criteria for a recommended standard....

OCCUPATIONAL EXPOSURE TO METHYL PARATHION

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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CRITERIA DOCUMENT:
RECOMMENDATIONS FOR AN OCCUPATIONAL
EXPOSURE STANDARD FOR METHYL PARATHION

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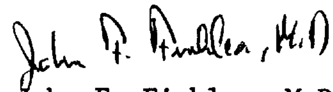
PREFACE

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 methyl parathion by members of my staff and the valuable constructive comments by the Review Consultants on Methvl Parathion, by the ad hoc committee of the American Conference of Governmental Industrial Hygienists, and by Robert B. O'Connor, M.D., NIOSH consultant on 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 methyl parathion. Lists of the NIOSH Review Committee members and of the Review Consultants appear on the following pages.



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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 methyl parathion. The Division review staff for this document consisted of J. Henry Wills, Ph.D., Frank L. Mitchell, D.O., Herbert E. Christensen, D.Sc., and Richard Rhoden, Ph.D., with Charles C. Hassett, Ph.D., and Seymour D. Silver, Ph.D. (consultants).

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

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I. RECOMMENDATIONS FOR A METHYL PARATHION STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to methyl parathion in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and safety of employees for up to a 10-hour workday, 40-hour workweek, over a working lifetime. Compliance with all sections of the standard should prevent adverse effects of methyl parathion on the health and safety 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. The criteria and standard will be subject to review and revision as necessary.

"Methyl parathion" is defined as O,O-dimethyl O-p-nitrophenyl phosphorothioate, regardless of production process, alone or in combination with other compounds. "Occupational exposure to methyl parathion" is defined as employment in any area in which methyl parathion or materials containing methyl parathion, alone or in combination with other substances, is produced, packaged, processed, mixed, blended, handled, stored in large quantities, or applied. If employees are occupationally exposed to other chemicals, such as pesticide vehicles, diluents, or emulsifiers, or other pesticides, provisions of any applicable standards for such other chemicals shall also be followed. Adherence to all provisions of the standard is required in workplaces using methyl parathion regardless of the airborne methyl parathion concentration because of serious effects produced by contact with the skin, mucous membranes, and eyes. Since methyl parathion

does not irritate or burn the skin, no warning of skin exposure is likely to occur. However, methyl parathion is readily absorbed through the skin, mucous membranes, and eyes and presents a potentially great danger from these avenues of absorption. It is extremely important to emphasize that available evidence indicates that the greatest danger to employees exposed to methyl parathion is from SKIN CONTACT.

Section 1 - Environmental (Workplace Air)

(a) Concentration

Occupational exposure to methyl parathion shall be controlled so that no employee is exposed to methyl parathion at a concentration greater than 0.2 milligram/cubic meter of air determined as a time-weighted average (TWA) exposure for up to a 10-hour workday in a 40-hour workweek.

(b) Calibration, Sampling, and Analysis

Procedures for the calibration of sampling equipment and the collection and analysis of environmental air samples shall be as provided in Appendices I and II, or by any method shown to be equivalent in accuracy, precision, and sensitivity.

Section 2 - Medical

Medical surveillance (medical and biologic monitoring) shall be made available to workers occupationally exposed to methyl parathion as outlined below. Physicians responsible for workers who may be occupationally exposed to methyl parathion should be familiar with the information contained in Appendix III which describes the diagnosis and treatment of

intoxication by organophosphorus compounds.

(a) Medical Management

(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. Those workers with a history of glaucoma, cardiovascular disease, hepatic disease, renal disease, or central nervous system abnormalities should be considered for exclusion from assignments requiring exposure to methyl parathion.

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

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

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

(F) A judgment of the worker's physical ability to use negative or positive pressure respirators as described in 29 CFR 1910.134.

(2) Emergency first-aid services shall be established, under the direction of the responsible physician, to provide care to any

worker acutely intoxicated by methyl parathion (See Appendix III).

(3) Appropriate medical services and surveillance shall be provided to any worker with adverse health effects reasonably assumed or shown to be due to occupational exposure to methyl parathion.

(4) Medical records shall be maintained for all workers occupationally exposed to methyl parathion, and such records shall be kept for at least 5 years after termination of employment.

(5) Pertinent medical information shall be available to the designated medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employee or former employee, and of the employer.

(b) Biologic Monitoring

(1) Definitions

(A) "Preexposure baseline" for erythrocyte cholinesterase activity is defined as the mean of two cholinesterase activity determinations, each of which is derived from a separate sample of blood. The two samples shall be taken at least 1 day apart after a period of at least 60 days without known exposure to any cholinesterase-inhibiting compounds. If the determinations produce values differing by more than 15%, additional determinations on new samples of blood shall be performed until successive tests are within 15% of each other.

(B) "Working baseline" erythrocyte cholinesterase is defined as the mean of two cholinesterase activity determinations, each of which is derived from a separate sample of blood. The two samples shall be taken at least 1 day apart. The cholinesterase activities of the two samples shall differ by no more than 15%. Alternatively, the working

baseline may be the arithmetic mean of normal values as defined in paragraph (b)(1)(C) of this section for the appropriate control population. A working baseline is determined only for an individual whose work history does not permit determination of a preexposure baseline as specified in paragraph (b)(1)(A) of this section.

(C) "Mean of normal values" is defined as the arithmetic mean of erythrocyte cholinesterase activities as determined by the laboratory's experience with repeated analyses on samples from healthy individuals. This mean shall also be consistent with the mean baseline activities presented in Table XII-2 of Appendix IV.

(2) Routine Monitoring

(A) All employees who are to be occupationally exposed to methyl parathion shall have preexposure erythrocyte cholinesterase 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 erythrocyte cholinesterase determinations shall have working cholinesterase baseline determinations performed.

(B) Within 60 days after the effective date of this standard, all employees currently exposed to methyl parathion shall have their working baseline erythrocyte cholinesterase activities determined.

(C) Subsequent to the determination of a preexposure or working baseline, all employees occupationally exposed to methyl parathion shall have their erythrocyte cholinesterase activities determined at 4-week intervals, except for those employees in the following occupations who shall be tested at 2-week intervals: mixers, loaders,

ground applicators, aerial applicators, flaggers, personnel who clean or repair equipment or clean up methyl parathion spills, checkers or field workers entering fields still wet from application or otherwise presenting a reasonable potential for adverse exposure, and employees engaged in manufacturing or formulating in other than closed production, mixing, blending, transfer, or packaging systems. This 2-week interval shall be reduced to 1 week for any employee working longer than 12 hours during any workday. This shorter interval shall be maintained until at least one entire workweek has elapsed without a workday exceeding 12 hours.

(D) Unacceptable absorption of methyl parathion indicating a failure of control procedures or work practices is demonstrated when the enzymatic activity of erythrocyte cholinesterase is decreased to between 60 and 70% of the employee's preexposure baseline or working baseline level. The employee shall be advised of this finding, and an industrial hygiene survey shall be conducted in the workplace of the affected employee unless the cause of exposure is known and corrective action has been initiated. This survey shall include an assessment of the dermal exposure potential. Based on the results of this survey, necessary corrective action shall be accomplished.

In addition, an employee whose erythrocyte cholinesterase determination, as required by paragraph (b)(2) of this section or (a)(5) of Section 6, indicates that the employee's erythrocyte cholinesterase activity is decreased to 60% of, or below, preexposure or working baseline, shall be removed from potential exposure to methyl parathion and placed under medical observation. In such cases, an industrial hygiene survey shall be conducted in the workplace of the

affected employee unless the cause of the exposure is known and corrective action has been taken. This survey shall include an assessment of the dermal exposure potential. Based on the results of this survey, necessary corrective action shall be accomplished.

(E) An employee who has been removed from methyl parathion exposure shall be prohibited from returning to work involving exposure to methyl parathion until the erythrocyte cholinesterase activity has returned to at least 75% of the working or preexposure baseline value.

(F) Each employee shall be given, as soon as possible, a copy of the results of said employee's initial, periodic, or special cholinesterase tests and a professional interpretation of the results.

(3) Blood Collection and Analysis

Procedures for collection and analysis of blood samples for erythrocyte cholinesterase activity shall be as provided in Appendix IV, or by any method shown to be at least equivalent in accuracy, precision, and sensitivity to those specified.

Section 3 - Labeling and Posting

(a) Labeling

Containers of methyl parathion shall be labeled with at least the following information:

DANGER!

POISON

CONTAINS METHYL PARATHION

3 HIGH HEALTH HAZARD (INCLUDES SKIN)

2 MODERATELY COMBUSTIBLE

CAN BE FATAL (If Swallowed
(If Inhaled
(If Left on Skin

(Note: The above items do not have to appear on labels for methyl parathion dust formulations.) If methyl parathion is dissolved in a combustible solvent, the label shall include a statement of flammability appropriate to the solvent.

WORK SAFETY RULES:

DO NOT breathe or allow vapor, mist, or dust to get into eyes or on skin or clothing. Do not rub eyes or face with hands or garments.

When possibility of contact exists, wear full-body coveralls or impervious apron, impervious boots and gloves, goggles, and, if required, respirator.

WARNING - Can penetrate leather or canvas shoes and sneakers.

Use fresh clothing daily. Shower with soap and water before leaving work. Do not wear work clothes home.

Wash hands thoroughly with soap and water before eating, chewing gum, smoking, using toilet, or urinating or defecating elsewhere. Store food and tobacco away from work area. Keep unattended containers tightly closed. Protect concentrated methyl parathion from all sources of ignition. Do not warm concentrated methyl parathion containers with open flame. Concentrated methyl parathion may explode when heated beyond 248 F (120 C). Do not smoke while handling methyl parathion.

EMERGENCY INFORMATION:

IF MATERIAL GETS ON SKIN, wash immediately with soap and water and call a physician. (Soap with a pH above 8.0 is more effective than neutral soap.) If clothes become contaminated, remove at once; wash skin with soap and water and call a physician. If sickness occurs during or after handling materials containing methyl parathion, call a physician. NOTE: Symptoms may occur several hours after end of work. If possible, take this label to the physician along with the patient.

IN CASE OF FIRE, use supplied-air respirator. Burning may produce highly poisonous combustion products.

IN CASE OF SPILLS (accidental discharges, leaks, ruptures, or other sources of contamination of equipment, facilities, or ground), place contaminated area or items under continuous surveillance; then decontaminate with strong alkali or other suitable decontaminating materials.

(b) Posting

(1) The following sign shall be posted in a readily visible location at or near all entrances to manufacturing, formulating, and storage areas containing methyl parathion:

POISON AREA
METHYL PARATHION

CAN BE FATAL (If Swallowed
(If Inhaled
(If Left on Skin

DO NOT SMOKE, EAT, OR SLEEP IN THIS AREA.

Use required personal protective equipment and clothing.

IF SKIN contact occurs, wash immediately with alkaline soap and water and call a physician.

IF CLOTHES are contaminated, go to a clean area and remove quickly. Wash skin with soap and water. Put on clean clothes and call a physician.

Warning signs shall be printed both in English and in the predominant language of non-English-reading workers. Employees unable to read posted warnings and labels, and those speaking languages other than English or the predominant non-English language, shall receive periodic training sufficient to ensure their understanding of the contents of the signs specified in this section and to provide a continuing reminder of their contents.

(2) The following sign shall be securely attached in a readily visible location to any vehicle (eg, truck, freight car) used to transport methyl parathion:

DANGER! POISON

CONTAINS METHYL PARATHION

IF LIQUID OR POWDER HAS LEAKED,
DO NOT ENTER

CAN BE FATAL (If Inhaled
(If Swallowed
(If Left on Skin

If skin contact occurs, wash immediately with alkaline soap and water and call a physician.

Section 4 - Personal Protective Equipment and Clothing

(a) Skin Protection

(1) Unless separately provided in this section, an employee who engages in filling containers of, pouring, mixing, formulating, loading, applying, or otherwise handling methyl parathion (including open-system manufacturing processes) shall be provided with, and required to

wear, protective head covering, goggles and face shield, impervious gloves, full-body coveralls, impervious apron or rainsuit, and impervious footwear. Impervious gloves should have reverse gauntlets and coveralls should be of a closely-woven material (siliconized fabric, such as nylon or cotton, is especially protective) and without cuffs. Whenever the word impervious appears in this document, it means highly resistant to the penetration of methyl parathion.

(2) Employees handling sealed, nonleaking containers of methyl parathion shall be provided with, and required to wear, full-body coveralls, or the equivalent, and impervious gloves.

(3) Employees operating open equipment for ground (non-aerial) application of methyl parathion shall be provided with, and required to wear, protective head coverings or face shields, impervious gloves, full-body coveralls or impervious rainsuits, and impervious footwear.

(4) Employees applying methyl parathion from closed-cockpit aircraft shall be provided with impervious gloves. Employees applying methyl parathion by open-cockpit aircraft shall be provided with, and required to wear, full-body coveralls or impervious rainsuits and goggles, and shall be provided with impervious gloves.

(5) Employees acting as flaggers (other than those flagging from enclosures) in the aerial application of methyl parathion shall be provided with, and required to wear, full-body coveralls or impervious rainsuit, protective head and neck covering, impervious footwear, and impervious gloves.

(6) Where toxic residues present a reasonable potential for exposure, employees entering areas treated with methyl parathion shall be provided with, and required to wear, impervious gloves, full-body coveralls or impervious rainsuits, face shields (if foliage is likely to contact the face), and impervious footwear.

(7) Laundry personnel handling clothing contaminated with methyl parathion shall be provided with, and required to wear, impervious gauntlet gloves, impervious footwear, and, in addition to ordinary clothes, impervious aprons.

(8) Employees applying methyl parathion in greenhouses or other enclosures, or entering such enclosures while foliage is still wet from an application or while dust is still airborne, shall be provided with, and required to wear, impervious rainsuits, hoods, neck coverings, impervious gauntlet gloves, and impervious boots.

(9) Employees (such as cleanup personnel) entering areas contaminated with methyl parathion shall be provided with, and required to wear, impervious gloves, full-body coveralls or impervious rainsuits, impervious footwear, impervious aprons, and such other personal protective equipment as may be required for adequate protection against the particular hazards present.

(10) Protective clothing shall not be taken home by employees. The employer shall provide for maintenance and laundering of protective clothing.

(b) Respiratory Protection

(1) Engineering controls shall be used wherever feasible to maintain methyl parathion concentrations below the TWA environmental limit

recommended in Section 1(a). Compliance with the recommended workplace environmental limit may not be achieved by the use of respirators except:

(A) During the installation, testing, maintenance, or repair of required engineering controls.

(B) For operations, such as maintenance or repair activities, causing brief exposures to methyl parathion at concentrations in excess of the workplace environmental limit.

(C) During emergencies.

(2) When a respirator is permitted by paragraph (b)(1) of this section, it shall be selected and used in accordance with the following requirements:

(A) For the purpose of determining the type of respirator to be used, other than supplied-air positive pressure respirators, the employer shall make a determination of the atmospheric concentration of methyl parathion in the workplace initially (and thereafter whenever pertinent working conditions are altered) and shall choose the appropriate respiratory protection specified in Table I-1. The employer shall ensure that no employee is being exposed to methyl parathion in excess of the TWA environmental limit recommended in Section 1(a) because of improper respirator selection, fit, use, or maintenance, or because of changes in working conditions.

(B) Employees experiencing breathing difficulties while wearing respiratory protective devices shall be medically examined to determine their ability to wear such devices. If it is determined that an employee cannot breathe adequately while wearing a respirator, the employee shall be assigned to work which does not require the use of a respirator.

This provision does not relieve the employer of any of the requirements of Section 2(a).

(C) A respiratory protective program meeting the requirements of 29 CFR 1910.134 shall be established and enforced by the employer.

(D) The employer shall provide respirators in accordance with Table I-1 that comply with the provisions of 30 CFR 11 and shall ensure that the appropriate respirator is worn.

(E) Canisters or cartridges shall be discarded and replaced with fresh canisters or cartridges as recommended by the manufacturer, or immediately if the user has difficulty breathing, if the user smells methyl parathion or methyl parathion-containing formulations, diluents, emulsifiers, or solvents while using the respirator, or if a breakthrough indicator (if any) indicates that the absorbent is saturated. Filters shall be changed whenever canisters or cartridges are changed, or after every 4 hours of use, or if breathing becomes difficult, whichever occurs first. Unused canisters or cartridges shall be discarded and replaced when the seals are broken, or on the expiration of the manufacturer's recommended storage life if the seals are unbroken.

(F) The employer shall ensure that respirators are adequately cleaned and maintained, and that employees are instructed on the use of respirators assigned to them and on methods for leakage testing.

(G) Respirators specified for use in higher concentrations of methyl parathion may be used in atmospheres with lower concentrations.

(H) Except in emergencies, respirators other than the cooled supplied-air type shall be used no longer than 15 minutes if ambient temperature exceeds 85 F in the workplace.

(I) Where an emergency develops which could result in overexposure of employees to methyl parathion, the employer shall provide respiratory protection as indicated in Table I-1.

TABLE I-1

RESPIRATOR SELECTION GUIDE

Concentration of Methyl Parathion	Respirator Type
2 mg/cu m or less	(1) Half-mask pesticide respirator (2) Type C supplied-air respirator, demand type (negative pressure), with half-mask facepiece
10 mg/cu m or less	(1) Fullface gas mask (chin style or chest- or back-mounted type) (2) Type C supplied-air respirator, demand type (negative pressure), with full facepiece
200 mg/cu m or less	(1) Type C supplied-air respirator, continuous-flow type, with full facepiece or suit (2) Pressure-demand type respirator with full facepiece and impervious plastic shroud
Emergency (includes entry to vessels, bins, or other containers which are likely to be contaminated with methyl parathion)	(1) Self-contained breathing apparatus, positive pressure type, with full facepiece (2) Combination supplied-air respirator, pressure-demand type, with auxiliary self-contained air supply

(3) For purposes of this section, application of methyl parathion or methyl parathion formulations is a routine operation in which respirators must be used if the recommended TWA environmental limit is exceeded. Engineering controls, such as enclosed filtered-air tractor cabins or cockpits, shall be used where the environmental conditions encountered, alone or in combination with the application method selected, present a reasonable likelihood of the recommended environmental limit being exceeded. Where filtered-air enclosures are used, air levels of methyl parathion shall be regularly monitored to ensure compliance with the recommended environmental limit.

Section 5 - Informing Employees of Hazards from Methyl Parathion

(a) Before beginning work, all new and reassigned employees who may be occupationally exposed to methyl parathion shall be informed of the hazards from methyl parathion, relevant symptoms of overexposure to methyl parathion, appropriate emergency procedures, and the conditions and precautions required for its safe handling.

(b) Within 30 days of the promulgation of a standard based on these recommendations, all employees whose duties currently involve potential exposure to methyl parathion shall be informed as specified in paragraph (a) of this section.

(c) A continuing education program shall be instituted within 30 days after the effective date of the standard. The program shall be designed to ensure that all employees occupationally exposed to methyl parathion 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.

(d) In addition to the requirements of paragraph (c) above, employees occupationally exposed to methyl parathion shall be kept currently informed through posting as specified in Section 3(b) and shall be instructed as to the availability of biologic monitoring. 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 methyl parathion may occur. In addition, employees shall be informed of the results of their biologic monitoring as specified in Section 2(b)(2)(F).

(e) 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) Emergency Procedures

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

(2) Unless otherwise specified in this paragraph, employees occupationally exposed to methyl parathion shall have readily accessible 25 gallons of water/person or 100 gallons, whichever is greater, plus alkaline soap and towels for use in emergencies. No emergency water supplies are required in agricultural aircraft. Tractors shall have at least 10 gallons

of water stored in closed containers. Mixing vehicles shall have at least 20 gallons of water stored in closed containers.

(3) Facilities for the manufacture, formulation, or fixed mixing of methyl parathion shall have emergency showers.

(4) Whenever methyl parathion contaminates clothing or personal protective equipment other than the outside of impervious clothing, the employee shall move away from the area of exposure; contaminated articles shall be immediately removed; and the employee required to wash with alkaline soap and water.

(5) Before externally contaminated impervious clothing is removed, its surface shall be washed with alkaline soap and water, or other decontaminant of equal or superior effectiveness.

(6) When an employer has reason to suspect that an employee has been overexposed to methyl parathion, or the employee suspects overexposure (eg, is aware of overexposure or has obvious signs or symptoms of poisoning), medical observation shall be instituted until a determination is made by the physician in accordance with Section 2(b)(2) that the employee is capable of returning to work.

(7) Persons responsible for fire protection shall be informed of the significance of the flashpoint and explosion hazard of methyl parathion formulations, of the high toxicity of its vapors and combustion products, and of the necessity for using supplied air respirators while suppressing fires involving methyl parathion formulations.

(b) Engineering Controls

(1) Engineering controls, such as process enclosures, filling equipment with automatic shutoff devices, mechanical metering and transferring devices, and ventilation systems, shall be used to ensure that the recommended workplace environmental limit specified in Section 1(a) is not exceeded, and to minimize skin exposure to methyl parathion.

(2) Control of Unit Operations

Unit operation controls of equivalent or superior effectiveness may be substituted for those specified below.

(A) All fittings, hoses, tubing, pumps, valves, and associated equipment operated at positive pressure shall be sufficient to withstand 2.5 times the maximum pressure encountered and shall be examined at least weekly for leaks and other signs of deterioration.

(B) All hoses, pipes, and tubing used for filling tanks on loading or application vehicles shall be equipped with quick-acting shutoff valves, or other devices at the discharge end, to prevent dripping.

(C) To prevent back-siphoning, the discharge end of hoses used for filling vessels, tanks, or other containers with methyl parathion, or for adding any other liquid if the container already contains some methyl parathion shall be submerged only if the level in the supply source is higher than the highest possible level of liquid in the receiving container.

(D) When positive displacement pumps are used with hoses, pipes, or tubing equipped with shutoff valves at the discharge end, a relief device shall be installed to bypass liquid back to the low-

pressure side of the system to prevent rupture of hoses, pipes, tubing, or pumps.

(E) All application equipment with two or more nozzles shall have the distribution manifold shielded to minimize operator exposure in the event of malfunction.

(F) Opaque tanks used for mixing, loading, or application of methyl parathion shall be equipped with indicators of the level of liquid within the tank.

(G) Loading equipment shall be fitted with an automatic shutoff device to prevent overfilling.

(H) Tank covers shall be constructed to minimize the possibility of contents spilling in the event of rollover or aerial accident.

(3) Ventilation

(A) Ventilation systems shall be designed to remove methyl parathion from the breathing zones of exposed workers and to prevent the accumulation and recirculation of methyl parathion in the workplace.

(B) Exhaust ventilation systems discharging to outside air should conform with applicable local, state, and federal air pollution regulations.

(C) A program of periodic preventive maintenance, cleaning, and inspection shall be established to ensure maximum effectiveness of ventilation systems. This program shall include airflow measurements, inspection of ductwork for leaks, and examination of the collecting elements. These procedures shall be performed before manufacturing or formulating operations begin and at least twice a month

during manufacture or formulation. A written record shall be kept indicating the conditions observed and measures taken.

(c) Storage

(1) All locations in which methyl parathion is stored shall be fenced and locked or shall have access limited by other means. All storage locations shall be posted as specified in Section 3(b).

(2) Provisions for the storage of containers, applicable to methyl parathion or its formulations, are given in 29 CFR 1910.106. Containers of methyl parathion, or of its combustible or flammable formulations, shall be protected from heat, corrosion, mechanical damage, and sources of ignition.

