated widely from alertness to complete stupor. Skeletal muscle weakness increased, so that by 38 hours after ingestion of the insecticide the patient exhibited severe weakness of the trunk muscles and all extremities, with somewhat more power in the pelvic girdle and leg muscles and in muscles of the arms. He was able to initiate only a very weak muscular contraction, which fatigued after 5-10 seconds, followed by tremors involving the entire limb. This in turn was succeeded by flaccid paralysis of the limb. He had moderate ptosis of the eyelids with normal power of the extraocular muscles. There was weakness of the upper and lower facial muscles. He was able to open his mouth for 3-5 seconds but unable to protrude his tongue. On attempts to phonate, his palate elevated symmetrically. Therapy with 2-PAM was begun 48 hours after ingestion of malathion with 500 mg administered iv at 48 and 54 hours and 1 g iv each hour for 3 hours beginning 72 hours after ingestion. It was discontinued thereafter. The patient's level of

consciousness continued to fluctuate for 5 days. He then began to regain muscle strength and endurance. Erythrocyte ChE activity, which measured less than 10% of laboratory normal in the first 48 hours, began to rise after the first 7 days. He was discharged from the hospital on the 28th day after ingestion and was not seen again until the 56th day. At that time, his erythrocyte ChE activity had risen to 66% of normal. No description of the clinical course between the 7th and 56th days was given, and no further followup visits were reported.

Amos and Hall [20] described the case of a 14-year-old boy weighing 165 pounds who was admitted to the hospital 20 minutes after ingestion of approximately 4 ounces (120 ml) of a malathion preparation of unstated composition. At the time of admission, he had abdominal cramps, nausea, vomiting, excessive salivation, difficulty in breathing, and severe muscle weakness. Within several minutes of admission to the emergency room, he became cyanotic, developed pulmonary edema, and lapsed into coma. There were muscular fasciculations of the face, eyelids, and neck accompanied by mild muscular twitchings of the entire body. Pupils were pinpoint, round, regular, equal, and nonresponsive to light. Neurologic investigation revealed the absence of deep tendon reflexes and the presence of marked motor weakness. The patient was atropinized with 1 intravenous (iv) dose of 0.4 mg and with intramuscular (im) doses of 0.4 mg, 0.6 mg, and 0.6 mg in the 1st hour; and doses of 2 mg iv every 30 minutes from the 3d hour after admission onward; the authors reported total atropine dosage of 54 mg in the first 48 hours. After 3 hours, the state of deep coma, areflexia, and nonresponse to painful stimuli began to abate. The deep tendon reflexes returned and a slight increase in the size of the pupil with

pupillary reaction to light was noted. The patient regained consciousness for several minutes and then became combative, confused, and disoriented. Several hours later, he appeared alert with no evidence of motor paralysis. The day after admission, the patient began to deteriorate again, becoming progressively weaker with shallow respiration, rapid thready pulse, and a cloudy sensorium. There was the return of excessive salivation, difficult respiration, pinpoint pupils, muscular fasciculations of the face and neck, and twitching of the entire body as if convulsions were imminent. The patient was critically ill for the next 12 hours and required tracheostomy. Atropinization was continued and, after another 24 hours, his vital signs improved and respiration was again satisfactory. On the 3d hospital day, miotic pupils were again noted; his respiration was shallow and abdominal in type with no intercostal muscle function. No muscle twitching was present, but there was profound muscular weakness with inability to move the lower extremities more than a few inches from the bed. Ptosis of the eyelids suggested a severe myasthenia gravis-type weakness. At this time, the patient was rational with clear sensorium. Because of progressive respiratory failure complicated by pneumonia, it was decided to treat the patient with 2-PAM, 500 mg iv during 5 minutes, whereupon muscle function improved. During the next 24 hours, respiratory paralysis recurred, so that repetition of treatment with 2-PAM seemed necessary and was performed. After 72 hours, the hemogram, urinalysis, and ECG were normal. Atropine dosage was reduced to 0.5 mg/hour, and on the 7th day to 1 mg in every 4 hours. The patient was discharged from the hospital on the 15th day in satisfactory condition.

Harris et al [40] described the case of a 45-year-old woman who had ingested an indeterminate amount of malathion. She was admitted to hospital no more than 6 hours after ingestion and, by then, was unconscious and areflexic. She was in total cardiac and respiratory arrest. No involuntary motor activity was evident, although seizures did develop about 8 hours later. Some mucus about the mouth had been seen by the patient's husband at home, but no salivation or frothy sputum was observed thereafter. Pupils were of intermediate size and unreactive to light. There was no excessive sweating, diarrhea, or retching. She had not been incontinent. Moderate bradycardia, without gross arrhythmia, was noted. Laboratory tests at the time of admission showed hyperglycemia and 4+ glycosuria, but subsequent estimations of concentrations of glucose in the plasma were within the normal range. Ventilation via an endotracheal tube was required and levarterenol was administered iv. The authors [40] noted that voluntary respiratory effort was inadequate throughout most of the patient's hospital course. For the next 36 hours, maintenance of adequate blood pressure was dependent upon administration of levarterenol. The patient was initially given 4 mg of atropine iv. Throughout hospitalization, therapy was continued with 2-PAM, 1 g iv every 12-24 hours, and atropine, 1-2 mg iv or im every 1-4 hours. Two days after her admission, the patient showed slight voluntary movement and responded momentarily to external stimuli. Her pupils were dilated and there seemed to be stronger respiratory effort. However, ventricular fibrillation occurred 4 hours thereafter and, following this, the patient remained comatose. ChE activity was absent from both erythrocytes and plasma. The patient expired 5.5 days after malathion ingestion. Autopsy revealed

generalized edema, including severe pulmonary edema, and bronchopneumonia. These were probably indirect effects of shock and respiratory failure. A small subdural hematoma was also found, but no associated abnormalities to indicate head trauma were observed.

Windsor [44] reported the case of a 37-year-old woman admitted to the hospital after swallowing 60-85 ml of a malathion preparation (55% malathion, 35% crude naphthal extract), a dose the author calculated as equivalent to 35-50 g of malathion. She was an epileptic who was taking barbiturates, chloral hydrate, chlorpromazine, phenelzine, and phenytoin, and was under psychiatric care and had attempted suicide with chlorpromazine 2 years prior to this incident. On admission, the patient was described as "severely collapsed" and deeply cyanosed, with profoundly depressed respiration and bubbling rales throughout the chest. Pupils were pinpoint, but reflexes were detectable and symmetrical. Endotracheal intubation and bronchial aspiration were performed, and she was placed on a respirator. Gastric lavage resulted in the recovery of large, but unspecified, amounts of the malathion mixture. Atropine was administered in 2-mg doses every 15 minutes; pralidoxime chloride was administered iv in doses of 1 g at 2 and 6 hours after admission. The patient's pupils dilated and respiration improved, although during this time she had "several bouts" of diarrhea and generalized muscular fasciculations. The respirator was removed, but had to be replaced 24 hours after admission. Atropinization was continued until the morning after admission. It was resumed 14 hours later at a rate of 2 mg every 15 minutes, together with 1 g of pralidoxime every 4 hours. Serum ChE activity was determined to be about 20% of the normal minimum 3 days after malathion ingestion and

increased to about 45% of normal 1 week after the incident. Pralidoxime chloride was discontinued on the 5th hospital day, but atropinization was maintained until the 11th day, by which time a total of 1,065 mg of atropine had been administered. The respirator was withdrawn, and her recovery proceeded uneventfully.

Namba et al [25] reported the case of a 63-year-old man who was poisoned and admitted to a hospital after he drank between 120 and 180 ml of a malathion preparation (50% malathion, 42.4% xylene, and 7.6% inert ingredients) diluted in milk. Although roughly equivalent to 60-90 g of malathion, the quantity actually absorbed was probably less, according to the authors, as the subject had vomited and gastric lavage had been performed on him. The patient, an epileptic for 20 years, had been treated for that disorder with diphenylhydantoin and primidone. Upon admission to the emergency room, he was reportedly comatose and dyspneic. His blood pressure and radial pulse could not be recorded, mucous membranes were cyanotic, eye movements were absent, his conjunctivae were injected, and he had pinpoint pupils which were unresponsive to light. A foul-smelling, thick, whitish secretion filled his mouth and pharynx. The heart was not enlarged as determined by percussion, but heart sounds were distant and muffled by bilateral coarse rales and ronchi. The patient's limbs were flaccid and unresponsive to painful stimuli; neither tendon nor pathologic reflexes were observed. Also absent were the oculocephalic and caloric stimulation reflexes, as well as muscle fasciculations. He was incontinent and vomited copious amounts of garlic-smelling fluid. Treatment was begun with cardiac massage, assisted respiration, frequent tracheobronchial suctioning, and administration of 2 mg of atropine sulfate.

Electrocardiographic abnormalities (incomplete right bundle branch block, S-T depression) were found, as were further neurologic abnormalities. During his first hospital day, the patient received 22 mg of atropine sulfate and 3 g of pralidoxime chloride iv. Plasma ChE activity was reduced to 13% of normal on the first day and 4% on the second, while the erythrocyte ChE level was reduced to 7% of normal on the second and 3% on the third day. An injection of 1 g of pralidoxime chloride on the second day was purportedly responsible for a "temporary" 24% elevation of both erythrocyte and plasma ChE activities. At the time of the victim's death, 6 days after exposure, no lasting recovery of plasma (erythrocyte not mentioned) ChE activity had been achieved, nor had the ECG abnormalities resolved. During the course of treatment, he had received 24.4 mg of atropine sulfate iv and 12.0 mg im, and 6 mg of pralidoxime chloride iv. Autopsy disclosed basal adhesive meningitis (believed to have been associated with his history of epilepsy), arteriosclerotic changes in the coronary arteries without evidence of myocardial infarction, ulceration of the pharynx and trachea because of endotracheal intubation, right lung bronchogenic carcinoma (with left lung, hilar, and paratracheal node metastases), telangiectases in the buccal mucosa and jejunum, granulomas of the spleen and liver because of old histoplasma infection, and status post posterior colic gastrojejunostomy. ChE activities were reduced to 32% of normal in the cerebrum, 3% in the cerebellum, 1% in muscle, 19% in the liver, and 13% in the kidney on post mortem determination.

Richards [45] described the case of a 46-year-old woman who was admitted to the hospital after drinking 50 ml of 50% malathion solution. She was cyanotic and had marked respiratory depression. Artificial

ventilation was instituted, and a total of 790 mg of atropine administered in the first 6.5 days of treatment was followed by 60 mg more in the 2 days following. Five hours after the malathion ingestion, 1 g of 2-PAM was administered as well. The patient recovered, despite her moribund status on admission.

Two incidents of malathion poisoning in Sarawak, Malaysia, subsequent to deliberate ingestion were reported by Mathewson and Hardy. [46] The first was that of a 31-year-old woman who drank 56 ml of 57% malathion solution, an amount equivalent to 35 g of malathion. On admission to the hospital a half hour later, she was conscious and not cyanosed. Gastric lavage was performed, and atropine administration im was begun at a rate of 1.8 mg every 10 minutes. One and one-half hours after admission, by which time she had received 18 mg of atropine, the patient showed cyanosis, sweating, profuse salivation, pinpoint pupils, and muscular fasciculation. The subject was placed on artifical respiration, and atropine administration was continued at the same dose but iv. The next morning, despite apparent improvement in her condition, with better muscle power, less constricted pupils, and adequate self-ventilation (permitting withdrawal of the respirator), she deteriorated within a half hour after the respirator was removed and had to be reintubated. Paraldehyde was administered (6 ml iv) to stop generalized convulsions, and atropinization was still continued every 10 minutes. Tracheostomy was performed on the 3d hospital day, and on the 4th day the patient was able to breathe spontaneously for only 4-5 minutes every 2 hours. Peripheral muscle power was described as poor, although she could lift her hands off the bed. Atropine was continued, with the dosage adjusted according to her pupil

size. Spontaneous breathing returned for gradually longer periods, but artificial respiration could not be completely withdrawn until the 19th day. A total of 589 mg of atropine was administered to the woman in 37 days, mostly by iv or im routes during the first two weeks, and by stomach tube thereafter. She was discharged to a mental hospital 46 days after admission.

The second case [46] was that of a 16-year-old boy who drank 6 or 7 tablespoonsful of 57% malathion solution, a dose of about 30 g of malathion. On admission to the hospital 1.5 hours later, he was cyanosed and incontinent, with shallow bubbling respiration and pinpoint pupils. He was placed on a respirator and given 1 g of pyridine aldoxime ethanosulphate (P2S) iv. Atropine was given 2.5 mg in every 15 minutes. Gastric lavage was performed. An additional gram of P2S was administered iv after 2.5 hours; artificial ventilation was discontinued after 4.5 hours. Atropinization was continued, and the patient still had pinpoint pupils. Eight hours later, artificial respiration had to be resumed and 1.2 g of P2S was administered in divided doses. A fall in blood pressure 3 hours later required a 24-hour infusion of metaraminol during which time an additional 1 g dose of P2S was given. Not until the 19th hospital day could the use of the respirator be discontinued; thereafter, small doses of atropine were administered, to a total of 613 mg by day 24 after admission.

Goldman and Teitel [47] reported in 1958 that a 34-month-old child, weighing 21 kg (unusually heavy for this age), consumed 8 cc of 50% malathion in xylene. He was immediately given a glass of milk, a hard-boiled egg, and milk of magnesia. Fifteen minutes after ingestion, the child became limp and was taken to a physician, who noted muscle

flaccidity, miosis, and drooling. Stomach lavage was performed and the odor of malathion was noted in the material removed. One hour and forty minutes after ingestion of the pesticide, the patient was admitted to the hospital emergency room, stuporous, retching, and with rapid, noisy respiration. Miosis, hypersalivation, and excessive mucus secretion were observed, as were moist rales and expiratory wheezes. The child's deep tendon reflexes were absent, but abdominal and cremasteric reflexes were present and equal, and both the gag reflex and the response to painful stimuli were present. Incontinence and vomiting occurred. Gastric lavage was again administered. The progressive increase in respiratory distress and slight cyanosis prompted administration of atropine (0.15 mg iv and 0.15 mg subcutaneously) 1 hour after admission, although it was noted that spontaneous resolution of these signs had begun immediately prior to drug treatment. Two and one-half hours after admission, the child was conscious, alert, oriented, and in no respiratory distress. His lungs were clear, pupils in mid-miosis, and salivation was normal. Three hours after admission, respiratory distress again appeared, but without rales. It was felt that this episode was in part a reaction to the local irritating effect of the mixture of malathion and xylene. High humidity, created by use of a nebulizer, was used to alleviate this, and by the 5th hour after admission (6 hours, 40 minutes after ingestion), the child was asymptomatic and without clinical signs of intoxication.

These case reports [19,20,25,39,40,44-47] are consistent with the signs and symptoms attributable to the inhibition of AChE. The authors of these papers concluded, therefore, that malathion produces its acute toxic effects by this means; NIOSH concurs in this opinion.

The major signs and symptoms of malathion poisoning are attributable to the potentiation of responses to the ACh released from preganglionic and postganglionic cholinergic and somatic motor nerve endings whenever nerve volleys reach the periphery. In milder cases, the postganglionic stimulation may predominate. As listed in the case reports described above, these signs and symptoms include nausea, [19,20,27] vomiting, [19,20,25] diarrhea, [19,25,39] excessive sweating, [19,20,23,27] salivation, [19,20,23-25,27] miosis, [20,23-25,27,39] increased bronchial secretion, [19,20,24,25,27,39] bronchial constriction, [20,24,27] and the appearance of generalized muscular fasciculations followed by weakness. [19,20,23,24,27,39] Central nervous system effects include anxiety, [20] restlessness, [19,24] headache [27] and, in more serious cases, tremors, [19,20,39] confusion, [19] drowsiness, [19,20] slurred speech, [19] coma, [20,23,25,27,39,40] loss of reflexes, [19,20,24,25,27,39,40] and convulsions. [24,40]

The full range of manifestations of ChE inhibition is given in Table III-2.

Nalin's [50] classification of the clinical status of a series of 264 people who ingested malathion with suicidal intent is exceptionally complete. He found that severity of illness could be classified as mild (56%), moderate (14%), or severe (30%) based on the clinical criteria tabulated in Appendix VI. Patients with mild cases frequently had about them the characteristic pungent odor of malathion. Nausea, vomiting, and dizziness were common.

Moderately ill patients [50] had a strong odor of malathion, which was present in the milky gastric aspirate. They had sialorrhea with

TABLE III-2

SIGNS AND SYMPTOMS ASSOCIATED WITH ACUTE AND SUBACUTE EXPOSURES TO MALATHION

	Effector Organ	Signs or Symptoms
(1)	Muscarinic manifestations	
	(a) Gastrointestinal	Anorexia, nausea, vomiting, abdominal cramps, diarrhea, tenesmus, involuntary defecation, eructation, "heartburn," sensation of substernal pressure
	(b) Sweat glands	Increased sweating
	(c) Salivary glands	Increased salivation
	(d) Lacrimal (tear) glands	Increased lacrimation
	(e) Cardiovascular system	Bradycardia, fall in blood pressure
	(f) Bronchial	Sensation of tightness in chest, wheezing suggestive of bronchoconstriction, dyspnea, cough, increased bronchial secretion, pulmonary edema
	(g) Pupils	Pinpoint (miosis) and nonreactive to light
	(h) Ciliary bodies	Blurring of vision
	(i) Bladder	Increased frequency of and involuntary urination
(2)	Nicotinic manifestations	
	(a) Striated muscle	Muscular twitching, fasciculation, cramping, weakness (including muscles of respiration)

TABLE III-2 (CONTINUED)

SIGNS AND SYMPTOMS ASSOCIATED WITH ACUTE AND SUBACUTE EXPOSURES TO MALATHION

Effector Organ	Signs or Symptoms
(b) Sympathetic ganglia	Pallor, tachycardia, elevation of blood pressure
(c) Adrenals	Elevation of blood pressure, elevation of blood glucose
(3) CNS manifestations	
	Uneasiness, restlessness, anxiety, tremulousness, tension, apathy, giddiness, withdrawal and depression, headache, sensation of "floating," insomnia with excessive dreaming (nightmares), ataxia, slurred and slow speech with repetition, drowsiness, difficulty in concentrating, confusion, emotional lability, coma with absence of reflexes, Cheyne-Stokes respirations, convulsions, hyperpyrexia, depression of respiratory and circulatory centers (with hypopnea or apnea and fall in blood pressure)

Derived from Grob et al [48] and Namba et al [49]

"foaming at the mouth," bronchospasm and bronchorrhea with rales or rhonchi, sweating, tearing, tachycardia, and sometimes mild stupor. Pupils were pinpoint except in a few milder cases. In 30% of the patients, transient glycosuria, as determined by reaction with glucose oxidase strips, was found. Three of sixteen of these patients had elevated concentrations of glucose in their blood. Blood urea concentrations

remained normal, but lactic dehydrogenase activities were elevated in the seven moderately ill patients tested. Serum calcium was determined in only seven cases and was not found to be elevated. Hematocrits were normal, but the white blood counts were reported to be acutely high. Specific values were not reported for these determinations.

Severely ill patients [50] had all of the above symptoms and signs, as well as hypotension, coma, cyanosis, areflexia, and sometimes convulsions, fasciculations, involuntary defecation, and Cheyne-Stokes respiration. Death occurred in 80% of the severely intoxicated patients despite intensive therapy. Nine of the severely ill patients had elevated blood pressures (mean, 170/110). Seven of these nine cases (four of them fatal) were females. Twitching of the eyelids, ankle clonus, muscle spasms, and acroparesthesias were occasionally noted.

Respiratory insufficiency was the cause of death in most reported cases of fatal malathion poisoning. [25] This terminal event was a consequence of one or more of the following: bronchial hypersecretion, weakness or paralysis of the intercostal muscles and diaphragm, and depression of the respiratory centers of the brain. [51]

The time of onset of signs and symptoms of poisoning after malathion exposure has varied from a few minutes [20,39,52] to several hours, [19] and to as long as 14 hours in the case of a child poisoned by the application of a 50% malathion-xylene hairwash solution. [27]

Hyperglycemia and glycosuria have been reported by three authors in connection with six patients with malathion poisoning, [25,27,40] although the pathophysiologic significance of this occurrence is unknown. Reports on three of these six patients noted the absence of acetone in the urine.

No comment on this finding was made in the other two cases. One case of glycosuria without hyperglycemia has been reported. [40] In one near-fatal accidental ingestion of malathion, the blood sugar was normal, and only a small amount of sugar was found in the urine. [19] Nalin [50] found transient glycosuria in 30% of the moderately ill cases. Five other reports of malathion intoxication [20,23,24,45,53] did not mention blood or urine glucose determinations. The degree of elevation of blood sugar that occurs in some cases of acute malathion poisoning has been shown to be much less than the levels associated with diabetic coma. [25]

Trinh Van Bao et al [54] conducted a study of 14 patients admitted to the hospital for malathion intoxication from either vocational exposure or attempted suicide. Blood samples were taken from all 14 patients within 3-6 days and thereafter at approximately 30 and 180 days from 12 of the group, one having died and another having declined to participate further in the study. Lymphocyte cultures were examined for chromosomal abnormalities and compared with those from 13 male and 2 female healthy unexposed controls. Stable chromosomal aberrations (ie, those containing deletions, translocations, and inversions) increased significantly immediately after intoxication, remained at a high level after 1 month, but returned to levels comparable with those seen in the controls after 6 months. The incidence of stable aberrations was not correlated with the dose of malathion. Of the patients examined, all were treated with atropine, and 9 (8 of the 12 completing the study) of the 14 also received Toxogonin (bis(4-hydroxyimino methylpyridinium(1)methyl)ether dichloride). The authors commented that they had not observed chromosomal damage in patients not poisoned by malathion but "treated with atropine shock." They

had no information to enable them to allow for the possible effects by Toxogonin, solvents, or vehicles involved in the poisoning and treatment on chromosomal structure.

Czeizel (unpublished manuscript) reported further data on the same 14 patients studied by Trinh Van Bao et al. [54] The malathion implicated in these studies was manufactured in Czechoslovakia. "Peripheral blood" samples, as cited by Trinh Van Bao et al, [54] revealed an "outstandingly high number of structural chromosome aberrations." The results of undefined animal experiments with malathion dissolved in cooking oil showed a higher frequency of break-isobreaks and deletions in bone marrow cells after 24 and 48 hours of treatment, and a higher occurrence of XY univalents and translocations in testicular tissue. This unpublished manuscript stated no doses, no correlation of the frequency of abnormalities with dose, and no numbers or types of experimental animals involved. In the absence of significant experimental details, such as dose and number of animals, and of independent confirmation in other laboratories, the significance of these unpublished observations for the human population is unknown. To this time, no human reproductive effects attributable to malathion seem to have been reported.

