

criteria for a recommended standard....

**OCCUPATIONAL EXPOSURE
TO
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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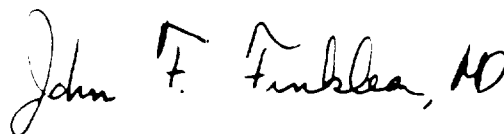
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PREFACE

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 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 parathion by members of my staff, the valuable and constructive comments presented by the Review Consultants on Parathion, by the ad hoc committees of the American Academy of Occupational Medicine and the American Conference of Governmental Industrial Hygienists, by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, and by Bruce J. Held on respiratory protection. The NIOSH recommendations for standards are not necessarily a consensus of all consultants and professional societies that reviewed this criteria document on parathion. Lists of the NIOSH Review Committee members and of the Review Consultants appear on the following pages.



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The Sequoia Groups, Berkeley, California, developed the basic information for consideration by NIOSH staff and consultants under contract No. HSM-99-72-35. Jon R. May, Ph.D., had NIOSH program responsibility and served as criteria manager.

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I. RECOMMENDATIONS FOR A PARATHION STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to parathion in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and safety of workers for up to a 10-hour work shift, 40-hour workweek during a working lifetime. Compliance with all sections of the standard should prevent adverse effects by 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.

“Parathion” is defined as O,O-diethyl O-p-nitrophenyl phosphorothioate, regardless of production process, alone or in combination with other compounds. “Occupational exposure to parathion” is defined as employment in any area in which parathion or materials containing parathion, alone or in combination with other substances, is produced, packaged, processed, mixed, blended, handled, stored in large quantities, or applied. If employees are potentially exposed to other chemicals, such as pesticide vehicles, diluents, or emulsifiers, or other pesticides, provisions of any applicable standards for such other chemicals shall also be followed. Adherence to all provisions of the standard is required in workplaces using parathion regardless of the airborne parathion concentration because of serious effects produced by contact with the skin, mucous membranes, and eyes. Since parathion does not irritate or burn the skin, no warning of skin exposure is likely to occur. However, 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 parathion is from SKIN CONTACT.

Section 1—Environmental (Workplace Air)

(a) Concentration

Occupational exposure to parathion shall be controlled so that no employee is exposed to parathion in a concentration greater than 0.05 mg/m³ of air determined as a time-weighted average (TWA) exposure for up to a 10-hour work shift and a 40-hour workweek.

(b) Sampling and Analysis

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

Section 2—Medical

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

(a) Medical Examinations

(1) Preplacement and periodic medical examinations shall include:

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

(B) A physical examination which shall be directed towards, but not limited to, evidence of frequent headaches, 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 parathion.

(C) Initial medical examinations shall be made available to all workers within 60 days of the promulgation of this recommended standard.

(D) Periodic examinations shall be made available on an annual basis 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 Section (b) Biologic Monitoring).

(F) A judgment of the worker's physical ability to use negative or positive pressure respirators as defined 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 parathion (See Appendix IV).

(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 parathion.

(4) Medical records shall be maintained for

all workers occupationally exposed to 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 is defined as the mean of 2 cholinesterase activity determinations, each of which is derived from a separate sample of blood taken at least 1 day apart, after a period of at least 60 days without known exposure to any cholinesterase-inhibiting compounds. If the determinations produce values differing by more than 15%, additional determinations on new samples must be performed until successive tests do not differ by more than 15%.

(B) "Working baseline" for erythrocyte cholinesterase is defined as the mean of 2 cholinesterase activity determinations, each of which is derived from a separate sample of blood taken at least 1 day apart and differing by no more than 15%, or the arithmetic mean of normal values for an appropriate control population of adults for that laboratory, whichever is higher. A "working baseline" is determined only for an individual whose work history does not permit a preexposure baseline to be determined as specified in paragraph (b)(1)(A) of this section.

(C) "Mean of normal values" is defined as the arithmetic mean of erythrocyte cholinesterase activities for healthy adults as determined by the laboratory's experience with repeated analyses, but which is not inconsistent with the mean baseline activities presented in Table XI-2 of Appendix III.

(2) Routine Monitoring

(A) All employees who are to be occupationally exposed to parathion shall have preexposure erythrocyte cholinesterase baselines determined whenever their work history allows an accurate preexposure determination, as specified in paragraph (b)(1)(A) of this section. Those new employees with work histories precluding preexposure baseline cholinesterase determinations shall have working baseline determinations performed.

(B) Within 60 days after the effective date of a standard based on this recommendation, all present employees occupationally exposed to parathion shall have working baseline erythrocyte cholinesterase activity determined.