(3) Containers shall be inspected upon receipt, and at least monthly thereafter, for corrosion, leaks, breaks, tears, or other defects.

(4) Partially full and empty methyl parathion containers shall be tightly closed and kept in locked storage areas until disposed of properly, except where direct supervision is maintained continuously.

(5) Methyl parathion shall be stored only in containers which bear the label required in Section 3(a).

(6) No containers which are normally used for storage or preparation of food, feed, or drink shall be used for storage of methyl parathion.

(7) No persons shall be allowed to eat, sleep, or smoke in any area in which methyl parathion is stored.

(8) Outdoor storage facilities shall be located at least 20 feet from any dwelling or populated area and shall be equipped with a sprinkler system where feasible.

(d) Personal Hygiene

(1) The employer shall provide areas where employees can change their street and work clothing. These areas shall have facilities for storing street and spare work clothes free from contamination.

(2) All required personal protective clothing and protective equipment shall be provided by the employer and shall be laundered or cleaned daily. The employer shall ensure that all impervious personal protective clothing is free from cracks, pinholes, or other signs of deterioration.

(3) Personal protective clothing grossly contaminated with methyl parathion shall be decontaminated and laundered separately from other clothing.

(4) The employer shall make extra clothes available at each worksite for use when protective or personal clothing becomes contaminated with methyl parathion.

(5) Employees occupationally exposed to methyl parathion shall be required to wash their hands and face with alkaline soap and water before eating, drinking, smoking, and before urinating or defecating.

(6) Employees occupationally exposed to methyl parathion shall be required to shower at the end of each workday before leaving work. The employer shall provide alkaline soap and clean towels.

(e) Housekeeping, Decontamination, and Waste Disposal

(1) All methyl parathion spills shall be cleaned up as soon as possible. If feasible, continuous surveillance of spills shall be provided until decontamination is completed. Contaminated areas shall be roped off and posted.

(2) All floors that may be contaminated by methyl parathion shall be cleaned with a strong alkaline solution, or with an equivalent or superior decontaminating solution, at least weekly.

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

(4) Equipment or fixtures contaminated with methyl parathion, including operator compartments or control positions on application and loading equipment, shall be washed as soon as possible with a strong alkaline solution, or with an equivalent or superior decontaminating solution.

(5) Drip pans containing absorbent material shall be utilized to facilitate decontamination in locations where leakage is likely to occur.

(6) Unless local, state, or federal regulations provide otherwise, clothing, rags, bags, and fiber drums heavily contaminated with methyl parathion shall be disposed of at a sanitary landfill or shall be incinerated. Adequate precautions shall be taken to prevent inhalation of potentially toxic fumes, combustion products, and vapors produced during disposal.

(7) All empty containers contaminated with methyl parathion that are to be disposed of in a sanitary landfill shall be decontaminated with a strong alkaline solution, or with an equivalent or superior decontaminating solution, and punctured before disposal.

(8) Empty metal drums or containers contaminated with methyl parathion that are to be reclaimed shall be decontaminated with a

strong alkaline solution or with an equivalent or superior decontaminating solution before shipment. The reclaimer shall be informed of the methyl parathion contamination.

(9) Whenever it is necessary for an employee to perform maintenance or repair work on equipment contaminated with methyl parathion, such as a vessel, pump, valve, pipe, nozzle, etc, the employer shall ensure that the equipment has been decontaminated before maintenance or repair is undertaken.

(10) Reusable clothing that has been exposed to, or is actually contaminated with, methyl parathion shall be placed in a plastic bag or container and labeled with a suitable warning.

(f) Other Work Practices

(1) Employees handling methyl parathion concentrates shall work in groups of two or more. In addition, regardless of the concentration of the material, all mixers, loaders, flaggers, and applicators shall maintain periodic communication with a person capable of summoning emergency aid.

(2) Employees exposed to methyl parathion while spraying shall remain upwind from the spray whenever possible.

(3) Aerial applicators shall mix or load pesticides containing methyl parathion only when closed mixing or loading systems are used. This provision shall not prevent an aerial applicator from supervising mixing or loading operations involving open systems.

(4) Only materials free of methyl parathion shall be used when testing mixing, loading, or application equipment for leaks; when

testing for clogged valves, lines, or strainers; or when calibrating equipment.

(5) No dispersal equipment containing methyl parathion shall be turned on outside the area to be treated. Except in an emergency, methyl parathion shall be dumped from application, mixing, or loading vehicles only when proper disposal procedures are followed.

(6) Employees piloting agricultural aircraft shall be prohibited from flying through the drift of an application, starting or continuing an application if wind creates a drift hazard to themselves or others, and spraying or dusting over waterways, canals, buildings, dwellings, vehicles, or persons, including flaggers.

Section 7 - Sanitation

(a) Food Facilities

Storage, preparation, dispensing (including vending machines), or eating of foods or beverages shall be prohibited in areas where methyl parathion is present. Employees may not carry food while working in these areas because of the risk of contamination. The employer shall provide an area free from methyl parathion contamination in which employees may store lunches and other foods, beverages, or tobacco products.

(b) Smoking

Smoking shall be prohibited in areas where methyl parathion is present. Employees may not carry tobacco products while working in these areas because of the risk of contamination.

Section 8 - Monitoring and Recordkeeping

(a) Environmental Monitoring

(1) Each employer involved in the manufacture or formulation of methyl parathion shall monitor environmental air levels of methyl parathion at least monthly, except as specified otherwise by a professional industrial hygienist. The initial monthly environmental air sampling shall be completed within 6 months of the effective date of a standard incorporating these recommendations. If monitoring of an employee's exposure to methyl parathion reveals that the employee is exposed at concentrations in excess of the recommended TWA environmental limit, control measures shall be initiated and the employee shall be notified of that exposure and the control measures being implemented to correct the situation. 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). Monthly monitoring may then be resumed.

(2) Air samples shall be collected in the breathing zone of employees to permit calculation of TWA values for every methyl parathion exposure area. For each TWA determination, a sufficient number of samples shall be taken to characterize each employee's exposure during each workday. 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

(1) Sampling records shall be maintained so that exposure information is available for individual employees. These records shall indicate, in addition to the results of air sampling, the type of personal protective device, if any, in use by each employee at the time of sampling. All employees shall be able to obtain information on their individual environmental exposure.

(2) Records shall be maintained and shall include sampling and analytical methods, types of respiratory devices used, and TWA airborne concentrations found. In addition, the following records shall be maintained for each employee occupationally exposed to methyl parathion:

(A) Preexposure baseline erythrocyte cholinesterase activity or working baseline cholinesterase activity, whichever is applicable.

(B) All cholinesterase activities measured during employment.

(C) Medical records compiled during employment (including preplacement examinations) in accordance with Section 2(a).

(3) Records required by this section shall be maintained for 5 years after the worker's employment has ended and shall be made 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 recommended standard which were prepared to meet the need for preventing occupational diseases arising from exposure to methyl parathion. 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 any 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 methyl parathion are part of a continuing series of criteria developed by NIOSH. The proposed standard applies only to the manufacture, formulation, application, or other occupational exposure to methyl parathion as applicable under the Occupational Safety and Health Act of 1970. The standard was not designed for the population-at-large, and any extrapolation beyond occupational exposures is not warranted. It is intended to (1) protect against acute systemic poisoning by methyl parathion, (2) be measurable by techniques

that are available to industry and to governmental agencies, and (3) be attainable with existing technology.

Because of (1) the widespread agricultural use of methyl parathion, both alone and in combination with other pesticides, (2) the particular exposure hazard presented by its absorption through the skin, and (3) the absence of investigations into the fraction of methyl parathion which is actually converted to methyl paraoxon prior to exposure, the recommended environmental air limit is insufficient by itself to protect most employees occupationally exposed to methyl parathion. Included with the air limit, therefore, are work practices to limit exposure and biologic monitoring, and other medical surveillance, for the detection of significant exposure to anticholinesterase compounds. Exposure must be detected early to prevent acute intoxication by continued exposure to methyl parathion or other anticholinesterase compounds.

While exposure to concentrated methyl parathion presents unequivocal hazards, the hazards to employees from exposure to residues of methyl parathion on crops, foliage, or soil vary with the age of the residue, extent of conversion to methyl paraoxon, wetness of crop surfaces, ambient temperature and humidity, prevalence of rain after application, contact with foliage and soil characteristic of the work activity and of the crop, time spent in the treated area, concentration of applied material, modifications in toxic qualities because of mixed ingredients, and other factors. Since many incidents of systemic poisoning have been reported for workers entering fields in which organophosphorus insecticides, including methyl parathion, have been applied, the reentry interval concept has been developed to protect such workers. Reentry intervals define the time

between application of the insecticide and entry of workers for any activity involving extensive contact with insecticide residues. Discussion of the protection of field workers from the potentially hazardous effects of methyl parathion residues on crops, foliage, or soil through the establishment of safe reentry intervals has been intentionally omitted from the recommended standard, since the US Environmental Protection Agency is presently the regulatory agency responsible for this area.

In the course of developing a recommended standard for occupational exposure to methyl parathion, deficiencies in the available data were recognized in the following areas: (1) epidemiologic studies on the chronic effects, if any, of occupational exposure to methyl parathion and methyl paraoxon and on those effects, if any, due to cholinesterase inhibition; (2) animal studies on the toxic effects of methyl parathion in combination with other chemicals; (3) studies on the permeability of human skin to methyl parathion and methyl paraoxon; (4) human studies on the correlation of cholinesterase inhibition with dermal and respiratory exposure to methyl parathion and methyl paraoxon; (5) development of more precise and uniform sampling methods for methyl parathion; and (6) determination of the fraction of exposure which is due to methyl paraoxon in different occupational settings and under various environmental conditions. To fill these information gaps, a concerted effort is required of those involved with the health and safety of employees exposed to methyl parathion.

III. BIOLOGIC EFFECTS OF EXPOSURE

Anticholinesterase compounds, including methyl parathion, exert their generally recognized acute toxic effects by inhibiting the enzyme responsible for hydrolyzing acetylcholine, with the subsequent accumulation of endogenous acetylcholine. [1] Acetylcholine is the substance which mediates the transmission of nerve impulses in preganglionic autonomic fibers, postganglionic parasympathetic fibers, and in some postganglionic sympathetic fibers. [2] These fibers innervate the heart, irises, salivary glands, stomach, small intestine, urinary bladder, bronchial glands, eccrine sweat glands, and other organs and tissues. [2] Acetylcholine also has a transmitter function at neuromuscular junctions (motor endplates) and at certain synapses between neurons within the central nervous system (CNS). [2]

In humans, there are two principal types of enzymes which hydrolyze choline esters: acetylcholinesterase, or true cholinesterase, and butyrylcholinesterase, frequently called plasma cholinesterase, serum cholinesterase, or pseudocholinesterase. [2] Acetylcholinesterase is found in neurons, at the neuromuscular junction, in erythrocytes, and in certain other tissues. Butyrylcholinesterase is found in various types of glial cells in the central and peripheral nervous systems, as well as in the plasma, liver, and other organs. [2]

As with other phosphorothioates, methyl parathion has only a slight inhibitory action on acetylcholinesterase and butyrylcholinesterase, but its active metabolite, methyl paraoxon, is a potent inhibitor of both these enzymes. [3,4] Because the resultant phosphorylated enzyme is stable,

hydrolysis leading to reactivation of the enzyme occurs slowly. [5] Recovery of cholinesterase activity is thought to occur as a result of hydrolysis of inhibited enzyme and by synthesis of fresh enzyme. [5,6] Hydrolysis is limited by another spontaneous reaction, aging, which leads to a stable phosphorylated cholinesterase refractory to spontaneous or induced hydrolysis. [2] Aging of the inhibited enzyme has been explained as a partial dealkylation of the phosphoryl moiety which results in a more stable phosphorylated enzyme. [2,7]

Extent of Exposure

Methyl parathion (O,O-dimethyl O-p-nitrophenyl phosphorothioate) is a nonproprietary organophosphorus insecticide. [8] Depending on storage conditions and on the use of stabilizing ingredients, methyl parathion isomers and methyl paraoxon may also be present. Some physical properties of methyl parathion are presented in Table XVI-1. Common trade names and synonyms for methyl parathion appear in Table XVI-2.

Methyl parathion is produced by the esterification of phosphorus pentasulfide with methanol, chlorination of the ester with molecular chlorine, and condensation of the chlorinated ester with the sodium salt of paranitrophenol to form methyl parathion. [9] Technical methyl parathion was produced by four US manufacturers in 1974. [9] Emulsifiable liquid, wettable powder, and dust products were being prepared from technical methyl parathion by 84 formulators registered with the US Environmental Protection Agency as of October 1974. Of these, 32 were registered for 5 or more different formulations. [10] Many of these formulations were mixtures of methyl parathion with other organophosphorus and organochlorine

insecticides. Methyl parathion is presently registered as a "restricted use" pesticide by the US Environmental Protection Agency. According to the 1972 amendments to the Federal Insecticide, Fungicide, and Rodenticide Act of 1947, "restricted use" pesticides may only be used by or under the supervision of a certified applicator. State certification programs must meet federal standards issued by the US Environmental Protection Agency. These standards appeared in the Federal Register 39:36446-52, 1974.

In 1972, methyl parathion was produced in greater quantity than any other organophosphorus insecticide in the United States. [9] Domestic production was estimated at 51 million pounds in 1972. Of the 40 million pounds of methyl parathion used domestically in 1972, 33.5 million pounds were used on cotton, 3.1 million pounds on soybeans, and the balance on other field, vegetable, and fruit crops. [9] In 1972, an estimated 75% of the methyl parathion applied in the United States was used in the south central states. [9] Regional distribution of methyl parathion use in 1972 is shown in Figure XVI-1. [11]

A list of occupations with potential exposure to methyl parathion is provided in Table XVI-3. [12] NIOSH estimates that approximately 150,000 US workers are potentially exposed to methyl parathion in occupational settings.

Historical Reports

The first indications that some organophosphorus compounds might be highly toxic appeared during the early 1930's when symptoms of acetylcholine poisoning were experienced by persons synthesizing dimethyl and diethyl phosphorofluoridates. In 1936, Schrader studied the phosphorus

compounds during an investigation of synthetic insecticides, and in 1937 he patented the general formula for organophosphorus (OP) contact insecticides. [13]

Although organophosphorus insecticides induce compound-specific toxic effects, those studied have at least one characteristic in common. All are cholinesterase inhibitors in mammalian systems. Because of this common toxic property, the signs and symptoms of acute systemic poisoning by organophosphorus compounds have been well characterized experimentally and from case studies. From these data, Holmstedt [14] compiled a table of signs and symptoms of anticholinesterase effects in humans. These effects are shown in Table XVI-4. Reports cited in this document strongly suggest that this list is applicable to acute systemic poisoning by methyl parathion.

Methyl parathion was introduced in 1949 by Farbenfabriken Bayer, Germany, as indicated by Spencer. [15] The first reported cases of methyl parathion intoxication in an occupational setting apparently occurred in 1956. Grigorowa [16] wrote that the incidence of reported systemic cholinergic symptoms among examined workers occasionally was as high as 38-83% during 1959 in a Wofatox (methyl parathion) dust-formulating plant in Germany. Symptoms typical of those observed for systemic poisoning by anticholinesterase compounds were accompanied by depression of plasma cholinesterase activity. Erythrocyte cholinesterase activities were not reported. Systemic poisonings were attributed to inadequate work practices and engineering controls. Workers wore neither gloves nor protective clothing and did not use respirators. Exposed skin and clothing showed yellowish-green discoloration. Although the author [16] reported that

pesticide dust measurements performed in the plant showed levels far in excess of "permissible amounts," the actual concentrations were not reported. Intoxications were especially frequent during hot summer periods. The author [16] stated that the symptoms of intoxication rapidly subsided in a majority of cases after seasonally high temperatures ended. Details provided on some of the cases indicated that poisoning had been responsible for actual injuries or had increased the risk of physical injury from other sources. For example, one employee who became dizzy in a mixing room was injured in a fall down some steps.

Effects on Humans

Fazekas [17] and Fazekas and Rengei [18,19] performed autopsies on 30 persons who died of methyl parathion poisoning between 1964 and 1969 in Hungary. Twenty-six cases involved ingestion (primarily suicidal) of an estimated 50-300 g of material, while four cases involved poisoning by dermal and respiratory exposures during spraying. The 20 male and 10 female victims ranged in age from 18 to 82 years. The victims died 2 hours-9 days after exposure; exact times of death were not reported. Autopsies were performed 4-12 hours after death. All organs were examined for gross and microscopic changes. Results of the autopsies indicated generalized edema, together with pooling and stagnation of blood and petechial hemorrhages in the liver, heart, and spleen. The gastrointestinal tract was severely irritated and exhibited petechial hemorrhages and inflammation. The pharynx, larynx, bronchi, and trachea were inflamed, and pulmonary edema and focal pneumonitis were evident. Petechial hemorrhages, congestion, and edema were observed in the kidneys

and adrenals. Blood stagnation and edema in the brain were also observed. These papers do not give any clear indications of the incidences of these various changes. Microscopic examination confirmed the gross autopsy findings, providing evidence of severe cellular degeneration. According to the authors, the most severe changes were found in the liver, kidneys, and brain, and in the vascular systems of these organs. Fazekas [17] acknowledged that the gross and microscopic changes observed could not be regarded as specific to methyl parathion poisoning. The author also indicated that the role, if any, of cholinesterase inhibition or of therapeutic agents in the observed changes was unclear. The possible role of ingested solvents (where present) in producing or altering toxic effects was not discussed. Since the report did not specify precisely how soon after death the autopsies were performed, it is impossible to separate the damage caused by methyl parathion poisoning from post-mortem changes.

Case histories [18,19] were provided for 7 of the 30 victims. None of the case histories described any of the four occupational fatalities, nor were cholinesterase activities reported. A 50-year-old woman ingested 200 g of methyl parathion while drunk and died 24 hours later, despite treatment of an unspecified nature. [19] A 28-year-old woman developed signs of anticholinesterase effects (eg, severe perspiration, vomiting, diarrhea) 30 minutes after drinking 100 g of methyl parathion in water. [19] Despite therapy with atropine (a competitive inhibitor of response to acetylcholine by effectors innervated by the parasympathetic nervous system), she died 27 hours later from respiratory complications. A 44-year-old man experienced nausea, vertigo, vomiting, and salivation immediately after drinking 300 ml of a methyl parathion solution of unknown

concentration. [19] Although atropine and pralidoxime chloride (a cholinesterase reactivator) were administered, the patient's condition suddenly deteriorated 70 hours after ingestion, and he died. A 31-year-old man ingested 100-200 g of methyl parathion and received atropine plus pralidoxime chloride therapy when hospitalized later in the day. [19] Thirty-three hours after ingesting the pesticide, he had muscle spasms over his entire body along with an "attack of asphyxia" and died within a few minutes, despite cardiac and respiratory support. A 57-year-old man ingested methyl parathion with wine while drunk. [19] Upon admission to a hospital 5 hours later, he exhibited skeletal muscle spasms, nausea, miosis, and, later, mydriasis. Although he received atropine and pralidoxime chloride therapy, he died from cardiac failure and pulmonary edema 20 hours after the ingestion. A sixth case involved a patient, age unknown, who displayed miosis along with severe perspiration and diarrhea upon hospital admission. [19] Although atropine, pralidoxime chloride, and strophanthin (a cardiac glycoside used to increase the force of myocardial contraction) were given, the victim died from respiratory arrest 65 hours after ingestion. A 50-year-old man drank an estimated 1.8 g of methyl parathion suspended in an unspecified liquid and was discovered dead. [18]

Organs examined in these cases showed detectable quantities of paranitrophenol (PNP), a degradation product of methyl parathion. [18,19] The examinations included the brain (pons, medulla oblongata, white matter, gray matter, stem ganglia, and cerebellum), stomach, spleen, liver, heart, lungs, small intestine, blood, kidneys, and urine. The sudden and unexpected death of many of the patients was not explained, but Fazekas [17] suggested that pericapillary hemorrhages observed in the myocardium

and medulla oblongata were probably involved. From these reports, it appears that the lethal dose for adults ingesting methyl parathion is less than 1.8 g.

During February and July 1959, Grigorowa [16] investigated methyl parathion poisonings in a German plant producing Wofatox. Eighteen of the 47 workers examined in February reported mild symptoms regardless of length of employment, which ranged from a few months to 6 years. Symptoms included lack of appetite, gastric distress, visual disturbances, lack of sleep, fatigue, nervousness, and slight headaches. Plasma cholinesterase activity was apparently measured but not reported. Of 35 persons examined in July, 29 reported severe symptoms. Twenty-seven of these had plasma cholinesterase activities that were between 31.6 and 89.0% of their winter measurements; 21 workers had inhibitions of more than 30%. Preexposure baseline activities were not available. Cholinesterase activity was measured by a colorimetric method. The author [16] stated that signs indicative of CNS involvement were most frequent. Symptoms included headache, dizziness, nausea, insomnia, fatigue, visual disturbances, increased perspiration, shooting pains in the heart, loss of appetite, vomiting, and stomach pains. Fibrillar muscular twitches in the eyelids and numbness of the legs, arms, or fingers were also reported frequently. No times of onset of these specific symptoms were provided. While the routes of exposure were not specified, a yellowish-green discoloration was observed on fingernail edges, fingertips, interdigital skin areas, lower arms, and neck, as well as on work shirts and foot wrappings of many workers. None of the workers in the plant wore respirators, gloves, or other protective clothing. The increase in the number and severity of

poisoning episodes in the summer over those in the winter apparently had been observed in the previous 3 years also.

Grigorowa [16] speculated that the greater incidence and severity of poisonings in hot weather were caused by increased respiratory rate, greater volatilization of methyl parathion, and increased conversion of methyl parathion to its active oxon and isomeric forms at elevated temperatures. Not mentioned was the possibility that skin absorption also may have been increased if clothing worn in summer months was either lighter in weight, left more skin exposed, or if dilation of superficial blood vessels had taken place. Since all workers had been employed in the factory for at least a few months and some for as long as 6 years, plasma cholinesterase activities measured during the winter probably were below those that would have been determined prior to exposure to anticholinesterase compounds. As a result, the actual extent of inhibition of cholinesterase activity in the summer examinations may have been greater than those reported. Correlation of the severity of poisoning with inhibition of plasma cholinesterase cannot be made because preexposure levels were not reported.

The author [16] described in slightly greater detail three of the poisoning incidents. In the first, a worker became dizzy, fell down the steps of the mixing room, and suffered considerable injuries. No additional details on this case were given. In the second, a 49-year-old worker with 5 years' work experience developed a headache and became weak and dizzy while filling bags with methyl parathion dust. The worker lost consciousness for a few minutes at home after work. Identical symptoms recurred when work was resumed. He reported that his left hand had been

numb for a few days, that his right hand had little feeling, and that he had experienced frequent twitching of the eyelids. At the first examination, in February, he had complained of insomnia. Plasma cholinesterase activity determined during the July examination showed an inhibition of 64.4% (reduction to 35.6%) of the winter value. In the third case, a 27-year-old worker with a year's experience had no complaints during the February examination, but he complained of severe headaches, loss of appetite, nausea, watering of the eyes, and insomnia at the July examination. For 8 weeks, he had experienced arm and leg numbness, with arm impairment sometimes involving only two or three fingers. While he was chopping wood at home, the ax had fallen from his hands. In the July examination, his plasma cholinesterase activity was inhibited by 60.2% (reduction to 39.8%) of the winter value.