Mattson and Sedlak [55] measured the ether-extractable phosphates in the urine of an adult man who had been administered malathion in a single oral dose of 58 mg (0.84 mg/kg). A total of 23% of the ingested dose was recovered in the ether-extractable, urinary phosphate fraction of the urine during the first 16.3 hours. Ninety-seven percent of this recovered dose was excreted in the first 7.5 hours. A smaller dose of 11 mg (0.16 mg/kg) gave a similar excretion pattern. Based on experiments in rats injected ip

or fed 32P-labeled malathion, the authors [55] found an average of 69 and 36%, respectively, of the malathion excreted in the urine to be recoverable in the ether-extractable fraction.

Moeller and Rider [21] fed 10 healthy men daily doses of malathion dissolved in corn oil to determine the amount of malathion which can be ingested over an extended period of time without causing ChE activity depression. Five subjects each received 16 mg/day of malathion for 47 days, and five were given 24 mg/day for 56 days. Control ChE activities for these same subjects were determined twice weekly for 2 weeks preceding the experiment. The observed decrease in ChE activity reached a maximum 3 weeks after discontinuation of administration of malathion. Both erythrocyte and plasma ChE activities rebounded to normal quite rapidly thereafter, erythrocyte ChE reaching the baseline value and plasma ChE leveling off at about 93% of baseline within 10 days. The erythrocyte ChE overshot the baseline value during the month following a 20-day postdose observation period, whereas the plasma ChE remained at 90-95% of baseline during this period. It is possible that some reservoir of malathion or some persistent effect of malathion on AChE and BuChE was exhausted about 21 days after the cessation of daily doses.

Studies of humans exposed to malathion aerosols were reported by Golz. [56] For 42 consecutive days, three groups of four men each received a total of 84 1-hour exposures to malathion aerosols sprayed once into exposure-room air at calculated initial concentrations of 5.3, 21.2, or 84.8 mg/cu m. Since the aerosol concentrations represented a static exposure which must have declined rapidly, the actual dose received by each subject cannot be calculated. No significant decrease of ChE activity in

either plasma or erythrocytes was noted, nor were any cholinergic signs or symptoms found at any time during the study.

In 1960, Mattson and Sedlak [55] described a chemical method to measure exposure to malathion, which entailed the study of the urinary excretion of malathion-derived materials in humans. The method was developed using laboratory animals. In the first experiment conducted, one male and one female rat were given 100 mg/kg of 32P-labeled malathion intraperitoneally (ip) daily for 5 consecutive days, and one male and one female rat were given peanut oil only by the same route. A device which separated urine and feces was used, and both were collected for each 24-hour period. This separation, however, did not rule out the possibility of cross-contamination. The urine was first assayed for the total amount of radioactive materials present. The percentage of dose recovered ranged from 20 to 73 (average 46%) for the 5-day period. The authors [55] noted that, as no extraordinary attempt was made to obtain quantitative recovery of all the urine, some of the variation in percentage recovery might have been due to collection losses. They reported that assay for total malathion metabolites established the presence of large amounts of these in the rat urine. Samples at 48, 72, and 96 hours after cessation of treatment showed a rapid decline in the amount of metabolites recovered, although it was still measurable after 96 hours.

The acidified urine was extracted with carbon tetrachloride followed by ether. [55] The extracted urine was analyzed colorimetrically by both the procedure of Fiske and Subbarrow [57] and the Chen et al modification [58] of the Ammon and Hinsberg method, [59] with the latter method determined to be four times as sensitive as the former. The urinary

metabolites were calculated in terms of malathion.

Ether extracted 13-43% of the daily dosage from acidified urine for the treatment period. This represented 47-78% (average 66%) of the total malathion-derived material excreted in the urine. Using this extremely sensitive method, ether-soluble, malathion-derived materials were also found to be excreted up to at least 96 hours after cessation of treatment.

The dose was next reduced to 25 mg/kg, with the other experimental parameters maintained the same. Urinary excretion of the total daily intake ranged from 37 to 47% (average 42%), and daily urine samples taken at 24-hour intervals after treatment showed amounts of malathion-derived material detectable by radioassay. Ether-extractable materials ranged from 38 to 75% of the total daily intake, averaging 69%, which the authors [55] concluded was within the same range (average 66%) as for the higher level of intake. The authors deemed the amounts of ether-extractable urinary phosphates to be almost directly proportional to the dose of malathion at both doses used.

Malathion labeled with 32P administered orally to male and female rats at a dose of 100 mg/kg was excreted to the extent of 24 and 48%, respectively, in the urine, of which 31 and 36%, respectively, was ether-soluble. [55]

According to the authors, [55] colorimetric determination of phosphates in the ether-soluble materials gave good correlation with the radioassay. Ether extracts from the urine of control animals were reported to show no detectable amounts of organic phosphate.

The same method [55] was applied to human urine obtained from a man who ingested 58 mg of technical malathion (0.84 mg/kg). This dose was

below that capable of causing any detectable ChE inhibition. Preexposure urine samples showed no detectable amounts of ether-extractable phosphates. The amount of ether-extractable phosphates was seen by the authors [55] to rise quickly after dosage and then decrease to the predosage level. A total of 23% of the dose was recovered after 16.5 hours and 97% of this was excreted in the first 7.5 hours. The rate in mg/hour was greatest in the sample taken 1.3-3 hours after ingestion. A smaller dose of 11 mg of malathion (0.15 mg/kg) gave a similar result so far as the percentage recovered was concerned. However, metabolites could be detected for a shorter time after ingestion of the smaller dose of malathion, even though the more sensitive method for detection was used.

Application [55] of malathion in a talc dust to the skin of a man resulted in the appearance of ether-extractable phosphatic materials in the urine. One hundred milligrams of malathion as a 1% dust was applied for 14 hours; 1% of the dose was recovered during this period. It was reported that with higher amounts of malathion the percentage recovery of metabolites from the urine was of the same order. No ChE inhibition was detected.

Using the method described by Mattson and Sedlak, [55] Hayes et al [32] studied the urinary excretion of malathion-derived material after dermal application of various doses on human volunteers, as well as the effect of these applications on blood ChE activity. The malathion (minimum 95% purity) was formulated in talc at concentrations of 0, 1, 5, and 10%. Each volunteer was issued 90 g of powder 5 days/week for up to 16 weeks. After showering and contributing a blood sample if necessary, each volunteer dusted his entire body except head, neck, and genitalia with

powder. This required only 25-30 g, and the rest was sifted into the clothing. Hands and forearms were washed immediately after dusting. Prior to and after the experiment, physical examinations were conducted. Blood ChE activity was measured by the Nelson procedure [60] several days each week for the first few weeks, and weekly thereafter. Urine samples were collected in a hospital during an approximate 6-hour period every 6th night, both volume and sampling duration being recorded.

The initial review of symptoms [32] indicated no complaints resulting from significant illness and no increased prevalence of symptoms in one group. Only two complaints, burning of the skin and visible dermatitis, were noted during the course of the experiment. Results of the bromsulphalein test remained normal (less than 10% retention) throughout the course of the experiment.

A Student's t-test showed that erythrocyte ChE activity values determined [32] on paired samples by the methods of Nelson [60] and Michel [61] could not be distinguished. The experimental design did not allow prediction of either the minimum dose necessary to produce a statistically significant inhibition of AChE activity or the dosage necessary to produce clinical symptoms of intoxication.

The highest rate of malathion excretion [32] was 9.57 mg/hour, and the highest concentration of ether-extractable phosphate was 107 ppm calculated as malathion. The coefficient of correlation between body surface and the excretion of malathion-derived material ranged from 0.43 to 0.64 for the groups receiving 5 and 10% malathion; no correlation was found in the 1% group.

The mean malathion excretion rate [32] was 0.30 ± 0.19 mg/hour for 1% dusting powder, 1.74 ± 1.65 mg/hour for 5%, and 1.99 ± 1.25 mg/hour for 10% powder. Given 28 g as the amount of dusting powder actually applied, the formulations made available 0.28-2.8 g of malathion. Mean minimum amounts of 7.8, 41.76, and 48 mg/day, respectively, of the malathion in the 1, 5, and 10% formulations, were excreted as measured ether-extractable material. As shown by Mattson and Sedlak, [55] these figures are in the order of one-third lower than the actual excretion rate because of the extraction of only a part of the malathion and its metabolites. Only with the 10% malathion dust was there any evidence of possible depression of ChE, suggesting that the human body can be safely exposed to up to 2.8 g of malathion in talc powder/day applied to the skin. This is equal to an absorbed dose of 40 mg/kg for a standard 70-kg man.

Mammalian tissues effectively detoxify malathion. [62,63] An enzyme which hydrolytically cleaves one ethyl alcohol moiety from malathion has been partially purified from human liver specimens by Main and Braid. [62] In addition to malathion, the enzyme preparation (termed aliesterase) was found to hydrolyze several aliphatic and aromatic esters. The half-maximal velocity (Km) of the enzyme was estimated to be 48 μM. The maximum capacity of human liver homogenates to degrade malathion was estimated to be 7.9 μM/g of liver/minute. Since only 1 mole of a titratable acid was released for each mole of malathion, the authors concluded that the reaction product was malathion monoacid. Since neither malathion monoacid nor malaoxon monoacid is a ChE inhibitor, the catalytic detoxification of malathion by aliesterase is an important aspect of mammalian resistance to malathion-induced intoxication. Because most other commercial

organophosphates do not contain a carboxy ester as a functional group, they are not substrates for aliesterase and are not detoxified by this mechanism. This fact probably contributes to the relatively low order of toxicity of malathion for mammals in comparison with that of other organophosphates. [64]

Matsumura and Ward [63] investigated the in vitro degradation of malathion by fresh human liver samples. Tissue samples from livers frozen no later than 16 hours post mortem were homogenized in Kronecker's saline solution at a concentration of 20 mg of tissue/ml. Aliquots of 1 ml of homogenate were incubated with 0.00001 M malathion for 1 hour. Unreacted malathion and soluble metabolites were extracted twice from the aqueous fraction with an equal volume of chloroform. The combined solvent phase was reextracted with sodium phosphate buffer. The aqueous phase was washed with chloroform. All solvent phases were combined, dried over sodium sulfate, and analyzed by thin layer chromatography. The results were given by the authors in terms of percentage of substrate added. The authors [63] stated that the accuracy of recovery of their procedure was 96.7 ± 8.5%.

Six samples of human liver homogenate tested [63] hydrolyzed 99.57, 95.28, 98.45, 98.44, 97.94, and 98.53% of the added malathion. Of the hydrolysis products, 3.97-5.71% appeared as desmethyl malathion, 0.07-1.23% as diethyl mercaptosuccinate, 0.08-0.48% as diethyl malate, 85.51-90.76% as carboxyesterase products, and 0.09-7.38% as "others." Although the data suggested that malathion is efficiently detoxified by humans through the action of the carboxyesterase. Walker et al [65] found that in the human liver, this same carboxyesterase is beta-aliesterase. [64,66] Although the results of the Matsumura and Ward in vitro study [63] reinforce the

knowledge that carboxyesterase activity is of prime importance in the detoxification of malathion in humans, they cannot be taken as an absolute indication of the proportions of metabolites to be expected in vivo.

Milby and Epstein [67] studied the contact-sensitizing effect of malathion on skin under both experimental and field conditions. The experimental study utilized 87 healthy male volunteers divided into four groups. The first group was exposed for 2 days to 10% malathion in ethanol on a skin site previously irritated by a 3-second freeze with dichlorodifluoromethane (Freon 12). There were no controls for the first group. Group 2 was exposed to the 10% malathion solution applied to a nonirritated site. Groups 3 and 4 received the Freon 12 irritation and were then exposed to 1.0 and 0.1% solutions of malathion in ethanol, respectively. All applications were made under occlusive dressings. After 30 days, all subjects were retested at a new site with a nonirritating dose of malathion (1% in ethanol). The areas were graded after 2, 4, and 6 days for intensity of cutaneous response (1+, erythema and edema, to 4+, bullae). Ten percent malathion was found to induce contact sensitization readily and the reactions were marked. To further examine the degree of sensitization, five highly malathion-sensitive subjects were tested with weak solutions of malathion in acetone and in water. A 1:10*6 (* means to the power of) concentration in acetone evoked 4+ reactions, and a commercial product consisting of 0.9% malathion in water with an unidentified suspending agent evoked positive responses as well. The field study comprised two occupationally exposed groups, the first composed of 157 sprayers, mechanics, and supervisors from mosquito abatement districts (93% of the total work population of those districts), and the second of 43

poultry-rancher volunteers (10% of the area's ranchers) who had used malathion for at least one season during the past 3 years. Each subject was interviewed for history of past or present asthma, hay fever, allergy, skin disease, and systemic poisoning by pesticides. Records were made of each individual's exposure to malathion and other organophosphate pesticides. Exposure was quantified according to the total years of malathion use and an estimate of the number of times it was used. The subjects then were tested with an emulsion of 1% malathion in distilled water applied on a cloth pledget under adhesive tape to the skin of the upper arm for 2 days. Three days later, the reaction was observed and graded. Four of the 157 workers in the first group (3%) showed positive reactions. They were all considered heavily affected by the grader. Three of the four had previous histories of undiagnosed skin eruptions. The greatest number of sensitized individuals was found in a district which exclusively employed No. 2 diesel oil as the spray vehicle. The authors speculated that the properties of the oil may have contributed to the apparent skin sensitization. Two of the 43 poultry ranchers had positive reactions (5%). While these reactors had not been as heavily exposed as the mosquito abatement reactors, they also had histories of unexplained dermatitis. The results of these studies indicate that malathion may act as a contact skin sensitizer in humans, and that clinically significant dermatitis may occur under conditions of heavy field use. A chi-square test associating patch-test reactivity and history of dermatitis in mosquito abatement district workers was significant at the 5% level.

Several investigators have studied the exposure of workers to malathion in agricultural pest and vector control operations. [35-37,68,69]

These measurements of respiratory and skin exposure were undertaken to determine the margin of safety between exposure dose and estimated toxic dose. ChE activities, where determined, verified the absence of significant depression as a consequence of exposure to occupational field-encountered concentrations of malathion. These reports are described in Chapter IV.

Epidemiologic Studies

Only two epidemiologic reports on the effects of occupational exposure to malathion were found. Grech [69] examined alterations of the activities of serum BuChE, SGOT, SGPT, and serum aldolase, and the concentration of serum albumin in 12 agricultural workers exposed to malathion over a period of 6 months. Two groups of controls were used, consisting of 30 blood samples each, the first from randomly selected healthy blood donors and the second from healthy blood donors engaged in manual labor. The mean BuChE activity of the agricultural workers at the end of the exposure period was not significantly different from that of either group of controls. However, the author [69] stated that the enzyme activity of any single subject changed significantly after exposure. A reduction in BuChE activity was noted in 11 of 12 agricultural workers, and 6 showed a sustained fall until the end of the study. Two showed slight increases over their preexposure activities at the end. Both SGOT and SGPT were found to be without significant difference between the two groups of controls, or between the mean values of the agricultural workers and those of the controls. The largest percent changes in the mean values of the agricultural workers during exposure to malathion were decreases in the

activities of serum aldolase, SGOT, and SGPT, with that of BuChE changing the least of the four serum enzymes studied. No significant differences were observed in serum albumin concentrations. This study indicates that BuChE depression secondary to malathion exposure under field conditions does occur.

In 1968, the New Jersey State Department of Health [70] studied the medical records of 35 malathion- and/or Thiophos- (parathion-) manufacturing employees, 11 of whom had been employed in this capacity for 15 years or more. Medical examinations by the company had been done on a preemployment basis, and at 1-1.5 yearly intervals thereafter. The Department of Health reviewed the medical records of 16 employees who had averaged 15.5 years of work in the organophosphate-production facilities. Eleven of these men had been exposed primarily to malathion, with sporadic exposure to the organophosphates Abate, Zinophos, and parathion. After carefully reviewing and analyzing the company medical records, the Department of Health concluded that the 16 men were suffering no adverse chronic health effects from exposure to the materials used in the manufacture of the organophosphates. Beginning in March 1953, monthly ChE testing was done on workers in the manufacturing unit, which had begun operation in 1951. All employees were required to wear protective coveralls, helmets, and boots upon entering the work area, as well as rubber gloves and respirators when in the work area or engaged in manufacturing operations. Accidental splash exposures occurred in two of the long-term workers: one because of a leak (following which the employee showered and changed, but developed headache, nausea, and redness and itching of the arms and chest); the other by malathion being sprayed on the

face (no symptoms developed). ChE activities measured 33 and 34 days later, respectively, were within normal limits (erythrocyte 0.93 delta pH, plasma 1.1 delta pH in the first worker; bromthymol blue test, 90-100% activity in the second).

Animal Toxicity

Malathion is absorbed through the intestinal tract, [10,33] the skin, [10,33,71] and the respiratory tract. [33] Following absorption, it is transported via the circulatory system to the liver, where it is metabolized in part to products which are not inhibitors of ChE [72] and in part to its oxygen analog, malaoxon, a potent ChE inhibitor. [73] In the liver, both malathion and malaoxon are rapidly hydrolyzed, and thus detoxified, by an esterase enzyme system, [73,74] which itself is inhibited to some extent by malaoxon. [73,74] Hydrolysis of malathion is not restricted to the liver but occurs also in human brain, where two highly active esterases, two moderately active ones, and six others of lesser activity have been separated electrophoretically by Sakai and Matsumura. [75] This rapid enzymatic hydrolysis accounts for the low toxicity of malathion [76] to mammals as compared with insects, which have relatively less capacity to hydrolyze malathion. [77] The metabolites of malathion are listed in Table XV-4. Compounds such as EPN which inhibit this system of enzymatic hydrolysis tend to enhance the toxicity of malathion. [78-80] Compounds which induce the enzymes tend to decrease malathion's toxicity. [66]

After formation in the lungs, kidneys, liver, and other organs, malaoxon is transported via the circulatory system to the nervous system

and to muscle, where it sets in motion the following sequence of events: inhibition of ChE activity at synapses and motor endplates; accumulation of ACh at these sites; and the appearance of signs and symptoms of ChE inhibition or ACh poisoning. [64] The biochemical mechanism by which malaoxon inhibits the enzyme ChE involves phosphorylation of the active site of the enzyme. The phosphorylated enzyme is incapable of hydrolyzing ACh. [64] In time, spontaneous reactivation of the enzyme occurs or the inhibited enzyme "ages," becoming nonsusceptible to reactivation by 2-PAM and other oximes. [81]

The signs of acute intoxication which appear in animals poisoned with these agents are similar to those which occur in humans. These are listed in Table III-2. [82] Other manifestations of malathion toxicity which are unrelated to ChE inhibition are discussed later in this chapter.

The LD50's for rats, mice, and guinea pigs by various routes of exposure are given in Table XV-5.

The sex difference in susceptibility to the effects of malathion is generally confined to rodents. Sex differences in toxicity have been found for most organophosphorus pesticides. In a study [78] of the inhibition of the ChE's of the blood by malathion, the authors observed that larger doses were required to produce given inhibition of the enzymes in the male than in the female because of the male's higher rate of metabolism of malathion by oxidative microsomal enzymes. [79] Species differences have been investigated and attributed to differences in rates of detoxification by hydrolytic enzymes.

Golz [33] reported Hazleton's results on the acute iv toxicity of malathion in dogs. A dose of 100 mg/kg had no apparent effect, while 200

mg/kg produced severe signs and marked ChE inhibition and 250 mg/kg was lethal. No details of the purity of the malathion or of the ages, sexes, or numbers of dogs used were provided, nor was there any clarification of the observed signs.

The subchronic toxicity of malathion in rodents also has been investigated. Ten male and ten female rats [33] were given 90% technical malathion at a concentration of 5,000 ppm in the diet for 4-6 weeks. The average daily intake was 62 mg/kg for the male rats and 68 mg/kg for the females. All animals survived until killed after the 4th, 5th, or 6th week of feeding. No signs of adverse effects and no physical or behavioral changes were noted. ChE activity determinations were made on brain, plasma, and erythrocytes. Essentially all tests showed ChE inhibition of at least 50%, presumably compared with control animals although this was not stated. Also unspecified were the sex distribution and distribution relative to week of killing for the five animals showing 100% erythrocyte ChE inhibition. In another study, [33] an unspecified number of rats of unstated age and sex were fed 90% technical malathion at 5,000 ppm in the diet (77.9 mg/kg/day) for 63 weeks. At termination, the exposed animals weighed 12% less than the controls. ChE activity was not determined. The author reported that no other effects were detected. Another group of six rats of unspecified age and sex was given 99% malathion at 20,000 ppm in the diet (275 mg/kg/day) for 68-70 weeks. Four of the animals died before the conclusion of the experiment; the two survivors weighed 36% less than the control rats.

Clyne and Shaffer [17] reported the results of 2-year feeding studies of technical grades of malathion (90% technical and 99+% technical, both as

25% wettable powder formulations) in male and female albino rats. Survival, effects on food intake and growth, and degrees of plasma, erythrocyte, and brain ChE inhibition determined when the animals were killed were measured for comparison with control group values. The 90% technical grade malathion was administered at concentrations of 100 ppm (6 mg/kg of malathion) to 20 males, of 1,000 ppm to 20 males and 10 females (60 mg/kg and 80 mg/kg, respectively), and of 5,000 ppm (350 mg/kg) to 20 males. The control group comprised 20 males and 10 females. Of the controls, 10/20 males and 5/10 females were alive after 2 years. Survival rates in the 100-, 1,000-, and 5,000-ppm groups were: 15/20 males, 11/20 males and 8/10 females, and 14/20 males, respectively. No effects on food intake or growth were reported below the 5,000-ppm concentration; at that level, a retardation of growth was observed. Plasma, erythrocyte, and brain ChE activities were depressed 10-30% in the 100-ppm group. The 1,000-ppm males showed 10-30% plasma, 60-95% erythrocyte, and 10-30% brain ChE inhibition, while the females in this group showed no plasma inhibitions, but otherwise were the same as the males. Inhibition of 60-95% in both plasma and brain ChE's and total inhibition of erythrocyte ChE were found in the 5,000-ppm males.