(C) Subsequent to the determination of a preexposure or working baseline, each employee occupationally exposed to parathion shall have his erythrocyte cholinesterase activity determined at 4-week intervals, except for those employees in the following occupations: (1) mixers, loaders, ground applicators, flaggers, and manufacturing or formulating employees working with other than closed production, mixing, blending, transfer, and packaging systems—all of whom shall be tested at 1-week intervals. This 1-week interval shall be reduced to testing every 3 days for any employee working with parathion for a period exceeding 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; (2) personnel who clean or repair equipment or clean parathion spills and aerial applicators (ie, agricultural pilots) not engaged in loading operations shall be tested at 2-week intervals.

(D) Unacceptable absorption of parathion indicating a failure of control procedures and/or work practices is demonstrated when the enzymic activity of erythrocyte cholinesterase is decreased to between 60-70% 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 the 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 his erythrocyte cholinesterase activity is decreased to 60% or below of his preexposure baseline or working baseline shall be removed from potential exposure to 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 parathion exposure shall not be allowed to return to work involving occupational parathion exposure until his erythrocyte cholinesterase ac-

tivity has returned to at least 75% of the working or preexposure baseline values or unless the responsible physician has approved his return.

(F) Each employee shall be given a copy of the results of his initial and periodic tests, and of any special cholinesterase test results as soon as possible after the test, plus an interpretation.

(3) Blood Collection and Analysis

Procedures for collection and analysis of blood samples for RBC ChE activity shall be as provided in Appendix III 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 parathion used in the workplace shall be labeled with at least the following information:

DANGER! POISON
CONTAINS PARATHION
EXTREME HEALTH HAZARD (includes skin)
CAN BE FATAL { If Swallowed
 { If Left on Skin
 { If Heated and Inhaled

If parathion is dissolved in a combustible solvent, the label shall include a statement of flammability appropriate to the solvent.

The following list of safe work practices and emergency information shall be made available to each employee as informational material.

SAFE WORK PRACTICES

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

When possibility of contact exists:
Wear full-body coveralls or impervious apron, goggles, impervious boots and gloves, and, if required, a 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, defecating, or urinating. Store food and tobacco away from work area. Keep containers tightly closed whenever unattended. Protect concentrated parathion from all sources of ignition. Do not warm concentrated parathion containers with open flame. Do not smoke while handling parathion.

EMERGENCY INFORMATION

If liquid gets on skin, wash immediately with alkaline soap and water and call a physician. If clothes become contaminated, remove at once. Then wash your body with soap and water and call a physician. If sickness occurs while handling materials containing parathion, or after handling such materials, call a physician. NOTE: Poisoning symptoms may occur several hours after work ends. 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 in which there is occupational exposure to parathion:

POISON AREA
PARATHION
CAN BE FATAL { If Swallowed
 { If Left on Skin
 { If Heated and Inhaled

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.

DO NOT SMOKE, EAT, OR SLEEP IN AREA.

Warning signs shall be printed in English and in the predominant language of non-English-reading employees. Employees unable to read posted warnings and labels and those unfamiliar with English or with the predominant non-English lan-

guage shall receive periodic training sufficient to ensure their understanding of the contents of the label and poster specified in this section, and to provide a continuing reminder of these contents.

(2) The following poster shall be securely attached beside the entrance to any vehicle (eg, truck, freight car) used to transport parathion at all times that parathion is contained therein:

DANGER — POISON
CONTAINS PARATHION
IF LIQUID OR POWDER HAS LEAKED,
DO NOT ENTER
CAN BE ABSORBED THROUGH SKIN
OR BY BREATHING
IF SKIN CONTACT OCCURS,
WASH IMMEDIATELY
WITH ALKALINE SOAP AND WATER
AND CALL A DOCTOR AT ONCE

Section 4—Personal Protective Equipment and Protective Clothing

(a) Skin Protection

(1) Unless separately provided in this section, an employee who engages in filling, pouring, mixing, formulating, loading, applying, or otherwise handling parathion (including in open-system manufacturing processes) shall be provided with, and required to wear, protective head covering; goggles or face shield; impervious gloves; full-body coveralls, impervious apron, or impervious rainsuit; and impervious footwear. Impervious gloves should have reverse gauntlets and coveralls should be of a closely-woven material (siliconized fabric [nylon or cotton] is especially protective) without cuffs. Whenever the word impervious appears in this document, it means highly resistant to the penetration of parathion.

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

(3) Employees operating open equipment for ground (non-aerial) application of parathion shall be provided with, and required to wear, a protective head covering, preferably wide-brimmed and waterproof, or face shield, impervious gloves, full-body coveralls or an impervious rainsuit, and impervious footwear.