During a period of approximately 10 years, Rider and Moeller, [20] Rider et al, [21-25] and Moeller and Rider [26-28] performed dose-response studies with several organophosphorus insecticides on prisoners to determine the minimum effective dose for significant cholinesterase depression. One of the substances tested was methyl parathion, which was administered orally in capsules containing corn oil. For each test dose, a different group of seven men, five as test subjects and two as controls, were utilized. Erythrocyte and plasma cholinesterase activities were determined over a 41-day pretest period. Methyl parathion was then ingested on a daily basis for approximately 30 days. Cholinesterase activity determinations were made twice weekly during the test period. All cholinesterase tests were done by the electrometric method of Michel. [29] The dose was increased in successive studies from 1 mg/day, [26] by

increments of 1/2, 1, [23] or 2 mg, to 30 mg/day. [25] The authors considered cholinesterase activities significant if 20-25% lower than preexposure baselines. Doses of 1-22 mg/day did not inhibit either erythrocyte or plasma cholinesterase activities significantly. After 24 mg/day, [24] two of five men had significant cholinesterase inhibitions. Maximum decreases in cholinesterase activities during the test for these individuals were 24 and 23% of plasma preexposure baselines and 27 and 55% of their erythrocyte preexposure baselines. After 26 mg/day, [24] two of five men showed significant cholinesterase inhibition, with maximum decreases of 25 and 37% of the preexposure baseline activities of the erythrocytes; their plasma cholinesterase activities were decreased less than 20%, however. After 28 mg/day, [25] three of five men had significant inhibitions of erythrocyte cholinesterase activity at the end of the test period. Plasma cholinesterase activities were not reported after the 28 and 30 mg/day doses. With 30 mg/day, [25] the mean maximum inhibition of erythrocyte cholinesterase activity for all five men during the 30-day test period was reported to be 37%. The authors stated that, by contrast, the mean maximum erythrocyte cholinesterase inhibition was 18% with the 26 mg/day dose [24] and 19% with the 28 mg/day dose. The study with the 30 mg/day dose [25] did not give individual cholinesterase activities for the subjects given methyl parathion. Since, for the 30 mg/day methyl parathion study, the only values reported were the mean maximum cholinesterase inhibitions (no cholinesterase activities during various times of the test period were given), it is impossible to determine whether cholinesterase inhibition was still changing at the end of the test period or had leveled off. The inconsistent reporting of individual values [25] also makes it

impossible to determine whether methyl parathion-induced inhibition of cholinesterase activities varied as greatly between test individuals as did those induced by parathion itself in a similar study performed by Rider et al. [23] In the study with parathion, [23] a 7.5 mg/day dose inhibited plasma cholinesterase activities in five volunteers to 97, 82, 69, 52, and 50% of their preexposure baselines by day 16 of the test interval. At this point, the two subjects with the lowest values withdrew from the study to avoid acute intoxication. A third volunteer was dropped on day 23 when his erythrocyte cholinesterase activity had declined to 54% of baseline. The two volunteers completing the 35-day test had plasma cholinesterase activities depressed to 86 and 78% of their preexposure levels. While Rider et al [25] did not report any clinical illnesses, observation for effects other than those associated with acute inhibition of cholinesterases was not reported.

Van Bao and Szabo [30] examined the abilities of organophosphorus insecticides to produce mutations in the lymphocytes of persons exhibiting systemic anticholinesterase effects. They reported that 14 of 15 exposed individuals (3 had been poisoned by methyl parathion) showed chromosomal anomalies in a mean of 2.53% (p less than 0.001) of metaphase cells examined. Only 4 of 10 controls exhibited chromosomal anomalies in 0.5% of control metaphase cells examined. None of the 15 poisonings was fatal. Anomalies in the methyl parathion cases were not quantified separately.

In a subsequent paper, Van Bao et al [31] examined lymphocyte cultures from 31 persons having systemic poisoning from organophosphorus insecticides. Nine of these persons were occupationally exposed. Of the 31 cases, 5 (4 men, 1 woman) had been exposed to Wofatox (methyl

parathion). Three blood samples were taken, the first 3-6 days after exposure, the second at 30 days, and the third at 180 days. The authors stated that the severity of intoxication was serious in two of the individuals, medium in one, and mild in the other two. All patients had received 16-360 mg of atropine (over unspecified time intervals), and one patient in each severity category had received an experimental cholinesterase reactivator, Toxogonin (bis (4-hydroxyiminomethylpyridinium-1-methyl) ether dichloride). Lymphocyte cultures from 15 controls (13 men, 2 women) were also examined. One hundred cells in metaphase were scored from each blood sample after incubation and air-drying. In the 3- to 6-day samples, 9.80% of 51 metaphase preparations karyotyped ($p = 0.05$) had translocations or deletions. In the 30-day samples, 26.00% of 50 cells in metaphase karyotyped ($p = 0.001$) had translocations or deletions. In the 6-month samples, 10.20% of 49 metaphase cells karyotyped had translocations or deletions. This last figure was not significantly different ($p = 0.05$) from that for the controls. The control group showed a deletion frequency of 3.33% and no translocations.

When data from all 31 patients were pooled without regard to the organophosphorus compound to which the patients had been exposed, the cells collected 3-6 days after the exposure had 17.83% deletions and translocations when the cells were arrested in metaphase. [31] In this sample, 34.30% of the cells with a deletion also included an acentric fragment. The cells collected at 30 days and 6 months after the exposures had 22.00% and 5.60%, respectively, metaphase cells with translocations or deletions. The increases in the percentage of cells with translocations and deletions were statistically significant in every severity group for

methyl parathion, phosdrin, malathion, and trichlorfon in both the 3- to 6-day and the 30-day samples. The frequencies of chromosomal aberrations did not differ significantly between the occupationally exposed and the suicidal cases. In their examination of case histories of the exposed and control individuals, the authors did not adequately document exposure to known mutagenic agents or high doses of ionizing radiation that could have accounted for, or contributed to, the observed abnormalities. Moreover, possible effects of pesticide solvents and vehicles, atropine, or Toxogonin were not properly considered. However, Toxogonin had been administered to only 12 of the 31 patients, and the authors [31] stated that atropine had not shown mutagenic activity in an unpublished study performed in their laboratory. The possibility of mutagenic effects occurring in response to preintoxication factors was rejected because of the correlation of systemic intoxication with subsequent increases in chromosomal aberrations in the 3- to 6-day and 30-day samples and the return to near control levels in the 6-month samples. While the number of cases in each severity group was too small to make a firm judgment, the authors noted that a dose-effect relationship was not apparent. The investigation did not determine whether chronic exposure to low levels of the compounds also would have produced chromosomal aberrations. This possibility merits investigation, because aberrations were observed in this study, even in cases of mild poisoning.

Yoder et al [32] studied chromosomal aberrations in lymphocytes of 16 crop dusters, formulators, spray rig operators, and farmers exposed to a variety of insecticides. Sixteen control individuals were selected from nonexposed, nonagricultural occupations. Experimental subjects had been exposed to a mixture of insecticides, in which the constituents, other than

parathion, were unknown. Methyl parathion, however, was included in a group of insecticides to which experimental subjects had been exposed less often. The number of chromosomal breaks in cultured lymphocytes of peak-season (high exposure) experimental subjects was five times higher than that for off-season (low exposure) experimental subjects, for off-season controls, and for peak-season controls. Because of the variety of possible substances (including solvents), the indeterminate exposure of test subjects, and the inadequacy of controls, no conclusions about the mutagenicity of methyl parathion can be drawn from this study.

A summary of the effects on humans from methyl parathion exposure is shown in Table XVI-5.

Epidemiologic Studies

No epidemiologic studies of persons occupationally exposed to methyl parathion were found. Exposure studies in which cotton checkers entered methyl parathion-treated fields are described in Chapter IV.

Animal Toxicity

Results of studies on the anticholinesterase effects of methyl parathion are presented immediately below. Other manifestations of methyl parathion toxicity, not necessarily related to cholinesterase inhibition, are discussed later in this section.

Gaines [33] reported that a single oral administration to rats of technical methyl parathion (80% methyl parathion in xylene) in peanut oil in graded doses produced LD50 values of 14 and 24 mg/kg for 68 male and 60

female animals, respectively. The sex-related difference observed is consistent with the observation by Johnsen and Dahm [34] that liver microsome fractions from male rats were more efficient at converting methyl parathion to methyl paraoxon than were those of female rats. This sex difference in LD50's was statistically significant in the study by Gaines [33]; confidence limits at the 0.95 level were 12-17 mg/kg for males and 22-28 mg/kg for females. Application of methyl parathion dissolved in xylene to the intact skin of 69 male and 50 female rats produced LD50 values of 67 mg/kg for both sexes, with confidence limits of 63-72 mg/kg at the 0.95 level.

Kimmerle and Lorke [35] reported that the median lethal concentrations (LC50) of technical methyl parathion for 20 male rats after 1- and 4-hour inhalation exposures were 0.2 mg/liter (200 mg/cu m) and 0.12 mg/liter (120 mg/cu m), respectively. Concentrations of methyl parathion in the air within the exposure chamber were determined by an unspecified analytical technique. Exposure was limited to breathing via the inhalation apparatus of Niessen et al. [36] The postexposure observation period lasted 14 days.

Newell [37] examined the acute systemic toxicity in rats of technical methyl parathion (74-76%) administered in propylene glycol. Fasting rats weighing approximately 200 g were used for all tests. The oral LD50's were 12.0 mg/kg for males and 18.0 mg/kg for females. The iv LD50's were 9.0 mg/kg for males and 14.5 mg/kg for females. The dermal LD50's were 110 mg/kg for males and 120 mg/kg for females. The 1-hour LC50's were 257 mg/cu m for males and 287 mg/cu m for females. The author stated that these LC50 values corresponded to 1.23 mg/kg and 1.38 mg/kg, respectively.

Miyamoto et al [38] examined the acute toxicities and anticholinesterase effects of methyl parathion, Sumithion, and their oxon derivatives in rats, guinea pigs, and mice. Test materials were synthesized in the laboratory and administered in aqueous emulsions. LD50 values were calculated after a 5-day observation period. The oral and iv LD50 values determined for methyl parathion and methyl paraoxon appear in Table III-1.

TABLE III-1

ACUTE TOXICITIES OF METHYL PARATHION AND METHYL PARAOXON
(LD50, MG/KG)

Animal (Sex)	Route	Methyl Parathion	Methyl Paraoxon	Potency Ratio
White rat (M)	Oral	24.5	4.5	5.4
(170-190 g)	iv	4.1	0.5	8.2
Guinea pig (M)	Oral	417	83	5.0
(290-320 g)	iv	50	2.2	22.7
Mouse (M,F)	Oral	17	10.8	1.6
(13-18 g)	iv	13	-	-

*Adapted from Miyamoto et al [38]

Miyamoto et al [38] also examined the iv dose required to reduce the cholinesterase activities in brain and plasma in rats and guinea pigs to half their initial values within 1 hour after dosing. Results of these tests appear in Table III-2.

TABLE III-2

SINGLE INTRAVENOUS DOSES REQUIRED TO REDUCE CHOLINESTERASE ACTIVITIES TO 50% OF INITIAL VALUES

Animal	Methyl Parathion (mg/kg)	Methyl Paraoxon (mg/kg)	Potency Ratio
White rat			
plasma	1.8	0.4	4.5
brain	2.1	0.3	7.0
Guinea pig			
plasma	24	2.0	12.0
brain	28	1.5	18.7

Adapted from Miyamoto et al [38]

From the data in Tables III-1 and III-2, it appears that, in rats and in guinea pigs, the single iv dose of methyl parathion required to reduce plasma cholinesterase activity to 50% of the initial value was 43.9% and 48.0% of the iv LD50 dose, respectively. For methyl paraoxon, the single iv dose sufficient to produce the same inhibition was 80% of the iv LD50 dose in rats and 91% in guinea pigs. These comparisons show a relatively small margin between the doses of methyl paraoxon necessary to inhibit the cholinesterase activity by 50% in the plasma and to kill 50% of the animals. Methyl parathion had a 1.8 times bigger margin between these two doses than its oxon analog in the rat and 1.9 times in the guinea pig. Furthermore, it is also clear that in each species tested methyl paraoxon was significantly more toxic than methyl parathion when given iv or orally in acute doses--the potency ratio ranged from 1.6 (oral LD50, mice) to 22.7 (iv LD50, guinea pigs). This [38] and other LD50 studies [33,35,37,39-42]

for methyl parathion are summarized in Table XVI-6.

Williams et al [43] fed technical methyl parathion to mixed breed dogs for 90 days at levels of 5, 20, or 50 ppm. Five plasma and five erythrocyte cholinesterase activity determinations were performed on four control and two experimental animals during a 4-week pretreatment period. Similar tests were performed every 2 weeks during the 90-day test period and at unspecified intervals during the 8-week recovery period. The investigators found the cholinesterase activities of the erythrocytes to be about 65% and 60% of baseline values in animals ingesting the 20- and 50-ppm diets, respectively. These decrements were statistically significant. Erythrocyte cholinesterase activities for animals on the 20- and 50-ppm diets were still declining at the end of the test period. This led the authors [43] to suggest that the cumulative inhibition (from an excess of inhibition over recovery) caused by methyl parathion probably was more pronounced than had been observed for Chlorthion, Dipterex, or Diazinon. The return of erythrocyte cholinesterase activity during the recovery period occurred at a rate of approximately 1%/day in the dogs fed the two highest dosages. This recovery rate is consistent with that reported by Grob et al [6] for related organophosphorus compounds (see Chapter IV).

Metcalf and March [41] compared the oral toxicities of methyl parathion and its heat-induced isomers in mice. Mortality over a twenty-four-hour period was used to determine LD50 values. Purified methyl parathion, heated for 4 hours at 150 F, was 84.7% "isomerized." While no separate quantifications of S-phenyl and S-methyl isomers were reported, the authors stated that analysis by paper chromatography showed that the S-methyl isomer was the principal constituent. The isomer mixture was 80

S-methyl isomer was the principal constituent. The isomer mixture was 80 times more effective than purified methyl parathion at inhibiting mouse brain cholinesterase in vitro. However, the same isomer mixture was reported to have been significantly less toxic than purified methyl parathion when given orally to mice in propylene glycol. The LD50 for purified methyl parathion was stated to be 100-200 mg/kg, while that for the isomer mixture reportedly was greater than 200 mg/kg. The investigators also demonstrated that UV radiation could isomerize purified methyl parathion. This finding was not confirmed in the study of UV-irradiated methyl parathion performed by Koivistoinen and Merilainen. [44] These authors separated the mixture by paper chromatography and reported only one product of UV-irradiated methyl parathion with anticholinesterase activity, which they suggested was methyl paraoxon. Metcalf and March [41] postulated that the difference between in vivo and in vitro inhibitions of cholinesterase observed for several isomerized alkyl phosphorus compounds was because of the far greater instability to hydrolytic detoxification of the isomer mixtures than of the purified normal forms. Examination showed that the hydrolysis of the mixed isomers of methyl parathion was incomplete. Therefore, the postulate of Metcalf and March [41] was not supported by their study. The results indicate the importance of using purified methyl parathion in investigations of mammalian toxicity to obtain the true toxicity of isomer-free methyl parathion. These data do not support the suggestion by Grigorowa [16] that heat-induced isomerization of methyl parathion contributed to the increased incidence of human intoxications during formulating runs in the summer.

Brodeur and DuBois [39] examined the effects of age on susceptibility to intoxication by organophosphorus compounds, including methyl parathion, in weanling (23-day-old) and adult male rats. Methyl parathion was administered ip to 58 weanlings and to 24 adults. The LD50's were 5.8 mg/kg for adults and 3.5 mg/kg for weanlings. Systemic toxicity at earlier ages was not examined. Since the rate of conversion of organophosphorous compounds to their active metabolites in the liver of immature animals has been shown to be lower than that in adults, [45] the increased toxicity observed in weanlings was assumed by the authors to be attributable to an incompletely developed ability to metabolize and detoxify these compounds, in this case, methyl parathion. [46]

Vandekar et al [47] examined the correlation of the ED50 (median effective dose for producing a selected first sign) for methyl paraoxon with its LD50 in dose-response tests with rats. Animals were injected iv or im with methyl paraoxon dissolved in propylene glycol or glycerol; ED50 values were measured by observing the slightest evoked tremors in rats dropped at 5-minute intervals from heights of 5-10 cm, and LD50 values were determined from 24-hour mortalities. Four rats were injected at each dose level. The LD50 for methyl paraoxon administered iv was about five times its corresponding ED50 (0.457 mg/kg and 0.084 mg/kg, respectively). The LD50 for methyl paraoxon administered im was about four times its corresponding ED50 (1.69 mg/kg and 0.402 mg/kg, respectively).

Tolerance of rabbits to repeated doses of methyl parathion was reported in 1967 by Orlando et al. [48] Twenty test animals were divided into two groups. One group received one dose of 15 mg/kg of methyl parathion by the im route 7 days before receiving 12.5 mg/kg methyl

parathion iv. The other group was treated with 15 mg/kg im every 15 days during a 5-month period prior to receiving a lethal iv dose, 12.5 mg/kg. After receiving the lethal dose, neither group of test animals showed the marked ECG changes found in animals given only the lethal dose in previous studies. Correspondingly, the other clinical signs of intoxication were comparatively mild. The first group of test animals showed some ECG abnormalities, including extrasystolic bigeminy as well as slight alterations in ventricular and atrial repolarization, which tended to disappear within 1 hour. The ECG tracings returned to normal after 2 hours and remained normal for 10 days. Clinical signs in this group included agitation, tremor, dyspnea, lacrimation, excessive salivation, and urinary and fecal discharges. The signs of acute intoxication disappeared after 1 hour. In the second group of test animals, no repolarization disorders were observed. One rabbit had a brief (less than 5 minutes) run of extrasystolic trigeminy. Signs of intoxication by the iv dose were limited to dyspnea and diffuse tremors lasting only a few minutes. This study shows that rabbits may develop tolerance to methyl parathion; however, because only one species was studied, extrapolation of these results to humans is impossible.

In 1957, Frawley et al [49] simultaneously administered EPN (O-ethyl-O-p-nitrophenyl benzenethiophosphonate) and malathion to rats and dogs. There was more inhibition of whole blood cholinesterase in rats and plasma and erythrocyte cholinesterase in dogs than would have been expected from the known inhibitory potencies of the components of the mixture. No studies were found demonstrating similar potentiation for methyl parathion in combination with either other pesticides or common pharmaceuticals.

Investigations into the toxic effects on humans of the interactions of methyl parathion with active co-ingredients in the most popular formulations (eg, with parathion or with toxaphene) have not been found in the published literature. In 1975, Plapp [50] described the increasingly popular combination of methyl parathion with chlordimeform, a synergist. While no human data have been found, he indicated that, when methyl parathion and chlordimeform were applied in equal amounts (1:1), the toxicity of methyl parathion to tobacco budworms was increased 2.8 times. These data cannot be extrapolated to humans.

Gaines [51] examined 30 organophosphorus and 9 carbamate compounds for evidence of neurotoxic effects in chickens. In this screening study, the latency of effects from these compounds was compared to the characteristic 8- to 14-day delay in onset of flaccid paralysis of legs observed in chickens, cats, and humans as discussed by Davies, [52] for the known neurotoxic compound, triorthocresyl phosphate. The highest no-effect dose of methyl parathion tested was 32 mg/kg. The lowest effective dose tested, 64 mg/kg, was approximately 1/3 of the lowest lethal dose tested, 200 mg/kg. The number of chickens tested was not specified. Although no histologic examinations were performed in this study, the neurotoxic signs in chickens treated with methyl parathion did not show the characteristic latency or persistence of classical neurotoxic agents. Onset of leg flaccidity at this dose occurred within 24 hours and lasted 3-28 days. These results suggest that methyl parathion is not a demyelinating agent and confirm those reported earlier by Barnes and Denz. [53]

Shcherbakov [54] reported in 1970 that 24 rats given single ip doses of 4 mg/kg of methyl parathion, said to be nonlethal, developed signs of

mild poisoning. These disappeared within 2 hours, but animals killed and examined at that time were said to have exhibited evidence of interference with the integrity of both central and peripheral neurons. These included swelling, chromatolysis, shrinkage and fragmentation of neurons, and swelling and fragmentation of myelin sheaths.

In a later paper, the same author [55] injected 40 rats ip with 20 mg/kg of methyl parathion. These rats died after 12-15 minutes. Despite the short times of survival, Shcherbakov [55] reported changes similar to those in the previous study [54] with the smaller dose of methyl parathion but a longer period of survival. In this paper, [55] the results of some experiments with another organophosphorus compound, tabun, rather than methyl parathion, are reported. One of the findings was that administration of atropine prevented death from poisoning by tabun, but did not decrease the degree of hydration of neurons in the rats. Shcherbakov [55] suggested, therefore, that the alterations in the neurons following administration of cholinesterase inhibitors are in part due to changes in the electrolyte composition of the nerve cell and are only indirectly related to the pseudocholinergic activity of the cholinesterase inhibitors. This suggestion is supported by reported alterations in the activities of acid phosphatase and adenosinetriphosphatase (ATPase) within neurons.

These two papers by Shcherbakov [54,55] are difficult to interpret. The rapidity with which the reported changes must have taken place has not been corroborated. In particular, the fragmentation of myelin within 2 hours after a nonlethal dose of methyl parathion reported by the author is difficult to believe because changes in myelin typically require days rather than hours. [53,56-59] Furthermore, the unfixed tissues used for

histochemical study of enzymes in brain and peripheral nerve [55] are of only questionable value in demonstrating localization of hydrolytic enzymes. Shcherbakov used these structural changes in the neurons and the results of the histochemical study as partial justification for suggesting that cholinesterase inhibition may produce structural changes in the neuronal terminals as a secondary effect.

The first paper [54] did not mention the use of control rats for comparison, but the second [55] stated that six control animals were used. Presumably, therefore, the reported changes in the rats given methyl parathion or tabun were different from those seen in the control rats; however, no actual information on the controls was provided. Therefore, NIOSH is skeptical about the validity of these observations but would welcome additional study of the early effects of nonfatal doses of methyl parathion on neuronal and glial integrities.

Akhmedov and Danilov [60] reported pathologic changes in the organs of adult rats in a 3-month inhalation study in which animals were exposed for 24 hours/day, 7 days/week, to aerosolized methyl parathion. Fifteen rats were exposed at each of the airborne levels tested: 0.072, 0.024, and 0.008 mg/cu m. An additional group of 15 rats served as controls. With the highest level tested (0.072 mg/cu m), the most marked changes were reported in the CNS. They were described as perivascular, pericellular edema, and vacuolar dystrophy of the cytoplasm of the ganglionic cells. In addition, the authors reported several other histopathologic effects at this dose level. Lymphoid infiltrations in the connective tissue of the heart were noted. The liver showed hemorrhagic, dystrophic, and necrotic changes. Hyperplasia of the red pulp of the spleen and moderate atrophy of

the follicles were observed. In the adrenal glands, the authors reported atrophy of the zona glomerulosa, granular dystrophic changes in the zona fasciculata, and hyperchromatosis in the cortical cells. At the intermediate level, 0.024 mg/cu m, similar but less marked changes were observed in these organs, but CNS effects were not reported. With the lowest level tested, 0.008 mg/cu m, the authors found no significant changes in the organs of experimental animals by comparison with those of controls. On the basis of these data, the authors recommended a maximum allowable concentration (MAC) of 0.008 mg/cu m for methyl parathion in urban atmospheric air. Interpretation of this study is impossible because of inadequate characterization of pathologic changes.