The 99+% technical grade malathion [17] was administered at concentrations of 500 ppm to four male and four female rats (30 and 40 mg/kg, respectively), of 1,000 ppm to four males and four females (60 and 80 mg/kg, respectively), of 5,000 ppm to three males and four females (380 mg/kg for both sexes), and of 20,000 ppm to three males and three females (720 and 1,800 mg/kg, respectively). Survivals after 2 years for these groups were 2/4 males and 3/4 females at 500 ppm, 2/4 males and 1/4 females

at 1,000 ppm, 3/3 males and 3/4 females at 5,000 ppm, and 0/3 males and 2/3 females at 20,000 ppm (all males having died within 20 days at this level). No effects on food intake or growth were noted in males at 500 ppm, or in either males or females at 1,000 ppm. No results for the 500-ppm females were given. At doses of 5,000 ppm, both males and females exhibited reduced food intakes, and growth in males was retarded. Because of the early death of the 20,000-ppm males, only data for reduction of food intake and retardation of growth for the females were given. No inhibition of plasma or brain ChE was noted, but erythrocyte ChE was inhibited by 60-95% in both sexes at the 500-ppm concentration. At 1,000 ppm, no inhibition of plasma ChE, 60-95% inhibition of erythrocyte ChE in males and complete inhibition in females, and 30-60% inhibition of brain ChE in males and 10-30% in females were reported. ChE inhibitions at 5,000 ppm were 10-30% in plasma and 100% in erythrocytes of both sexes; brain ChE was inhibited 30-60% in males and 10-30% in females. In the surviving female fed 20,000 ppm, both plasma and brain ChE activities were inhibited by 60-95% and erythrocyte ChE by 100%. Gross and microscopic tissue examinations reportedly revealed no anatomic lesions attributable to the action of malathion. [17]

The experimental results of Fogelman on the effects of chronic feeding of malathion to rats were submitted to NIOSH (CB Shaffer, written communication, March 1976). Groups of three or four weanling albino rats (Carworth Farm strain) of each sex were fed diets containing 500, 1,000, or 5,000 ppm of 99% malathion for up to 104 weeks. In a parallel experiment with 90% malathion, 20 male rats and up to 10 female rats by group were fed 0, 100, 1,000, or 5,000 ppm of malathion for up to 104 weeks. At autopsy,

tissues from the liver, kidney, adrenal, spleen, large intestine, small intestine, brain, lung, bladder, and for females from the uterus, were examined microscopically from six animals of each group. Although no evidence of neoplasia was reported, the number of animals used was insufficient to allow a firm conclusion with respect to the induction of cancer by malathion in either this or any other species.

Using 32P-malathion, Mattson and Sedlak [55] measured the urinary excretion of all 32P-containing metabolites from one male and one female rat that had been injected ip with 100 mg/kg of the material. The total number of rats in each group and sex distribution were not specified. During the 24 hours after each of the five daily injections, the rats excreted a mean of 46% of the daily dose. After the end of daily dosing, the excretion rate fell rapidly but was still measurable after 96 hours. Male and female rats given 100-mg/kg oral doses of 32P-malathion excreted totals of 24 and 48%, respectively, in their urine. One male and one female rat injected ip with 25 mg/kg of 32P-malathion on each of 5 consecutive days excreted a mean of 42% of the injected dose during each 24-hour period following a dose. [55] The male excreted an average of 45% and the female 38%. After the daily injections were stopped, the label was detected in the urine for up to 5 days; between 24 and 120 hours after the last dose, the male excreted 1.5% of the daily dose and the female 5.1%. In the urine obtained after ip injections of 32P-labeled malathion, an average of 68% of the radioactivity was extracted from the urine by diethyl ether, whereas only 34% was similarly extractable after oral administration. Although a device was used to separate the urine and feces during collection, the authors [55] admitted that some cross-contamination

may have occurred. Fecal excretion of 32P-labeled material was not measured.

Hazleton and Holland [10] reported the results of inhalation studies on rats, guinea pigs, mice, rabbits, and dogs. Unspecified numbers of rats and guinea pigs were exposed to air bubbled through 90% technical malathion at 30 C, 8 hours/day, 5 days/week, for 2 weeks. No fatalities, no signs suggestive of ChE toxicity, and no significant lowering of ChE activity were observed. The estimations of ChE activity were made by an unspecified electrometric method, and the chamber concentration of malathion was not measured. Mice, rats, guinea pigs, and rabbits (numbers unspecified) were exposed to an aerosol of 90% malathion at a concentration of approximately 60 ppm for 6 hours/day for 2 days. The only responses noted were sneezing and rhinorrhea. Erythrocyte, plasma, and brain ChE activities were observed to be within normal limits for rats and guinea pigs, but they were not reported for mice and rabbits. Rats, guinea pigs, and a dog were exposed for 7 hours/day, 5 days/week, for 4 weeks to aerosolized malathion at a concentration of 5 ppm. The dog and guinea pigs lacrimated, but no tremors, salivation, or other signs of intoxication by organophosphate compounds were seen. No significant reduction in the ChE activities of plasma, brain, or erythrocytes were found, and no gross pathologic changes were detected at necropsy. Microscopic examination disclosed thickening and leukocytic infiltration of the intraalveolar septa.

Rats, guinea pigs, and dogs [10] exposed for 7 hours/day, 5 days/week, for 6 weeks to an aerosol containing dust equivalent to 5 ppm of malathion showed no gross evidence of toxicity. Moderate inhibition of plasma, erythrocyte, and brain ChE's were noted in the rats. The guinea

pigs had no significant inhibition of these ChE activities; one of two dogs had slightly inhibited plasma and erythrocyte ChE activities. Again, analytical methods were not detailed.

Weeks et al [83] exposed groups of 6 male New Zealand white rabbits and 20 Coturnix quail to aerosols of technical (95%) malathion and of 6% malathion in No. 2 fuel oil for periods of 6 hours. At concentrations of 6 and of 34 mg/cu m of aerosolized technical malathion, there were no toxic signs or significant decreases in blood ChE activities of the rabbits. At 34 mg/cu m, reductions in plasma ChE activity which averaged 51% were noted in the quail immediately after exposure, but no reduction was observed at 24 hours nor at 7 days postexposure. Plasma ChE activity was reduced in quail by 84% immediately following and by 63% at 24 hours after exposure to malathion at 65 mg/cu m, but it was not affected 7 days postexposure. No toxic signs or changes in blood ChE activities were found at this concentration (65 mg/cu m) in rabbits, although at 123 mg/cu m, significant decreases in ChE activities were found in plasma at 24 hours, and in erythrocytes at 24 and 72 hours and at 7 days. Quail exposed to 123 mg/cu m had significantly decreased plasma ChE activities immediately following exposure and at 24 hours, but not at 7 days. Microscopic examination of the tissues and organs of the test animals killed 7 days after exposure showed no pathologic changes due to the compound. From these data, quail appeared to react to malathion exposure in qualitatively the same way as rabbits, but to be slightly more sensitive to the compound at these concentrations and this duration of exposure.

Six-hour exposures [83] of groups of the same species and numbers of animals to aerosols of 6% malathion in No. 2 fuel oil resulted in the same

minimal effects of ChE depression in quail at concentrations equivalent to 24 and 34 mg/cu m of malathion as did exposures to aerosols of the 95% compound. Particle sizes were 12 μm mass median diameter (mmd) for the 95% formulation, and 25 μm mmd for the 6% formulation. Thus, it would appear that particle size had no effect on the responses of quail and rabbits to these aerosols. Exposures to 6% malathion in No. 2 fuel oil at levels of 66 and 128 mg/cu m resulted in mortalities due to respiratory distress, rather than to ChE inhibition, in both quail and rabbits. The respiratory difficulty appeared to have been caused by the heavy concentration of fuel oil in the formulation. One may conclude, then, that the possible toxic effects from the fuel oil may be a greater risk than those from malathion itself under these experimental conditions.

Oral administration of single doses of 0, 12, 120, 300, 600, or 1,200 mg/kg of technical malathion in corn oil to groups of six rabbits of the same strain was undertaken by Weeks et al [83] for comparison with the aerosol exposure results. They found that an oral dose of 300 mg/kg caused approximately the same inhibition of AChE as did the estimated dose of about 15-20 mg/kg inhaled by rabbits exposed to an aerosol containing 123 mg/cu m for 6 hours. These results indicated a greater hazard from inhalation than from ingestion of equivalent amounts of malathion.

Murphy et al [5] compared the abilities of malathion and its oxygen analog, malaoxon, injected ip, to inhibit the ChE activity in groups of four mice, of two or four chickens, and four of each of two fish species. They found that mice appeared to be 25 times more susceptible to malaoxon than to malathion, chickens 13 times, and bullheads about 80 times. The findings on sunfish were not appropriate for this kind of analysis, but the

authors indicated that this species was much more susceptible to the effects of malaoxon than to those of malathion. These results were adduced from brain ChE inhibition assays conducted in duplicate according to the manometric method of DuBois and Mangun. [84]

The occurrence and significance of in vivo interactions between malathion and other organophosphorus pesticides [53,80,85-91] and between malathion and certain drugs and chemicals [92,93] have been the subjects of numerous reports.

In 1957, Frawley et al [86] studied the effects of both single and coadministration of malathion and O-ethyl O-p-nitrophenyl phenylthiophosphonate (EPN) on 35 Osborne-Mendel strain adult male rats, and in male and female dogs. Rats in groups of five received ground diets containing 500 ppm malathion, 100 ppm malathion, 25 ppm EPN, 5 ppm EPN, 25 ppm EPN with 500 ppm malathion, or 5 ppm EPN with 100 ppm malathion. During a 4-week pretreatment period, five whole blood ChE activity determinations were done on each rat. One group was kept as a control. ChE activity of whole blood was measured on each animal after 1, 2, 4, 6, and 8 weeks on the test diet. Marked ChE inhibition (21% of pretreatment level) was observed in the group fed the combination of 25 ppm EPN and 500 ppm malathion, and minimal but significant inhibition occurred in the 25-ppm EPN group.

One dog of each sex was placed for 12 weeks on a diet containing 250 ppm of malathion, 100 ppm of malathion, 25 ppm of malathion, 50 ppm of malathion, 20 ppm of EPN with 100 ppm of malathion, or 3 ppm of EPN with 8 ppm of malathion, followed by a control diet for 8 additional weeks. Two dogs of each sex were maintained as controls throughout the experiment.

Both plasma and erythrocyte ChE determinations were made on five blood samples drawn during the course of 4 pretreatment weeks, and after 1, 2, 4, 5, 6, 8, 10, and 12 weeks on the experimental diet and 3 and 8 weeks on the terminal control diet. Only slight, but significant, inhibition of erythrocyte ChE was found at the 250-ppm dietary level, while 250 ppm of malathion and 50 ppm of EPN together caused up to 60% inhibition of plasma ChE and 93% inhibition of erythrocyte ChE activities. A combination of 100 ppm of malathion and 20 ppm of EPN caused questionable inhibition of plasma ChE, but up to 68% inhibition of erythrocyte ChE. Up to 24% inhibition of erythrocyte ChE was noted after 8 weeks on the diet containing 8 ppm of malathion and 3 ppm of EPN, but the ChE activity of the erythrocytes returned incompletely to pretreatment levels during the recovery period, thereby complicating the interpretation of the data. No animals exhibited gross manifestations of poisoning during the experiment.

Shortly thereafter, Cook et al [94] and Murphy and DuBois [78] demonstrated the capacity of the liver in vitro to alter malathion to a form not susceptible to conversion to malaoxon or any other active inhibitor of ChE. This activity was inhibited by EPN and Diazinon more markedly than by any other organophosphate compounds tested. Murphy and DuBois [78] also demonstrated that single ip doses of 13 mg/kg of EPN (1/2 LD50) clearly reduced the capacity of male and female Sprague-Dawley rats to detoxify malaoxon. This suggested that EPN increased the toxicity of malathion by inhibiting the enzymes responsible for its detoxification. Principal among these enzymes are the carboxyesterases. Cook et al [94] found that a number of organophosphorus compounds, after oxidation with bromine if they were thiophosphates, were inhibitors not only of ChE but

also of malathionase; here, EPN and Diazinon were particularly effective. Cook and Yip [74] showed that the change in the constitution of malathion by malathionase was caused by the formation of a monoacid homolog in the removal of one alcoholic residue from the diethylsuccinate portion of the malathion molecule. DuBois [80] found that when 50 compounds being tested for use as pesticides were given simultaneously in pairs to rats, potentiation occurred with four pairs. Among these were malathion with EPN, Dipterex, or Co-Ral. Certain other organophosphorus pesticides, such as Ronnel, [91] Delnav, [91] Dipterex, and Baytex, [79,88,95-98] and drugs of the phenothiazine family, [99] when administered for a period of days before exposure to malathion, have been found to potentiate the toxicity of malathion.

In addition to their studies on human liver homogenates, which were discussed in the preceding section, Main and Braid [62] analyzed the in vivo inhibition of serum aliesterase by malathion in male Sprague-Dawley rats. Initial serum aliesterase activities were measured, and single oral doses of 1,250, 1,500, or 1,700 mg/kg of 96.8% malathion were administered. Aliesterase activity was measured colorimetrically (pH 6.3 and 25 C) at 0.5, 1, 2, 3, 4, and 5 hours after dosing. The results are shown in Table III-3. The data suggest that high doses of malathion inhibit aliesterase, an enzyme which detoxifies it in vivo. The data may have been influenced by an epizootic infestation in the animal colony, but this was not experimentally verified.

Male rats (weighing 200 ± 50 g) [62] were administered practical grade tri-o-tolyl phosphate (TOTP) in single oral 0.5-mg/kg doses. Serum, erythrocyte, and brain ChE, and liver and serum aliesterase activities were

TABLE III-3

IN VIVO INHIBITION OF SERUM ALIESTERASE BY MALATHION IN RATS

Malathion (mg/kg)	Initial Activity (μ moles/ml of serum/min)	% Initial Activity Remaining					
		0.5 hr	1 hr	2 hr	3 hr	4 hr	5 hr
1,700	12.67	73.2	48.2	31.2	25.8	21.3	-
1,700	3.06	25.5	0.0	0.0 Death after 2 hr			
1,500	11.18	69	56.7	37.8	35.5	36.8	35.0
1,500	13.70	48	39.2	31.5	30.3	28.5	-
1,250	0.79	Death before 0.5 hr					
1,250	5.80	76.5	35.3	12.0	-	6.5	9.8

Adapted from Main and Braid [62]

measured during 5-25 hours. Serum aliesterase activity was reduced to zero within 60 minutes, and that of liver to 12% of its initial activity. After 24 hours, liver aliesterase activity was only 1.5% of the initial value. The effect of an identical TOTP pretreatment on the oral LD50 of 96.8% malathion was then examined in rats fasted for 24 hours before administration of malathion. Without TOTP, the oral LD50 of malathion was determined to be 1,600 mg/kg. This value fell to 35 mg/kg when malathion was given 1 hour after 0.5 mg/kg TOTP, and further still to 20 mg/kg when

malathion was administered 24 hours after the same dose of TOTP. While the eightyfold decrease in the LD50 of malathion cannot be attributed unequivocally to inhibition of the aliesterase, these data support this hypothesis by agreeing with the findings by Cook et al, [95] Murphy and DuBois, [78] and Frawley et al [86] of potentiation of the toxicity of malathion by EPN, demonstrated by these authors [78,86,94] to follow inhibition by EPN of carboxy-ester hydrolysis of malathion.

Welch and Coon [66] studied the effects of drug pretreatment on malathion toxicity. Young adult, unfasted, male Swiss-Webster mice (weighing 18-25 g) were pretreated for 4 days with SKF-525A, chlorcyclizine, phenobarbital, or cyclizine before administration of technical malathion (95%). Malathion (1,500 mg/kg) was given orally in corn oil 24 hours after the last pretreatment dose, which had been given in amounts equivalent to about 1% of body weight: chlorcyclizine, cyclizine, SKF-525A (each at 25 mg/kg, twice a day for 4 days), and phenobarbital (35 mg/kg, twice a day for 4 days). They concluded that mice pretreated with chlorcyclizine and phenobarbital were less susceptible to the lethal activity of malathion than control mice.

Interactions in which organophosphorus compounds affect the metabolism of other drugs or chemicals have not been reported to any great extent. Rosenberg and Coon [100] reported that malathion, along with OMPA, EPN, chlorthion, and phostex, but not DFP and TEPP, increased markedly the time during which a given dose of hexobarbital removes the ability of mice to right themselves from a position on one side. Malathion did not alter the toxicity of hexobarbital. Stevens et al [101] reported that several organophosphorus pesticides, including malathion, impaired the metabolism

of hexobarbital and aniline, as evaluated by hexobarbital sleeping time and para-hydroxylation of aniline. Male Swiss-Webster mice (25-35 g), Wistar rats (150-200 g), albino rabbits (900-1,200 g), and mongrel dogs (9-14 kg) were the experimental animals. Malathion (99.6%) dissolved in corn oil was administered orally at a dose of 5 ml/kg. First, the oral LD50 in mice was determined to be 5,896 μmoles/kg. Mice were then dosed with 1/8, 1/4, or 1/2 the LD50 of malathion. The hexobarbital sleeping time (HST) was measured at 30-minute intervals, beginning 1 hour after malathion administration. HST was designated as "the time interval elapsed from the loss to the recovery of the righting reflex after an ip injection of 100 mg/kg of hexobarbital sodium." [100] The results indicated that the pretreatment with malathion significantly increased the HST.

Stevens et al [101] reasoned that this increase in HST caused by malathion might be related to an interference with the metabolism of hexobarbital in the liver and demonstrated this through in vitro experiments. Malathion at a concentration of 2 x 10*5 M (* means to the negative power of) significantly inhibited hexobarbital metabolism by liver in vitro. No inhibition by 2 x 10*6 M malathion, however, was observed. Further experiments showed that malathion (0.01-M range) consistently inhibited the metabolism of hexobarbital in all species (mice, rats, rabbits, dogs, and humans) studied. Stevens and Greene [102] were able to show that, despite the apparent interference with the metabolism of hexobarbital by malathion, such effects were not correlated highly with effects of this compound on the oxidation of nicotinamide adenine dinucleotide phosphate (reduced form), reduction of cytochrome C, or reduction of cytochrome P-450 in liver microsomal preparations in vitro.

It is likely, therefore, that at least some of the metabolism of hexobarbital is performed by other than the mixed-function oxidase system.

Certain factors other than drug or chemical interactions have been shown to influence malathion toxicity. Brodeur and DuBois [103] studied the differences between mature and immature rats in malathion toxicity. Twenty 23-day-old weanling (50-60 g) and 18 adult male (200-300 g) Holtzman rats were used. Undiluted malathion was administered to the adults and was dissolved in a mixture of 20% ethanol and 80% propylene glycol for administration to weanlings. The LD50 of malathion was determined to be 340 mg/kg for weanling rats and 750 mg/kg for adults. Death or complete recovery occurred within the first 7 days after doses were administered. In a later study, Brodeur and DuBois [104] further investigated the previously documented [103] observation that weanlings were more susceptible than adult rats to malathion. The metabolism in the liver involves both the conversion of malathion to malaoxon, which is the active metabolite responsible for ChE inhibition, and splitting off by hydrolysis of one of the alcoholic residues in the diethylsuccinate portion of the molecule to produce a molecule that cannot be activated by the replacement of S with O. [74] Brodeur and DuBois [104] concluded that the age difference in susceptibility was due to relatively low levels of malathionase in the liver and other organs (especially, perhaps, brain) in young rats.

Weanling rats (23 days old, 50-60 g) and adult male and female rats (200-300 g and 175-250 g, respectively) were injected ip with malathion dissolved in a mixture of 20% ethanol and 80% propylene glycol. [104] Malathion was administered in amounts equivalent to 0.2% and 0.1% of

weanling and adult body weights, respectively. ChE activity was determined by the method of DuBois and Mangun. [84] The livers of the males were 2.5 times more active than those of the females in hydrolyzing malaoxon. Also, the detoxification process was more active in adults than in weanlings and young rats.

In addition, studies [104] indicated that ChE activity was decreased to 37 or 28% of normal in weanlings by 100 or 150 mg/kg of malathion. In adults, the same degree of inhibition resulted only after doses of 600 mg/kg. The LD50 for young, 12-day-old rats was 125 mg/kg; for adults, it was 900 mg/kg. Eighteen-day-old rats tolerated 100 mg/kg of malathion; the LD50 was 200 mg/kg. Thirty-day-old rats tolerated 400 mg/kg with little ChE depression. The LD50 for the 30-day-old rats was 600 mg/kg, and 800 mg/kg for the 42-day-old rats.

The effect of dietary protein on malathion toxicity has been studied by a number of investigators, among them Boyd et al. [105] At weaning, male albino rats were put on diets containing various amounts of casein for 28 days. Oral LD50's of malathion were then determined for each group as follows: Group I - 51 rats, 0% casein, LD50 539 ± 42 mg/kg; Group II - 110 rats, 3.5% casein, LD50 599 ± 138 mg/kg; Group III - 52 rats, 9% casein, LD50 759 ± 91 mg/kg; Group IV - 108 rats, 26% casein, LD50 1,401 ± 99 mg/kg; Group V - 51 rats, 81% casein, LD50 649 ± 51 mg/kg. Group IV (26% casein) represented normal dietary protein intake. The authors noted that prior to inclusion of malathion in the diet, the highest protein intake (Group V, 81% casein) had the following effects on the rats: diarrhea, diuresis, polydipsia, and other unspecified effects. The highest casein concentration in the diet may have produced an unappetizing diet. The mean

weight of the 28-day-old rats in Group V was only 70% of that of the rats in Group IV. This diet was noted also to cause definite pathognomonic changes, eg, renal capillary congestion and diarrhea, among others. The postulated inappetence and the observed diarrhea both would operate to decrease the absorption of protein into the body from the diet of Group V. Boyd et al [106] concluded that the toxicity of malathion was inversely proportional to dietary protein intake, except at extremely high protein levels.

Boyd and Tanikella [106] administered technical malathion (95%) in cottonseed oil by intragastric intubation to young male albino rats to determine the oral LD50. The rats previously had been fed normal (Group II, 26% casein) or low-protein (Group III, 3.5% casein) diets on days 28-56 of age or until they weighed 5-10% more than Group I rats, which were on a lab chow diet. At the end of the modified-diet feeding period, malathion was administered in single oral lethal doses (predetermined in a pilot study) of 700-1,400 mg/kg to Group I; 1,000-2,000 mg/kg to Group II; and 200-1,200 mg/kg to Group III. Each dose was given to 10 rats on the experimental diets, with 15-45 controls receiving cottonseed oil only. LD50's were determined to be 1,090 ± 83 mg/kg for Group I; 1,041 ± 99 mg/kg for Group II; and 599 ± 138 mg/kg for Group III. The authors concluded that the twofold increase in malathion toxicity in Group III rats over that in Group II rats was due to their low-protein diet. The authors speculated that low-protein intake might result in hepatic enzyme activity reduction, thereby altering the animal's ability to detoxify malathion. This was not supported by either experimental data or theoretical considerations.

Marton et al [107] studied the effect of chronic malathion treatment on tolerance to cold. Sixty-eight Wistar rats were randomly divided into four groups of 17 each according to treatment and sex. The control group received Fox Chow. The other groups were given the same chow mixed with 95% technical grade malathion dissolved in corn oil. The concentration of malathion was 4,000 ppm, so that the daily intake of malathion approximated 240 mg/kg of body weight. After 5 months, during which malathion had little effect, the experimental groups were exposed to an environmental temperature of 1.5 ± 1 C. They were given water but no food. Blood ChE activity was determined 2-3 weeks prior to the experiment and again within 15 minutes after death. The rats fed malathion survived the cold for a significantly shorter period than did the control animals (P less than 0.01). ChE activity was also significantly lower in the malathion-fed animals but did not differ significantly between preexposure and cold exposure activities. Malathion-fed rats did not appear to have increased heat loss over the controls. Hence, the authors [107] inferred that malathion decreased the ability of rats to produce a high rate of heat continuously over a prolonged period of time.