Street and Sharma [61] reported that immunosuppressive effects of recrystallized methyl parathion were observed in dose-response studies with rabbits. Groups of seven animals each received methyl parathion-treated feed to yield doses of 0.036, 0.162, 0.519, or 1.479 mg/kg/day for 28 days before challenge with injected sheep erythrocytes. A control group of eight animals received untreated feed. While the test rabbits were continued on treated feed, immunosuppression was assessed during the following 28 days by a fluorescent antibody technique. The investigators examined leukocyte count, hemolysin titer, hemagglutinin titer, the concentration of gamma globulin in serum and its ratio to transferrin, the response of skin cells to intradermal injection of tuberculin, atrophy of germinal centers of the spleen, thymus cortical atrophy, and lymph node fluorescence. In the majority of these tests, results were inconclusive, inconsistent, or not statistically significant. Since only a relatively small number of animals of only one species was used and positive controls

were absent, definite conclusions cannot be drawn from this study. However, these data suggest that there may be a slight tendency for methyl parathion to suppress cell-mediated immune responses in rabbits.

Lybeck et al [62] demonstrated that methyl parathion had an inhibitory effect on iodine uptake by adult female rat thyroid in a study of 25 experimental animals, 25 positive controls (propylthiouracil), and 15 negative controls. Five experimental, five positive-control, and three negative-control rats were used for each of five test periods. Each experimental animal received ip 0.15 mg of methyl parathion in 3 ml of distilled water. The negative-control animals received ip injections of 3 ml of distilled water. The positive controls received ip 1 mg of propylthiouracil in 3 ml of distilled water. A few drops of acetic acid were added to each liter to stabilize the test solution. The animals were killed 8, 12, 16, 20, or 24 hours after receiving their injections. Two hours before the rats were killed, a dose of 20 microcuries of 131I was administered ip. Methyl parathion did not inhibit as much of the uptake of inorganic iodine by the thyroid gland as propylthiouracil, but it still produced a demonstrable effect: maximum inhibition by propylthiouracil was 95.5%, and that by methyl parathion was 65%. Both maximum effects occurred 8 hours after administration of the experimental compounds. A curious phenomenon observed in this study was that both propylthiouracil and methyl parathion apparently produced greater inhibition of uptake of iodine by the thyroid at 20 hours after the experimental compounds were given than at either 16 or 24 hours. The action of methyl parathion on the uptake of iodine by the thyroid therefore appears to be largely, if not completely, an indirect one. Lybeck et al [62] suggested that methyl parathion may

have an influence on the hypothalamic-pituitary level of control of thyroid activity, acetylcholine being thought to be the chemical mediator that initiates liberation of thyrotropin-releasing factor from the hypothalamus.

Mohn [63] examined the mutagenic potential of methyl parathion in Escherichia coli. Induction of 5-methyltryptophan-resistant mutations was determined by examining plate cultures after treatment with 0.01 M methyl parathion for 0, 60, 120, 180, or 240 minutes. Survival times were determined simultaneously on other plates without 5-methyltryptophan. The frequency of occurrence of mutant colonies in the cultures exposed to methyl parathion was not significantly different from that in the control cultures with doses which did not inactivate cells. For treatment times of 0 and 60 minutes, the survival fractions were 100 and 93%, and the mean numbers of mutant colonies/plate were 9.7 ± 6.5 and 11.3 ± 7.6, respectively. However, at higher doses, the frequency of occurrence of mutant colonies was significantly increased with a parallel decrease in survival. After contact times of 120, 180, and 240 minutes, survival fractions were 81, 69, and 53%, and mean numbers of mutant colonies/plate were 18.0 ± 7.9, 19.3 ± 7.6, and 12.7 ± 6.2, respectively. Mohn concluded in an abstract [64] of this study that methyl parathion was "probably mutagenic" and indicated [63] the need for further testing in several other mutation systems.

Plate tests with methyl parathion and eight other organophosphorus insecticides were performed by Dean [65] using E coli WP2. The author reported that methyl parathion did not induce reverse mutations in this system. Nine positive control compounds (alkylating agents known to be mutagenic) produced reverse mutations in this strain of bacteria; however,

two compounds, caffeine and urethane, which induce reverse mutations in certain bacterial test systems, had no mutagenic influence on E coli WP2. These findings confirmed the necessity for testing methyl parathion in several mutation systems before a firm judgment on its mutagenic potential can be made.

Simmon et al [66] examined the mutagenic potential of methyl parathion in several systems. The authors stated that their data showed no significant mutagenic effects in B subtilis, E coli, mice (dominant lethal test), Salmonella typhimurium (TA 98, TA 100, TA 1535, TA 1537, TA 1538), and unscheduled DNA biosynthesis. Results were reportedly inconclusive in a yeast test system. In the bacterial test systems, methyl parathion and methyl paraoxon were tested separately, since these organisms cannot perform desulfuration of the thio compound to form the oxon. Results in these test systems were negative for methyl paraoxon as well as for methyl parathion.

Huang [67] reported that, when three different human hematopoietic cell lines were treated with methyl parathion in concentrations of 25, 50, 75, and 100 μg/ml, the percentage of chromosomal aberrations in metaphase preparations was not increased in treated cultures. Doses of 5, 10, and 20 mg/kg of methyl parathion administered ip to mice did not produce significant chromosomal changes in cultures of bone marrow stopped in metaphase and examined 24 hours after exposure to methyl parathion.

Lobdell and Johnston [68] used the three-generation study design described by Fitzhugh [69] in 1959 to examine the effects of methyl parathion on reproductive performance in rats. Methyl parathion (99% pure) was administered by incorporation into the diets of experimental animals

(10 male and 20 female rats/group on each of two concentrations). [68] Daily dietary intake levels were adjusted to provide 10 ppm (1 mg/kg) and 30 ppm (3 mg/kg). With 30 ppm, tremors were observed only in a few of the original parent rats (F0). Reductions in survival time were observed in the first generation-first litter (F1a) and first generation-second litter (F1b) weanlings in the group fed the 30-ppm methyl parathion diet, and in the third generation-first litter (F3a) weanlings of that fed the 10-ppm diet. Of the second generation-second litter (F2b) females in the 30-ppm group, only 41% had litters after the second mating. Littering by the F2b females of the group fed 10 ppm was comparable with that of F2b controls. Rats in the 30-ppm F1b group had an elevated total number of stillbirths, but at each mating the numbers of litters containing stillborn pups did not differ significantly between the control and the treated groups. However, the authors concluded that dietary concentrations of 30 ppm or less of methyl parathion did not produce a consistent or dose-related toxic effect on the rat. This conclusion was based in part upon unpublished data from their laboratory.

Tanimura et al [70] examined the effects on rat and mouse fetuses of single doses of methyl parathion, dissolved in carboxymethyl cellulose, administered to the mothers. The material was injected ip into pregnant rats on day 12 of gestation and into pregnant mice on day 10 of gestation. Signs of cholinergic intoxication were seen approximately 30 minutes after administration at each dose (5, 10, and 15 mg/kg for rats; 20 and 60 mg/kg for mice). The animals were killed near term, on day 21 in rats, and on day 18 in mice. The fetuses were examined for intrauterine death, external malformations, and skeletal abnormalities. In rats, the only effects

observed were suppression of fetal growth and ossification. However, cleft palates were observed in fetuses of mice given doses of 20 mg/kg and 60 mg/kg. The higher dose was reported by the authors to be close to the LD50 for mice. With the lower dose, two cleft palates were observed among 143 fetuses. With the higher dose, 13 of 112 fetuses had cleft palates. In addition, fetal deaths in mice were dose-related: 22.3%, 4.2%, and 2.9% for the 60-, 20-, and 0-mg/kg groups, respectively. The authors suggested that the transient depression of maternal food intake in combination with the chemical action of this compound or its metabolites may have been responsible for the adverse prenatal effects. Since the distribution of deformities among the litters was not shown, the data presented cannot be properly analyzed. In addition, the single dose on day 10 (mice) or day 12 (rats) does not represent exposure to methyl parathion during all phases of organogenesis.

Fish [71] studied the effects on fetuses of methyl parathion given ip to pregnant rats. Single doses of 4 and 6 mg/kg in a vehicle of ethanol (20%) and propylene glycol (80%) were administered on day 9 or 15 of gestation. Controls received injections of the vehicle only. The author reported that the LD50 for methyl parathion in female rats was 24 mg/kg. Signs of acute intoxication appeared 5-10 minutes later and most maternal deaths occurred within the first 30 minutes after injection. Eight test animals (two treated with 4 mg/kg on day 9 of gestation, three treated with 4 mg/kg on day 15 of gestation, and three treated with 6 mg/kg on day 9 of gestation) and two controls were killed on day 21 of gestation. The author found no resorption or gross abnormalities in any of these animals; however, a diminished cerebral cortical cholinesterase activity was

observed in all fetuses of the treated groups. The fetal brain cholinesterase activity was determined using a histochemical technique. The data are qualitative, as no quantitation of the depth of staining was possible with this technique. The other rats, two test animals (one each treated with 4 mg/kg on days 9 and 15 of gestation) and two controls, were allowed to deliver. The author found no significant differences between pups derived from control and treated animals when measured by stillbirths, neonatal deaths, and gross developmental abnormalities. The small number of litters obtained from any one regimen makes any assessment of embryotoxicity speculative. However, the observed reduction in the cholinesterase activity of the fetal cerebral cortex suggested that methyl parathion had passed the placental barrier.

Ackermann and Engst [72] examined the passage of methyl parathion and methyl paraoxon across the placental barrier 1-3 days before parturition in four pregnant rats weighing 270 g. Methyl parathion, 3 mg dissolved in 0.4 ml ethanol (11.1 mg/kg), was administered orally. The placentas as well as the embryos were removed by surgery 30 minutes after administration. Maternal and fetal twitching, an early sign of methyl parathion poisoning, was observed at this dose. Animals were killed 30 minutes after the dose; maternal liver and placenta and fetal brain, liver, and muscle were sampled for assay. Methyl parathion and methyl paraoxon were found in fetal brain, liver, and muscle. Maternal liver and placenta contained residues of methyl parathion, but the authors stated that their analytical technique was not sufficiently sensitive to detect methyl paraoxon in these tissues. The presence of methyl paraoxon in fetal liver but not in maternal liver tissue was attributed to the threefold greater esterase activity observed

in maternal liver than was found in fetal liver.

Miyamoto [73] used 32P-labeled methyl parathion in tissue distribution studies. In male rats killed 2.5 minutes after iv injection, methyl parathion and methyl paraoxon were found in all tissues assayed (brain, liver, lung, heart, kidney, spleen, muscle, and blood). Methyl paraoxon was found primarily in liver tissue. Similar results were found in the guinea pig 2.5 minutes after iv injection of methyl parathion. Conversion of methyl parathion to methyl paraoxon and degradation of methyl paraoxon by liver microsomes have been confirmed in vitro for eight mammalian species by Johnsen and Dahm. [34]

Hollingworth et al [74] identified several metabolites of methyl parathion in the urine of mice. Single doses of 3 or 17 mg/kg of 32P-labeled methyl parathion in 0.15 ml of olive oil were fed to male mice. Urine collected during the following 24 hours was analyzed by ion-exchange chromatography. Excretion products from the 17 mg/kg dose were reported by percentage of radioactivity in urine as follows: dimethyl phosphoric acid, 31.9%; O-methyl-O-p-nitrophenyl phosphate, 23.1%; O-methyl-O-p-nitrophenyl phosphorothioate, 18.8%; dimethyl phosphorothioic acid, 12.9%; phosphoric acid, 5.8%; unknown, 3.1%; methyl paraoxon, 2.4%; methyl phosphoric acid, 2.0%. After both doses tested, 65-75% of the 32P administered was excreted in the urine within 18 hours. The authors suggested that urinary excretion of methyl paraoxon may be an important detoxification mechanism. The appearance of methyl paraoxon, but not of methyl parathion, in the urine was attributed [74] to the much higher water solubility of methyl paraoxon. [75] On the basis of this study, the authors proposed the metabolic pathways shown in Figure XVI-2.

Table XVI-7 summarizes the effects on animals reported in the studies discussed above other than LD50 studies.

Correlation of Exposure and Effect

Methyl parathion is absorbed through the gastrointestinal tract, [17-19,24,25,33,37,38,41,43,61,68] the skin, [33,37,76,77] and the respiratory tract. [35,37,60] Parathion is absorbed through conjunctivae, cuts, and abrasions [6]; methyl parathion is probably also absorbed through these routes.

The only confirmed effects on humans of exposure to methyl parathion are the signs and symptoms characteristic of systemic poisoning by cholinesterase-inhibiting organophosphorus compounds observed in the case studies cited. [16-19] These studies of methyl parathion intoxication, however, do not provide sufficient data for correlating plasma or erythrocyte cholinesterase activity with the various signs and symptoms of intoxication by methyl parathion. Despite this deficiency, the oral ingestion studies performed by Rider et al [24,25] suggest that manifestations of acute methyl parathion toxicity are absent in humans whose erythrocyte cholinesterase activity has been reduced to as little as 45% of their preexposure baselines. A study with dogs by Williams et al [43] lends support to this range of erythrocyte cholinesterase inhibition within which humans showed no clinical manifestations of acute intoxication by methyl parathion. Inhibition of erythrocyte cholinesterase to 60-65% of the preexposure baseline activities in dogs fed methyl parathion was not reported to produce signs of systemic intoxication. This range of inhibition within which humans and dogs appear asymptomatic is consistent

with the data compiled by Namba et al [78] (reported in Chapter IV), which showed that persons having symptoms of poisoning by parathion had more than 50% inhibition of the cholinesterase of their erythrocytes. Since no preexposure baseline determinations were made in the study by Grigorowa, [16] the range of plasma cholinesterase activities reported for workers with symptoms of methyl parathion intoxication may not reflect the true extent of cholinesterase inhibition. For this reason, true inhibition values were probably greater than those reported in the paper. In addition, the author reported only plasma cholinesterase activities. Plasma cholinesterase activity appears to return to baseline, after exposure to methyl parathion ceases, more promptly than erythrocyte cholinesterase activity. [43]

In their 1970 and 1971 studies, Rider et al [24,25] found that ingestion by humans of doses of methyl parathion of 24, 26, and 28 mg/day (five subjects each level) for 30 days was sufficient to inhibit erythrocyte cholinesterase activity by at least 20-25% in two, two, and three test subjects, respectively. With a 30 mg/day dose, the mean maximum cholinesterase activity of the erythrocytes for the test group was inhibited to 63% of the baseline activity. Return of erythrocyte cholinesterase activity to baseline value occurred at a rate of approximately 1%/day. Since Rider et al [25] did not consider the failure or possible failure of cholinesterase inhibition to level off at the end of the test intervals, 30 mg/day may not be the threshold doses for significant cholinesterase inhibition. The true threshold dose appears to be lower than 30 mg/day and may even be lower than 22 mg/day--the dose at which some of the test subjects in the 1970 study by Rider and coworkers

[24] first had inhibition of more than 25% of their erythrocyte cholinesterase by the end of the test.

Since none of the human experimental studies presented in this chapter examined the toxicity of methyl paraoxon, the active metabolite of methyl parathion, it is not possible from these data to confirm for humans the oxon:thion toxicity ratios observed in the Miyamoto et al [38] study with animals.

The data of Vandekar et al [47] from the rat show a relatively narrow range between median effective and median lethal doses for methyl paroxon. Data from human poisonings by methyl parathion, however, are not sufficiently detailed to identify the range between the doses producing first symptoms and those producing severe or fatal intoxication. Moreover, the routes of administration used in the animal study, iv and im, were not ones of occupational significance (ie, as compared to dermal, oral, and respiratory). From the data on human fatalities, [17-19] the minimum lethal dose of methyl parathion for adults appears to be less than 1.84 g.

No reports of inhalation or percutaneous dose-response studies with humans were found for methyl parathion. However, the data on rats by Newell [37] suggest that the methyl parathion is several times more toxic by inhalation than by oral administration.

None of the noncholinergic effects of methyl parathion reported in animal studies have been adequately confirmed or refuted, nor has their applicability to humans been determined.

No reports of investigations of the carcinogenic potential of methyl parathion in humans or in laboratory animals were found. However, Bedford and Robinson [79] have found that methyl parathion has about 1/300 and that

methyl paraoxon has about 1/160 the ability of dimethyl sulfate to methylate 4-(p-nitro benzyl) pyridine, a model of generalized protein with an aromatic type of amino group in a reactive form at pH 7.5. Although meaningful interpretation of the practical importance of alkylating activity is uncertain at best, one can guess that neither methyl parathion nor its oxon metabolite would be remarkably potent as either a mutagen or a carcinogen. Preussmann et al, [80] who stated that a strong positive response was given by methyl parathion as an alkylating agent, used a method of study that can be characterized as semiquantitative at best. Bedford and Robinson [79] modified the method to make it more reproducible and quantifiable. Their judgment on the alkylating propensity of methyl parathion is probably more reliable than that of Preussmann et al. [80]

Data from the reproductive studies considered [68,70-72] were not sufficient to reach a judgment on the teratogenic potential of methyl parathion. The reduced survival time observed in the study by Lobdell and Johnston [68] might be accounted for by the increased susceptibility of younger rats to methyl parathion, [45] especially in light of the report by Ackermann and Engst [72] that methyl parathion crosses the placental barrier in rats. This factor does not seem adequate, for the reasons given below, to explain the prevalence of cleft palates observed by Tanimura et al [70] in mouse fetuses from dams given a near-LD50 dose of methyl parathion ip on day 10 of gestation. On the other hand, the teratogenic potential for humans of methyl parathion can be neither confirmed nor refuted by the latter study, since the distribution of deformities within the litters was not shown. The work of Fish [71] does not determine whether or not methyl parathion has a teratogenic potential in rats. In

addition, it is impossible to determine from the study of Tanimura et al [70] whether terata and early fetal deaths were a direct result of exposure to methyl parathion (or its metabolites) or were simply a result of impaired maternal health. Furthermore, methyl parathion was not administered in the studies of Fish [71] and Tanimura et al [70] during all phases of organogenesis.

The study by Mohn [63] with bacterial cultures did not adequately confirm the mutagenic potential suggested by the human data of Van Bao and Szabo, [30] Van Bao et al, [31] and Yoder et al, [32] in light of negative results that Simmon et al [66] found in several test systems. However, the study by Huang [67] with cultures of mouse bone marrow and human hematopoietic cells and the dominant lethal (mouse) test by Simmon et al [66] do not conclusively demonstrate an absence of mutagenic potential in humans, but they do suggest the need for further research in this area.

IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION

Air Sampling

Sampling for airborne methyl parathion requires equipment suitable for simultaneously collecting vapors, airborne solids, and airborne droplets, since formulations in common use include emulsifiable liquids, wettable powders, and dusts. [9] No sampling method was found which has been adequately investigated for its accuracy in collecting all three forms.

The midget impinger is recommended as the device for sampling methyl parathion because of its small size which imparts greater adaptability to the air sampling procedure without sacrificing precision. Although studies have not been reported on the efficiency of midget impingers for collecting airborne methyl parathion, Roberts and McKee [81] studied the efficiency of midget impingers for collecting ammonia (1 ppm) with distilled water as the collection medium. Efficiency was highest (nearly 90% trapped by the first impinger) at the flow rate recommended for collection of particulates: 0.1 cu ft/min (2.8 liters/min).

During development of this document, NIOSH was informed (RH Hill Jr, written communication, March 1976) that gaps existed in the performance specifications for the sampling and analytical techniques recommended for methyl parathion. In addition, the Environmental Protection Agency has withdrawn the method utilizing a midget impinger charged with ethylene glycol, since "a controversy concerning the reliability of the data" has arisen using this method (RH Hill Jr, written communication, March 1976).

NIOSH currently recommends in the NIOSH Manual of Analytical Methods

[82] that an ethylene glycol-charged midget impinger be used for parathion sampling and that hexane be used to extract the trapped pesticide. Details of sampling and air-flow calibration procedures for methyl parathion are given in Appendix I. Other air sampling methods of equivalent or superior efficiency may be substituted for the recommended method.

Analysis of Air Samples

Because of the industrial practice of formulating mixed active ingredient products, [12] the analytical method must be able to differentiate methyl parathion from other pesticides. Common pesticide vehicles either must not interfere or must be readily extractable prior to analysis.

Although UV absorption [83] and colorimetric [84] methods have been reported for parathion analysis, no reports concerning the use of these methods for analysis of methyl parathion were found.

Phosphorus-specific detectors were introduced in 1964 and 1965 and have made gas-liquid chromatography (GLC) the analytical method of choice for organophosphorus compounds. [85,86] Both the alkali flame ionization (thermionic emission) detector introduced by Giuffrida [85] and the flame photometric detector developed by Brody and Chaney [86] exhibit relatively high sensitivity. Giuffrida [85] indicated that 24 ng of methyl parathion could be detected by a gas chromatograph with an alkali flame ionization detector. The linear working range of this system was reported to be 0.05-1.0 ng/injection volume. [85] Brody and Chaney [86] reported that the flame photometric detector, equipped with a narrow band-pass interference filter for isolating phosphorus emissions at 526 nm, was sensitive to

0.25 ng of parathion or malathion, with a linear response range of 0.0063-63.0 ppm. The method was reported to be highly specific for phosphorus compounds, thereby excluding interference by pesticide vehicles or chlorinated hydrocarbon coingredients.

The NIOSH Manual of Analytical Methods [82] recommends the use of GLC with a phosphorus flame photometric detector for analysis of hexane-extracted parathion air samples. Since different retention times are indicated in this method for methyl parathion, methyl paraoxon, parathion, and paraoxon, the method appears suitable for methyl parathion analysis. Precision and accuracy of the method were indicated as unknown.

Gas-liquid chromatography utilizing a phosphorus flame photometric detector is recommended as a suitable analytical technique for determining methyl parathion in hexane-extracted samples. The recommended method detailed in Appendix II identifies four separate chromatographic columns for obtaining discrete peaks when interfering phosphorus compounds are present. Also presented are data on additional columns suitable for analysis of samples containing methyl parathion. [87,88] Analytical techniques of equivalent or greater precision, accuracy, and sensitivity may be substituted for the recommended method.

Biologic Monitoring Methods

Two general approaches may be taken in evaluating occupational exposure to cholinesterase-inhibiting insecticides. Direct methods identify the amount of insecticide in the blood, [89-91] or of the insecticide, [90] its metabolites or its degradation products [92] in urine. Indirect methods measure cholinesterase activity in erythrocytes,

plasma, serum, or whole blood. [29,93-111]

Monitoring of methyl parathion, paranitrophenol, or alkylphosphates in urine, or of methyl parathion in blood, is unsatisfactory for determining the hazards to workers by exposure to methyl parathion. Neither method considers the increased susceptibility to intoxication by methyl parathion faced by workers whose cholinesterase activity has been lowered by recent or simultaneous exposure to other organophosphorus or carbamate pesticides. In addition, these methods are nonspecific; for example, the appearance of paranitrophenol in urine may be due to the degradation of methyl parathion, parathion, or EPN.

Reports cited in Chapter III indicate that symptomatic methyl parathion intoxication in humans, irrespective of dose or route of entry, causes profound inhibition of circulating cholinesterases. The validity of monitoring blood cholinesterases for determining the efficacy of engineering controls, personal protective equipment, and work practices depends on the extent to which the activity of one or both of these enzymes is predictive of the relationship of total anticholinesterase exposure to increased susceptibility to systemic poisoning upon continued exposure. This correlation has not been firmly established for methyl parathion in humans. However, a correlation between circulating serum cholinesterase activity in parathion-poisoned workers and severity of systemic poisoning has been compiled by Namba et al [78] based on several single-dose parathion poisoning incidents. Symptomatic intoxication was associated with inhibition of more than 50% of baseline serum cholinesterase activity. The level of serum cholinesterase activity paralleled the severity of manifestations: 21-50% of normal in mild poisoning, 11-20% of normal in

moderately severe poisoning, and 0-10% of normal in severe poisoning cases.

Grob et al [6] studied the rate of restoration of plasma and erythrocyte cholinesterase activity in 67 persons poisoned as follows: 18 by parathion, 35 by diisopropyl fluorophosphate (DFP), and 14 by tetraethyl pyrophosphate (TEPP). Initial rates of return (during the first 3 days following exposure) for all three pesticides were comparatively rapid. For parathion, erythrocyte cholinesterase activity increased by 10% over this interval, while for the plasma enzyme the figure was 27%. While the initial rate of return of activity differed for the three organophosphorus insecticides, restoration rates were identical from day 4 on. Rate of return for erythrocyte cholinesterase activity averaged 1-2%/day after day 3. For plasma cholinesterase, the average rate of return was 5%/day for days 4-10 and 3%/day for days 10-20. If this steeper rate of return of plasma cholinesterase activity applies to methyl parathion and exceeds the rate of recovery of functional (neuroeffector) cholinesterase, the use of plasma values for monitoring purposes could fail as an index of cumulative functional inhibition of neuroeffector cholinesterase. The divergence between plasma and erythrocyte cholinesterase activity would be especially significant where inhibition is due to extended low-level exposures to methyl parathion or other anticholinesterase compounds.

Several attempts have been made to determine a range of normal human cholinesterase activities for nonexposed persons. [93,112-114] Laboratories deriving their own normal values have been able to compare their results with those produced in these studies to validate their analytical methods. Laboratory norms are particularly useful when preexposure cholinesterase baselines are not available for a worker.

Asymptomatic employees (whose cholinesterase activities may already be inhibited) may thus be assigned a "working baseline" value: the arithmetic mean of a laboratory's normal values or the employee's current cholinesterase activity, whichever is higher. Values from four studies of cholinesterase levels in nonexposed human populations appear in Table XVI-8. [93,112-114]

Interpretation of cholinesterase assays should take into account the known nonoccupational sources of inhibition of cholinesterase activity. Such possibilities include liver disease, [115] pregnancy, [116] malignant neoplasia, [117,118] and tuberculosis. [118] Familial reduction in plasma cholinesterase activity was reported by Lehmann and Ryan [119] and by Kalow [120] and was subsequently found by Kalow and Genest [121] to be related to the presence of an atypical gene. About 1 in 3,000 individuals tested in a healthy Canadian population was homozygotic for this atypical gene [122] and thus could be expected to have a genetically determined deficiency in serum cholinesterase activity. The activity of erythrocyte cholinesterase has been found to be inhibited in certain pulmonary and extrapulmonary cancers [118] and in paroxysmal nocturnal hemoglobinuria. [123] Familial asymptomatic reduction in erythrocyte cholinesterase activity also has been reported. [124] The importance of these observations to susceptibility to organophosphorus insectide poisoning has not been determined.

Plasma and Erythrocyte Cholinesterase Analyses

Methods for determining plasma and erythrocyte cholinesterase activity may be classified as electrometric, manometric, colorimetric,

spectrophotometric, radiometric, titrimetric, or chromatographic.

Michel [29] developed a widely used electrometric method for cholinesterase analysis in 1949. The method depended on measurement of the quantity of acetic acid liberated during a fixed period of time (1-1.5 hours) by the action of cholinesterase on acetylcholine. Enzymatic activity was thus measured in terms of the change in pH of a buffered solution of sample plus substrate/unit time. The pH was determined with a glass electrode. Both erythrocyte and plasma cholinesterase activities were measurable. Correction tables were provided to adjust for nonenzymatic hydrolysis and to correct for variations in the rate of pH change with decreasing pH. The author compared the electrometric and the manometric methods by performing parallel analyses on 31 independent samples of plasma and 27 independent samples of erythrocytes from 12 persons. The standard deviations of the differences in cholinesterase activities determined by the two methods were reported to be 5.49% for plasma cholinesterase and 5.50% for that of the erythrocytes. Michel [29] stated that the electrometric pH method was preferable to the manometric one (discussed below) because of its simplicity, the minimum of required equipment, and its suitability for doing a large number of determinations in a relatively short time. Both the initial and the final pH readings required for each sample took 1 minute to perform.

Wolfsie and Winter [93] developed a micromodification of the Michel method [29] to adapt it to fingertip blood samples. The analytical procedure of Wolfsie and Winter, [93] however, is identical with that of Michel. [29] Witter et al [94] presented another modification of the Michel procedure. This method eliminated the initial pH reading, used

distilled water instead of a solution of saponin to hemolyze the erythrocytes, started the enzyme reaction by adding a mixture of buffer and acetylcholine to the diluted sample, and shortened the period of incubation from 90 to 60 minutes. The results were nearly identical with those obtained by the Michel method, but twice as many samples could be analyzed in the same period of time.

Witter [95] stated that the manometric technique was one of the most accurate and precise (to within ±1%) for the determination of plasma, erythrocyte, or whole blood cholinesterase activities. This method is based on the measurement of the amount of carbon dioxide liberated when acetic acid, produced by the enzymatic hydrolysis of acetylcholine, reacts with sodium bicarbonate. The author noted, however, that manometric techniques require 20-30 minutes to obtain a rate curve [95] and are thus too time-consuming for routine analysis.

Limperos and Ranta [96] described a rapid screening test for whole blood cholinesterase activity that could be used in the field without specialized equipment. In this visual colorimetric method, the change in pH resulting from the liberation of acetic acid from an acetylcholine-iodide substrate was estimated by the change in color of an indicator, bromthymol blue, after a 20-minute incubation with a drop of fingertip blood. Adjustments for temperature were not included but were subsequently proposed by Davies and Nicholls. [97] Separate determinations of erythrocyte and plasma cholinesterase activities were introduced in a modification by Fleisher et al [98] using different substrates specific for erythrocyte or plasma cholinesterase. Gerarde et al [99] adapted the basic visual colorimetric screening test by providing premeasured quantities of

stabilized reagents in capillary tubes. Forsyth and Rashid [125] used a field kit based on the colorimetric method of Edson [126] for the determination of the activity of cholinesterases in whole blood. WHO has sponsored field tests of this method. [127] While better adapted for field use than other methods, visual colorimetric techniques are either cumbersome, because of the requirement that the time necessary for a standard color change must be recorded for each sample, [98] or inadequate to determine separately the plasma and erythrocyte cholinesterases. [97,99]

Several investigators have described spectrophotometric methods for determining plasma, serum, whole blood, and erythrocyte cholinesterase activities. [100-104,112,128] Each method involves the hydrolysis of a substrate by plasma or erythrocyte cholinesterase, with measurement of the rate of loss of substrate [112,128] or the rate of appearance of hydrolytic products subsequently bound to indicators. [100-104] None of the spectrophotometric methods are as simple or as rapid as the electrometric methods, and few have been widely employed in laboratories.

Cholinesterase assays have also been performed using a 14C-labeled substrate, [105-107] a liquid membrane electrode highly selective for acetylcholine, [108] GLC, [109] titrimetric techniques, [95,110] or substrate-impregnated indicator papers. [111] The GLC, titrimetric, and liquid membrane electrode methods require more expertise than the electrometric methods. The radiometric micromethod developed by Winteringham and Disney [105-107] operates with very small samples and involves a simple counting technique to measure the appearance of labeled acetic acid but requires a counter and a supply of labeled acetylcholine.

Based on the foregoing discussion, the electrometric method of Michel [29] is recommended as a suitable method for plasma and erythrocyte cholinesterase analyses. This selection is made because it is the most widely documented method and is sufficiently precise. It requires ordinary laboratory equipment that is relatively inexpensive and simple to use. The Wolfsie and Winter [93] micromodification, when used in conjunction with the original electrometric method of Michel, [29] will provide sufficient precision in analysis without excessive bloodletting. This method has been automated. Details of the recommended method are presented in Appendix IV. Laboratories performing numerous or frequent cholinesterase assays may prefer to use a modified Ellman method in conjunction with an autoanalyzer. The pH-stat method is also considered an acceptable analytical method.

Environmental Levels

Few studies were found in which the skin and respiratory exposures of workers handling methyl parathion were measured. A study by Trefilov et al [77] was the only one found to report air levels of methyl parathion in manufacturing plants. Most samples were found to be below 0.1 mg/cu m, and very few reached 0.2 mg/cu m. Of the many opportunities for exposure during the performance of custom applications of methyl parathion, only cotton checking has been studied directly. [129-131] Indirect methods involving the monitoring of urinary metabolites have been used to assess the comparative exposures of different occupational groups to parathion. [92] The ranking of exposure potential derived from the latter study probably can be applied also to workers exposed to methyl parathion.

Three occupational exposure studies of cotton checkers were found.

[129-131] Cotton checkers, or scouts, typically enter recently sprayed fields to determine the effectiveness of an insecticide application in destroying target insects. This occupational group was selected because of its allegedly high exposure to dislodgeable foliar residues [129] and because more than 80% of the methyl parathion used domestically is applied to cotton. [9] According to Ware et al, [129] checkers move through sprayed foliage for up to 10 hours daily.

Quinby et al [131] examined methyl parathion exposures among cotton checkers in 1958. Methyl parathion was applied at the rate of 0.5 lb/acre with ground equipment under conditions of "high" relative humidity and temperatures ranging from 59 to 97 F. Exposure was determined for two test subjects during periods of 5-65 minutes, 1.5-3.5 hours, and 4-5 hours after the application. Gloves and cotton shirt sleeves showed the greatest contamination. Respirator pads showed no detectable quantities of methyl parathion by the analytical method used, which was sensitive to 20 μg for 1-hour samples and 10 μg for 2-hour samples. Contamination levels for leg and foot coverings were not reported, although much work by the checkers was done on hands and knees. One-hour exposures beginning 5 minutes after application resulted in an average retention of 2.69 mg/hour on gloves. For exposures during the periods 1.5-3.5 hours and 4-5 hours after application, the average rates of accumulation of methyl parathion on the gloves were 2.22 and 0.56 mg/hour, respectively. In trials performed during each postapplication interval, residues on gloves accounted for more than 80% of the total potential exposure reported. The authors stated that "blood cholinesterase" activity measured 24 hours after exposure of the checkers showed no significant inhibition. However, none should have been

expected, since opportunities for absorption were minimized (1) by the gloves, respirator, and clothing, (2) by the immediate change of clothing after the test exposure, (3) by the short exposure periods, which never exceeded 2 hours, and (4) by the absence of repeated exposures which could have resulted in cumulative inhibition of blood cholinesterase activities in checkers. The average total weight of methyl parathion extracted from garments worn by the checkers (gloves, shirtsleeves, T-shirts) declined with time. The total weights for the first, second, and third postapplication intervals averaged 3.2, 2.6, and 0.7 mg/hr, respectively. This decline was presumably due to both the absorption of methyl parathion by the foliage and the decay of the nonabsorbed fraction. Quantitative conclusions are difficult to draw from this study for two reasons. First, significant methyl parathion may have been lost from clothing during travel to the laboratory. The authors [131] were able to demonstrate such losses from artificially exposed garments saturated with saline to simulate sweat after incubation for 2-3 days, the approximate time that checker garments were in the mail. Second, it does not appear that the analytical method, the spectrophotometric technique of Averell and Norris, [84] measured methyl paraoxon separately from methyl parathion. Use of a method that measures the combined quantity of methyl parathion and methyl paraoxon would not be an accurate measure of the toxicologic hazard of methyl parathion exposure since the oxon form is the more toxic one to mammals. The half-life of dislodgeable foliar residues of methyl parathion was calculated by the authors to be "less than one hour." The significance of this half-life estimate for methyl parathion on cotton foliage is obscured, however, by the apparent failure to differentiate between residues of

methyl parathion and of methyl paraoxon.

Ware et al [129] examined the exposure of cotton scouts (checkers) to methyl parathion and to a mixture of parathion and methyl parathion in field studies. In each experiment, the plasma and erythrocyte cholinesterase activities of two volunteers were measured immediately before they entered sprayed fields of maturing cotton. The first experiment involved application of 1.0 lb of methyl parathion plus 4.0 lb of toxaphene in 5 gallons of spray mixture/acre. Canopy (top) foliage was dense and overlapping. Twelve aluminum foil sheets were placed in random horizontal positions on top of the canopy to determine the quantity of spray reaching the foliage. Urine was collected from the checkers at the time of entry into the sprayed fields and for 24 hours thereafter. Checkers entered the fields wearing fresh T-shirts and bluejeans at 3 minutes and at 4 hours after pesticide application. Portable air samplers were positioned just below the chin. Gauze patches were taped to the trousers at shin, thigh, and hip levels and to unprotected forearms. While in the field for 30 minutes, the subjects took four 100-leaf samples of cotton canopy and four 100-leaf bottom samples for subsequent foliar residue analysis. The report did not state whether checkers performed their usual task of opening cotton blossom squares to check for pests. Quinby et al [131] asserted that this latter task probably accounted for most of a checker's exposure. Hands of subjects were washed in hexane after each 30-minute test period. [129] Gauze patches and clothing were removed and sent to the laboratory. Analysis by GLC, using a flame photometric detector sensitive to phosphorus-containing substances, showed deposition of methyl parathion on the foil sheets of 0.17-1.99 lb/acre,

plus a "trace" of methyl paraoxon. Methyl parathion was most heavily deposited on the trousers and the hands of the checkers. When the subjects took canopy leaf samples, methyl parathion on the trousers averaged 15.9 mg, almost three times the amounts detected when samples of bottom leaves were collected. Entry into the fields 4 hours after spraying produced contaminations of hands and trousers during the collection of samples, but higher ones when bottom leaves were sampled. Of the gauze patches examined, those on thighs and hips held the highest amounts of methyl parathion. The airborne concentrations of methyl parathion were low during both the canopy and bottom leaf samplings at 3 minutes and 4 hours after application. For these trials, the highest value measured was 1.77 μg/cu m.

In a second experiment, Ware et al [129] used an aerial application of 0.5 lb of methyl parathion, 0.5 lb of parathion, and 2 lb of toxaphene in 5 gallons of spray/acre of mature cotton. The use of both parathion and methyl parathion in mixed active ingredient applications is commonplace. [10] After cholinesterase, paranitrophenol, and serum methyl parathion pretests, the same two test subjects who had taken part in the earlier experiments entered the fields for 30-minute periods beginning 10 minutes or 12, 24, 48, or 72 hours after application. [129] Neither gauze pads nor air samplers were worn in this experiment. Since the application was performed in the morning, test subjects were not in the fields during the hours of highest ambient temperature (high temperatures for the test days were 92-98 F, lows 62-68 F).

No significant depressions of plasma or erythrocyte cholinesterase activities were reported for subjects in either of the experiments, nor was

urinary PNP detected after exposure. [129] After the second 30-minute exposure in the first series of tests, serum parathion levels were 27 and 32 ppb for the two test subjects. Neither parathion nor methyl parathion was detected in serum following exposure in the second experiment. For the same reasons cited above, no significant inhibition of blood cholinesterase activity was expected under the circumstances. The authors estimated the total time in the field for cotton checkers in actual practice to be 5 hours/day and used this estimate to calculate 24- and 48-hour reentry exposure levels from the 30-minute exposure data. When entry was made 24 hours after application under these experimental conditions, it was estimated that 11.6 mg of the methyl parathion-parathion mixture had accumulated on hands and forearms, and 64.7 mg on clothing over a 5-hour exposure. The authors estimated that 3.6 μg of the mixture would be inhaled during this exposure. When the field was entered 48 hours after the application, estimated accumulations were 6.0 mg on hands and forearms and 45.2 mg on clothing, while approximately 1.8 μg of the parathion-methyl parathion mixture was inhaled. By assuming there was no absorption from the clothing and, because of the dryness of the residue from hands, forearms, and respiratory tract, the authors surmised that probably 5.8 mg are absorbed in a day with a 5-hour exposure (equivalent to 1 day of checking) when 24 hours elapsed between application and entry by the checker and 3.0 mg/day with an elapsed time of 48 hours. No data were reported to support the assumptions regarding the fraction of the insecticidal mixture absorbed by clothing, hands, forearms, and respiratory tract. It is unclear from the report how respiratory figures were calculated for the second series of trials, since no air sampling was

performed. No symptoms of systemic poisoning were reported in either series.

Ware et al [130] subsequently conducted a similar study in which four cotton checkers were exposed to methyl parathion for 5-hour working periods 24 hours after the last application. Methyl parathion was applied repeatedly to the test field at 5-day intervals for a total of four applications, each at the rate of 1 lb/acre, by high-clearance ground equipment. Subjects wore fresh T-shirts and blue jeans with an optional head covering. Portable air samplers, with the intake tubes attached to the upper front of the T-shirt of each subject, were used for 2.5 hours during the exposure period. The impingers were charged with ethylene glycol. The concentrations of methyl parathion in serum were determined before, during, and after the exposure period. Twenty-four-hour urinary paranitrophenol collections were performed before exposure and twice during the next 48 hours. Subjects simulated the activities normally performed by cotton checkers or entomologists, in addition to gathering leaf samples for residue analysis. Foliage was dense and was intertwined between rows, causing relatively high body contact and green stains on some parts of the clothing. No signs of systemic poisoning were observed. Physical activity at the prevailing environmental temperatures did cause sweating and dehydration. In tests immediately following the exposure period, no methyl parathion was detected in serum, nor were the cholinesterase activities of plasma or erythrocytes inhibited when measured by the Michel electrometric method. [29] The total amounts of paranitrophenol excreted in 48 hours by the four subjects were 0.15, 0.19, 0.44, and 1.20 mg, but the authors [130] cautioned that recoveries were inconsistent for the "lower" concentrations.

Again, the same type of data was absent in this report. When methyl parathion was recovered by hexane washes from clothing and from hands, the authors found the most methyl parathion (1.7 mg) and methyl paraoxon (39.0 μg) on the trousers. The discrepancy between these and the considerably greater quantities retained on clothing and hands in the earlier studies by Ware et al [129] were not discussed. Inhaled methyl parathion was estimated from the impinger data to be 1.2 μg over the 5-hour exposure, with an average pulmonary ventilation of 20 liters/minute assumed. The investigators concluded that 24 hours was a safe reentry interval for methyl parathion. This conclusion fails to recognize the many environmental variables and differences in the performance of applications that influence the decay rates of methyl parathion and methyl paraoxon on foliage and soil, as well as the amount which remains airborne. The data do, however, confirm the importance of wearing impervious gloves and fresh full-body clothing daily.

Arterberry et al [92] compared data from persons exposed to parathion in various job categories. These categories included mixing-plant personnel, part-time ground applicators, aerial application workers, commercial ground applicators, and workers in orchards. Erythrocyte and plasma cholinesterase and urinary paranitrophenol excretion were measured in a majority of these occupational groups. Generally, samples taken on the last day of mixing, heavy spraying, or other intensive contact with parathion were chosen to represent maximum exposure (period of exposure unspecified), and the results were compared with preexposure values. The ranges and the means of plasma cholinesterase activities for all job categories tested did not differ from the preexposure values. Similarly,

except for mixing-plant personnel, erythrocyte cholinesterase activities were lower than preexposure values. There was a 36% inhibition of erythrocyte cholinesterase activities in mixing-plant personnel, suggesting that low-level chronic exposures were responsible for this effect. The slower rate of erythrocyte cholinesterase reactivation [6,43] could have allowed its daily inhibition to exceed the rate of recovery, leading to a net reduction in erythrocyte cholinesterase activity. Paranitrophenol (a urinary degradation product of parathion, methyl parathion, fenitrothion, and EPN, and thus an index of exposure to these compounds) was found in five occupational groups. These, in order of decreasing paranitrophenol concentration in their urine, were commercial ground applicators, mixing-plant personnel, part-time ground applicators, aerial application workers, and workers in orchards. Results of this study were consistent with the findings of the California State Department of Food and Agriculture [132] which indicated that workers engaged in mixing, loading, and applying account for most of the reported severe occupational intoxications from pesticides.

Trefilov et al [77] studied clothing contamination and personal hygiene in a metaphos (methyl parathion) manufacturing plant. The authors found the highest degree of contamination of the special protective clothing of operators and mechanics in the chest area (16-190 mg/sq m/workday). For mechanics, trousers showed the highest contamination of the regular clothing, especially at the knees (640-720 mg/sq m/workday). Contamination of underwear ranged from 1 to 600 mg/sq m/workday. This latter finding is particularly significant for male workers because of the high absorbancy of parathion (and presumably methyl parathion) by scrotal

skin. [133] The authors also reported that showering with soap and water decreased the amount of methyl parathion in wrist washings from an initial range of 0.8-310 mg/sq m to 0.2 mg/sq m. Multiple skin washes from wrists, chest, forehead, and back of each operator and machinist confirmed the importance of dermal protection generally and of hand protection in particular. Dermal absorption was confirmed in the study by preexposure and postexposure erythrocyte and plasma cholinesterase tests on workers who wore gas masks.

Control of Exposure

Engineering controls and work practices for methyl parathion should have as their main objectives the control of vapor and aerosol concentrations, minimization of skin contact, and the prevention of fires. Closed systems and operator enclosures, properly operated and maintained, should be used where it is feasible to achieve all three of these objectives. Operations in which methyl parathion concentrates are poured or otherwise handled by workers should be eliminated, whenever possible, by transfer devices which minimize potential exposure. General room ventilation is necessary in methyl parathion-manufacturing and methyl parathion-formulating areas. Exhaust systems are needed at loaders, blenders, mixers, mills, packaging equipment, and at all other potential sources of vapor, spray, or dust containing methyl parathion. Liquid and dust exhaust systems must be designed so that neither the employees nor human and animal life in the surrounding area are endangered. Dust exhaust systems should be vented to a dust collector, not directly into the atmosphere. Exhaust air should not be recirculated. Detailed information

on the design and installation of methyl parathion vapor and dust exhaust systems should be sought from competent sources, such as ventilation engineers or industrial hygienists. Guidance for design can be found in Industrial Ventilation--A Manual of Recommended Practice, [134] or more recent revisions, and in ANSI Z9.2-1971. [135] Respiratory-protective equipment is not an acceptable substitute for feasible engineering controls but should be available for emergency purposes and for nonroutine maintenance and repair situations.