Durham et al [108] stated that the muscular weakness seen in the legs of chickens appeared to be the best available index of the possible paralytic effects of organophosphorus compounds in humans. They tested nine organophosphorus compounds, including malathion, for toxicity in atropinized chickens. Immediate muscle weakness appeared in 6 of 10 chickens given one subcutaneous injection of 1,000 mg/kg of malathion. The lowest dose of malathion that produced immediate muscle weakness was 100 mg/kg. Although the weakness was reversible and disappeared completely

within 4-21 days, the authors did not state whether this reversibility was a dose-related effect. Utilizing methods similar to those of Durham et al, [108] Gaines [109] investigated the effects of 9 carbamates and 30 organophosphates (in peanut oil suspension or solution) in an unspecified number of chickens. Within a few hours after the subcutaneous injection of malathion in doses of 100 mg/kg or more, leg weakness was observed and it persisted for 4-14 days. The results of microscopic examinations of tissues were not reported. Frawley et al [110] fed malathion to chickens at levels up to 10,000 ppm for 15 weeks. All of the birds died, but only one exhibited muscle weakness, and none showed microscopic evidence of nerve damage. O'Brien [64] pointed out that, while many known neurotoxic compounds are inhibitors of plasma ChE, most inhibitors of this enzyme do not produce neurotoxic effects. Malathion appears to be a ChE inhibitor that is not neurotoxic and does not induce demyelination of long axons.

Krause et al [111] administered 40 mg/kg of malathion (purity unstated) in corn oil to male rats on days 4 and 5 of age and 20 mg/kg to another group on days 4-24. Controls and experimental animals received 0.1 ml of corn oil/5 g body weight at each dose. Two rats from each group were killed for microscopic examination of the testes at 6, 12, 18, 26, 34, or 50 days of age. From the results obtained with this rather limited numerical base, the authors concluded that the weight of the testes and the mean diameter of the seminiferous tubules, as well as the number of Leydig cells, were reduced at some time during the experiment. All effects, however, disappeared by the rats' 50th day of life. The lesions in the testes caused by malathion were evaluated as "not very serious," and were limited essentially to the period of time during which the compound was

administered, because of the rapid excretion of the compound. All cell counts were reported to be normal after the 24th day of life.

Mohn [112] applied 0.2 M malathion to Escherichia coli K-12/gal Rs,8, a phenotypic gal-, and incubated it for up to 300 minutes. The resulting cultures were examined for forward mutations to 5-methyl tryptophan (5-MT) resistant colonies. In these experiments, the author reported using a concentration of 20μg 5-MT/ml and an inoculum containing 300,000-500,000 cells/ml. Cultures with spontaneous mutation rates of less than 25/plate were used. The mean number of cell generations was 8-9 during residual growth. According to the author, the results with malathion did not differ significantly from spontaneous values, even when 70% of the cells were inactivated. Malaoxon was not examined.

A study by Huang [113] also failed to reveal a mutagenic potential in malathion. Eighty thousand cells/ml from three different human hematopoietic cell lines were treated with malathion dissolved in dimethyl sulfoxide at concentrations of 50 and 100 μg/ml. Cells were harvested 6, 12, 24, and 50 hours after exposure to malathion. Colcemid at a concentration of 0.04 μg/ml was added to the cultures 2 hours before harvesting for chromosome preparation. [113] Cells were treated with 1% sodium citrate and fixed in acid-methanol (1:3). Flame-dried slides were stained with Giemsa's stain, and 100 metaphase figures were studied with an oil-immersion objective. Clear chromosome lesions (gaps, breaks, exchanges, dicentrics, pulverization, etc) were recorded for each group. Cell growth was inhibited, but returned to normal in cells placed in malathion at a concentration of 50 μg/ml after they were washed with fresh, pesticide-free medium. No resumption of growth was noted in cells placed

in malathion at a concentration of 100 μg/ml. Single gaps and breaks were found in 4% of the controls at 6 hours, 3% at 12 hours, 3% at 24 hours, and 2% at 50 hours. Similar counts had values of 2, 3, 5, and 0% at the same time periods for the 50-μg/ml concentration and of 5, 4, 5, and 5% for the 100-μg/ml concentration. These results, however, are contrary to the findings of Trinh Van Bao et al [54] reported in Effects on Humans.

The use of submammalian test systems and in vitro cell cultures should be regarded only as ancillary procedures to supplement mutagenic studies using intact mammalian test systems, according to a recommendation by a WHO Scientific Group in its 1971 report entitled Evaluation and Testing of Drugs for Mutagenicity: Principles and Problems. [114] NIOSH agrees with the general philosophy of this recommendation.

Kimbrough and Gaines [115] studied the possible teratogenic effects of several organophosphorus pesticides, including malathion, on rat fetuses after a single ip injection into the mother. Six dams were injected ip with 600 mg/kg of malathion and six others with 900 mg/kg on the 11th day of their pregnancy. The fetuses were removed on the 20th day of pregnancy. The higher dose of malathion produced a slight tendency for the weights of the placentas and the fetuses to be reduced and one instance of adactylia among 67 fetuses. The lower dose produced no evident effects. It should be noted that administration of the pesticide in a single dose on day 11 of gestation may have resulted in less teratogenic effect than either repeated or earlier doses.

Dobbins [116] conducted a screening study of the teratogenic potential of various malathion doses in 15 pregnant Wistar rats. The drug was dissolved in corn oil and administered by stomach tube on day 9 or 10,

or from days 8 to 12 or 12 to 15, of pregnancy. Seven control rats were untreated. On day 20 of gestation, the dams were killed and the fetuses examined. A suggestion of teratogenic effect on the urinary system was noted, but the data and the experimental detail were confused and insufficient for any conclusion. None of 74 control fetuses was considered to be abnormal; the usual rate of spontaneous abnormalities would be about 1%.

Lillie [117] fed seven groups of 20 Leghorn pullets a breeder diet containing either 0, 250, or 500 ppm of malathion, 250 or 500 ppm of carbaryl, 250 ppm each of malathion and carbaryl, or 500 ppm each of both pesticides. Observations during a 36-week period included changes in body weight, egg production, egg weight and specific gravity, feed consumption, mortality, fertility, hatchability, embryonic abnormalities, and performance of progeny. In the studies of performance by progeny, chicks from hens fed 0 or 500 ppm of malathion or malathion and carbaryl were fed a broiler diet supplemented with 0 or 500 ppm malathion or carbaryl for 4 weeks. The only significant effect was a smaller weight gain in adult birds fed the mixture of carbaryl and malathion. Decreased growth was observed in the progeny fed carbaryl, irrespective of maternal diet, but it was not seen in those fed malathion. In a separate 4-week study, [117] the incorporation of 500 ppm of malathion, of carbaryl, or of both, into the diet of Leghorn cocks produced no significant changes in fertility pattern, production of sperm, or embryonic abnormalities.

Greenberg and LaHam [118] injected malathion at concentrations of 3.99 or 6.42 mg/egg into the yolk sacs of 50 hens' eggs incubated for 4 or 5 days. Twenty-five control eggs were used. The eggs injected with

malathion produced chicks exhibiting sparse plumage, micromelia, overall growth retardation, and beak defects. The authors speculated that the observed abnormalities could be attributed to an in vivo retardation of cell growth and protein synthesis, but they did not provide any experimental support for this contention.

Ho and Gibson [119] injected hen's eggs with 0.1 ml of 2% malathion in corn oil on the 5th day of incubation. The treated embryos showed a generalized reduction in body size, delayed patterns of mineralization in certain endochondral bones, and micromelia. Tibiotarsi consistently exhibited retarded growth, cartilage necroses, and angulation. In another paper, [120] Greenburg and LaHam used the technique of injecting into the yolk sacs of 4- or 5-day incubated hens' eggs 6.42 mg/egg of malathion either alone or with various amino acids, vitamins, and nicotinamide adenine dinucleotide precursors to attempt to find means for preventing the malformations and retardation of growth induced by malathion. Nicotinamide (5 mg), nicotinic acid (5 mg), and quinolinic acid (4.3 mg) prevented the malformations, but growth was still stunted. Tryptophan (5.1 mg) was the only compound of 32 tested that prevented both malformation and growth retardation. Indole, indoleacetic acid, and serotonin had no antagonistic value. Indeed, in two of four experiments, indole had a more marked effect than malathion itself, and indoleacetic acid enhanced the effects of malathion. The authors suggested, therefore, that malathion may have had no direct metabolic effect on the egg but rather may have disturbed the electronic milieu within the egg, and that tryptophan nullified this effect by virtue of its particular ionization potential. Compounds having an ionization potential near that of tryptophan (adenine, guanine, alpha-

naphthol, beta-naphthol, indoleacetic acid, and quinoline) by themselves had no effect on the embryos, but did have a magnifying effect when given with malathion. Imidazole, with an ionization potential quite different from that of tryptophan, was neither therapeutic nor synergistic with malathion. The ionization potential appears, therefore, not to be the basis of either the ovotoxic effect of malathion or the protective action of tryptophan.

Wilson and Walker [121] reported that malathion in concentrations greater than 1 μg/ml was toxic to primary cultures of chick embryo fibroblasts.

While many of the basic concepts of teratology were initially investigated using avian eggs, the absence of anatomic and physiologic maternal-fetal relationships during incubation makes it difficult to extrapolate from the effects on the avian egg to teratogenic hazards to humans. The use of mammalian species for evaluation of possible teratogenic hazard is now recommended by the WHO Scientific Group on the Principles for the Testing of Drugs for Teratogenicity. [122] Because of the difference between the conditions within an egg and within the amniotic sac of mammals, the production of terata within eggs indicates a teratogenic potential but does not necessarily mean that mammals will be likely to develop terata on exposure of pregnant females to the same influence.

In a study using malathion administered in the diet at a rate of approximately 240 mg/kg/day, Kalow and Marton [123] found no effects attributable to malathion in the reproductive performance of 18 female and 12 male experimental rats mated after 10 weeks of feeding on the malathion-

containing diet compared with 18 female and 12 male control animals. However, the survival to weaning of the offspring of animals fed malathion was only 31.8% versus 64.7% in the control group. The mean gain in body weight of offspring from the malathion-fed rats was only about 85% of that of control offspring from weaning to 9 weeks of age. The authors suggested that this effect may have been due to a lowered resistance of the treated animals to infection or "other noxious influences" in the colony and not necessarily to ChE inhibition.

The effects of malathion on the reproductive capacity of rats in a three-generation reproduction study have been reported. [124,125] The test material (95% pure) was incorporated into the diets of all three generations of rats in concentrations of 100, 500, or 2,500 ppm (approximately 5, 25, or 125 mg/kg/day). Sixteen pairs of rats in each group were mated, beginning with the original weanling rats, as were an equal number of untreated paired controls. Signs of ChE inhibition were not present. The following effects ascribed to respiratory disease were observed in the 2,500-ppm group: death of 4 of 16 dams; lower ratios of litters to pregnancies and of pups weaned to pups aged 5 days plus lower pup weights in all 3 generations. Both matings of the second generation on the 2,500-ppm diet produced pups of lower body weight and reduced ratios of pups weaned to pups at 5 days, relative to the controls. The authors [124,125] suggested that this may have been due to a change of bedding material which, in turn, induced respiratory distress. The fertility of the rats used in the final mating at the 2,500-ppm level also was reduced, but no malformations in the pups were observed. Microscopic examinations of the pups from the third generation, first mating, of the control and

high-level groups revealed similar minor lesions. The data revealed no adverse effects at the 100- and 500-ppm levels. However, the respiratory distress, reduced fertility, reduced pup weights, and poor pup survival at the 2,500-ppm level may have been due to malathion.

Correlation of Exposure and Effect

A number of biologic effects associated with malathion exposure have been documented in humans and experimental animals. The effects of exposure are the complex group of signs and symptoms which result to an unknown extent from the accumulation of ACh at various neural synapses and motor endplates. These signs and symptoms are discussed in detail in Effects on Humans and are tabulated in Table III-2. [48,49] Death due to malathion intoxication has been attributed to depression of the respiratory center of the brain, [126] presumably as a result of accumulation of ACh.

In humans, ingestion of malathion has been shown to produce all of the signs and symptoms of cholinergic stimulation up to and including death. Nalin [50] reviewed 264 reports of attempted suicide collected over a period of 3 years in Guyana. All patients experienced signs and symptoms consistent with cholinergic stimulation, and 53 individuals (20% of the total) died.

Eight case study reports [19,20,25,39,44-46] found in the literature specified the amount of malathion ingested and the characteristic manifestations of cholinergic stimulation observed. In the first case, [20] a 14-year-old boy weighing 165 lb ingested approximately 4 ounces (approximately 118 ml) of malathion (purity not reported). The authors calculated this to be a dose of approximately 0.4 g/kg of body weight. The

victim exhibited a wide range of severe manifestations consistent with cholinergic stimulation. He was comatose and recovered only after intensive therapy. In another case, a 45-year-old man ingested 50-90 ml of 50% malathion in a petroleum hydrocarbon base. Although the patient's actual weight was not reported, assuming one of 70 kg, a maximum dose of approximately 0.8 g/kg can be calculated. The patient experienced the full range of cholinergic symptoms, including marked respiratory insufficiency requiring tracheostomy and mechanically assisted ventilation, cardiac arrhythmia, and unconsciousness. He survived only with intensive and prolonged therapy. In a third incident, [39] a 42-year-old woman ingested 120 ml of 50% malathion garden spray solution. Goldin et al [39] estimated the maximum intake at 1.0 g/kg. The victim displayed signs consistent with cholinergic stimulation, including coma and profound shock. After intensive therapy, she survived without sequelae. In five similar cases, [25,44-46] the estimated doses consumed, which resulted in severe poisoning that would have been fatal but for intensive therapy, were in the order of 0.5, 0.9, 0.7, 0.5, and 0.6 mg/kg. From the extremely grave clinical picture exhibited by these patients, it is clear that all had absorbed doses of malathion which would have been lethal without intensive and prolonged therapy. Based on these cases, each of which was stipulated by the authors to have been nearly fatal, it appears that without treatment, the acute oral lethal dose of malathion in humans would be somewhat below 1.0 g/kg.

In a human experimental study, [21] five men ingested 16 mg of malathion/day for 47 days. The malathion was administered as a corn oil solution in gelatin capsules. The subjects exhibited no clinical effects

and reported no subjective complaints during or after the study. There was no drop in blood ChE activity. If an average weight of 70 kg is assumed, the approximate daily dose for these men was 0.22 mg/kg.

In a similar study, [21] the same authors administered malathion at a daily oral dose of 24 mg to five men for 56 days. This dose would amount to 0.34 mg/kg, assuming an average weight of 70 kg. Although no clinical signs or symptoms of poisoning were observed, a statistically significant drop in plasma ChE activity was noted after 2 weeks. The maximum depression of 25% occurred after 3 weeks. However, the activity returned to normal throughout the remaining 5 weeks of the experiment. At 7 weeks, there was also a drop in erythrocyte ChE activity. This reached a maximum 2 weeks after completion of administration of malathion.

There are very few human data available that give a quantitative relationship between respiratory exposure to malathion and biologic effects. In Golz's study, [56] four volunteers were exposed to malathion in a room in which an aerosol was dispersed at the beginning of a 1-hour exposure period. The maximum theoretical air concentration at the beginning of the exposure period was approximately 2.4 g/1,000 cu ft, or approximately 85 mg/cu m of malathion. The true concentration to which the men were exposed probably was smaller than this since the aerosolized formulation may have settled out within a short time following its generation. The subjects were examined weekly during the 42-day period of twice-daily exposures, and no signs or symptoms consistent with excess ACh accumulation were observed. Several studies [35-37] have been performed in which respiratory exposure to malathion during actual application was estimated. In cases in which workers were exposed to malathion during its

application in field use, the respiratory rate of exposure ranged from approximately 0.01 to 1.23 mg/hour. The skin exposure rate was 10-100 times the respiratory rate, that is, the amount of malathion which could have been deposited was 10-100 times the amount they inhaled. In none of these studies [35-37] did the investigators look for signs or symptoms of poisoning related to the exposure, but it is reasonable to assume that, had there been any significant effects, they would have been reported.

Signs and symptoms of cholinergic stimulation attributed to absorption of malathion through the skin have been reported. [24] An 8-year-old girl developed signs and symptoms consistent with ACh accumulation after having her hair washed with a 50% malathion-xylene solution. She died 5 days after the hairwashing. No quantitative estimate of the malathion exposure can be made in this case. In addition, Quinby and Lemmon [127] reported a case study of clinical poisoning in a group of field workers who were exposed to malathion residues on crop foliage. Again, no quantitative estimate of the exposure is possible.

After iv injection of a dose of 14C-malathion into an unspecified number of normal male volunteers, [128] 90.2% of the label was recovered in the urine with a half-time of excretion of 3 hours. Using these figures to correct measured absorption from the skin, Feldmann and Maibach [128] found that 12 subjects absorbed an average of 6.8 ± 2.3% of malathion applied to the skin of the forearm during a period of 5 days after its application. In another study, [129] the skin of the axilla absorbed 4.2 times as much malathion as that of the forearm — the highest absorption measured with malathion. (Scrotal skin was not used.) Therefore, the maximum absorption (outside of the scrotum) was 28.5% of that applied to the skin.

The effects of malathion on laboratory animals are similar to those in man. Acute doses of malathion produce signs of anticholinesterase effects in dogs, rats, mice, and rabbits, [10,33,83] indicating a common analogous mechanism of action in these species.

Laboratory mammals can tolerate large quantities of malathion when it is absorbed at a moderate rate. [124,125] During the three-generation study, [124,125] rats survived average daily intakes of 125 mg/kg/day or 45 g/kg each year.

Animal experiments indicate that the dermal application of malathion can cause cholinergic effects and death. The transdermal LD50 of malathion in rats has been reported as greater than 4,400 mg/kg. [109] This dose is approximately 3-6 times larger than the oral LD50's in this species.

The study by Weeks et al [83] showed malathion aerosols to have no effect on blood ChE activity in concentrations of 6-8 mg/cu m in either rabbits or quail, and no effects at up to about 30 mg/cu m in rabbits or lasting effects (beyond 24 hours) in quail. The formulations tested were technical malathion (95% pure) and 6% malathion in No. 2 fuel oil. Particle size had no effect on toxicity, and the fuel oil component was found to be of greater toxic potential than malathion in the 6% formulation.

There are several experimental investigations whose results suggest a level of dermal exposure to malathion in humans below which no cholinergic effects can be detected. In three separate studies, [35-37] the dermal exposure of individuals during malathion application was estimated by using absorbent pads taped to various areas of the skin or clothing. Estimated dermal exposures ranged from 0.25 mg/hour to an extreme high of 194

mg/hour. These individuals were also exposed via the respiratory route. In none of the subjects were signs and symptoms of cholinergic stimulation looked for, but it may be assumed that any significant complaints would have been noted by the investigators. In another group of studies, [32,129,130] volunteers were dusted daily with powdered formulations containing various concentrations of malathion. Hayes et al [32] reported no significant changes in ChE activities in 60 male volunteers exposed to dermal doses of malathion contained in talc dusting powder during an 8- to 16-week period at levels sufficient to lead to urinary excretion of malathion-derived materials equivalent to a minimum of about 70 mg of malathion/day. Using Feldmann and Maibach's [128] figure for recovery of 14C administered as malathion, the gross values from this study indicate that about 78 mg of malathion were absorbed from the application of 2.8 g of malathion powder to the skin. This absorbed quantity of malathion may be regarded, therefore, as a no-effect or safe dose.

In summary, malathion can cause signs and symptoms in humans resulting presumably from accumulation of ACh at various effector sites after absorption. The approximate single oral lethal dose in humans is probably somewhat below 1.0 g/kg. Although respiratory and dermal exposures to malathion have been reported to cause clinical effects consistent with pseudocholinergic (anticholinesterase) activity, no clear-cut cases of fatal poisoning by these routes of entry have been reported, and no quantitative relationship between exposure and cholinergic effect via these routes has been established. It is evident that a brief exposure to atmospheric concentrations as high as 85 mg/cu m [56] and dermal exposure [55] sufficient to lead to urinary excretion of malathion-derived

materials equivalent to a minimum of about 48 mg of malathion/day, as determined by ether extraction (78 mg/day total), caused no significant depression of ChE activity.

No findings of carcinogenesis by malathion have been reported. There is some information on its possible teratogenic and mutagenic activities. [17,54,111-113,115-119,123-125] Because some of the papers on teratogenic activity are derived from studies on hens' eggs and some of those on mutagenesis relate to studies with unicellular organisms, little information applicable directly to mammals is available in this general field. The data are judged to be insufficient to establish the existence of significant risk of the occurrence of these effects in human populations exposed to malathion.

IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION

Sampling and Analytical Methods

Various complications arise in the atmospheric sampling for malathion due to its formulation as an emulsifiable liquid, wettable powder, or dust. [131]

Packed column adsorption is efficient for trapping vapors, but sample recovery from the column is difficult. [58] Filters, whether glass fiber or cellulose pad, permit passage of large volumes of air in a short time, but they have low efficiency for vapors and lose unknown amounts of both particulate and aerosol samples during the collection period. [37,92] Scrubbers are good for aerosols and vapors, but the use of sintered glass precludes particle collection. [132,133]

Miles et al [134] determined the collection efficiency of Greenburg-Smith impingers using ethylene glycol as the collection medium. They compared the amount originally present in a U-tube or a vaporization chamber to that collected in Greenburg-Smith impingers for parathion. Either the U-tube or the vaporization chamber was connected directly to two Greenburg-Smith impingers in series. The authors found that in a 240-minute sampling period, 94.8% of the parathion in the U-tube was collected by the first impinger connected to the U-tube, and 87.2% (19.8μg) of the parathion was collected by the first impinger connected to the vaporization chamber. The flowrate was not given. Miles et al [134] also determined the collection efficiency of Greenburg-Smith impingers for parathion dusts. In this study, they dispersed parathion dust in a chamber and collected the dispersed dust with three Greenburg-Smith impingers connected in series.

The flowrate again was not given. The results indicated that 99.9% (3,000μg) of the parathion dust was collected in the first impinger using ethylene glycol as the collection medium. NIOSH believes that these results are applicable to malathion as well. There is no reason to believe that the particle sizes are different, as the inert substrates for dry formulations of both malathion and parathion are the same. [135]

Culver et al [68] found that the collection efficiency of the midget impinger using ethyl alcohol as the collection medium was in excess of 90% for collecting malathion in the form of aerosolized liquid with a median diameter of 40-54 μ. No range of particle sizes within which this efficiency is applicable was given, and the method of determining the collection efficiency was not indicated. They also found that the midget impinger picked up particles of approximately the same size as did the upper respiratory tract. Since malathion may occur in air as vapor, as liquid droplets, or as an adsorbed film on solid particles, it is essential that the impinger be operated at a flowrate which will efficiently collect all forms of airborne malathion. Although no studies were found in which malathion or any other organophosphorus pesticide was used as the test compound, Roberts and McKee, [136] by comparing known concentrations of ammonia with those absorbed in midget impingers filled with distilled water, found that the most efficient air flowrate was 0.1 cu ft/min (2.8 liters/min).