Methyl parathion is very unstable to heat [136] and may explode at 248 F (120 C). [136] The flashpoint of 80% methyl parathion in xylene is 115 F (46 C). [136] Structures in which methyl parathion is manufactured or stored should be designed to reduce the possibility of fire or the spread of fire. Overheated drums of technical product may rupture violently. [136] Heat and air currents will vaporize methyl parathion and cause contaminated particles to become airborne, producing highly toxic fumes and smoke. Heat also will promote conversion of methyl parathion to the corresponding oxon with an increase in toxicity. [136] Since water and chemicals used for firefighting may spread contamination over a wide area, efforts should be made to dike the run-off water, where possible, so as to prevent its entering sewers or streams. [136] Firefighting personnel should wear impervious gloves, hats, suits, and footwear, and use supplied-air respirators.

Firefighting procedures should be developed in advance, and local fire departments, as well as plant employees, should be informed of the hazards involved. Additional information on firefighting precautions appears in the Safety Guide for Warehousing Parathions. [136]

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

The American Conference of Governmental Industrial Hygienists (ACGIH) [137] proposed in 1969 that its recommended threshold limit value (TLV) for methyl parathion be set at 0.2 mg/cu m. Included was a "skin" designation to indicate that measures must be taken to minimize skin exposure so that the TLV is not invalidated. According to the 1971 TLV Documentation, [138] the basis for this level was the lower toxicity of methyl parathion than that of parathion observed in human and animal studies. However, the greater toxicity of the oxon derivative of methyl parathion was not addressed in the basis given for the TLV. The TLV for parathion had previously been set at 0.1 mg/cu m. References were made in the Documentation to two animal studies [33,43] and one human study. [139] The 1974 TLV [140] is unchanged from the 1971 TLV.

Gaines' study [33] cited in the ACGIH Documentation reported the oral and dermal LD50's of methyl parathion in rats. The oral LD50's for male and female rats were 14 mg/kg and 24 mg/kg, respectively, while they were 13 mg/kg and 3.6 mg/kg, respectively, for parathion. The dermal LD50 for methyl parathion in rats of both sexes was 67 mg/kg; the dermal LD50's for parathion were 21 mg/kg (males) and 6.8 mg/kg (females).

The study by Williams et al [43] cited by the committee was an oral experiment in which technical methyl parathion was administered in the diet to dogs in concentrations of 5, 20, or 50 ppm daily for 90 days. The authors reported that the 50-ppm concentration resulted in inhibition of both plasma and erythrocyte cholinesterases to 50-60% of control values.

However, although it was not noted in the Documentation, the erythrocyte cholinesterase activity was still declining at the end of the test period in the dogs exposed to both the 20-ppm and the 50-ppm concentrations in the diet. It is likely that during a treatment period somewhat longer than 90 days, the dogs fed 20 ppm would have experienced inhibitions of blood cholinesterases equal to that of the dogs fed 50 ppm and those fed 50 ppm would have shown still greater cholinesterase inhibitions. The 50-ppm concentration corresponds to approximately 70 mg/day for a 70-kg person.

The human study cited in the Documentation was one of a series performed by Moeller and Rider. [139] In this study, groups of five men each were given methyl parathion in corn oil orally in doses of 7, 7.5, 8, or 9 mg/day for 30 days. Even with the highest dose tested, both plasma and erythrocyte cholinesterase activities were between 80-100% of preexposure values.

The methyl parathion TLV was also supported by ACGIH with the statement that: "The safety record of methyl parathion is considerably better than that of parathion." [138] The significance of the dermal absorption route was recognized in the 1971 Documentation by the word "skin" immediately following the recommended atmospheric level. Text explaining the "skin" notation stated that "this attention-calling designation is intended to suggest appropriate measures for the prevention of cutaneous absorption so that the threshold limit is not invalidated."

No standards governing the safe handling of methyl parathion by the American National Standards Institute (ANSI) or by the International Standards Organization (ISO) were found. Methyl parathion is not mentioned in the 1969 documentation of MAC's in Czechoslovakia. [141] The only

standard found governing methyl parathion exposure in a foreign country was the MAC for the USSR, 0.1 mg/cu m. [142]

Several states currently regulate the formulation, distribution, and use of pesticides. Of these, California presently has the most comprehensive regulations. In 1974, the California Department of Food and Agriculture issued pesticide-worker-safety regulations as reported by Maddy [132] for "moderately toxic" (Category 2) and "highly toxic" (Category 1) pesticides, but established no MAC or TLV levels. Methyl parathion was included in Category 1. From the 1,474 pesticide-related occupational illnesses reported in California during 1973, the occupations "mixer-loader" and "ground applicator" were identified as most hazardous. [132] The single most hazardous activity was reported to be the pouring of concentrates. Since California had no manufacturers (but many formulators) of methyl parathion in 1973, none of the reported illnesses could have been associated with the manufacture of technical grade methyl parathion. Thus, the identification of the most hazardous pesticide occupations bears that limitation, along with the absence of denominators for the high-risk job categories.

The California regulations applicable to pesticides in toxicity Category 1 provide for medical supervision, biologic monitoring, closed mixing and loading systems, and specific work practices, including supervised training, emergency procedures, minimum employee age for certain operations, changing room facilities, personal protective clothing and equipment, and restrictions on working alone. [132]

Summaries of activities of the various states in controlling the use of pesticides are presented in Appendices VI and VII.

Basis for the Recommended Environmental Standard

The recommended standard for methyl parathion includes (1) work practices and engineering controls designed to prevent absorption of methyl parathion (especially through the skin), (2) procedures for periodic biologic monitoring to screen overexposed workers, and (3) a workplace environmental limit. In addition to these components of the recommended standard, the use of personal protective equipment and clothing also is recommended to reduce exposure of employees to methyl parathion by inhalation and dermal routes of entry. The toxicity of methyl parathion by these routes of entry has been reported by a number of investigators. [16,17,76,143]

The study by Maibach et al [133] used 14C-labeled malathion, carbaryl, and parathion with urinary radioassays to determine the dermal penetration of these pesticides when applied to different sites of the human body. All anatomic sites studied--forearm, palm, ball of the foot, abdomen, hand dorsum, fossa cubitalis, scalp, jaw angle, postauricular area, forehead, ear canal, axilla, and scrotum--showed significant penetration of the substances tested. While absorption rates and efficiencies derived in this study are not directly applicable to methyl parathion, it is likely that methyl parathion would also be absorbed from all these regions. Therefore, personal protective equipment and clothing, which will limit exposure of most, if not all, portions of the body, are recommended. Goggles and faceshields are recommended to limit eye and facial exposure to the pesticide. The use of respirators may be necessary during emergencies and during installation, testing, and maintenance of engineering controls.

Work practices and engineering controls afford additional protection to the worker by minimizing inhalation of, or exposure of the skin to, methyl parathion. Work practices are recommended to control or reduce exposure resulting from spills, splashes, leaks, or other inadvertent release of methyl parathion into the workplace environment. Engineering controls, such as the use of closed manufacturing, formulating, mixing, and loading systems, should further reduce exposure resulting from accidental release of the pesticide in the workplace.

Employees should be informed that even small amounts of methyl parathion can be hazardous and should be instructed as to the proper workplace practices. The use of good work practices and of personal protective equipment and clothing may be affected by behavioral attitudes and environmental and other conditions. Increased environmental temperatures or extremely humid environments may cause workers to avoid using certain protective equipment. When workers become fatigued as a consequence of long workdays, which may be encountered during peak formulation and application seasons, they may fail to use good work practices. Instructions to workers, therefore, should emphasize that deviation from the recommended work practices, including improper use of protective equipment and clothing, even for brief periods of time, may be dangerous.

Compliance with these recommended work practices and engineering controls as well as with the recommended workplace environmental limit for methyl parathion should limit worker exposure to this pesticide. However, available data are inadequate to establish the significance in the causation of occupational poisoning by methyl parathion of mixed active

ingredient formulations or succesive exposures to residues of single- or multiple-ingredient formulations containing methyl parathion. Exposure of the worker to anticholinesterase compounds, in addition to methyl parathion, may pose a hazard because of the cumulative effects of cholinesterase inhibition. To assess these effects in asymptomatic persons, individual monitoring is necessary.

The method of personal biologic monitoring best suited for detection of asymptomatic, progressive poisoning by anticholinesterase compounds is the periodic assay of erythrocyte cholinesterase activity. Erythrocyte cholinesterase is found in all human beings, and its activity is relatively consistent and reproducible. Determination of erythrocyte cholinesterase activity can give guidance to the physician in deciding whether an exposed worker requires extended observation, removal from the job, treatment as an outpatient, or intensive treatment. This enzyme is also affected by other organophosphorus pesticides and, thus, will aid in determining whether overexposure from other pesticides commonly found in areas of exposure to methyl parathion has occurred.

It should be emphasized that biologic monitoring will not prevent poisoning but does provide an indication of the degree to which an individual has been exposed. In addition, it may help to identify those workers exposed to low doses of methyl parathion who presently are asymptomatic but may become symptomatic because of possible cumulative effects of repeated exposure to the pesticide.

To be of protective value, biologic monitoring must be performed frequently to detect short-term increases of susceptibility to further exposure caused by changes in work activities, defective equipment,

carelessness, and changes in environmental influences. The scheme of biologic monitoring proposed by the California State Department of Health (see Appendix VI and references 132 and 144) appears inadequate in one respect: it suggests a longer interval between consecutive examinations of blood for workers exposed to Category 1 or 2 compounds for up to 2 days/week than for those exposed 3 days/week or more, without having demonstrated lessened hazard to the first group or any other supporting evidence for this difference. NIOSH recommends an interval between tests of 2 weeks for mixers, loaders, ground applicators, aerial applicators, flaggers, maintenance and janitorial personnel, checkers entering fields still wet from an application, and for manufacturing or formulating employees not working with closed production, mixing, blending, transfer, or packaging systems. If any workday exceeds 12 hours, an employee covered by the 2-week testing interval should be tested at 1-week intervals until a week passes in which no workday exceeds 12 hours. NIOSH recommends that all other employees occupationally exposed to methyl parathion, including but not limited to those indicated in Table XVI-3 but not assigned to the above 2-week interval between blood samples, be tested at 4-week intervals. Times specified here should be construed as maximum test intervals which should be shortened when conditions warrant.

A workplace environmental limit for methyl parathion has been chosen on the basis of a careful review of the available literature on the pharmacologic and toxicologic effects of this and related pesticides on animals and on humans. The literature on the toxic effects on humans of occupational exposure to methyl parathion is, however, incomplete. In addition, information is unavailable on the experimental effects of human

respiratory exposure to methyl parathion. Moreover, data which would indicate the fraction of inhaled methyl parathion actually absorbed are unavailable from epidemiologic or other studies of workers exposed to this pesticide in an occupational environment. No data were found which would allow estimation of the deposition of droplets of methyl parathion in the various sections of the respiratory apparatus from the environmental air. Data are scanty on how factors such as airstream behavior, particle size and shape, and physiologic parameters affect deposition of methyl parathion in the lungs. The mechanism by which ciliated epithelium affects the clearance of methyl parathion from the lungs is poorly understood. Furthermore, there are inadequate data on the extent of individual variation in impaction, coalescence, and absorption of particulates within the tracheobronchial tree and the alveoli of the lungs.

In contrast, the information on parathion is more extensive than that on methyl parathion and includes inhalation studies with humans [145] and with rats and dogs (Unpublished report, Edgewood Arsenal, Md, 1976), as well as studies on the toxicity of parathion by other routes in other species. These studies were used by NIOSH to recommend a TWA workplace environmental limit of 0.05 mg/cu m for parathion. Reports have been found that compare the effects of methyl parathion with those of parathion on rats [33,35,37,39,138,146] and on humans. [20-28]

Table V-1 presents a summary of several studies wherein the acute toxicities to rats of methyl parathion were compared with those of parathion.

TABLE V-1

COMPARISON OF ACUTE TOXICITIES OF PARATHION AND METHYL PARATHION IN RATS

Routes of Exposure	Sex	LD50 (mg/kg) or LC50 (mg/l)		Toxicity Ratio	Reference
		Parathion	Methyl Parathion		
Inhalation (1 hr)	Female	0.115	0.2	1.7	35
po	"	3.6	24	6.7	33
	"	7.9	18	2.3	37
	Male	13	14	1.1	41
	"	13	14	1.1	33
	"	14	12	0.9	37
iv	Female	4.5	14.5	3.2	37
	Male	6.4	9.0	1.4	37
ip	-	5.5	3.5	0.6	146
	Female	2.7	7.4	2.7	42
	Male	4.8	6.8	1.4	42
	Male (adults)	3.6	5.8	1.6	39
	Male (weanlings)	1.5	3.5	2.3	39

Although there is considerable variation between the ratios of toxicities found by different authors, the data show that methyl parathion is generally less toxic than parathion. A sex-related variation is also apparent. This agrees with the observation of Hayes [147] that the rat shows a particularly marked variation between the sexes in its response to chemicals. Variability in responsiveness to drugs and chemicals is not uncommon in animals. It may be related to inherent differences in enzyme activation and inactivation mechanisms, to differences in experimental

designs and procedures between laboratories, or to the differences in purity of the chemical used.

However, these data indicate a trend in a number of acute toxicity studies carried out in rats which, based on toxicity ratios, show that methyl parathion is less toxic than parathion. This trend was confirmed by Newell, [37] who showed that methyl parathion was considerably less toxic than parathion in female rats administered the insecticide by oral, intravenous, dermal, and inhalation routes. In the same study, methyl parathion was reported to be also less toxic in male rats by the intravenous and dermal routes; however, methyl parathion was almost seven times more toxic than parathion by inhalation. The methyl parathion used in Newell's study was stated to have been 70-80% pure, whereas the parathion was said to have been 88-94% pure. There is the possibility, then, that the methyl parathion may have contained approximately 15% more of some comparatively toxic contaminant than the parathion. Furthermore, the fact that Newell's data for the inhalatory toxicities of parathion and methyl parathion for female rats agrees reasonably well with those of Kimmerle and Lorke, and that only those estimated for parathion for male rats differ greatly from those of the latter authors, raises a question about the validity of Newell's results for the male rat. These two areas of uncertainty about Newell's study lead NIOSH to feel uncomfortable with Newell's conclusion on the toxicity of parathion for male rats exposed to the insecticide by inhalation.

The series of studies by Rider and his colleagues [20-28] compares the anticholinesterase activity of parathion and methyl parathion in humans. These data show that the oral doses of methyl parathion and

parathion required to reduce erythrocyte cholinesterase activities by 25-30% in men are about 30 mg/day and 7.5 mg/day, respectively. These figures lead to an estimate that methyl parathion is one-fourth as toxic as parathion. By applying this estimate to the recommended environmental limit of 0.05 mg/cu m for parathion, a level of 0.2 mg/cu m for methyl parathion is derived. This is the same level as the TLV currently recommended by the ACGIH. NIOSH recognizes the limited value of developing an occupational exposure limit from comparative oral data in humans and toxicity data in rats and in dogs. Nonetheless, in the absence of solid evidence that it would be unsafe, and on the basis of the relatively safe work history of methyl parathion, NIOSH recommends a TWA workplace environmental limit of 0.2 mg/cu m.

It should be noted that the contribution to human toxicity of isomers of the oxon form of methyl parathion has not been considered in development of the proposed standard, because of the scarcity of information on the occurrence of these forms of the parent substance. Adherence to the recommendations in this standard on work practices and personal protective equipment and clothing will help to reduce exposure to these more toxic analogs as well as to the parent compound.

VI. WORK PRACTICES

Occupational pesticide exposure may occur by skin penetration (including through cuts and abrasions), through inhalation, and by ingestion. [148] Methods for preventing exposure by these routes have been discussed by several investigators and groups interested in occupational safety and health. [12,127,142,148-158]

According to Wolfe, [149] over 97% of the pesticide to which the body is subjected during most application processes is deposited on the skin. Wolfe [149] stated that, in parathion spraying operations, skin exposure was potentially 950 times greater than respiratory exposure. Feldmann and Maibach [159] indicated that the spraying or dusting of pesticides may result in the deposition on exposed skin surfaces of an amount of pesticide 20-1,700 times greater than that which reaches the respiratory tract. Studies by Nemec et al [76] showed that as much as 10 mg of methyl parathion was deposited on the arms and hands of cotton checkers entering a field 2 hours after spraying with ULV equipment. The ULV technique involves application of volumes of 0.5 gallon or less/acre. This technique was reported [160] to deposit more insecticide on crops than higher-volume, water-emulsion sprays and to provide longer residual toxicity. Exposure for a 5-minute period at 2, 24, and 2 hours, respectively, after three consecutive weekly ULV applications to the same field resulted in erythrocyte cholinesterase inhibition of approximately 30% (from 90 to 60% of baseline). From these studies, [76,149,159] it is evident that a program of sound work practices, including the use of personal protection

items, must be followed to minimize skin exposure to methyl parathion.

Wolfe [161] recommended that long-sleeved outer clothing, such as coveralls, be washed daily. The author noted that rubberized or plastic waterproof clothing may be too uncomfortable for outside use because of trapping and absorption of body heat. Wolfe [161] also recommended unlined rubber gauntlet gloves, a wide-brimmed waterproof hat, and waterproof shoes or boots. According to the author, use of goggles and a respirator would offer protection from absorption of pesticide through facial skin. If high environmental temperature precludes the use of such items, other means of protection must be used.

All equipment, surfaces, and objects that become contaminated with methyl parathion must be decontaminated with 5% sodium carbonate, or with solutions of equivalent or superior decontaminating capability, to prevent employee exposure. Finley et al [162] reported that alkaline media hydrolyze methyl parathion to PNP. It has been observed [12] that periodic and emergency decontamination procedures utilizing strong alkaline solutions are commonly accepted practices in methyl parathion industries. Finley and Rogillio [163] and Finley et al [162] found that machine washing of cotton clothes contaminated with methyl parathion was effective in reducing residues. Normal laundering removed 99% of the methyl parathion applied to cotton-polyester fabric and 93% of that applied to an all-cotton fabric. [163]

A second important occupational route of entry for methyl parathion is the respiratory tract. Since high levels of airborne methyl parathion may be encountered in uncontrolled atmospheres, [77] it is necessary that filtered air enclosures or personal respiratory protection be utilized as

specified in Chapter I whenever airborne concentrations cannot be limited by engineering controls to the recommended workplace air level.

A third route of methyl parathion exposure is the oral route. Every effort must be made to avoid contamination of foodstuffs, tobacco products, and other materials that are placed in or near the mouth. Prohibiting the carrying of food, tobacco products, gum, and candy, and requiring that hands and face be washed before eating and smoking are accepted practices in methyl parathion industries. [12]

Methyl parathion must never be stored in food containers or handled with food-dispensing equipment. This requirement is necessary to prevent poisoning of individuals unaware of the presence of methyl parathion or its residues.

Wolfe et al [164] and Mail et al [165] discussed the health problems presented by discarded pesticide containers and explained the necessity for decontaminating and destroying them. Information on proper methods of disposal is readily available. [37,165,166] Such methods are routinely practiced by methyl parathion formulators and applicators. [12]

Hayes [127] stated that employees exposed to insecticides should be informed of the pertinent hazards. Industrial experience indicates that written information on insecticides is often unavailable at the worksite. However, it is generally agreed that informing employees of the hazards from methyl parathion exposure is extremely important, [12] especially in view of the absence of exposure-limiting signs or symptoms early in the course of methyl parathion intoxication.

VII. RESEARCH NEEDS

Several aspects of current knowledge regarding the acute and chronic toxicities of methyl parathion need to be verified or extended. Studies should be performed to determine the effects of long-term exposure to methyl parathion, to methyl paraoxon, and to methyl parathion isomers. The concentration of methyl paraoxon and the S-alkyl isomer of methyl parathion in technical solutions, formulations, environmental residues, and air should be determined. Inhalation exposures due to different methods of application should be quantified. Although many studies have been reported on parathion, there is limited data on the absorption, distribution, metabolism, and inhalation toxicity of methyl parathion. Epidemiologic studies of occupationally exposed populations should be designed to develop more accurate and complete data on risk.

Of particular value to the improvement of existing work practices and of environmental monitoring would be (1) research toward providing a breakthrough indicator for respirator cartridges and canisters, (2) assessment of the effectiveness of soap and water for removing methyl parathion from skin, (3) determination of the protection afforded by different materials used for impervious protective clothing, (4) investigations into the contribution to methyl parathion toxicity of methyl paraoxon in occupational environments, (5) effects of elevated ambient temperatures on the absorption and toxicity of methyl parathion, and (6) research regarding the feasibility of using membrane filters for sampling

airborne methyl parathion.

Also of significant value would be investigations into improved biologic monitoring techniques.

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IX. APPENDIX I

SAMPLING METHOD FOR METHYL PARATHION

The recommended sampling method is based on the methods described by Miles et al, [167] and on that appearing in the NIOSH Manual of Analytical Methods. [82] As stated previously in Chapter IV, the sampling efficiency and the overall precision of the recommended sampling and analytical method are not completely known. In addition, the Environmental Protection Agency has withdrawn the impinger (with ethylene glycol) sampling method from its pesticide manual (RH Hill Jr, written communication, March 1976). However, the recommended method remains the best one presently available for collecting and determining the concentration of methyl parathion in air.

Atmospheric Sampling

When sampling is performed for determination of compliance with the recommended workplace air standard, the sample shall be taken within the breathing zone of the exposed employee to ascertain the employee's actual exposure to airborne methyl parathion. 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 the sample collection.

(a) Equipment

The sampling train consists of a midget impinger filled with 15 ml of ethylene glycol, an absorption tube, and an air pump.

(1) Midget impinger: All portions of the impinger which may contact the collection medium or the air stream before collection is effected must be made of glass. The collection medium is ethylene glycol. The ethylene glycol used must be free of substances that will produce interfering peaks upon hexane extraction and subsequent gas-liquid chromatographic (GLC) analysis. Consequently, the only ethylene glycol suitable is that which has been preextracted and found to be free of interfering substances by GLC with a flame photometric detector.

(2) Absorption tube: An absorption tube, loosely packed with a plug of glass wool, is inserted between the exit arm of the impinger and the air pump to protect against splash-over or water condensation.

(3) Air pump: Any air mover capable of drawing the desired flowrate through the impinger may be used, so long as the flowrate does 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 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.

(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. How often the calibration must be performed is dependent on the use, care, and handling of the pump. 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 both before they are used in the field and after they have been used to collect a large number of field samples. The accuracy of calibration is dependent on the type of instrument used as a reference. The choice of calibration instrument will depend largely upon where the calibration is to be performed. For laboratory testing, primary standards such as a spirometer or 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 appear below. 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 a midget impinger, the pump must be calibrated while operating with a representative midget impinger in line. The calibration train thus consists of a soapbubble meter, a midget impinger, a pressure gauge capable of measuring 20 inches of water, and an air pump.

(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. Then the inside of the soapbubble meter is moistened by immersing the buret in the soap solution and drawing bubbles up the inside until they are able to travel the entire buret length without bursting.

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

(4) A water manometer is checked to ensure that the pressure drop across the sampling train is maintained at approximately 12 inches of water at 2.8 liters/minute.

(5) A soapbubble is started up the buret, and the time it takes the bubble to move from one calibration mark to another is measured with a stopwatch.

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

(7) Calibration data which are recorded include the volume measured, elapsed time or number of strokes, pressure drop, air temperature, atmospheric pressure, serial number of the pump, date, and name of the person performing the calibration.

(c) Sampling Procedure

Breathing zone samples representative of the individual employee's respiratory exposure are collected with the midget impinger by fastening the impinger to a coat lapel or shirt collar, or by holding the impinger near the face of the employee during the sampling period. The duration of sampling shall be such that a concentration of 10% of the recommended environmental limit specified in Chapter I, Section 1(a), may be detected accurately by the recommended analytical method. An air sample of at least 50 liters must be taken. The temperature and pressure of the atmosphere being sampled are measured and recorded.