Miles et al [134] investigated a variety of solvents that may be used as collection media in impingers. By varying the solvents in otherwise identical trials, they found that iso-octane, toluene, and ethyl benzene trapped parathion with high efficiency (no percentage was given), but that

losses of solvent from the impinger sampling train were high. Sampling runs longer than 30 minutes could not be made because of saturation of the system. Aliphatic hydrocarbons of higher molecular weight, including normal nonane and normal decane, formed aerosols when air was passed through the impingers, with the resultant loss of an unstated amount of solvent. The higher molecular weight hydrocarbons were difficult to evaporate. The authors found that samples of 10.7 and 205 μg were trapped with 90% or better efficiency by ethylene glycol. In comparing the collection efficiency for a known amount of parathion vapor, it was found that with ethylene glycol the collection efficiency was not dependent upon sampling time, whereas with water the collection efficiency decreased from 100% for a 10-minute sample to 52.6% for a 60-minute sample.

Thomas and Seiber [137] evaluated the solid sorbent Chromosorb 102, an alternative to liquid solvents in impingers, for the collection of malathion. Collection efficiency for the vapor of 95% technical malathion (31.5 μg malathion in a U-tube through which 9 cu m of air were drawn) in the first of two tubes, each containing 4 g of Chromosorb 102, was determined to be 102%. Upon separation of 4 g of adsorbent from a single tube into 1-g segments after sampling, no penetration of malathion vapors beyond the second segment was found. Downwind trapping of aerosolized technical (95%) malathion by Chromosorb 102-charged impingers was compared with that of similar impingers filled with ethylene glycol. Two separate runs were made, at 100 and 150 feet from the spray source, with the two types of filled impingers side by side and each with a backup impinger. Chromosorb 102 at 100 feet collected 12.3 μg and less than 0.1 μg of malathion vapor and aerosol in the first impinger and in the backup

impingers, respectively; the ethylene glycol collected only 5.5 and 0.3 μg, respectively. At 150 feet, the Chromosorb 102 impingers collected 8.6 and 0.5 μg, respectively; no data were given for ethylene glycol at this distance. Although Chromosorb 102 appears to be a superior collecting medium, the breakthrough volumes, ideal sampling rate, and precision of the method still remain to be determined.

Pending further studies, the midget impinger [68] is recommended as the air sampling method of choice. Appendix I gives details of the sampling and airflow calibration procedures to be followed when using this method. Other air sampling methods which can be shown to be equivalent, or superior, in efficiency to the midget impinger [68] with ethylene glycol as the solvent [134] may be used.

In 1964, the thermionic emission or alkali flame ionization detector was introduced by Giuffrida. [138] In 1966, Brody and Chaney [139] introduced the flame photometric detector. Both detectors are modifications of the universal flame ionization detector and are highly specific for phosphorus. Since the development of phosphorus-specific detectors, gas liquid chromatography has been the preferred method for malathion analysis. Formerly, organophosphorus pesticide analysis was done by colorimetric [140] and ultraviolet spectrophotometric [141] techniques. These, however, were highly subject to interference.

A major advantage of the gas liquid chromatography-phosphorus specific detector method of analysis is that changes in the composition, filling, and temperature of the column permit the separation of peaks due to interfering compounds from the peak of the compound of interest. These column changes result in a variation of retention times of all substances

involved. Giuffrida [138] indicated that 0.024 μg (24 ng) of parathion could be detected using gas liquid chromatography with an alkali flame ionization detector. For normal analytical work, the convenient working range for the alkali flame ionization detector was between 50 and 1,000 pg (0.05-1.0 ng) in each injection volume. With acetone as the solvent, gas liquid chromatography combined with a flame photometric detector and a 526-nm filter were reported [139] to be sensitive to 0.25 ng of malathion; the response was linear from 0.0063 to 63 ppm. Since the flame photometric detector is the more sensitive method, it is recommended over the alkali flame ionization detector. Details of this method can be found in Appendix II.

Environmental Levels and Engineering Controls

Data on environmental levels of malathion in the workplace are scanty. The only information found was contained in articles describing workers exposed while applying malathion for purposes of agricultural pest and vector control.

Wolfe et al [35] studied the dermal and potential respiratory exposures to malathion of an unstated number of air-blast sprayers and aerosol machine operators who were applying malathion spray (0.04-0.08%, 3.4 lb/acre), dust (4%, 1.4 lb/acre), or aerosol (2.5-5.0%, application rate not specified) to fruit trees or pole beans. From absorbent gauze pads attached to the workers' exposed skin areas (the face, back of neck, "V" of chest, forearms, and hands) and respirator filter pads, the authors calculated the mean dermal exposure to have been 30 mg/hour for employees spraying fruit orchards with air-blast machines, and 67 mg/hour for

employees using high-pressure hand guns. Employees using a power duster on pole beans were calculated to have had a mean dermal exposure of 23 mg/hour. Potential respiratory exposure was calculated to have been 0.11 mg/hour for air-blast orchard sprayers, 0.09 mg/hour for the high-pressure hand-gun operators, and 0.73 mg/hour for those using a power duster to dust pole beans with malathion. These results indicate a potential for much higher dermal than repiratory exposure in the application of malathion. ChE determinations were not made in this study.

Culver et al [68] studied the dermal and potential respiratory exposure to 2.5% or 5% malathion (formulating solvent not stated) of two aerosol machine operators and three field observers from the drifting aerosol cloud during mosquito control application. Cellulose head and ankle bands and a cotton knit glove on one hand of each worker were used to estimate dermal exposure. Cellulose filter pads in front of the cartridge of toxic dust respirators were used to measure potential respiratory exposure. Atmospheric sampling in the breathing zone was done with all-glass midget impingers, with ethyl alcohol as the collecting medium. Exposures were intermittent and generally brief, lasting from 20 seconds to about 30 minutes, for a total of about 5 hours during a 2-week period. The atmospheric concentration, as determined from 145 samples taken at the same time as the dermal and respiratory samples, ranged from 0.52 to 7.70 mg/cu m, depending on application distances (10-75 yards). The jeep driver received the highest dermal exposure, 32-86 mg, of which more than 90% was deposited on the hands. The total potential respiratory dose range for the 2-week period was 11-21 mg, also from the jeep driver's samples. Erythrocyte and plasma ChE activities were measured by a microadaptation of

the Michel method. [61] Either two or three preexposure examinations and daily examinations during the 2-week application period were performed. The authors concluded that slight decreases observed in ChE activities were insignificant.

Caplan et al [37] measured the potential dermal and repiratory exposures of individuals who worked outside during a 2-week mosquito control project in which malathion was applied intermittently by aerosol machines. Dermal exposure was estimated from cellulose pads attached to various parts of the body, and respiratory exposure was calculated from atmospheric concentrations of malathion collected at several points during and again 1 hour after spraying. The authors found atmospheric concentrations of malathion as high as 0.67 mg/cu m. Skin exposure ranged from 0.45 to 2.62 μg/sq cm for a man working outdoors during the spraying operation. No ChE activities or other measurements of response were reported.

Jegier [36] measured the dermal and respiratory exposures of 52 individuals who operated tractor-driven, air-blast sprayers during application of insecticides to fields of grain and vegetables. Spray formulations consisted of malathion alone as well as mixtures of malathion and DDT. Malathion was applied in a concentration of 2 lb of 25% wettable powder/100 gal of water. Respiratory exposures were estimated from analysis of breathing-zone air samples and from respirator filter pads. Dermal exposure estimates were based on the amount of insecticide found on absorbent patches taped to the forehead and wrists of observers riding beside the tractor operator. In all, the exposure of four operators to malathion was estimated. Breathing-zone samples had a range of 0.41 to

0.76 mg/cu m, with a mean of 0.59 mg/cu m. The mean respiratory exposure dose was found to be 0.08 mg/hour of malathion (range, 0.03-0.13 mg/hour) and the mean dermal dose was 2.5 mg/hour (1.5-4.9 mg/hour). The authors did not report any signs or symptoms of malathion poisoning, nor did they report any ChE activity determinations.

Good industrial hygiene requires that adequate engineering controls and work practices be used, including personal protective equipment and, under certain conditions, respiratory protection. Exhaust systems are needed at loaders, blenders, mixers, mills, packaging equipment, and all other possible sources of vapor, spray, or dust containing malathion. Liquid and dust exhaust systems must be so designed that the health of employees and that of people or animals in the surrounding community is not endangered. Dust exhaust systems should be vented into a dust collector, not into the atmosphere. Guidance for design of a ventilation system can be found in Industrial Ventilation--A Manual of Recommended Practice, [142] or more recent revisions, and in ANSI Z9.2-1971. [143] Exhaust air should not be recirculated and should be scrubbed to prevent pollution of the outdoor air. Respiratory protective equipment is not an acceptable substitute for proper engineering controls, but should be available for emergencies and for nonroutine maintenance and repair purposes.

Biologic Evaluation

Indicators of response to absorption of malathion which have been reported include: determinations of erythrocyte and plasma ChE activities, [25] electromyography, [144] electroencephalography, [145] and direct measurement of serum malathion levels. [40] With additional study,

electromyography and electroencephalography eventually may prove to be useful diagnostic tools. Direct serum malathion measurement is of extremely limited use, as the compound disappears rapidly from the blood. Only one case report [40] was identified in which this phenomenon was examined. Although serum malathion levels were found to be zero 4.5 days after ingestion of the compound, the patient remained critically ill and died 1 day later. Estimation of circulating erythrocyte and plasma ChE activities is the most effective method for monitoring occupational exposure to malathion, as reduction of ChE activity has been found consistently in clinical cases of malathion poisoning and has been far more extensively studied and documented than either of the other two examinations. Also, plasma and erythrocyte ChE activities are related generally to the severity of acute poisoning. NIOSH recommends only erythrocyte ChE monitoring as an effective measure of acute or chronic exposure. However, as plasma ChE activities are often electively monitored as well, both parameters will be discussed, and analytical methods for both are given in Appendix IV.

DuBois [146] examined the relationship between the lethal effects of six organophosphorus pesticides and their respective abilities to inhibit ChE in rat serum, liver, and brain. The numbers of animals were not specified. He found that the correlation between lethality, as reflected by the ip LD50 in rats, and inhibition of brain ChE were much better than the correlation between the ip LD50 and serum or liver ChE inhibition. Freedman et al, [147] in 1948, studied the relationship between the severity of symptoms and inhibitions of erythrocyte and plasma ChE's in 94 adult male rats weighing 125-175 g and divided into groups of 20-25 each

for single subcutaneous injections of either 1 or 2 mg/kg di-isopropyl fluorophosphate (DFP) in saline. Signs were graded as severe (marked spontaneous trembling of the body, great hyperreactivity on tapping of the spine, varying degrees of muscular weakness culminating in paralysis, and excessive salivation), moderate (intermittent periods of trembling, marked motor restlessness, moderate hyperreactivity on tapping of the spine, and spontaneous fasciculations of the muscles in the flanks), or slight (transient fasciculations while standing erect on their hindlegs and motor restlessness). Brain, plasma, and erythrocyte ChE activities were measured manometrically, and control values were obtained from 17 normal rats for these same parameters. Correlation between clinical signs and brain ChE activity was consistently significant at the 1% level. Erythrocyte ChE activity correlated less well with severity (2-5% significance), and plasma ChE activity only with severe signs (by classification). In the presence of toxic signs, erythrocyte and brain ChE activities remained closely parallel, and the correlation coefficient of erythrocyte with brain ChE was found to be 0.7 after a 1.0-mg/kg dose of DFP. Therefore, erythrocyte ChE activity seems to serve more accurately than that of plasma to approximate ChE activity in the brain in both the acute and recovery phases. The authors [147] pointed out the importance of the rapidity with which ChE activity in the circulating blood is lowered as an indicator of the severity of poisoning by organophosphorus compounds.

In a discussion of clinical case reports of organophosphorus poisoning in humans, Namba et al [49] stated that, for diagnostic purposes, estimation of erythrocyte ChE (AChE) activity was preferable because it indicated the degree of inhibition of synaptic ChE, ie, the extent of

inhibition directly determining the degree and visible manifestations of poisoning. Also, as observed in one of the cases described, following pralidoxime administration, erythrocyte ChE indicated the effectiveness of pralidoxime; plasma or serum ChE indicated the prior presence of ChE inhibition even after restoration of erythrocyte ChE activity by pralidoxime. They [49] reported that manifestations of acute poisoning in humans generally accompanied serum ChE inhibition of 50% or more. The ranges of serum ChE activity were 20-50% of normal in mild poisoning, 10-20% of normal in moderately severe poisoning, and less than 10% of normal in severe poisoning. Gage [148] pointed out that, while the inhibitory action of parathion and certain other organophosphorus compounds was more marked on the plasma enzyme than on the erythrocyte enzyme, various other organophosphates, notably the dimethyl esters, inhibited the erythrocyte enzyme first. Clinical case reports detailed in Chapter III [19,24,25,27,39,40] have all indicated that symptomatic malathion intoxication in man, irrespective of dose or route of entry, was characterized by profound inhibition of circulating ChE's, as determined by laboratory measurement. Where both erythrocyte and plasma ChE activities were determined, both were clearly depressed [25,39,40]; and where either erythrocyte or plasma ChE activity was examined, depression was uniformly evident. [19,24,27] The consistent presence of this phenomenon in malathion poisoning, no matter which blood fraction was examined, reinforces the case for measurement of ChE activity as a clinical diagnostic test in cases of possible malathion poisoning.

Frawley et al [86] found that diets containing malathion at concentrations up to 250 mg/kg of body weight inhibited ChE activity in the

erythrocytes of three dogs without significantly altering the activity of plasma ChE. Crowley and Johns [19] described a case of malathion ingestion in which erythrocyte ChE activity was reduced to less than 10% of normal during the first 7 days after ingestion and rose gradually (at the rate of about 1%/day) to 66% of normal 56 days after ingestion.

Initially, biologic assays were used to measure ChE activity. [149] Now outmoded, they have been replaced by methods classified as manometric, titrimetric, electrometric, colorimetric, radiometric, and chromatographic.

Witter [150] stated that the Warburg manometric technique, based on the measurement of carbon dioxide released when acetic acid reacts with bicarbonate, was one of the most accurate and versatile ChE measurement methods. Such techniques, however, are unsuitable for use with large populations because they require bulky apparatus and time-consuming procedures.

Methods of determination wherein ChE activity is indicated by discernible color changes have been described. The method of Limperos and Ranta [151] required only a very small blood sample; the authors found it reasonably accurate and reproducible away from the laboratory. Others who described modifications of such methods were Davies and Nicholls [152] who modified the Limperos and Ranta technique; Fleischer et al [153] who altered the Davies and Nicholls' modification; and Gerarde et al [154] who modified the procedures described by Wolfsie and Winter, [155] Limperos and Ranta, [151] and Hestrin. [156] All such methods are less accurate because the solutions used are not buffered, but they may be applicable for field screening use.

Spectrophotometric methods have been described by Ellman et al [157] and Garry and Routh, [158] and by Dietz et al, [159] who modified the Garry and Routh method.

Baum [160] reported on a method utilizing a liquid membrane electrode highly selective for ACh that correlated well with Hestrin's method. [156] Descriptions of a variety of other methods of ChE activity determination have included titrimetry by Jensen-Holm et al [161]; specially impregnated test papers which yield an obvious visible result to be matched against standard colors by Oudart and Holmstedt [162]; radiometry by Winteringham and Disney [163-165]; and gas liquid chromatography by Cranmer and Peoples. [166]

The most widely used electrometric method has been that of Michel. [61] The Michel method, which utilizes readily available apparatus, depends on measurement of the activity of H^+ ions released from acetic acid produced by the catalytic action of ChE in the hydrolysis of ACh. The change in the pH of a standard buffer resulting from the enzymatic activity during a definite period of incubation at 25 C is measured by a glass electrode and associated pH meter. The pH range of 6-8 was found to be appropriate for the change in ChE activity which one would expect to find in malathion poisoning. The method was applicable to both erythrocytes and plasma, with different buffers and certain variations in technique. Michel concluded that the electrometric pH method was preferable to the manometric method because of its simplicity, minimal equipment requirements, and capacity for processing a large number of determinations in a relatively short (less than 1 minute/reading) time. It should be noted that a 1974 report by Ellin and Vicario [167] showed that, when measured by the Michel

method, [61] ChE levels varied with changes in temperature. A change of 1 degree from the 25 C prescribed by Michel resulted in a 5.5% change in plasma ChE activity and in a 3.9% change in erythrocyte ChE activity, whether or not the enzyme was inhibited. It is, therefore, necessary to carefully control temperatures when using this method. Wolfsie and Winter [155] developed a micromodification of the sampling technique used in the Michel method which was as accurate as the original.

Witter et al [168] presented a modification of the Michel method. [61] Theirs eliminated the initial pH reading, the enzyme reaction being started by adding a mixture of buffer and ACh to the diluted sample. The results are identical to those obtained with the Michel method, but twice as many samples can be analyzed in the same period.

It has been accepted generally that electrometric methods (in which delta pH is measured) and colorimetric methods are the preferred methods for measuring ChE activity because they utilize less expensive equipment and require less expertise for their operation. As colorimetric methods are subject to decreased accuracy by solution turbidity, such as would occur with erythrocytes, these methods can only be used to measure plasma ChE activity. An electrometric method is therefore recommended, specifically Wolfsie and Winter, [155] a microadaptation of the Michel method. [61] It is presented in Appendix IV.

The establishment of normal values for plasma and erythrocyte ChE in humans has become increasingly important as the use of organophosphorus pesticides has become more widespread. Therefore, a range of normal values for comparison with ChE activities in potentially exposed people has become a necessity.

Several studies in which normal ChE activities were determined have been reported. These ranges are given in Table XII-2. Further data may be found in Appendix IV. Pearson et al [169] calculated formulae to convert delta pH values to international enzyme units. These were given as: μM/ml/min = 23.15 delta pH/hr - 5.805 for erythrocyte ChE; and μM/ml/min = 3.26 delta pH/hr + 0.15 for plasma ChE.

Vorhaus and Kark [170] determined the serum ChE in 120 healthy individuals for whom the range of activity was 0.58-1.37 delta pH/hour. Fremont-Smith et al [171] reported mean serum ChE activities of 0.95 delta pH/hour for 20 "normal" men and of 0.78 delta pH/hour for women. Wolfsie and Winter [155] tested 255 healthy men and reported ranges for plasma and erythrocyte ChE values of 0.408-1.652 and 0.554-1.252 delta pH/hour, respectively. Callaway et al [172] studied a group of 247 healthy adults, 66 of whom were women, and concluded that "sex, age, occupation, and season are without effect upon the level of plasma enzyme."

Sidell and Kaminskis [173] studied the temporal variation of plasma and erythrocyte ChE activity, as opposed to laboratory-induced artifact. Eight female and fourteen male volunteers, aged 23-67, were tested biweekly throughout 1 year for ChE activity and simultaneously questioned on their medications, illnesses, alcohol intake, and exposure to ChE inhibitors. The average test period attendance was 23 times, and no subject was present every time. Nine healthy soldiers, aged 19-24, had blood drawn each working day for 3 weeks and completed questionaires similar to those of the aforementioned subjects. No correlation was obtained between ChE activity and age. A significant difference (P less than 0.01) was obtained in plasma ChE activity between men and women, but no seasonal variation in

enzyme activity was noted for either sex. Six subjects handled organophosphates. One volunteer, who had hung insecticide strips at home, experienced a 20% decrease in plasma ChE during the subsequent 6 weeks. The coefficient of variation for plasma ChE was reported to be about 6% for both sexes, with a mean of 25.7% for men and 24.3% for women.

Erythrocyte ChE activities in this study [173] were reported to be more constant, with an average coefficient of variation of 4.1%/single subject, 2.1% for men, and 3.1% for women. The average range of variation of erythrocyte ChE activity was ± 7.9% for men and ± 12.0% for women.

During the course of this study, measurements were made of packed cell volume, hemoglobin content, erythrocyte counts, mean corpuscular volume, erythrocyte ChE activity/unit volume, and ChE activity/erythrocyte. All of these were reported to vary more than the overall erythrocyte ChE activity above.

In a population studied twice at 1-year intervals, [173] the average change in plasma ChE was 9.3% for men and 16.5% for women. Changes in erythrocyte ChE activity of 6.3% for men and 6.7% for women were found at this same time. The results of this study [173] serve to vindicate the method employed as reliable within the demonstrated limits of temporal variation for this small sample. The nine control subjects, who were reported to have engaged in strenuous physical exercise, with occasional heavy drinking during the evenings, exhibited a maximum difference of 5.13% in erythrocyte and 12.8% in plasma ChE activity over the 3-week observation period.

Plasma ChE reportedly has been depressed by a variety of conditions unrelated to exposure to chemical anticholinesterase agents. Such

conditions include, but probably are not limited to, liver diseases (such as hepatitis and cirrhosis), [174] cachexia, [174] pregnancy, [175] malignant neoplasia, [175,176] pulmonary tuberculosis, [175] anemia, acute infections and chronic debilitating disease, and malnutrition. [170] Familial incidence of low plasma ChE activity was reported by Lehmann and Ryan [177] and by Kalow [178] and subsequently found to be related to the presence of an atypical gene. [179] About 1 in 5,000 healthy Canadians was found to be homozygous for this autosomal allele [178] and to have a genetically determined deficiency in plasma ChE. Heterozygotes were reported to have a mixture of normal and abnormal serum ChE. The frequency for the abnormal gene in a healthy population was reported to be 0.019 ± 0.002. [180] The importance of these observations to susceptibility to organophosphorus pesticide poisoning does not appear to have been determined. However, in interpreting the results of ChE activity tests, it is necessary to consider the above-noted factors which could cause deceptively low activities.

The activity of erythrocyte ChE has been depressed by certain pulmonary and extrapulmonary cancers [175] and in paroxysmal nocturnal hemoglobinuria. [181] Familial asymptomatic reduction in erythrocyte ChE activity has also been reported. [182]

Drugs, such as caffeine and related xanthine compounds, [183] chloroquine and other antimalarial drugs, [74] chloroform, [184] ether, [184] narcotic analgesics such as morphine and codeine, [76] and thiamine [185] have been shown to depress the activity of serum (ie, plasma) ChE activity. A few drugs have been reported to depress erythrocyte ChE activity, including quinine, [74] other antimalarial drugs, [74] and echothiophate. [186]

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

The American Conference of Governmental Industrial Hygienists' (ACGIH) recommendation of a threshold limit value (TLV) for malathion of 15 mg/cu m was published in 1962. [187] A TLV of 10 mg/cu m was recommended in 1971 in a general reduction of the TLV's for "nuisance" dusts. [188] The TLV remained at that figure in 1975, without indication of an intended change in 1976. This TLV was based on studies both in experimental animals and in humans. The Documentation [188] cited the review of Johnson et al [189] in which the authors concluded that in animals, malathion was not more than 1/100 as toxic as parathion. The report of Tousey [190] was cited in support of this opinion, as was the work of Hazleton and Holland, [10] which showed little or no inhibition of blood or brain ChE activity and no other injury to rats fed malathion at a concentration of 200 ppm for 2 years. The authors of the Documentation suggested that this animal exposure was equivalent in humans to 350 mg/day. However, they did not present the assumptions underlying this estimate.