After a sample is taken, the impinger stem is removed and washed with 2-5 ml of ethylene glycol. This wash solution is included in the impinger, and the amount of washing solution recorded. The top of the impinger is sealed tightly with a plastic stopper. The impinger is placed upright in a carrying case, with care taken to prevent losses because of spillage or evaporation. The trapped methyl parathion (and methyl paraoxon, if present) is extracted into hexane and analyzed as described in Appendix II. Other collection methods shown to be equivalent or superior may be used.

X. APPENDIX II

ANALYTICAL METHOD FOR METHYL PARATHION

The method presented in the _NIOSH Manual of Analytical Methods_ [82] for analysis of parathion (ethyl) in air is recommended for the analysis of methyl parathion.

Principle of the Method

Methyl parathion in workplace 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 solution of methyl parathion in hexane is concentrated and subjected to GLC analysis using a phosphorus-specific flame photometric detector.

Range and Sensitivity

The linear range of the flame photometric detector is 0.5-25 ng for methyl parathion. For a 50-liter air sample, carried through the following procedure to solution in 5 ml of hexane, 2 µl of which is injected into the GLC, the range of workplace air concentrations over which analysis is linear is 25-1,250 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 GLC.

Interferences

Phosphorus compounds having retention times close to that of methyl parathion will interfere with the analysis. The equipment used must be scrupulously cleaned to remove any traces of phosphate detergents. Glassware should, in addition, be rinsed with hexane immediately prior to use.

Advantages and Disadvantages

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

(b) 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 parameters. Contamination can occur easily through equipment and reagents. If interfering compounds are anticipated, a lengthy cleanup procedure is required.

Apparatus

(a) Forceps.

(b) Glass stirring rods.

(c) Separatory funnels, 125-ml.

(d) Beakers, 100-ml.

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

(f) Glass wool, silanized.

(g) Hot water bath.

(h) Kuderna-Danish evaporator concentrator, consisting of a 125-ml Erlenmeyer-type flask, 3-ball Snyder column, and 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-liquid chromatograph, with attendant equipment, including a phosphorus-flame photometric detector.

(n) Gas-liquid chromatography column, 6-ft x 4-mm ID, borosilicate glass (silanized), 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 (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 conditioned by heating 2-4 days at 240-250 C under nitrogen flowing at 60 ml/minute, then primed by repeated injections of standard methyl parathion solution under the conditions of analysis given below. Column 3 is conditioned by heating 12 hours at 225-230 C under nitrogen flowing at 60 ml/minute. Column 4 is conditioned for at least 3 days at 245 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 ID glass tubing) is then attached 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 20M column is subsequently removed.

Reagents

(a) Ethylene glycol, interference-free.

(b) Hexane, interference-free.

(c) Distilled water, interference-free.

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

(e) Anhydrous sodium sulfate.

(f) Methyl parathion of known purity.

Procedure

(a) The sample in 17-20 ml of ethylene glycol is transferred to a 125-ml separatory funnel. (The reagent quantities below apply to a sample in 20 ml of ethylene glycol and must be scaled for different volumes of collection media). 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.

(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. When the extract has eluted, 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 ml. Remove the assembly from the bath and, after it is cool, 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, dilute to exactly 1.0 ml, and stir.

(e) Inject an aliquot of the hexane solution into the GLC 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 temperature	235 C
Switching valve temperature	235 C
Carrier gas (nitrogen) flow	60 ml/minute

The retention times (relative to methyl parathion) at these conditions for methyl parathion and some interfering organophosphorus insecticides are shown in Table X-1.

TABLE X-1

RELATIVE RETENTION TIMES OF METHYL PARATHION
AND OTHER ORGANOPHOSPHORUS (OP) INSECTICIDES

OP Compound	Column 1	Column 2	Column 3	Column 4
Methyl parathion	1.00 (3.2 min)	1.00 (6.2 min)	1.00 (4.0 min)	1.00
Methyl paraoxon	0.77	1.13	1.20	1.11
Ethyl parathion	1.37	1.28	0.85	1.33
Ethyl paraoxon	1.05	1.45	1.04	1.47
Amino parathion	1.42	1.00		
Dursban	1.37			
Fenthion	1.33			
Ruelene		1.29		
Phosphamidon				1.36

Adapted from reference 82

The solvent-flush sample injection technique is recommended. Duplicate injections should be made. The hexane which precedes the methyl parathion and methyl paraoxon should be vented so that the detector flame is not extinguished. The conditions of the run should be such that no methyl parathion is lost during the venting process.

(f) By comparison to standard curves for methyl parathion, the average of the area under the methyl parathion peak is converted to the amount (ng) of methyl parathion seen by the detector.

Calibration and Standards

(a) Prepare at least three standard solutions in the concentration range 100-10,000 ng/ml from a stock solution of methyl parathion in hexane.

(b) Make duplicate injections of aliquots of each methyl parathion standard solution and determine the peak areas.

(c) Plot the amount (ng) of methyl parathion seen by the detector vs the peak area. A straight line passing through the origin should result. If these conditions are not observed, 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 in order to monitor detector sensitivity.

Calculations

(a) Determine the total weight (ng) of methyl parathion present in the sample:

$$\text{Sample weight of methyl parathion (ng)} = \text{ng(0)} \times \frac{\text{Soln vol}}{\text{Inj vol}}$$

where:

ng(0)	=	nanograms of methyl parathion determined from calibration curve based on peak area responses
Soln vol	=	volume in μl of the final hexane solution
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 (25 C, 760 mmHg):

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

where:

V(s) = volume of air in liters at 25 C, 760 mmHg

V = volume of air in liters as measured

P = barometric pressure in millimeters of mercury

T = temperature of air in degrees centigrade

(c) The concentration of methyl parathion (or methyl paraoxon) can be expressed in ng/liter or μg/cu m:

$$\mu g/\text{cu m} = \text{ng/liter}$$

or

$$\mu g/\text{cu m} = \frac{\text{total ng}}{V(s)}$$

XI. APPENDIX III

DIAGNOSIS AND MEDICAL MANAGEMENT OF ORGANOPHOSPHORUS INTOXICATION

The text appearing immediately below is excerpted from a publication entitled "Prevention and Management of Organophosphate Poisoning." [168] This material, which was approved in 1970 by the AMA Committee on Occupational Toxicology of the Council on Occupational Health, originally appeared in the Journal of the American Medical Association in 1971.

Diagnosis

"A diagnosis of organophosphate intoxication is based primarily on a definite history of exposure to an organophosphate six 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 cholinesterase 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 cholinesterase 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 cholinesterase determination should

state the units involved along with the appropriate normal range. Based on the Michel method the normal range of red blood cell cholinesterase 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 cholinesterase 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 cholinesterase test may be necessary to establish a definite diagnosis.

"Cholinesterase is an enzyme which hydrolyzes acetylcholine. Two types are clinically significant: The first is true or acetyl cholinesterase, found principally in nervous tissue and in the red blood cell; the other, plasma or pseudo cholinesterase, 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 cell 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 cholinesterase regenerates at approximately 1% per day, whereas the enzyme in the plasma regenerates at a more rapid rate, approximating 25% in the first seven to ten days.

"Circulating red blood cell and plasma cholinesterase 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 cholinesterase values drop to 25% to 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 cholinesterase depression should not be allowed to return to work with organophosphate pesticides until his

cholinesterase 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 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 to 4 mg of atropine promptly should be given intravenously. *This dose is approximately ten times the amount which is administered for other conditions in which atropine is considered therapeutic* (emphasis in text). This dose should be repeated at five to ten minute intervals until signs of atropinization appear (dry, flushed skin, tachycardia as high as 140 beats per 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 (Protopam) chloride, is a commercially available antidote which complements atropine and hastens the reactivation of cholinesterase enzymes. For adults, in the moderate to severe case, it should be used along with atropine, injected intravenously as an initial dose of 1 gm at a rate not in excess of 500 mg/minute. After an hour, a second dose of 1 gm 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 to 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 to 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 cholinesterase 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 FOR BIOCHEMICAL DETERMINATION OF CHOLINESTERASE ACTIVITY IN BLOOD

Although NIOSH recommends only erythrocyte cholinesterase determinations for routine cholinesterase tests, plasma cholinesterase may be screened in the same blood samples as a further diagnostic indicator. The method of Wolfsie and Winter, [93] a micromodification of the Michel method, [29] is the procedure recommended for the measurement of both erythrocyte and plasma cholinesterase activities.

Reagents

All reagents should be at least ACS reagent grade.

(a) Buffer solutions

Prepare each according to the following directions, noting that pH will decrease over a period of several weeks. The pH should be checked before a solution is used, and, if it has dropped more than 0.03 pH units, the solution should be discarded and a fresh one prepared.

(1) Erythrocyte

For 1 liter of buffer, dissolve 4.1236 g sodium barbital (0.02 M), 0.5446 g potassium orthophosphate, di-H (0.004 M), and 44.730 g 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 add distilled water to a volume of 1 liter. The pH should be 8.10 at 25 C.

(2) Plasma

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

(b) Acetylcholine substrates

A few drops of toluene are added to each acetylcholine substrate solution as a preservative, and the solutions are kept refrigerated when not in use. These solutions should not be kept for more than a week.

(1) Erythrocyte

Prepare a 0.11-M acetylcholine chloride solution (2.000 g in 100 ml of distilled water).

(2) Plasma

Prepare a 0.165-M acetylcholine chloride solution (3.000 g in 100 ml of distilled water).

(c) Saponin solution

For both plasma and erythrocyte cholinesterase determinations, prepare a 0.010% saponin solution (100 mg in 1,000 ml of distilled water).

Apparatus

(a) Centrifuge capable of 3,500 rpm and of 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.

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

(f) Heparinized capillary tubes.

(g) A Bunsen burner.

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 one end free by 1-1.25 inches to permit flame-sealing of the tip of the tube without overheating the blood sample.

The finger should be pricked deeply and care should be taken to collect only free-flowing drops of blood to guard against the initiation of the clotting process before the blood contacts the heparin on the wall of the capillary.

One end of the capillary is plugged with solid (room temperature) paraffin and the other (free) end is sealed in the flame of a Bunsen burner. The capillary may now be 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 the equivalent. When the sample has been so treated, it may be shipped to a laboratory, if necessary, or stored for several days (preferably in a refrigerator) without appreciable change.

Analysis

For analysis, the capillary is cut cleanly with a sharp ampule file. From the packed-cells 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) into 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 transfer of 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 is discharged into 1.0 ml of distilled water, the Sahli pipet being rinsed into the solution (three times) as with the erythrocytes.

Erythrocyte Cholinesterase Assay

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

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

(c) Two-tenths milliliter of 0.11 M acetylcholine solution is added with rapid mixing; the time is recorded.

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

The beaker containing the solution should be shaken when the glass electrode is introduced to speed equilibration.

Note: Erythrocyte buffer solution is designed to yield a pH of 8.00

after the addition of hemolyzed human erythrocytes.

Plasma Cholinesterase Assay

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

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

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

(d) Two-tenths milliliter of 0.165 M acetylcholine solution is added with rapid mixing.

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

Calculations

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

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

where:

pH(i) = initial pH

pH(f) = final pH

t(f) - t(i) = time elapsed in hours between reading pH(i) and reading pH(f)

b = nonenzymatic hydrolysis corresponding to pH(f)

c = correction for variations in delta pH/hour with pH, corresponding to pH(f)

The b and c correction factors are given in Table XII-1. [
Average baseline values of erythrocyte and plasma cholinesterase activit
determined by this method for healthy nonexposed men and women, are give
in Table XII-2. [93,112]

TABLE XII-1

CORRECTION FACTORS FOR USE IN THE EQUATION FOR DELTA pH/HOUR

pH(f)	Erythrocyte Cholinesterase Corrections		Plasma Cholinesterase Corrections	
	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	0.01	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 reference 29

TABLE XII-2

MEAN BASELINE ERYTHROCYTE AND PLASMA CHOLINESTERASE VALUES IN MEN AND WOMEN (DELTA pH/HR)

	Erythrocyte Cholinesterase	
	Men	Women
Mean	0.861	0.843
	Plasma Cholinesterase	
Mean	0.953	0.817

Adapted from references 93 and 112

The average erythrocyte cholinesterase activity value for men is drawn from Wolfsie and Winter. [93] The value for women uses the product of the average erythrocyte cholinesterase activity figure for men [93] times the ratio (of mean delta pH/hour for women to mean delta pH/hour for men) formed from the data of Rider et al. [112] The use of the data from Wolfsie and Winter [93] allows for increased packing of erythrocytes in the capillary tubes above that obtained in more usual types of centrifuge tubes as well as for possible contamination of erythrocytes by plasma. Plasma cholinesterase values were selected from Rider et al, [112] since their larger data base probably provides a closer approximation of the true population mean of normal values for plasma cholinesterase activity. For the same reason, their data appear to provide the most reliable women/men ratio for erythrocyte cholinesterase activity.

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 a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

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

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

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

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

(c) Section III. Physical Data

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

(d) Section IV. Fire and Explosion Data

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

(e) Section V. Health Hazard Information

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

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

Skin Contact--single short contact, no adverse effects likely; prolonged or repeated contact, possibly mild irritation.

Eye Contact--some pain and mild transient irritation; no corneal scarring.

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

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

(f) Section VI. Reactivity Data

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

(g) Section VII. Spill or Leak Procedures

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

(h) Section VIII. Special Protection Information

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

(i) Section IX. Special Precautions

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

(j) Signature and Filing

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

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

MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION

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

II HAZARDOUS INGREDIENTS

MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA

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

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	

FLAMMABLE LIMITS IN AIR, % BY VOL.	LOWER		UPPER	

EXTINGUISHING MEDIA	
SPECIAL FIRE FIGHTING PROCEDURES	
UNUSUAL FIRE AND EXPLOSION HAZARD	

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN:

INHALATION:

INGESTION

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY STATEMENTS

OTHER HANDLING AND STORAGE REQUIREMENTS

PREPARED BY

ADDRESS:

DATE:

XIV. APPENDIX VI

SUMMARY OF ACTIVITIES OF THE STATE OF CALIFORNIA IN CONTROLLING USE OF PESTICIDES, 1974

Under the California regulations, [132] employers must arrange medical supervision for all workers who mix, load, apply, or flag Category 1 (highly toxic) pesticides for more than 30 hours in any 30-day period. According to these regulations, methyl parathion is considered a Category 1 pesticide. This supervision includes preexposure baseline cholinesterase determinations and periodic biologic monitoring of erythrocyte and plasma cholinesterase activities. It also includes authority for the physician to instruct the employer to remove an employee from all occupational exposure to organophosphates and carbamates should monitoring reveal inhibition of plasma cholinesterase to 50% of the preexposure baseline or erythrocyte cholinesterase to 40% of the preexposure baseline. Both cholinesterase activities must return to within 20% of the preexposure baseline before the employee can resume exposure to organophosphates or carbamates. Whenever a cholinesterase test indicates an inhibition of 30% or more, a retest is required. Laboratories performing cholinesterase assays must be approved by the California State Department of Health.

Closed mixing and loading systems are required to prevent exposure, especially to concentrated solutions, caused by spills in the course of pouring. [132] Ground- and aerial-application tanks must have an external means for determining the internal liquid level, or the filler hose must have an automatic shutoff device to prevent overfilling. Such transfer

hoses must be equipped with a device to prevent dripping from the outlet end after filling. In addition, no unshielded flexible hoses carrying liquid pesticide may pass through the driver's compartment of an application vehicle.

If employees have not received previous training, employers must instruct employees on the safe handling of pesticides used, including personal protective equipment, common poisoning symptoms, the necessity for eating and smoking rules, availability of emergency medical treatment, and the rationale for biologic monitoring. [132] Close supervision is required during training.

Employers must make prior arrangements for emergency medical services and must take an employee to a physician immediately "when the employer has reasonable grounds to suspect a pesticide illness or when an exposure to a pesticide has occurred that might reasonably be expected to lead to an illness." [132] To prevent the simple masking of symptoms, atropine may be taken by an employee only under direction of a physician.

Neither pilots of agricultural aircraft nor employees under the age of 18 are permitted to mix or load pesticides in Category 1 or 2 unless closed mixing or loading systems are used. [132] Persons handling pesticides in Category 1 are not allowed to work alone. Radio, telephone, or personal contact at least once every 2 hours during the day or every hour at night may be substituted for the presence of a second person. Operators of ground vehicles who are able to see each other's application vehicles or operating lights are not considered to be working alone. Pilots and either mixer-loaders or flaggers are not considered alone when working as a team.

Changing areas equipped with towels, soap, and sufficient water are required for mixers, loaders, applicators, and flaggers handling pesticides in Category 1 or 2 who work for more than 30 hours in any 30-day period. [132] Contaminated equipment or work clothing may not be taken home by employees. In addition, minimum amounts of water are required at worksites, along with soap and towels, for routine or emergency washing.

Mixers, loaders, applicators, and flaggers handling Category 1 or 2 pesticides must be provided with clean outer clothing daily by the employer. Contaminated clothing must be immediately removed. [132] Mixing and loading sites must have at least one change of clean outer clothing. The employer is required to provide respiratory and other personal protective equipment, to clean it as necessary, and to provide new respirator filter pads and cartridges according to the manufacturer's instructions. Employees who service or repair mixing, loading, or application equipment must be informed of the hazards associated with exposure to residues and must be provided with suitable protective equipment and clothing by their employer.

Subsequent to the issuance of the above regulations in 1974, the California State Department of Health sought to guide physicians providing medical supervision in the selection of cholinesterase testing intervals. [144] The table (XIV-1) immediately following was provided in a letter to physicians with the warning that immediate testing was indicated in the event of accidental exposure from splashes, spills, or other mishaps. Only workers exposed to Category 1 or 2 pesticides for 30 hours or more in a 30-day period were covered.

TABLE XIV-1

RECOMMENDED FREQUENCY OF CHOLINESTERASE TESTING
IN NUMBER OF WEEKS BETWEEN ROUTINE TESTS,
CALIFORNIA STATE DEPARTMENT OF HEALTH, MAY 1975

Work Activity	Exposure/Week	
	2 Days or Less	3 Days or More
Mixer-loader*	2	1
Ground applicator	4	2
Agricultural pilot	4	3
Flagger	4	2

*When closed mixing and loading systems are used exclusively, increase the interval between cholinesterase tests by 1 week for this group.

Adapted from Kahn [144]

XV. APPENDIX VII

SUMMARY OF ACTIVITIES OF VARIOUS STATES OTHER THAN CALIFORNIA IN CONTROLLING USE OF PESTICIDES

Of the 53 administrative units in the United States and its possessions, all except Guam have at least one law relating to the control of pesticides. The pesticide laws of Nebraska and American Samoa are quite general, without specific provisions. In all other administrative units except Michigan, statutes give to the responsible government authority the power to regulate storage, transportation, and disposal of pesticides, to restrict their uses, and to hold disciplinary hearings on alleged infractions of regulations. In 35 of the 53 administrative units, the responsible agency is given the power to license dealers in pesticides. In 49 administrative units, this agency licenses or certifies custom applicators of pesticides; in 35, the agency also certifies private applicators using restricted pesticides.

In most of the administrative units, the responsible agency is some government department, most commonly the state agricultural department or its equivalent. Departments of environmental protection or of conservation are the designated agencies in several administrative units. Other state governmental entities (eg, Department of Natural Resources, Department of Health, State Chemist, or Director of Regulatory and Public Service Programs of Clemson University) appear occasionally as responsible authorities. Thirty-nine administrative units provide for pesticides

boards, councils, or committees. In most cases, these have advisory capacities only, but a few have been made responsible for controlling the use of pesticides and for licensing or certifying custom or private applicators of pesticides.

In 22 administrative units other than California, the governing statute gives to the designated agency the power to require reports of illness caused by accidental pesticide exposure. These administrative units are: Alaska, Arkansas, Colorado, Florida, Hawaii, Indiana, Iowa, Louisiana, Missouri, Nevada, New Mexico, North Dakota, Ohio, Pennsylvania, Rhode Island, South Carolina, South Dakota, Texas, Vermont, Virginia, the Virgin Islands, and Washington. This power generally has been available for only a short time in administrative units other than California; there it has existed since the passage in 1949 of the Injurious Materials Law. California has, therefore, a particularly extensive but not necessarily complete inventory of illnesses caused by pesticides.

In general, the various administrative units have no statutory authority to require information on the use of pesticides. In Maine, New Hampshire, and Rhode Island, however, the law provides that renewal of a license or certification requires full reporting of pesticide use during previous periods of licensure or certification. A number of the other administrative units do have a means for obtaining some information when required use or purchase permits for pesticides are obtained. Maine, New Hampshire, and Rhode Island use this mechanism as a check on the required reporting of pesticide uses.