Studies in humans cited in support of the 10-mg/cu m TLV include those by Culver et al, [68] Golz, [56] Rider et al, [191] and Hayes et al. [32] The ACGIH TLV Documentation [188] reported that Culver et al [68] found that "a group of entomologists with a maximal exposure of 5 hours at a peak of 56 mg/cu m and an average of 3.3 mg/cu m had normal ChE levels." The study group consisted of two entomologists, and the exposure period comprised multiple 20-second to 30-minute exposures which totaled 5 hours during a 2-week period. With reference to the aerosol studies of Golz,

[56] the ACGIH committee wrote that "groups of 4 men each received 84 one-hour exposures in 42 consecutive days at dosages of 0, 0.15, 0.6, and 2.4 g of malathion/1,000 cu ft (5.3, 21.2, and 84.8 g/cu m)." In this study, the malathion was dispersed as an aerosol into the exposure room air in a single application. The amount released was calculated to be sufficient to produce an initial peak concentration at the stated level. No additional malathion was released into the air during the 1-hour exposure period. Since the air concentration of aerosol had probably decreased by an unknown and undeterminable amount during the 1-hour exposure period, the actual dose received by the subjects cannot be calculated. The subjects did not manifest cholinergic signs or symptoms, nor did they exhibit dose-related changes in blood ChE activities.

The dermal exposure studies of Hayes et al [32] found that men exhibited no significant decreases in blood ChE activity when exposed 5 days/week for 8-16 weeks to malathion-containing dusting powder to an extent sufficient to lead to urinary excretion of malathion-derived materials extractable from acidified urine by ethyl ether equivalent to about 48 mg of malathion/day. Since the ether-extractable phosphates represent about 69% of the total urinary metabolites, the data suggest dermal absorption of malathion of about 78 mg/day. The preliminary investigations of Rider et al [191] found no effect on blood ChE activities when malathion was fed to human volunteers for a total of 88 days as follows: 47 days at a dose of 16 mg/day alone, followed by 41 days with the same dose of malathion and 3 mg/day of EPN, a synergist of malathion.

The present federal standard for occupational exposure to malathion is 15 mg/cu m as a TWA limit (29 CFR 1910.93, published in the Federal

Register 39:23543, June 27, 1974). The American National Standards Institute (ANSI) has made no recommendations for a malathion standard to date. Foreign standards for malathion listed in 1970 by the International Labour Office (ILO) [192] were given as 0.5 mg/cu m for Bulgaria and the USSR and 15 mg/cu m for Finland, Yugoslavia, and Rumania. The scientific bases for these standards are not known to NIOSH. The ILO publication [192] gave the standard for malathion in the Federal Republic of Germany as 15 mg/cu m and stated that it was based on the 1966 Documentation on Threshold Limit Values of the ACGIH.

Basis for the Recommended Standard

As shown by the case reports in Chapter III, [19,20,23-25,27,39] the main signs and symptoms of malathion intoxication are increased bronchial secretion and excessive salivation, [19,20] nausea, [27] vomiting, [25] excessive sweating, [23] miosis, [24,39] and muscular weakness and fasciculations. [20] These signs and symptoms are induced by the inhibition of functional AChE in the nervous system. [1,2]

Malathion has been responsible for a number of nonoccupationally related cases of human poisoning, many of which have been fatal. [22,39,50,188] All known reports of such fatalities in humans have involved ingestion of large quantities of malathion, mainly in attempted suicide. [22,39,50] In the adult human, the approximate lethal oral dose can be estimated to be of the order of 0.4-1.0 g/kg based on case reports of ingestion. [19,20,25,44-46] Only extreme emergency measures, including massive therapy with atropine and 2-PAM and extensive artificial life-support systems over prolonged time periods, managed to save these

patients. Serious poisoning by dermal exposure has been reported in a few isolated instances. [27]

Only a few instances of occupationally related poisonings have been documented. [17,38,42,182] Following heavy dermal exposure to malathion for 3 or more days, applicators experienced mild-to-moderate intoxication with typical signs of inhibition of ChE. [182] In the carefully controlled experiments of Hayes et al, [32] repeated daily dustings of the entire body for 8 or more weeks with a 10% talc formulation of malathion did not produce any signs or symptoms of ChE inhibition. Liquid preparations of malathion, either as technical grade or as formulations, probably represent more pronounced dermal hazards than a 10% talc formulation. Protection for the worker can be achieved by wearing protective clothing while handling or applying malathion. Following dermal exposure to large amounts of malathion from splashes and spills, the skin should be cleansed to prevent further absorption of the material.

The study by Culver et al [68] of workplace exposure under field conditions revealed a maximum mean atmospheric concentration of malathion of 7.70 mg/cu m at a 10-yard distance from the source of the spray. The jeep driver, who had the greatest total dermal exposure, formulated the insecticide from technical grade malathion and transferred all the material from mixing cans to the aerosol rigs. The exposure was intermittent over a 2-week period. His minimum total dermal exposure was in the range of 32-86 mg (calculated as 0.5-1.23 mg/kg by the authors) over a total of 5.23 hours comprising 23 separate runs. Of this exposure, 84-93% was determined to be on his hands. Total respiratory exposures for the same jeep driver were measured at 11-21 mg over the same time span. Measurement of his

erythrocyte and plasma ChE activities revealed maximum decreases of 19 and 27%, respectively. No symptoms were reported other than "some signs of generalized fatigue," attributed by the authors to the work schedule. Since the exposure was intermittent during 2 weeks, spontaneous recovery of the ChE activity may have occurred. The authors [68] also calculated that, from the highest integrated total exposure during a month on a 40-hour workweek basis, without protective clothing, skin exposures of 17-45 mg/kg would have occurred.

A study by Jegier [36] of exposures to malathion during field-spraying operations reported a mean air concentration of 0.59 mg/cu m in the breathing zone of the tractor operator (a range of 0.41-0.76 mg/cu m). The mean rates of exposure of workers were 2.5 mg/hour by dermal contact and 0.8 mg/hour by the respiratory route. The maximum rate of exposure, both respiratory and dermal, was calculated as 5.03 mg/hour, according to the procedure described by Durham and Wolfe. [133] Jegier's procedure was based on comparisons between the measured respiratory and dermal exposures and the animal toxicities given in Clinical Memoranda on Economic Poisons. [193] No toxic effects were noted in the workers examined, although it was reported that 85% of the operators disregarded safety precautions and usual working procedures.

Studies by Weeks et al [83] demonstrated no effects on ChE activity levels in either rabbits or quail exposed for one 6-hour period to aerosols of technical malathion (95% pure) at 65 mg/cu m. ChE activity was significantly reduced when the rabbits were exposed to malathion at a concentration of 125 mg/cu m for 6 hours. The mass median diameter of the aerosolized particle was 12μm. The total amount of malathion absorbed

under these experimental conditions cannot be estimated. While the data indicated that extremely high concentrations of malathion aerosols can be tolerated by rabbits for 6 hours, it is not possible to draw any conclusions from this study about the effects on humans of repeated exposures at low concentrations.

In view of the low vapor pressure of malathion (0.00004 mmHg at 30 C, 0.05 ppm), concentrations of malathion in the workplace can exceed the current environmental limit only when significant amounts of aerosols and dusts are present. The current environmental limit is consistent with the standard for protection against physical irritation initiated by the presence of physical matter. The present federal standard for malathion in the air of the workplace is 15 mg/cu m as a TWA limit (29 CFR 1910.93). The few reported cases of occupational poisoning have resulted from violation of sound work practices. [17,38,42,182] The toxicologic evidence [17,32,36,42,68,83] suggests that the current standard provides an adequate margin of safety for the worker. Therefore, NIOSH recommends that the current workplace TWA limit be maintained.

While it is unlikely that poisoning will occur because of occupational exposure, the possibility does exist for it to occur in extreme circumstances. Case studies by Namba et al [49] have indicated that toxic effects caused by malathion appear when ChE activity is reduced to 50% of baseline. It is recommended that workers exhibiting erythrocyte ChE inhibition to 60% of baseline be removed from their jobs until recovery to 75% of baseline is observed, and that, if any worker's erythrocyte ChE is found to be reduced to 70% of baseline, an immediate evaluation of work practices be undertaken to determine that they are properly observed.

VI. WORK PRACTICES

Based on personal research, Wolfe [194] stated that over 97% of the pesticide to which the body is subjected during most exposure situations is deposited on the skin. Feldmann and Maibach [128] indicated that spraying or dusting with pesticides may result in the deposition on the exposed skin surface of an amount of pesticide 20-1,700 times greater than that which reaches the respiratory tract. Maibach, in the Report to the Federal Working Group on Pest Management, [195] stated that pesticide skin depositions of 718-1,755 mg/hr were observed during spraying operations. Studies by Maibach et al, [31] in which they applied malathion to various skin sites of human volunteers, indicated that dermal absorption ranged from 5.8% on the palm to 28.7% at the axilla. Because of this demonstrated deposition of pesticides on exposed skin surfaces and the experimentally reported dermal absorption of malathion, personal protective measures should be observed insofar as possible to limit malathion exposure.

For personal protection against pesticide exposure, Wolfe [194] recommended long-sleeved outer garments, such as coveralls, that can be washed daily, rather than rubberized or plastic waterproof clothing which may be too uncomfortable because of heat absorption and trapping of body heat. Wolfe [194] also recommended wide-brimmed waterproof hats, unlined waterproof boots or shoes, gauntlet gloves, goggles, and respirators for additional protection. When skin exposure does occur, the affected area should be washed promptly and medical surveillance instituted to determine whether overexposure has occurred. The rate of dermal absorption will vary with the composition of the formulation, but measurements of the degree of

variation have not been found in the literature.

Malathion-contaminated equipment and surfaces should be decontaminated to minimize exposure. Although only qualitative results were given, treatment of malathion by alkali has been shown by Kennedy et al [196] to degrade malathion to an inorganic phosphate. The use of alkali decontaminants, however, could be damaging to wooden surfaces. El-Refai and El-Essawi [197] found that laundering in detergent removed up to 98% of the malathion contamination from cotton fabric.

Another important route of entry is through the respiratory tract. If exposure to airborne concentrations of malathion cannot be reduced either by engineering controls or by administrative measures to the level specified in Chapter I, Section 1(a), then respiratory protection as specified in Chapter I, Section 4(b) must be utilized.

The other potential route of exposure is oral. Hence, effort should be made to avoid contamination of foodstuffs and their containers, tobacco products, and other materials placed in or near the mouth. Handwashing before eating, as recommended by NIOSH, is a common practice in malathion industries. [131]

Wolfe et al [198] and Mail et al [199] discussed the health problems of discarded pesticide containers and stressed the necessity of decontaminating and destroying them. Mail et al [199] recommended that fiber drums used as pesticide containers be crushed, and metal containers washed and punctured prior to their disposal. Lime slurry may be a highly effective agent for both destroying and immobilizing malathion. Floor sweepings containing malathion should not be sent to a public sanitary landfill, but rather disposed of by trained plant personnel. Wolfe [194]

recommended two thorough rinsings with water as a minimum decontamination procedure for 5-gallon metal drums after removal of their pesticide content. Both sets of recommendations by Mail et al [199] and by Wolfe [194] were based on studies of parathion decontamination. Containers may also be returned to the supplier or sold, burned, or buried 18 inches deep in isolated areas. However, when containers are sold, buyers must be informed of their previous use with pesticides, and decontamination must be accomplished by washing the outside with water and the inside with water and caustic soda (2 lb/55-gal drum). Glass containers should be broken, plastic containers punctured and mutilated, and metal containers punctured and crushed. [200]

The thermal decomposition of a commercial malathion formulation (5 lb/gal) was measured [196] to be from 95.3 to 96.7% at temperatures of 600-1,000 C. At 900 C, decomposition products of burning analytical grade malathion were determined [201] to be carbon monoxide, carbon dioxide, sulfur dioxide, hydrogen sulfide, oxygen, and four unidentified products. Stojanovic et al [202] also tentatively identified diethyl succinate, diethyl maleate, and diethyl fumarate as thermal decomposition products. Some of the undecomposed fraction of burning malathion will vaporize, and contaminated particles will become airborne. The National Agricultural Chemicals Association (NACA) [203] recommends that self-contained breathing apparatus, rubber gloves, hats, suits, and boots be worn by firefighters in the case of parathion fires, and that these be cleaned before being removed. Firefighters are advised [203] to shower thoroughly and change to clean clothing after the operations have ended. Workers should avoid being downwind of the fire, and only those workers essential to the firefighting

operation should remain in the vicinity of the fire.

NIOSH recommends that the procedures advised by NACA [203] for parathion fires be followed for malathion fires as well. Attention should be given to the possibility of concomitant exposure to considerably more toxic organophosphates or to other pesticides and compounds which may also be burning in warehouse fires, and appropriate precautions should be observed.

The WHO Expert Committee on Insecticides, [41] in its 16th report, recommended that employees exposed to pesticides be properly informed of the associated hazards. Industrial experience indicates that written information on pesticides is sometimes not readily available at the worksite. [131] Recognizing the need for employees to have information on the materials with which they work, the WHO stressed the importance of employees being informed of the hazards of malathion. [41]

VII. RESEARCH NEEDS

Several aspects of the available information on malathion need extension, verification, or development. Information on the mutagenic and carcinogenic potentials of malathion is very scanty. Studies designed to detect the induction of these deleterious effects in at least two species over their entire lifetimes should be initiated as soon as possible.

The ingestion study of Moeller and Rider [21] needs confirmation. The results of 47 days of malathion administration indicated that the threshold of significant erythrocyte ChE inhibition was somewhat greater than 24 mg/day for 8 weeks.

The rate and mechanism of skin absorption of the various types of malathion formulations need to be determined. In particular, the enzymes or biochemicals which metabolize or activate the compound during dermal absorption need to be determined. This is the most likely area of exposure to malathion by way of liquid spills and splashes, atmospheric dust deposits, etc. It would be beneficial to better understand the degree of hazard posed via this route of exposure.

The physiologic significance of aliesterase inhibition should be examined further. The kinetics of inhibition and regeneration of aliesterase should be studied as functions of the dose and route of malathion administration.

An accurate field test for ChE activity should be developed. Current methods are unsuitable as they require special laboratory equipment or lengthy procedures, or are insufficiently quantitative.

The quantitative relationship between skin and respiratory exposure to malathion and the excretion of metabolites in the urine should be determined and correlated with the rate of AChE inhibition in vivo. Such knowledge would facilitate the development of a noninvasive technique for measuring malathion exposure.

Alternative methods, such as filters, for the collection of malathion dusts, vapor, and aerosols in the workplace should be further investigated. The efficacy of charcoal tubes in the collection of malathion vapor should be investigated.

The equilibrium constant for the reaction of malaoxon with purified AChE and the rate of aging of the dimethylphosphoryl AChE derivative should be measured. Such information is necessary to determine the rate of accumulation of dimethylphosphoryl AChE as a function of dose route and dose rate.

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IX. APPENDIX I

METHOD FOR SAMPLING MALATHION IN AIR

The sampling and analytical methods presented in Appendices I and II are taken from those described by Culver et al, [68] by Brody and Chaney, [139] and in the NIOSH Manual of Analytical Methods. [204]

Atmospheric Sampling

Breathing zone samples representative of the individual employee's exposure shall be collected. A description of sampling location and conditions, equipment used, time and rate of sampling, and any other pertinent information shall be recorded at the time of sample collection. Enough samples shall be collected to permit calculation of a TWA concentration for every operation or location in which there is exposure to malathion.

The midget impinger recommended in Chapter IV of this document must be operated in a uniform and consistent way if data obtained are to have meaning in the assessment of environmental conditions. The impinger should be made of glass in all portions that may contact the collection medium or the air stream before collection is effected. It should be emphasized that the ethylene glycol used as a collection medium must be free of contaminants that produce interfering peaks when extracted with hexane and analyzed by gas liquid chromatography (GLC). Consequently, only ethylene glycol that has been preextracted and found to be free of interfering

substances by GLC utilizing a flame photometric detector can be used.

(a) Equipment

The sampling train consists of an all-glass midget impinger filled with 10 ml of ethylene glycol. The sampling pump is protected from splash-over or water condensation by an adsorption tube loosely packed with a plug of glass wool and inserted between the exit arm of the impinger and pump or, preferably, by a water trap inserted in the same location.

(b) Calibration

Since the accuracy of an analysis can be no greater than the accuracy of the air volume measurement, the accurate calibration of a sampling pump is essential to 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. Pumps should also be recalibrated if they have been misused 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. 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, primary standards, such as a spirometer or a soapbubble meter, are recommended, although other standard calibration instruments, such as a wet-test meter or dry gas meter, can be used. The actual setups will be similar for all instruments.

Instructions for calibration with the soapbubble meter follow. If another calibration device is selected, equivalent procedures should be used. Since the flowrate given by a pump is dependent on the pressure drop of the sampling device, in this case an impinger, the pump must be calibrated while operating with a representative impinger in line. The calibration system should be assembled in series following this order: soapbubble meter, water manometer, midget impinger, and pump, as shown in Figure XV-2.

(1) The voltage of the pump battery is checked with a voltmeter to ensure adequate voltage for calibration. The battery is charged if necessary.

(2) The pump is turned on and the inside of the soapbubble meter is moistened by immersing the buret in the soap solution and drawing bubbles up the inside until they travel the entire buret length without bursting.

(3) The pump rotameter is adjusted to provide the desired flowrate.

(4) A soapbubble is started up the buret and the time required for it to move between calibration marks is measured with a stopwatch.

(5) The procedure in (4) above is repeated at least twice, the results averaged, and the flowrate calculated from the volume between the preselected marks divided by the time required for the soapbubble to traverse the distance.

(6) Data for the calibration include the volume measured, elapsed time, pressure drop, air temperature, atmospheric pressure, serial

number of the pump, date, and name of the person performing the calibration.

(c) Sampling Procedure

Any air mover capable of drawing the desired flowrates through the impingers may be used, so long as flowrates do not vary more than ± 5% during the sampling period. The sampling pump must be capable of operating at a pressure drop of 1 inch of mercury while providing the designated flow of 2.8 liters/minute.

An air sample is taken using a flowrate of 2.8 liters/minute. The flowrate of the pump must be calibrated and this calibration checked periodically to ensure that it has not changed.

When atmospheric samples are taken for determination of compliance with the recommended environmental limit, the impinger is placed within the breathing zone of the exposed employee to determine the employee's actual exposure to airborne malathion. This may be done by placing the midget impinger in a holster and fastening it to a lapel of a coat or coliar of a shirt. The individual conducting the evaluation may also hold the impinger near the face of the employee during the sampling period.

The duration of sampling shall be such that the recommended analytical method may detect concentrations as low as 1/10 the recommended environmental limit, ie, 1.5 mg/cu m.

The contents of the impinger should be transferred to a sample bottle for shipping. The impinger and stem should be washed with 2-5 ml of ethylene glycol, the solution used for washing included in the sample bottle, and the exact amount of ethylene glycol used recorded. The bottle should be sealed tightly and placed upright in a carrying case. Every

attempt should be made to prevent any loss due to spillage or evaporation.

The trapped malathion is extracted from the ethylene glycol with hexane and analyzed as described in Appendix II. Other collection methods shown to be equivalent may be used.

X. APPENDIX II

ANALYTICAL METHOD FOR MALATHION

The method presented in the NIOSH Manual of Analytical Methods [204] for analysis of parathion in air is recommended for malathion.

Principle of the Method

Malathion from the air is trapped in ethylene glycol contained in a midget impinger. The ethylene glycol solution is diluted with water and extracted with hexane. The resulting hexane solution containing the malathion is concentrated and subjected to gas chromatographic analysis using a phosphorus flame photometric detector.

Range and Sensitivity

The linear range of the flame photometric detector is 0.5-25 ng for malathion and for a 50-liter air sample carried through the following procedure to solution in 1 ml of hexane, 2 μl of which are injected into the gas chromatograph, ie, 5-250 μg/cu m. These limits can be lowered or raised by changing (1) the volume of air sampled, (2) the volume of the final hexane solution, or (3) the size of the aliquot injected into the gas chromatograph.

Interferences

Phosphorus compounds having retention times close to that of malathion will interfere with the analysis. Retention ratios, relative to ethyl parathion, have been tabulated for malathion on columns identical to column 4 as specified (see Apparatus Section), but operated at slightly different temperatures, by Thompson. [200] These indicate possible interference by malaoxon and methyl parathion. Resolution of such interference can be accomplished by varying the column compositions and temperatures used. The equipment used must be scrupulously cleaned to remove any traces of phosphate detergents.

Advantages and Disadvantages of the Method

(a) Advantages: The method is very sensitive, and the detector exhibits high specificity for phosphorus compounds. The analysis is performed directly on malathion. Separation and quantitation are accomplished in a reasonable amount of time.

(b) Disadvantages: The cost of the equipment and supplies may tax the budget of some laboratories. The sensitivity of the equipment depends on careful adjustment of the operating conditions. Contamination can occur easily through equipment or reagents. If interfering compounds are anticipated, a lengthy cleanup procedure is required.

Apparatus

(a) Forceps.

(b) Glass stirring rods.

(c) Separatory funnels, 250-ml.

(d) Beakers, 100-ml.

(e) Funnels, 65- or 75-mm (diameter at top).

(f) Glass wool.

(g) Hot-water bath.

(h) Kuderna-Danish evaporator-concentrator, consisting of a 125-ml Erlenmeyer-type flask, 3-ball Snyder column, and a 10-ml receiver graduated in milliliters.

(i) Glass beads, 3-mm.

(j) Volumetric flasks for standards.

(k) Graduated cylinders, 25- or 50-ml.

(l) Syringes, 5- or 10-μl and 100-μl.

(m) Gas chromatograph, with attendant equipment, including a phosphorus flame photometric detector.

(n) Gas-chromatography column constructed from 6-ft x 4-mm inside diameter borosilicate glass packed with one of the following:

(1) 10% DC-200 (12,500 cst) on 80-100 mesh Gas Chrom Q.

(2) 7.5% QF-1 (10,000 cst)/5% DC-200 (12,500 cst) on 80-100 mesh Gas Chrom Q.

(3) 2% diethylene glycol succinate (DEGS) (C6 stabilized) on 80-100 mesh Gas Chrom Q.

(4) 4% SE-30/6% OV-210 on 80-100 mesh Chromosorb W, HP.

Columns 1 and 2 are heat-conditioned for 2-4 days at 240-250 C under nitrogen flowing at 60 ml/minute, then primed by repeated injections of standard malathion solution under the conditions of analysis given below. Column 3 is conditioned by heating for 12 hours at 225-230 C under nitrogen

flowing at 60 ml/minute. A column of 10% Carbowax 20M on 80-100 mesh silanized support (2-in x 4-mm inside diameter glass tubing) is then inserted before Column 4, and the assembly is heated at 230-235 C for 17 hours under nitrogen flowing at 20 ml/minute. The 10% Carbowax 20 M column is subsequently removed.

Reagents

(a) Ethylene glycol, chromatoquality.

(b) Hexane, pesticide quality.

(c) Distilled water, interference-free.

(d) Saturated aqueous sodium chloride, interference-free.

(e) Anhydrous sodium sulfate.

(f) Malathion of known purity.

Analysis of Samples

(a) Transfer the sample in 17-20 ml of ethylene glycol to a 125-ml separatory funnel. Wash the sample container with a measured amount of water and add the washings to the separatory funnel. Dilute the ethylene glycol with a total of 70 ml of water.

(b) Extract the aqueous solution three times with 12 ml of hexane, and discard the aqueous layer. Should an emulsion be formed, saturated aqueous chloride can be used to disperse it.

(c) Dry the hexane solution by passing it through 2.6 g of anhydrous sodium sulfate contained in a funnel with a glass-wool retaining plug at the top of the stem. Collect the eluate in a 125-ml Kuderna-Danish

flask which has been fitted with a 10-ml receiving tube containing one 3-mm glass bead. Rinse the separatory funnel with three consecutive 2-ml portions of hexane, washing down the walls of the funnel. Allow each rinse to elute before adding the next. Finally, rinse the funnel and the sodium sulfate with two more 2-ml portions of hexane.

(d) Place the Kuderna-Danish assembly in a boiling water bath and concentrate the extract to a volume of approximately 5.0 ml. Remove the assembly from the bath, and after it has cooled, disconnect the receiving tube from the flask, rinsing the joint with a little hexane. Place the tube under a nitrogen stream at room temperature and further concentrate the extract to approximately 0.5 ml. Rinse down the wall of the tube with hexane delivered from a 100-μl syringe, diluting the extract to exactly 1.0 ml, and stir.

(e) Inject a suitable aliquot of the hexane solution into the gas chromatograph and obtain a chromatogram. The chromatographic conditions are:

Column temperature	220 C for columns 1 and 2 210 C for column 3 200 C for column 4
Injection port temperature	225 C
Detector temperature	200 C
Transfer line and switching valve temperature	235 C
Carrier gas (nitrogen) flow	60 ml/minute

The solvent-flush sample injection technique is recommended. Duplicate injections should be made. The hexane, which precedes the malathion, should be vented so the detector flame will not be extinguished.

The conditions of the run should be such that no malathion is lost during the venting process.

(f) The average of the areas under the malathion peaks is converted to the amount (ng) of malathion seen by the detector by comparing it to a standard curve for malathion.

Calibration and Standards

(a) Prepare at least three standard solutions in the concentration range of 100-12,500 ng/ml from a stock solution of malathion in hexane.

(b) Make duplicate injections of aliquots of each standard solution into the gas chromatograph and determine the peak areas.

(c) Plot the amount (ng) of malathion seen by the detector against the peak area. A straight line passing through the origin should result. If this result is not obtained, either the linear range of the detector has been exceeded or a system malfunction has occurred.

(d) Injections of standards should be interspersed among sample injections so that a watch can be maintained on detector sensitivity.

Calculations

(a) Determine the total amount in ng of malathion present in the sample:

$$\text{Total ng} = \text{ng(o)} \times \frac{\text{Soln vol}}{\text{Inj vol}}$$

where:

ng(o) = nanograms of malathion determined from calibration curve based on peak area responses

Soln vol = volume in μl of the final hexane solution (usually 1,000 μl)

Inj vol = volume in μl of the aliquot of the final hexane solution injected into the gas chromatograph

(b) Convert the volume of air sampled to standard conditions of 25 C and 760 mmHg:

$$Vs = V \times \frac{P}{760} \times \frac{298}{(T + 273)}$$

where:

Vs = volume of air in liters at 25 C and 760 mmHg

V = volume of air in liters as measured

P = barometric pressure in mmHg where sample is collected

T = temperature (degrees C) of air sampled

(c) The concentration of malathion can be expressed in ng/l or μg/cu m:

$$\mu g/cu\ m = ng/liter$$

$$\mu g/cu\ m = \frac{total\ ng}{Vs}$$

XI. APPENDIX III

NOTES ON THE DIAGNOSIS AND MEDICAL MANAGEMENT OF ORGANOPHOSPHORUS INTOXICATION

The following paragraphs have been adapted from an article entitled "Prevention and Management of Organophosphate Poisoning" which appeared in the Journal of the American Medical Association and which was approved by the AMA Committee on Occupational Toxicology of the Council on Occupational Health. [205]

Diagnosis

A diagnosis of organophosphate intoxication is based primarily on a definite history of exposure to an organophosphate 6 hours or less before onset of illness and clinical evidence of diffuse parasympathetic stimulation. Laboratory verification is based on depression of plasma and red blood cell ChE activities to a level substantially (50% or more) below preexposure values if these are available. If preexposure values are not available, one can use laboratory normal ranges, observing, of course, the usual caution in interpreting such figures. There are many different methods for estimation of ChE content of blood, and associated with each method is a different set of normal values and a different set of reporting units. The laboratory report of a ChE determination should state the units involved along with the appropriate normal range. Based on the Michel method, [61] the normal range of red blood cell ChE activity (delta pH/hr) is 0.39 to 1.02 for men and 0.34 to 1.10 for women. The normal range of

the enzyme activity (delta pH/hr) of plasma is 0.44 to 1.63 for men and 0.24 to 1.54 for women.

In actual practice, the ChE test is often of more value as a confirmatory, rather than a diagnostic, procedure. For moderate-to-severe intoxication, the clinician should act on his clinical impression and on the history of exposure rather than wait for laboratory confirmation.

Initial signs and symptoms of intoxication are headache, nausea, vomiting, sweating, blurred vision, weakness, diarrhea, abdominal pain, and pallor. In moderate-to-severe cases of intoxication, signs and symptoms may also include dyspnea, salivation, lacrimation, muscle fasciculation, convulsions, cyanosis, shock, and cardiac arrhythmias, coma, and death. In the case of mild poisoning where the differential diagnosis may be puzzling, the results of the ChE test may be necessary to establish a definite diagnosis.

ChE is an enzyme which hydrolyzes ACh. Two types are clinically significant: the first, true or acetylChE, is found principally in nervous tissue and in the red blood cell; the other, plasma or BuChE, is found in nervous tissue and in the circulating plasma. Whereas the action of both is inhibited by organophosphate compounds, only depression of the amount of enzyme in the red blood cells is a specific response to these toxins. The level of the enzyme in the plasma may vary with a number of diseases or toxic states. A relatively wide variation exists in the normal levels of both enzymes from one individual to another as well as in the same individual at different times. Once enzyme activity is inhibited, the regeneration times differ between the two types. Red blood cell ChE regenerates at approximately 1%/day, whereas the enzyme in the plasma

regenerates at a more rapid rate, approximating 25% in the first 7-10 days.

Circulating red blood cell and plasma ChE may be conveniently thought of as a buffer system which serves to protect the individual against the nervous system effects of organophosphate toxins by binding the pesticide in the circulating blood, thereby preventing it from reaching the nervous system. Although this is an oversimplified explanation, it is a clinically useful one. In practice, an individual who has been chronically exposed to organophosphate pesticides should be withdrawn from further exposure when his ChE activity values drop to 25-50% of normal and should not be allowed to return until these values rise to at least 75% of normal. The individual who has been acutely poisoned and has shown marked ChE activity depression should not be allowed to return to work with organophosphate pesticides until his ChE levels have returned to approximately 75% of normal.

Treatment

Treatment of organic phosphate poisoning ranges from simple removal from exposure in very mild cases to the provision of very rigorous supportive and antidotal measures in severe cases. In the moderate-to-severe case, because of pulmonary involvement, there may be a need for artificial respiration using a positive pressure method. Careful attention must be paid to removal of secretions and to maintenance of a patent airway. Anticonvulsants, such as thiopental sodium, may be necessary. The critical point is that respiration must be maintained since death usually results from weakness of the muscles of respiration and accumulation of excessive secretions in the respiratory tract. As soon as cyanosis has

been overcome, 2-4 mg of atropine iv should be administered promptly. This dose is approximately 10 times the amount which is administered for other conditions in which atropine is considered therapeutic. This dose should be repeated at 5- to 10-minute intervals until signs of atropinization appear (dry, flushed skin, tachycardia as high as 140 beats/minute, and pupillary dilatation). A mild degree of atropinization should be maintained for at least 48 hours. Atropine is contraindicated in a cyanotic patient because of the possibility of inducing ventricular fibrillation.

Although atropine remains the drug of choice, particularly if the treatment has to be continued for more than a day or two, pralidoxime chloride (Protopam chloride) is a commercially available antidote which complements atropine and hastens the reactivation of ChE enzymes. For adults, in the moderate-to-severe cases, it should be used along with atropine, injected iv as an initial dose of 1 g at a rate not in excess of 500 mg/minute. After an hour, a second dose of 1 g is indicated if muscle weakness has not been relieved. After an overwhelming inhalation or skin exposure to or after ingestion of the toxic agent, the doses may be doubled. For children, the dose may be 25-50 mg/kg of body weight. Treatment with pralidoxime chloride will be most effective if given within 24 hours after poisoning. (Its usefulness after 36-48 hours is questionable.) Together, the two antidotes, atropine and pralidoxime chloride, are more effective than either one alone. Morphine, aminophylline, and the phenothiazines are specifically contraindicated.

It is of great importance to decontaminate the patient. The stomach should be lavaged and a saline cathartic administered if the toxin has been

ingested. Contaminated clothing should be removed at once and the skin should be washed with generous amounts of soap or detergent and a flood of water, which is best accomplished under a shower or by submersion in a pond or other body of water if the exposure occurred in the field. Careful attention should be paid to cleansing of the skin and hair. The patient should be attended and monitored continuously for not less than 24 hours, since serious and sometimes fatal relapses have occurred because of continuing absorption of the toxin or dissipation of the effects of the antidote.

Atropine is antagonistic to the muscarinic effects, which include anorexia, nausea, vomiting, abdominal cramps, sweating, salivation, constricted pupils, pulmonary edema, and cyanosis. Atropine has no effect on the nicotinic manifestations, which include muscle fasciculation and weakness. Pralidoxime chloride acts to regenerate ChE and to reverse muscle weakness. Muscle weakness, specifically weakness of the muscles of respiration, is responsible for respiratory impairment and death in the fatal case. A fully atropinized patient may die of respiratory insufficiency.

XII. APPENDIX IV

METHOD OF SAMPLING AND ANALYSIS FOR BIOCHEMICAL DETERMINATION OF CHOLINESTERASE ACTIVITY

The method of Wolfsie and Winter, [155] a micromodification of the Michel method, [61] is recommended for the measurement of ChE activity.

Sample Handling and Preparation

Blood is collected from a clean, dry fingertip in a heparinized glass capillary tube. The blood is allowed to flow into the capillary tube until the tube is approximately 3/4 full, leaving 1-1.25 inches free at one end to permit flame-sealing of the tip of the tube without overheating the blood sample. The finger should be pricked deeply and care taken to collect only free-flowing blood to prevent clotting before the blood contacts the heparin lining the wall of the capillary tube.

One end of the capillary tube is plunged into solid (room temperature) paraffin and the other (free) end sealed in the flame of a Bunsen burner. The capillary tube is labeled with an adhesive tape tag bearing a serial number or name and date. The sample should then be centrifuged at 3,000-3,500 rpm for 50-60 minutes or its equivalent. When so treated, the sample may be shipped to a laboratory for immediate analysis. The sample should be stored in the cold, insofar as is feasible under field conditions.

Reagents

All reagents should be at least ACS reagent grade.

(a) Buffer solution I (for erythrocytes)

For 1 liter of buffer, dissolve 4.1236 g of sodium barbital (0.02 M), 0.5446 g of potasium orthophosphate, di-H (0.004 M), and 44.730 g of potassium chloride (0.60 M) in 900 ml of distilled water. Add 28.0 ml of 0.1 N hydrochloric acid while shaking the solution, and bring the flask to volume with distilled water. The pH of buffer I should be 8.10 at 25 C.

(b) Buffer Solution II (for plasma)

For 1 liter of buffer, dissolve 1.2371 g of sodium barbital (0.006 M), 0.1361 g of potassium orthophosphate, di-H (0.001 M), and 17.535 g of sodium chloride (0.30 M) in about 900 ml of distilled water. Add 11.6 ml of 0.1 N hydrochloric acid before bringing to volume. The pH of buffer II should be 8.00 at 25 C.

The pH of a buffer solution may decrease over a period of several weeks. The pH should be checked before use. If it has dropped more than 0.03 pH units, the solution should be discarded and a fresh one made.

(c) ACh substrate (for erythrocytes)

This is 0.11 M ACh chloride. Dissolve 2.000 g in 100 ml of distilled water.

(d) ACh substrate (for plasma)

This is 0.165 M ACh chloride. Dissolve 3.000 g in 100 ml of distilled water.

A few drops of toluene may be added to the ACh solutions as a preservative. The solutions must be refrigerated when not in use and discarded at the end of 2 weeks.

(e) Saponin solution

This is 0.01% saponin. Dissolve 100 mg in 1,000 ml of distilled water.

Apparatus

(a) Centrifuge capable of maintaining 3,500 rpm and holding capillary sample tubes.

(b) A pH meter, calibrated to 0.01 pH units.

(c) 0.02-ml Sahli-type hemoglobin pipet.

(d) Constant-temperature bath, 25 C ± 0.1.

(e) 100- and 1,000-ml volumetric flasks.

Analysis

For analysis, the capillary tube is cut cleanly with a sharp ampule file. From the packed-cell section of the capillary, draw 0.02 ml directly into a Sahli-type hemoglobin pipet. The ends of the capillary must be cut evenly to provide satisfactory juxtaposition with the tip of the pipet. Discharge the contents of the pipet directly into 1.0 ml of 0.01% saponin in a microbeaker, and rinse the pipet well (three times) in the solution. Glass vials, 1 inch (2.5 cm) deep by 3/4 inch (19 mm) in diameter, are convenient for electrometric testing. They will fit in the carrier of a standard pH meter and, when used with a clean rubber stopper, will eliminate transferring the sample from a test tube for each pH measurement. Plasma is taken from the appropriate section of the capillary in the same manner as the packed erythrocytes and discharged into 1.0 ml of distilled

water, the Sahli-type pipet being rinsed in the solution (three times) as with the erythrocytes.

Erythrocyte Assay

(a) One milliliter of hemolyzed erythrocyte solution is added to 1 ml of buffer solution I and placed in a 25 C water bath.

(b) After a 10-minute equilibration period, the initial pH (pH(i)) is determined to the nearest 0.01 pH unit with the pH meter.

(c) A volume of 0.2 ml of 0.11 M ACh solution is added with rapid mixing and the time is recorded.

(d) The reaction proceeds for 1-1.5 hours and then the final pH (pH(f)) is noted.

The beaker containing the solution should be shaken when the glass electrode is introduced to expedite the establishment of equilibrium.

Note: Buffer solution I is designed to yield a pH of 8.00 after the addition of hemolyzed human erythrocytes.

Plasma Assay

(a) One milliliter of diluted plasma is mixed with 1 ml of buffer solution II.

(b) The solution is allowed to equilibrate in a 25 C water bath for 10 minutes.

(c) At the end of 10 minutes, the pH (pH(i)) is noted to the nearest 0.01 pH unit.

(d) A volume of 0.2 ml of 0.165 M ACh solution is added with rapid mixing.

(e) The reaction mixture is incubated for 1-1.5 hours and the final pH (pH(f)) is noted.

Calculations

The final units derived from this assay are delta pH/hour:

$$\text{Delta pH/hour} = \frac{c(pH(i)) - pH(f)}{t(2) - t(1)} - cb$$

where:

pH(i) = initial pH

pH(f) = final pH

t(2) - t(1) = time elapsed in hours between pH(i) and pH(f) readings

b = nonenzymatic hydrolysis corresponding to pH 2

c = correction for variations in delta pH/hour with pH corresponding to pH 2

The b and c correction factors are given in Table XII-1. Average baseline values of erythrocyte and plasma ChE activities in men and women determined by this method are given in Table XII-2.

TABLE XII-1

CORRECTION FACTORS FOR USE IN EQUATION 1

	Erythrocyte ChE Corrections		Plasma ChE Corrections	
pH 2	b	c	b	c
7.9	0.03	0.94	0.09	0.98
7.8	0.02	0.95	0.07	1.00
7.7	0.01	0.96	0.06	1.01
7.6	0.00	0.97	0.05	1.02
7.5	0.00	0.98	0.04	1.02
7.4	0.00	0.99	0.03	1.01
7.3	0.00	1.00	0.02	1.01
7.2	0.00	1.00	0.02	1.00
7.1	0.00	1.00	0.02	1.00
7.0	0.00	1.00	0.01	1.00
6.8	0.00	0.99	0.01	1.00
6.6	0.00	0.97	0.01	1.01
6.4	0.00	0.97	0.01	1.02
6.2	0.00	0.97	0.01	1.04
6.0	0.00	0.99	0.01	1.09

Adapted from Michel [61]

TABLE XII-2

NORMAL VALUES FOR CIRCULATING CHOLINESTERASES IN HEALTHY NONEXPOSED PERSONS*

Subjects	Erythrocyte ChE Activity (delta pH/hr)			Plasma ChE Activity (delta pH/hr)			Reference
	Range	Mean	SD	Range	Mean	SD	
400 men	0.58 -0.95	0.766	0.081	0.52 -1.39	0.953	0.187	112**
400 women	0.56 -0.94	0.750	0.082	0.38 -1.25	0.817	0.187	112**
255 men	0.554-1.252	0.861	0.091	0.408-1.652	0.912	0.112	89***
120 men and women	-	-	-	0.58 -1.37	0.94	0.16	113
20 men	-	-	-	-	0.95	0.24	114
20 women	-	-	-	-	0.78	0.12	114

*All analyses by method of Michel [61]
**Ranges, means, and standard deviations estimated from data extrapolated to age 40; highest 1% and lowest 1% values eliminated from ranges
***Analytical method modified for smaller blood samples

XIII. APPENDIX V

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 an 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, ie, "100 ppm LC50-oral-rat," "25 mg/cu m LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.93," 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. Flammable or reactive data

could be flash point, shock sensitivity, or other brief data indicating nature of the hazard.

(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 flash point 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, mild irritation and possibly some blistering.
>
> 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 workers.

(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 workers 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," "Suitable for dusts not more toxic than lead," 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 workers potentially 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 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 _____

XIV. APPENDIX VI

CLINICAL CLASSES OF MALATHION POISONING

Class	Criteria
I Clinically insignificant exposure	No significant signs or symptoms, vital signs normal, physical examination negative; history of minimal exposure-inhalations, skin contact, mouth-rinse or ingestion - some malingerers - sometimes no malathion odor
II Mild nonspecific clinical symptoms	Nausea, vomiting, dizziness; malathion odor detected
III Mild to moderately severe specific clinical symptoms	Sialorrhea, with foaming if taken po, few rales of rhonchi, pupils small (sometimes not pinpoint); conscious, sometimes stuporous; glycosuria not infrequent
IV Severe specific clinical symptoms	As above, but more marked, including hypotension; Cheyne-Stokes respirations, involuntary defecation, coma, cyanosis, areflexia, and convulsions or fasciculations

From Nalin [50]

XV. TABLES AND FIGURES

TABLE XV-1

PHYSICAL PROPERTIES OF MALATHION

Chemical name	O,O-dimethyl S-(1,2-dicarboethoxyethyl) dithiophosphate
Common name	Malathion (ISO)
Molecular formula	C10H1906PS2
Molecular weight	330.36
Color and form	Colorless to light amber liquid
Odor	Penetrating (garlic)
Vapor pressure	0.00004 mmHg at 30 C
Boiling point	156-157 C at 0.7 mmHg
Melting point	2.85 C
Specific gravity	1.232 at 25 C
Solubility	Slightly soluble in water (145 ppm) at 25 C, miscible with many organic solvents
Flash point	Above 325 F TOC
Conversion factors at 25 C and 760 mmHg	1 mg/cu m = 0.075 ppm 1 ppm = 13.333 mg/cu m

Adapted from 11 and 17

TABLE XV-2

TRADE NAMES AND SYNONYMS FOR MALATHION

S-(1,2-bis(aethoxycarbonyl)-aethyl)-0,0-dimethyl-dithiophasphat (Ger)

S-(1,2-bis(ethoxy-carbonyl)-ethyl)-0,0-dimethyl-dithiofosfaat (Ned)

S-(1,2-bis(ethoxycarbonyl)ethyl,0,0-dimethyl phosphorodithioate

S-(1,2-bis(etossi-carbonil)-etil)-0,0-dimetil-ditiofosfato (It)

S-1,2-bis(ethoxycarbonyl)ethyl-0,0-dimethyl thiophosphate

Dicarboethoxyethyl 0,0-dimethyl phosphorodithioate

S-(1,2-di(ethoxycarbonyl)ethyl dimethyl phosphorothiolothionate

1,2-di(ethoxcarbonyl)ethyl 0,0-dimethyl phosphorodithioate

Diethyl mercaptosuccinate, 0,0-dimethyl dithiophosphate, S-ester

Diethyl mercaptosuccinate, 0,0-dimethyl phosphorodithioate

Diethyl mercaptosuccinate, 0,0-dimethyl thiophosphate

0,0-dimethyl S-(1,2-bis(ethoxycarbonyl)ethyl)dithiophosphate

0,0-dimethyl-S-(1,2-dicarbethoxyethyl)dithiophosphate

0,0-dimethyl S-(1,2-dicarbethoxyethyl)phosphorodithioate

0,0-dimethyl S-(1,2-dicarboethoxyethyl) dithiophosphate

0,0-dimethyl S-1,2-di(ethoxycarbamyl)ethyl phosphorodithioate

0,0-dimethyldithiophosphate diethylmercaptosuccinate

TABLE XV-2 (CONTINUED)

TRADE NAMES AND SYNONYMS FOR MALATHION

Dithiophosphate de 0,0-dimethyle et de S-(1,2-dicarboethoxyethyle) (Fr)

Phosphorodithioic acid, 0,0-dimethyl ester, S-ester with diethyl mercaptosuccinate

American Cyanamid 4,049
Carbetox
Carbophos
Chemathion
Compound 4049
Cythion
ENT 17,034
Ethiolacar
Fosfothion
Fosfotion
Four thousand forty-nine
Insecticide No. 4049
Karbofos
Malacide
Malakill
Malagran
Malamar 50
Malaphos
Malaspray
Malathion
Malathion LV concentrate
Malathion (Pol)
Malatol
Malatox
Mercaptothion
Oleophosphothion
Phosphothion
Sadofos
Sadophos
SF 60
Siptox 1