XVI. TABLES AND FIGURES

TABLE XVI-1

PHYSICAL PROPERTIES OF METHYL PARATHION

Chemical name	0,0 dimethyl 0-p-nitrophenyl phosphorothioate [also: 0,0-dimethyl 0-(4-nitrophenyl) thiophosphate; or dimethyl p-nitrophenyl thionophosphate
Common name	Methyl parathion
Molecular weight	263.3
Volatility	1.40 mg/cu m at 20 C (pure)
Boiling point	Thermally unstable
Melting point	37 C (pure); 29 C (technical)
Crystallization temperature (80% in xylene, stabilized)	17 C (62.6 F)
Flashpoint (80% in xylene, tag open cup)	46 C (115 F)
Vapor pressure	0.000097 mmHg at 20 C
Autoignition temperature (80% in xylene)	120 C (248 F)
Odor	Garliclike (technical)
Color	Tan-to-brown (technical); white (pure)
Solubility	55-60 ppm in water at 25 C; slightly soluble in light petroleum and mineral oils; soluble in most other organic solvents; slightly soluble in lipids and fats
Specific gravity	1.358 at 20 C (pure); 1.22 at 20 C (technical)
Conversion factors (at 760 mmHg, 25 C)	1 ppm = 10.5 mg/cu m 1 mg/cu m = 0.095 ppm

Adapted from Monsanto Corporation, [8] National Agricultural Chemicals Association, [136] and Agency for International Development [169] publications

TABLE XVI-2

SYNONYMS, INCLUDING TRADE NAMES, FOR METHYL PARATHION

Azofos
Azophos
Bay 11405
Bayer E601
Dalf
0,0-Dimethyl-0-p-nitrofenylester kyseliny thiofos (Czech)
0,0-Dimetyhl-0-(4-nitro-fenyl)-monothiofosfaat (Dutch)
Dimethyl p-nitrophenyl monothiophosphate
0,0-Dimethyl-0-(4-nitro-phenyl)-monothiophosphat (German)
0,0-Dimethyl 0-(p-nitrophenyl) phosphorothioate
0,0-Dimethyl-0-(4-nitrophenyl)phosphorothioate
0,0-Dimethyl 0-(p-nitrophenyl)thionophosphate
0,0-Dimethyl-0-(p-nitrophenyl)-thionophosphat (German)
Dimethyl-p-nitrophenyl thionphosphate
Dimethyl p-nitrophenyl thiophosphate
0,0-Dimethyl 0-p-nitrophenyl thiophosphate
Dimethyl parathion
E601
ENT 17,292
Folidol M
Folidol 80
8056HC
M-Parathion
Metacid 50
Metacide-50
Metacide
Metaphor
Metaphos
Methyl-E 605
Metylopartion (Polish)

TABLE XVI-2 (CONTINUED)

SYNONYMS, INCLUDING TRADE NAMES, FOR METHYL PARATHION

Methylthiophos
Metron
p-Nitrophenyldimethylthionophosphate
Nitrox
Nitrox 80
Parathion methyl
Parathion-Metile (Italian)
Partron M
Phenol, p-nitro-,O-ester with O,O-dimethylphosphorothioate
Thiophenit
Thiophosphate de O,O-dimethyle et de O-(4-introphenyle) (French)
Vafatox
Vofatox
Wofatox
Wofotox

Adapted from Encyclopaedia of Occupational Health and Safety, [142] Registry of Toxic Effects of Chemical Substances--1975 Edition, [170] and 1968 Evaluations of Some Pesticide Residues in Food [171]

TABLE XVI-3

OCCUPATIONS WITH POTENTIAL EXPOSURE TO METHYL PARATHION

Aerial application personnel	Flag persons
Area cleanup crews	Ground applicator vehicle drivers
Bagging machine operators	Janitorial personnel
Basic manufacturing employees	Laundry workers
Haulers of laundry	Maintenance personnel
Drum fillers	Mixer and blender operators
Drum reconditioning personnel	Refuse haulers
Dump personnel	Tractor tank loaders
Field checkers	Truck loaders
Fieldworkers (eg, exposed to residues on crops and foliage)	Warehouse personnel

Adapted from reference 12

TABLE XVI-4

SIGNS AND SYMPTOMS ASSOCIATED WITH PARATHION POISONING

Effector Organ	Signs and Symptoms
MUSCARINIC Manifestations	
(a) Gastrointestinal	Anorexia; nausea; vomiting; abdominal cramps; diarrhea; tenesmus; involuntary defecation; eructation; "heartburn"; 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 tree	Tightness in chest; wheezing suggestive of bronchoconstriction; dyspnea; cough; increased bronchial secretion; pulmonary edema
(g) Pupils	Pinpoint (miosis) and non-reactive
(h) Ciliary body	Blurring of vision
(i) Bladder	Frequent or involuntary urination
NICOTINIC Manifestations	
(a) Striated muscle	Muscular twitching; fasciculation; cramps; weakness (including muscles of respiration)
(b) Sympathetic ganglia and adrenals	Pallor; tachycardia; elevation of blood pressure

TABLE XVI-4 (CONTINUED)

SIGNS AND SYMPTOMS ASSOCIATED WITH PARATHION POISONING

Effector Organ	Signs and Symptoms
CNS Manifestations	
	Uneasiness; restlessness; anxiety; tremulousness; tension; apathy; giddiness; withdrawal and depression; headache; sensation of "floating"; insomnia with excessive dreaming (nightmares); ataxia; slurred, 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 dyspnea and fall in blood pressure)

Derived from references 6 and 78

TABLE XVI-5

EFFECTS OF METHYL PARATHION (MP) EXPOSURE ON HUMANS

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	References
Dermal and respiratory	4 humans	(Unknown conc)	Death; marked microscopic changes in liver, kidneys, and brain; paranitrophenol in all tissues examined	17-19
"	3 humans	MP (unknown conc)	No deaths; chromosomal anomalies in 2.53% of metaphase lymphocytes in 14 of 15 patients; 0.5% anomalies in controls	30
	12 humans	Organophosphorus pesticides (unknown conc)		
	10 controls			
"	16 exposed farm workers	Organophosphorus pesticides including MP (unknown conc)	Peak-season chromosomal break frequency in metaphase lymphocytes 5 times greater than that of off-season	32
"	47 humans (winter) 35 humans (summer)	MP dust (unknown conc) 3 mon - 6 yr in formulating plant with poor work practices	Signs and symptoms independent of length of employment, "mild" at 18 winter exams, "severe" at 29 summer exams; CNS involvement, headache, dizziness, nausea, insomnia, fatigue, visual disturbances, nervousness, shooting pains in heart, loss of appetite, vomiting, stomach pains, numbness of extremities, fibrillar muscle twitching; summer plasma cholinesterase activities 30% or more below winter values in 21 of 29 symptomatic workers	16

TABLE XVI-5 (CONTINUED)

EFFECTS OF METHYL PARATHION (MP) EXPOSURE ON HUMANS

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	References
Oral, dermal, and respiratory	4 men and 1 woman	MP (unknown conc)	Translocations or deletions in 9.80% of metaphase lymphocytes at 3-6 d after exposure, 26.00% at 30 d, 10.20% at 180 d	31
	26 humans	Organophosphorus pesticides (unknown conc)	For these plus above, translocations or deletions in 17.83% at 3-6 d, 22.00% at 30 d, 5.60% at 180 d	31
	15 controls (13 men, 2 women)		For controls, 3.33% deletions and no translocations	31
Oral	26 humans	1.84 - 200 g	Death in 2 hr-9 d; marked microscopic changes in liver, kidneys, and brain; paranitrophenol in all tissues examined	17-19
"	7 men at each dose level: 5 subjects, 2 controls	1 - 22 mg/d in corn oil x 30 d	Average erythrocyte or plasma cholinesterase activity not inhibited more than 20% below baseline	20-23, 26-28
"	7 men: 5 subjects, 2 controls	24 mg/d in corn oil x 30 d	More than 20% inhibition in 2 of 5 subjects (plasma, 24 and 23%; erythrocyte, 27 and 55%)	24

TABLE XVI-5 (CONTINUED)

EFFECTS OF METHYL PARATHION (MP) EXPOSURE ON HUMANS

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	References
Oral	7 men: 5 subjects, 2 controls	26 mg/d in corn oil x 30 d	More than 20% inhibition in 2 of 5 subjects for erythrocyte cholinesterase only (25 and 37%); maximum mean inhibition, 18%	24
"	7 men: 5 subjects, 2 controls	28 mg/d in corn oil x 30 d	More than 20% inhibition in 3 of 5 subjects for erythrocyte cholinesterase; maximum mean inhibition, 19%	25
"	7 men: 5 subjects, 2 controls	30 mg/d in corn oil x 30 d	Maximum mean inhibition of erythrocyte cholinesterase activity, 37%	25

TABLE XVI-6

LD50S FOR MICE, RATS, AND GUINEA PIGS

Routes of Exposure	Animals	Number and Sex	Material	LD50 or LC50	References
Oral	Mice	- -	Methyl parathion, 84.7% isomerized	Greater than 200 mg/kg	41
"	"	- -	Methyl parathion, not isomerized	100-200 mg/kg	41
"	Mice 15 - 20 g	- -	Methyl parathion* in mucine	58 mg/kg	40
"	"	- -	Methyl parathion* in propylene glycol	18.5 mg/kg	40
"	Mice 13 - 18 g	- -	Methyl parathion in aqueous emulsion	17 mg/kg	38
"	Rats 170 - 190 g	- M	"	24.5 mg/kg	38
"	Rats 200 g or larger	60 F	Methyl parathion* in peanut oil	24 mg/kg	33
"	Rats 200 g	10 F	Methyl parathion* in propylene glycol	18 mg/kg	37
"	Rats 175 g or larger	68 M	Methyl parathion* in peanut oil	14 mg/kg	33
"	Rats 200 g	10 M	Methyl parathion* in propylene glycol	12 mg/kg	37
"	Guinea pigs 290 - 320 g	- M	Methyl parathion in aqueous emulsion	417 mg/kg	38
iv	Mice 13 - 18 g	- M, F	"	13 mg/kg	38
"	Mice 15 - 20 g	- -	Methyl parathion* in propylene glycol	2.3 mg/kg	40

TABLE XVI-6 (CONTINUED)

LD50S FOR MICE, RATS, AND GUINEA PIGS

Routes of Exposure	Animals	Number and Sex	Material	LD50 or LC50	References
iv	Rats 200 g	- F	Methyl parathion* in propylene glycol	14.5 mg/kg	37
"	"	- M	"	9 mg/kg	37
"	Rats 170 - 190 g	- M	Methyl parathion in aqueous emulsion	4.1 mg/kg	38
"	Guinea pigs 290 - 320 g	- M	"	50 mg/kg	38
ip	Mice 15 - 20 g	- -	Methyl parathion* in mucine	32.0 mg/kg	40
"	"	- -	Methyl parathion* in propylene glycol	8.6 mg/kg	40
"	Rats 200 - 300 g	24 M	Methyl parathion in ethanol (20%) and propylene glycol (80%)	5.8 mg/kg	39
"	Rats 50 - 60 g	58-	"	3.5 mg/kg	39
Sub-cutaneous	Mice 15 - 20 g	- -	Methyl parathion* in propylene glycol	18.0 mg/kg	40
Dermal (clipped fur)	Rats 200 g	- F	"	120 mg/kg	37
"	"	- M	"	110 mg/kg	37
"	Rats 200 g or larger	69 M	Methyl parathion in xylene (0.0016 ml/kg)	67 mg/kg	33
"	Rats 175 g or larger	50 F	"	67 mg/kg	33

TABLE XVI-6 (CONTINUED)

LD50S FOR MICE, RATS, AND GUINEA PIGS

Routes of Exposure	Animals	Number and Sex	Material	LD50 or LC50	References
Respiratory	Rats 200 g	- F	Methyl parathion* in propylene glycol	287 mg/cu m (1.38 mg/kg) for 1 hr	37
"	"	- M	"	257 mg/cu m (1.23 mg/kg) for 1 hr	37
"	Rats	- M	Methyl parathion*	0.2 mg/1 for 1 hr 0.12 mg/1 for 4 hr	35

*Technical grade

TABLE XVI-7

EFFECTS OF METHYL PARATHION EXPOSURE ON ANIMALS

Routes of Exposure	Animals	Number and Sex	Material	Exposure Concentration and Duration	Effects	References
Oral (in food)	Rats*, F0, F1, F2	10 M, 20 F (for each generation, including F1)	Methyl parathion, 99% pure	3 mg/kg/d x 27 wk	No consistent or dose-related effects on reproduction; reduced survival of F1 weanlings; fewer litters from F2 dams than from controls	68
"	"	"	"	1 mg/kg/d x 27 wk	No consistent or dose-related effects on reproduction; reduced survival of F3 weanlings	68
Oral	Rats 270 g	4 F	Methyl parathion, unspecified grade	11 mg/kg (3 mg in 0.4 ml ethanol)	Twitching in dams and fetuses after dose 1-3 d before expected parturition; methyl parathion in liver and placenta of dams killed 30 min postdose; methyl parathion and methyl paraoxon in fetal brain, liver, and muscle	72
Oral (in food)	Rabbits ca. 2 kg	7 M, 7 M, 7 M, 7 M	"	1.479 mg/kg/d, 0.519 mg/kg/d, 0.162 mg/kg/d, 0.036 mg/kg/d x 56 d (Immunization with sheep erythrocytes 28th d)	Slight suppression of cell-mediated immune responses; slight decrease in spleen weights	61
"	Dogs 6-10 kg	1 M, 1 F	Methyl parathion, technical grade	50 ppm/d x 90 d	Plasma and erythrocyte ChE inhibition	43
"	"	1 M, 1 F	"	20 ppm/d x 90 d	"	43
"	"	1 M, 1 F	"	5 ppm/d x 90 d	No appreciable plasma or erythrocyte ChE inhibition	43
iv	Rats	- M	Methyl parathion in aqueous emulsion	2.1 mg/kg	50% brain ChE inhibition	38
"	"	- M	"	1.8 mg/kg	50% plasma ChE inhibition	38
"	Guinea pigs	- M	"	28 mg/kg	50% brain ChE inhibition	38
"	"	- M	"	24 mg/kg	50% plasma ChE inhibition	38
"	Rabbits	- -	Methyl parathion	12.5 mg/kg	Death	48
im, iv	"	- -	"	15 mg/kg im every 15 d for 5 mo and then 12.5 mg/kg iv	Like those in rabbits given only 1 im dose before iv dose (see below) but shorter lasting and less marked	60
"	"	- -	"	15 mg/kg im and 7 d later 12.5 mg/kg iv	Slight bradycardia after im dose, neutralization of iv dose (lethal to other rabbits) by im doses, slight electrocardiographic alterations and ChE inhibition effects after iv dose	48

TABLE XVI-7 (CONTINUED)

EFFECTS OF METHYL PARATHION EXPOSURE ON ANIMALS

Routes of Exposure	Animals	Number and Sex	Material	Exposure Concentration and Duration	Effects	References
ip	Mice	14 F	Methyl parathion in sodium carboxy-methyl cellulose (0 5%)	60 mg/kg d 10 of gestation	22.3% offspring dead, 13/112 cleft palates, low offspring body weights; variations in cervical rib formation and caudal vertebrae ossification	70
"	"	11 F	"	20 mg/kg d 10 of gestation	None	70
"	Rats	13 F	"	15 mg/kg on d 12 of gestation	Slight retardation of ossification of caudal vertebrae and lower body weights in offspring	70
"	"	10 F	"	10 mg/kg d 12 of gestation	No malformations in offspring	70
"	Rats 225 g	12 F	Methyl parathion (unspecified grade) in ethanol (20%) and propylene glycol (80%)	6.0 mg/kg or 4.0 mg/kg on d 9 or d 15 of gestation	Fetal brain ChE inhibition, reduced erythrocyte ChE activity, symptoms of ChE inhibition, and lower average weight gain in dams	71
"	Rats	10 F	Methyl parathion in sodium carboxy-methyl cellulose (0.5%)	5 mg/kg d 12 of gestation	No malformations in offspring	70
"	"	5 F, 5 F, 5 F, 5 F, 5 F	Methyl parathion in distilled water	0 15 mg in 3 ml water at 8 hr, 12 hr, 16 hr, 20 hr, 24 hr before 131I ip injection	Inhibition of thyroid 131I uptake, maximum inhibition at 8 hr, less inhibition when more time between methyl parathion and 131I injections	62
Sub-cutaneous	Chickens, atropinized	- -	Methyl parathion, unspecified grade	200 mg/kg	Lowest lethal dose tested, leg flaccidity beginning in 24 hr and lasting 3-28 d	51
"	"	- -	"	64 mg/kg	Lowest effective test dose	51
"	"	- -	"	32 mg/kg	Highest no-effect test dose	51
Respiratory	Rats	15 -	Methyl parathion, unspecified grade, aerosolized	0 072 mg/cu m 3 mo	Marked changes in liver, spleen, heart, adrenal glands, and CNS	60
"	"	15 -	"	0.024 mg/cu m 3 mo	Less marked changes than at 0.072 mg/cu m	60
"	"	15 -	"	0.008 mg/cu m 3 mo	No specific morphologic changes	60

*Three-generation study. F0=original parents; F1, F2, and F3=1st, 2d, and 3d generation, respectively

TABLE XVI-8

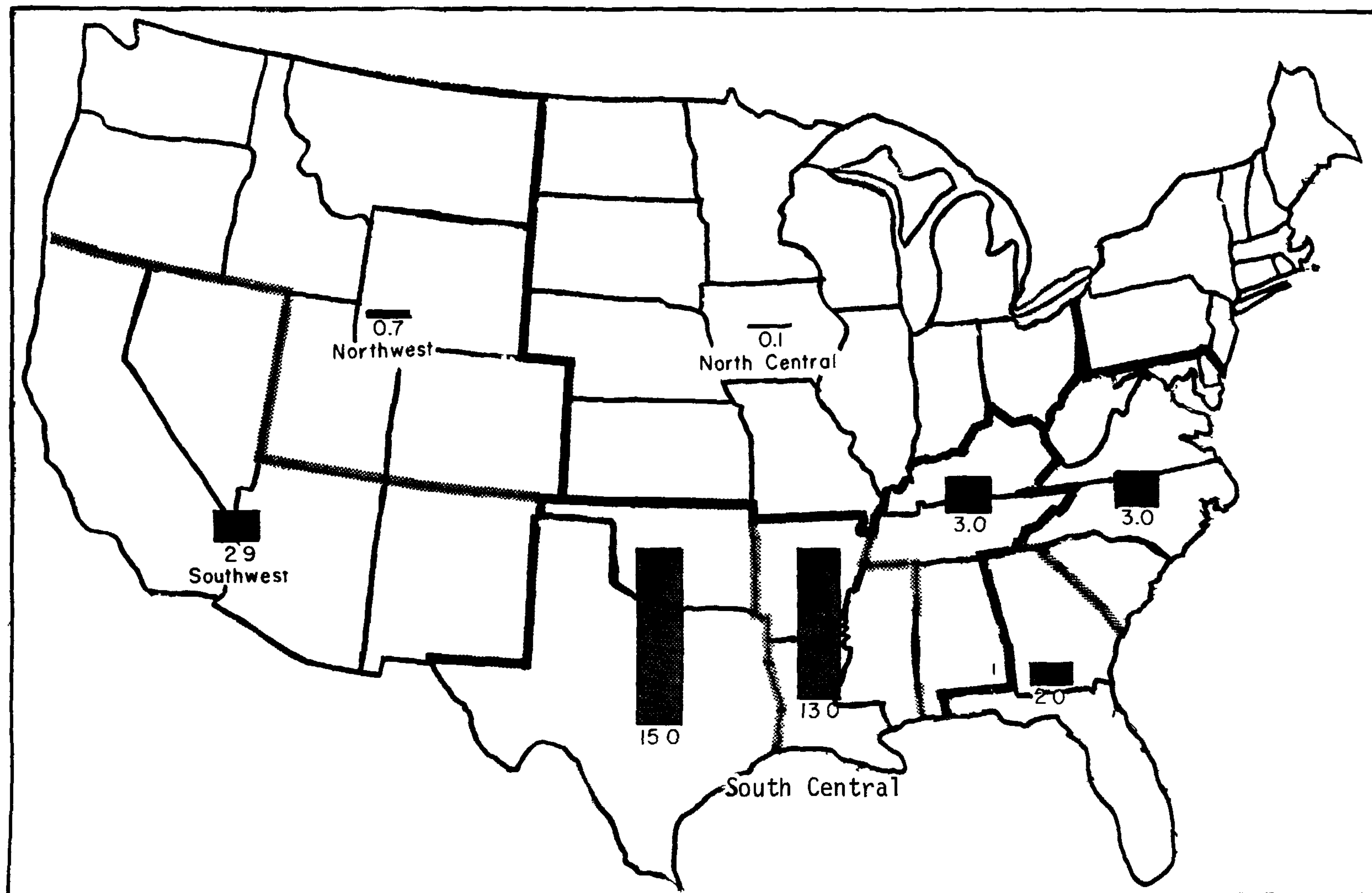
NORMAL VALUES FOR CIRCULATING CHOLINESTERASES
IN HEALTHY NONEXPOSED PERSONS*

Subjects	Erythrocyte Cholinesterase Activity (delta pH/hr)			Plasma Cholinesterase 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	93***
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 performed by method of Michel [29]
**Ranges, means, and standard deviations estimated from data extrapolated to age 40; highest 1% and lowest 1% values eliminated from ranges
***Analytic method modified for smaller blood samples

FIGURE XVI-1

GEOGRAPHIC DISTRIBUTION OF DOMESTIC METHYL PARATHION USE, 1972*

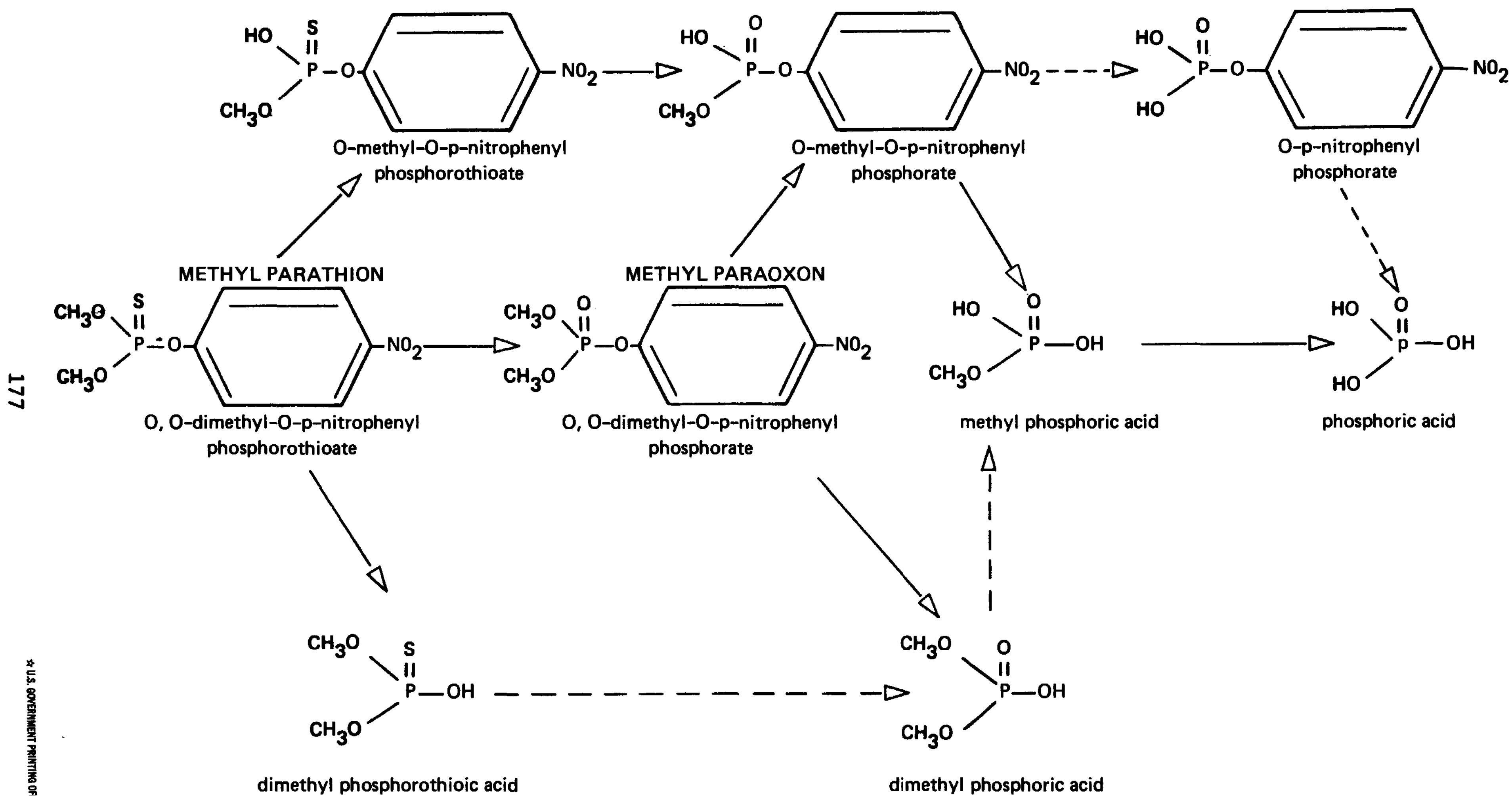


*Figures in millions of pounds of active ingredient

Adapted from US Environmental Protection Agency [11]

FIGURE XVI-2

METABOLISM OF METHYL PARATHION IN MICE*



* Dashed lines indicate hypothetical pathways

NOTE: Since only 32P-labeled metabolites were identified, paranitrophenol, a known degradation product of methyl parathion, does not appear in the figure.

Adapted from Hollingworth et al [74]

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