Adapted from Registry of Toxic Effects of Chemical Substances 1975 Edition [12]

TABLE XV-3

PARTITION COEFFICIENTS OF MALATHION AND MALAOXON

Malathion and:	
Carbon tetrachloride	34
Chloroform	37
Hexane	27
Malaoxon and:	
Carbon tetrachloride	2.9
Chloroform	5.8
Hexane	0.42

From O'Brien and Dannelley [71] and O'Brien [206]

TABLE XV-4

SOME METABOLITES OF MALATHION

Product	Species	Location	Reference
Dimethyl phosphate	Cow	Feces	186
	Human	Urine	207
Dimethyl phosphorothioate	Human	Urine	200
Dimethyl phosphorodithioate	"	"	200
Dimethyl thiophosphate	"	"	200
Dimethyl dithiophosphate	"	Urine and serum	207
Desmethyl malathion	Cow	"	64
	Rat	"	64
	Dog	"	64
	Mouse	"	64
Malathion diacid	Cow	"	64
	Rat	"	64
	Dog	"	64
Phosphatase products	Mouse	"	76
Malaoxon	Mammal	Tissue	64

TABLE XV-5

LD50's (MG/KG) FOR RATS, MICE, AND GUINEA PIGS

Species	Exposure Route			Reference
	Oral	Dermal	ip	
Rats	1,400 - 1,500 M			208
"	1,401 M			105
"	1,375 M 1,400 F	Exceeds 4,400 M and F		109
"	480 M			209
"			750 adult M 340 weanlings	103
"			619.4 F	211
"	200 F		136 F	
"	200 F		136 F	210
Mice	885 M			209
"	775 M			208
"			193 M	211
Guinea pigs			500 F	208
Dogs			1,400 M	211

TABLE XV-6

EFFECTS ON HUMANS FROM MALATHION EXPOSURE

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	Reference
Dermal, oral, respiratory	3 men	(Unknown conc) 35 - 40 d 4.5 mo	No signs or symptoms, no ChE activity changes	17
"	"	(Unknown conc) 3 d	Symptoms of ChE poisoning in 2 for 3 days, in 1 for 1 day	182
"	1 man	(Unknown conc) 10 d	"Obvious manifestations of organo-phosphorus intoxication"	38
Respiratory, possibly oral and dermal	12 men	5.3 mg/cu m 21.2 mg/cu m 84.8 mg/cu m 84 hourly over 42 d	No changes in ChE activity; no cholinergic signs or symptoms	56
Dermal	30-40 men	0 % in talc 1 % " 5 % " 10 % " 5 d/wk*	No changes (1 and 5%), nonsignificant decrease (10%), in erythrocyte ChE activity; no illness	32
Oral	1 man	120 ml (Spray 50%)	Coma, bronchial hypersecretion, miosis, diarrhea, areflexia, fasciculations, reduced erythrocyte ChE activity, ECG changes	39
"	"	50 - 90 ml (Spray 50%)	Nausea, vomiting, diarrhea, incontinence, bronchial hypersecretion, areflexia, altered sensorium, blepharoptosis, reduced erythrocyte ChE activity	91

TABLE XV-6 (CONTINUED)

EFFECTS ON HUMANS FROM MALATHION EXPOSURE

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	Reference
Oral	1 man	Appr 120 ml	Bronchial hypersecretion, coma, fasciculations, areflexia, miosis, excessive sweating, blepharoptosis	20
"	10 men	16 mg/d x 47 d	No signs or symptoms; reduced ChE activity only after termination of study	21
"	5 men	24 mg/d x 56 d	"	55
"	264 humans	-	Vomiting, sweating, bronchorrhea, miosis, incontinence, areflexia, fasciculations, hypotension, stupor, death	50
"	1 child	8 ml (50% in xylene)	Excessive mucus secretion, hypersalivation, vomiting, incontinence, miosis, absence of deep tendon reflexes, stupor	47
"	1 woman	-	Miosis, coma, areflexia, pulmonary edema, respiratory and cardiac arrest, death	40
"	1 man	0.84 mg/kg	No effects; 23% recovered from ether-extractable urine fraction	55
"	1 woman	0.7 g/kg (liquid 57%)	Sweating, cyanosis, salivation, miosis, fasciculations	46

TABLE XV-6 (CONTINUED)

EFFECTS ON HUMANS FROM MALATHION EXPOSURE

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	Reference
Oral	1 woman	0.6 g/kg (liquid 55% in 35% naphtha extract)	Cyanosis, respiratory distress, miosis, diarrhea, fasciculations	44
"	1 man	0.5 g/kg (liquid 57%)	Cyanosis, incontinence, respiratory distress, miosis, hypotension	46
"	"	0.5 g/kg (liquid 50% in 42.4% xylene and 7.6% inert ingredients)	Coma, respiratory distress, hypertension, bronchial hypersecretion and constriction, areflexia, miosis, vomiting, incontinence, reduced ChE activity, ECG abnormal, death	25
"	1 woman	0.5 g/kg (liquid 50%)	Cyanosis, respiratory distress	45

*For an estimated whole body maximum of 28 g

TABLE XV-7

EFFECTS ON ANIMALS FROM MALATHION EXPOSURE

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Respiratory	Rabbits	6 M	128 mg/cu m 6% aerosol in No. 2 fuel oil 6 hrs	Respiratory distress, death: 1 dead immediately after exposure, 4 dead by 24 hrs, 1 dead by 72 hrs, all dead by 7 d	83
"	"	"	123 mg/cu m 95% aerosol 6 hrs	Plasma ChE inhibition of 32% by 24 hrs, 35% by 72 hrs, normal by 7 d; erythrocyte ChE inhibition of 34% by 24 hrs, 51% by 72 hrs, 45% by 7 d	83
"	"	"	66 mg/cu m 6% aerosol in No. 2 fuel oil 6 hrs	Respiratory distress during and for 7 d after exposure, 1 dead after exposure, 1 dead by 72 hrs	83
"	"	"	65 mg/cu m	No significant inhibition of blood ChE; no toxic signs	83
		"	34 mg/cu m 95% aerosol 6 hrs		
"	"	"	30 mg/cu m	"	83
		"	24 mg/cu m 6% aerosol in No. 2 fuel oil 6 hrs		
"	"	"	6 mg/cu m 95% aerosol 6 hrs	"	83

TABLE XV-7 (CONTINUED)

EFFECTS ON ANIMALS FROM MALATHION EXPOSURE

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Respiratory	Quail	20	128 mg/cu m 6% aerosol in No. 2 fuel oil 6 hrs	All dead at end of exposure	83
"	"	20	123 mg/cu m 95% aerosol 6 hrs	Significant plasma ChE inhibition, 95% immediately after exposure, 75% at 24 hrs, normal by d 7	83
"	"	20	66 mg/cu m 6% aerosol in No. 2 fuel oil 6 hrs	Death of 14 during exposure, 4 by 24 hrs; 2 survivors	83
"	"	20	65 mg/cu m 95% aerosol 6 hrs	Significant plasma ChE inhibition, 84% immediately after exposure, 63% at 24 hrs, normal by d 7	83
"	"	20	34 mg/cu m 95% aerosol 6 hrs	Significant plasma ChE inhibition, 51% immediately after exposure, normal by 24 hrs	83
"	"	20	30 mg/cu m 6% aerosol in No. 2 fuel oil 6 hrs	Significant plasma ChE inhibition, 54% immediately following exposure, 28% at 24 hrs, normal by 7 d	83

TABLE XV-7 (CONTINUED)

EFFECTS ON ANIMALS FROM MALATHION EXPOSURE

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Respiratory	Quail	20	24 mg/cu m 6% aerosol in No. 2 fuel oil 6 hrs	Significant plasma ChE inhibition, 45% immediately after exposure, normal by 24 hrs	83
"	"	20	6 mg/cu m 95% aerosol 6 hrs	No significant inhibition of blood ChE	83
"	Rabbits Guinea pigs Rats Mice	- - - -	60 ppm 90% aerosol 6 hrs/d x 2 d	Normal brain, plasma, and erythrocyte ChE activity in guinea pigs and rats; pulmonary hyperemia all species; no "gross pathology"	10
"	Guinea pigs Rats Mice Dogs	- - - 1	5 ppm 90% aerosol 8 hrs/d 5 d/wk x 4 wks	No deaths; no signs of ChE inhibition	10
"	Guinea pigs	-	5 ppm 5% dust 7 hrs/d 5 d/wk x 6 wks	No inhibition of brain, plasma, or erythrocyte ChE	10
"	Rats	-	5 ppm 5% dust 7 hrs/d 5 d/wk x 6 wks	Moderate inhibition of brain, plasma, and erythrocyte ChE	10

TABLE XV-7 (CONTINUED)

EFFECTS ON ANIMALS FROM MALATHION EXPOSURE

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Respiratory	Dogs	-	5 ppm 5% dust 7 hrs/d 5 d/wk x 6 wks	"Mild" ChE inhibition in 1; no inhibition of plasma or erythrocyte ChE in 1	10
Oral	Rats	388	200 - 2,000 mg/kg x 28 d	Decreased toxicity with increased dietary protein	106
"	"	21 F	900 mg/kg in corn oil d 9 or d 10, d 8 - d 12, or d 12 - d 15 of gestation	No dose-related effects	116
"	"	5 M	500 ppm or 100 ppm 8 wks	No significant effects	86
"	"	5 M	500 ppm with 25 ppm EPN* 8 wks	Whole blood ChE inhibition of 79%	86
"	"	5 M	100 ppm with 5 ppm EPN 8 wks	No significant effects	86
"	"	192 M	1,600 mg/kg	LD50 reduced to 20-35 mg/kg by previous administration of 0.5 g trio-tolyl phosphate	62

TABLE XV-7 (CONTINUED)

EFFECTS ON ANIMALS FROM MALATHION EXPOSURE

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Oral	Rats	6	275 mg/kg/d 68 - 70 wks	Body weight of 2 survivors 36% below controls	33
"	"	17 M 17 F	240 mg/kg 5 mos	Significant decrease in cold temperature survival time	107
"	"	8 M 8 F	100 mg/kg/d x 5 d	Average total urinary excretion of 24% (M) and 48% (F)	55
"	"	-	77.9 mg/kg/d x 63 wks	Body weight 12% below controls	33
"	"	10 M 10 F	62 mg/kg/d 4 - 6 wks 68 mg/kg/d 4 - 6 wks	Minimum 50% brain, plasma, and erythrocyte ChE inhibition; 100% erythrocyte ChE inhibition in 5	33
"	"	2 M	40 mg/kg on d 4 and d 5 of age or 20 mg/kg on d 4 - d 24 of age	Reductions in testicular weight, tubular diameter, number of Leydig cells; all cell counts normal by d 24 of age; reversal of all effects by d 50	111
"	Rats Mice Dogs	- 15 -	5 ml/kg 99.6% in corn oil	Significant increase in hexobarbital sleeping time	101

TABLE XV-7 (CONTINUED)

EFFECTS ON ANIMALS FROM MALATHION EXPOSURE

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Oral	Mice	42 M	1,400 - 1,500 mg/kg 95% in corn oil	Decrease in toxicity after 4-d pretreatment with SKF-525A, chlorcyclizine, cyclizine, or phenobarbital; no deaths	66
"	Mice	10 M	500 mg/kg in corn oil followed 30 min later by 200 or 250 mg/kg of hexobarbital ip	Toxicity of hexobarbital not altered at either dose; all dead in 30 min	100
"	Rabbits	6 M	1,200 mg/kg 95% in corn oil	Death	83
"	"	"	600 mg/kg 95% in corn oil	Rapid, shallow breathing; miosis	84
"	"	"	300 mg/kg 95% in corn oil	Same degree of erythrocyte ChE inhibition as respiratory exposure to 123 mg/cu m x 6 hrs	83
"	"	"	120 mg/kg 95% in corn oil	Inhibition of plasma (41%) and erythrocyte (32%) ChE after 6 hrs	83
"	Dogs	1 M 1 F	250 ppm 100 ppm 12 wks	No effects on plasma ChE; slight but significant erythrocyte ChE inhibition at 250 ppm	86

TABLE XV-7 (CONTINUED)

EFFECTS ON ANIMALS FROM MALATHION EXPOSURE

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Oral	Dogs	1 M 1 F	250 ppm with 50 ppm EPN 12 wks	Up to 60% inhibition of plasma ChE and 93% inhibition of erythrocyte ChE	86
"	"	1 M 1 F	100 ppm with 20 ppm EPN 12 wks	Questionable inhibition of plasma ChE; up to 68% erythrocyte ChE inhibition	86
"	"	1 M 1 F	8 ppm with 3 ppm EPN 12 wks	Significant inhibition up to 24% of erythrocyte ChE at wk 8; incomplete recovery to pretreatment level	86
"	Chickens	-	up to 10,000 ppm 15 wks	No nerve damage, muscle weakness in 1; death of all	110
ip	Rats	16 F	900 mg/kg or 600 mg/kg on d 11 of gestation	No toxic effects; no fetal malformations	115
"	"	18 M	750 mg/kg	LD50 (adults)	103
"	"	20 M	340 mg/kg	LD50 (weanlings)	103
"	Rats	8 M 8 F	25 mg/kg x 5 d	Average total urinary excretion 42%	55

TABLE XV-7 (CONTINUED)

EFFECTS ON ANIMALS FROM MALATHION EXPOSURE

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
ip	Mice	4	1,500 mg/kg 99.5% in corn oil	Death of 2 in 2 hr	5
"	"	4	1,000 mg/kg 99.5% in corn oil	No deaths	5
"	"	4	500 mg/kg 99.5% in corn oil	"	5
"	Chickens	2	500 mg/kg 99.5% in corn oil	Death of 1 in 2 hr	5
"	"	4	250 mg/kg 99.5% in corn oil	No deaths	5
"	Sunfish	4	400 mg/kg 99.5% in corn oil	Death of 1 in 2 hr	5
"	Bullheads	4	400 mg/kg 99.5% in corn oil	"	5
iv	Dogs	-	250 mg/kg	Death	33
"	"	-	200 mg/kg	"Severe symptoms"; marked ChE inhibition	33
"	"	-	100 mg/kg	No effects	33
Subcutaneous	Chickens	24	50 - 1,600 mg/kg	Acute cholinergic signs in 21; immediate muscle weakness in 8; 4 deaths	108
"	"	-	100 mg/kg	Leg weakness for d 4-14	109

TABLE XV-7 (CONTINUED)

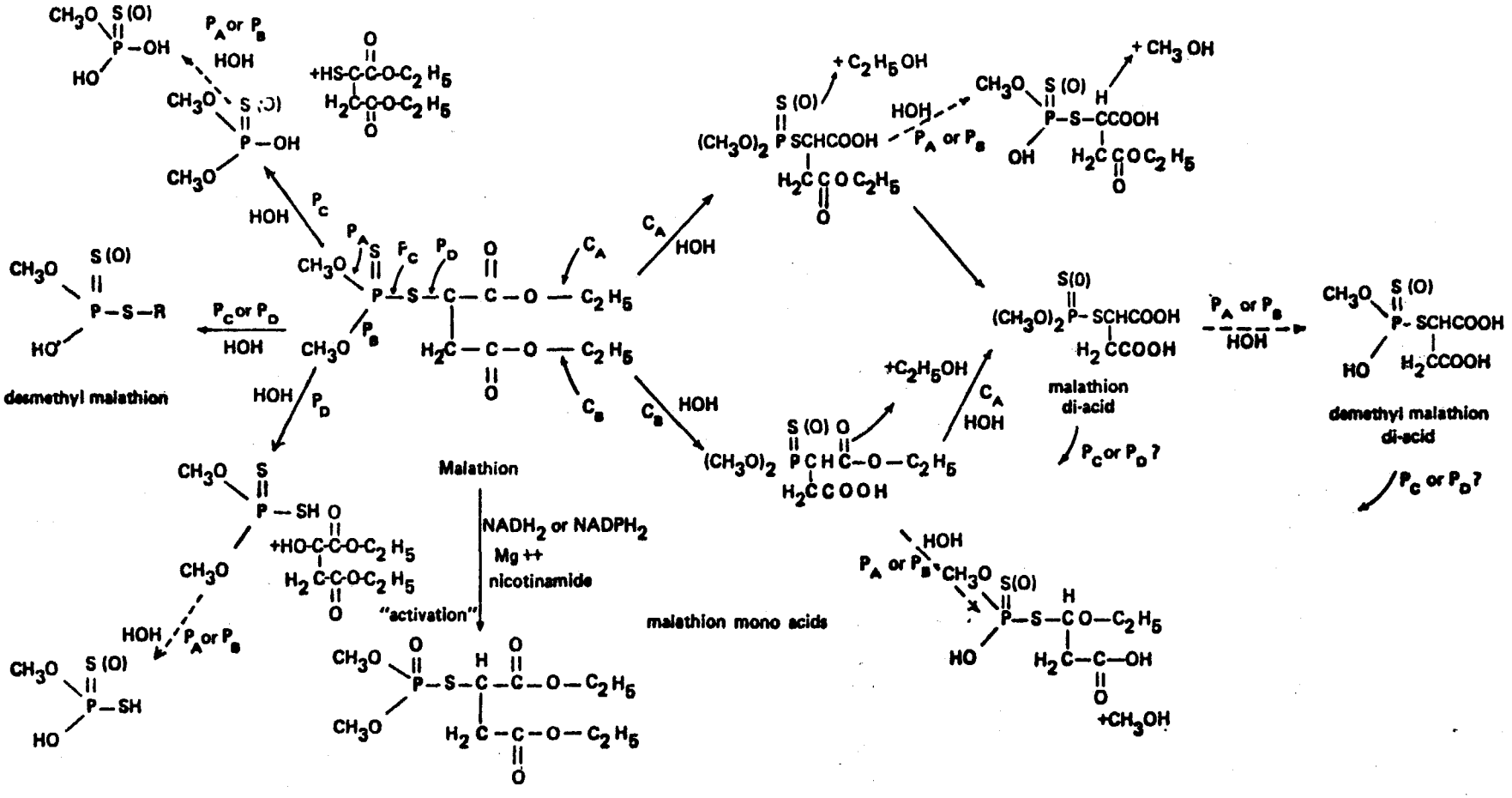
EFFECTS ON ANIMALS FROM MALATHION EXPOSURE

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Injection into yolk sac	Chick embryo	25 25	6.42 mg/egg at d 5 3.99 mg/egg at d 4 95% in corn oil	Sparse plumage, micromelia, overall growth retardation, beak defects in 15 d	120

*O-ethyl O-p-nitrophenyl phenylthiophosphonate

FIGURE XV–1

MALATHION METABOLISM



Malaoxon may undergo the same metabolism as malathion, shown above, and is indicated by (O) in the pathway scheme.

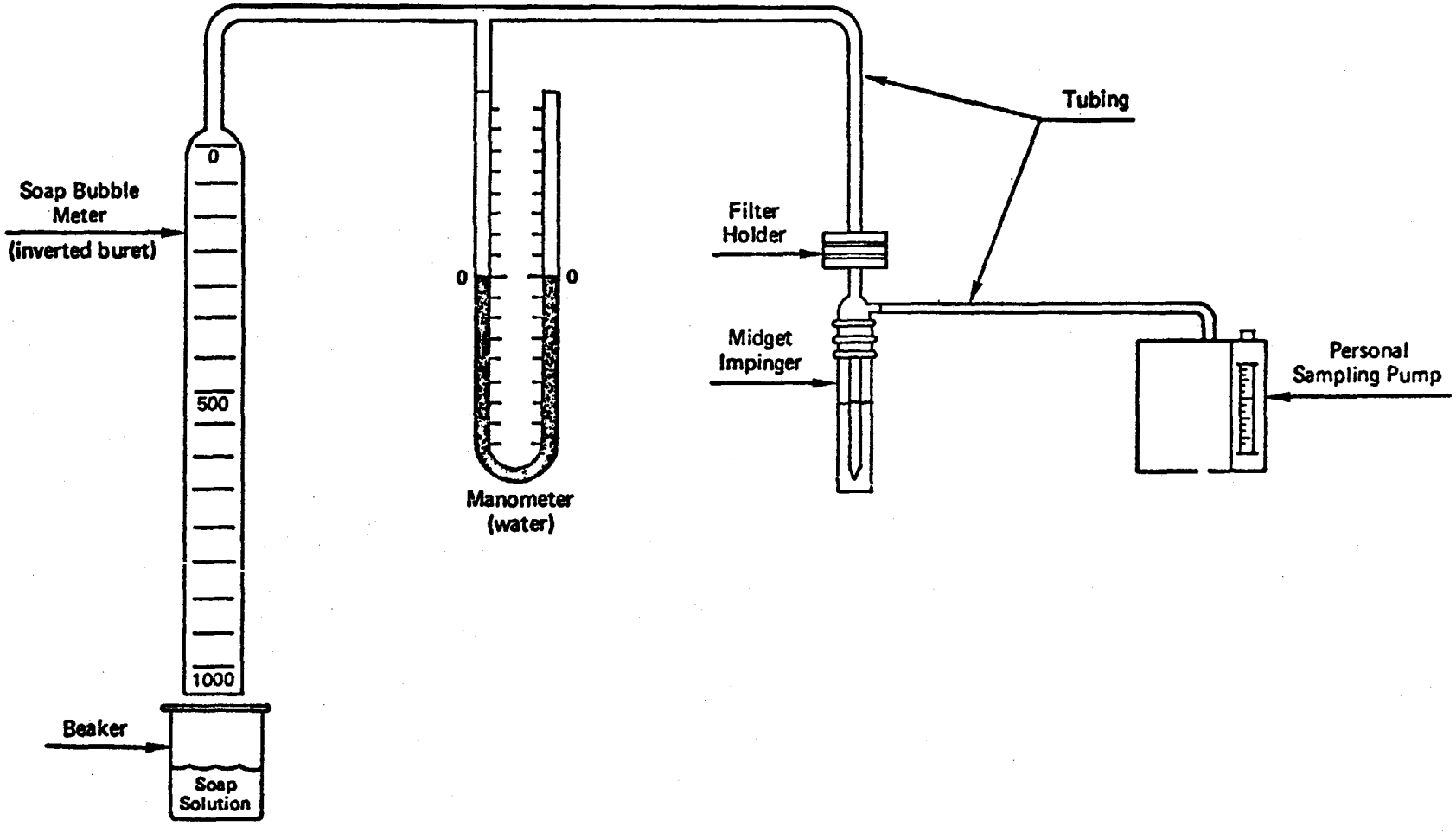
P = "phosphatases"
C = "carboxyesterases" } have not been specifically identified

Aliesterase(s) may act at the same sites as both P and C.

Adapted from Mattson and Sedlak [@65], Main and Braid [@62], Matsumura and Ward [@63], Walker et al [@65], and Welch and Coon [@66]

FIGURE XV-2

CALIBRATION SETUP FOR PERSONAL SAMPLING
PUMP WITH FILTER HOLDER AND MIDGET IMPINGER



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