(4) Employees applying parathion by closed-cockpit aircraft shall be provided with im-

pervious gloves. Employees applying parathion by open-cockpit aircraft shall be provided with, and required to wear, full-body coveralls or impervious rainsuit, goggles, and impervious gloves.

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

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

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

(8) Laundry personnel handling clothing contaminated with parathion shall be provided with, and required to wear, impervious gauntlet gloves, impervious shoes, and, in addition to ordinary clothes, an impervious apron.

(9) The employer shall ensure that all personal protective devices are inspected regularly and maintained in clean and satisfactory working condition.

(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 airborne parathion concentrations below the workplace air limit specified in Section 1(a). Compliance with the 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 nonroutine operations, such as maintenance or repair activities, where brief exposure to parathion at concentrations in excess of the permissible exposure limit could occur.

(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 parathion in the workplace initially (and thereafter whenever pertinent working conditions are altered) and shall choose the appropriate respiratory protective device specified in Table I-1. The employer shall ensure that no employee is being exposed to parathion in excess of the limit specified 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 not be allowed to work in any operation requiring the use of a respirator. This provision shall 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 and 30 CFR 11 which incorporates the American National Standard Practices for Respiratory Protection Z88.2-1969 shall be established and enforced by the employer.

(D) The employer shall provide respirators in accordance with Table I-1 and shall ensure that the employee uses the respirator provided.

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

(F) Canisters or cartridges shall be discarded and replaced with fresh canisters or cartridges in accord with the manufacturer's specifications, or if the odor of parathion, parathion-containing formulations, diluents, emulsifiers, or solvents is detected while using the respirator, or if a breakthrough-indicator (if any) indicates the absorbent is saturated, whichever occurs first. 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.

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

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

(I) Respirators, except cooled supplied-air type, shall not be used for more than 15 minutes if ambient temperature exceeds 85°F in the particular workplace, except in emergencies.

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

(3) For purposes of this section, the application of parathion formulations is not to be considered a nonroutine operation for which respirators may be used in exposure situations where the environmental limit is exceeded. Engineering controls, such as enclosed filtered-air tractor cabins and aircraft cockpits, shall be used where the environmental conditions encountered or the application method selected present a reasonable likelihood of the environmental limit being exceeded. Where filtered-air enclosures are used, air levels of parathion shall be regularly monitored to ensure compliance with the standard.

Section 5—Informing Employees of Hazards from Parathion

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

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

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

TABLE I-1
RESPIRATOR SELECTION GUIDE FOR PROTECTION
AGAINST PARATHION

Concentration of Parathion	Respirator Type
0.5 mg/cu m or less	Half-mask pesticide respirator. or Type C supplied-air respirator, demand type (negative pressure), with half-mask facepiece
2.5 mg/cu m or less	Fullface gas mask (chin-, chest-, or back-mounted type) or Type C supplied-air respirator, demand type (negative pressure), with full facepiece.
50 mg/cu m or less	Type C supplied-air respirator, continuous flow type with full facepiece or suit or Pressure-demand type respirator with full facepiece and impervious plastic shroud
Emergency (includes entry into vessels, bins, or other containers which are probably contaminated with parathion)	Self-contained breathing apparatus with positive pressure in full facepiece or Combination supplied-air respirator, pressure demand type with auxiliary self-contained air supply

under this paragraph.

(d) In addition to the requirements of paragraph (c) above, employees occupationally exposed to 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 information. The information specified in Section 2(b)(2) shall be kept on file and shall be readily accessible to each employee at or near each workplace where exposure to parathion may occur. In addition, each employee shall be informed of his or her biologic monitoring results 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 parathion exposure can occur.

(2) Unless otherwise specified in this paragraph, employees occupationally exposed to parathion shall have provided to them in a readily accessible site either 25 gallons of water for each

person or 100 gallons, whichever is greater, plus alkaline soap and towels, for use in emergencies. Emergency water supplies are not 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) Parathion-manufacturing, -formulating, and fixed mixing facilities shall have emergency showers.

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

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

(6) When an employer, a supervisor, or the affected employee suspects overexposure to parathion (eg, known exposure, obvious signs or symptoms of poisoning), the employee shall be placed under medical observation 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 that formulations of parathion in combustible solvents are being used, of the high toxicity of the products of combustion, and of the necessity for using supplied-air respirators in suppressing fires involving parathion.

(8) Any emergency or accidental release (eg, application to incorrect field) of parathion from agricultural aircraft shall be reported immediately to people resident in the area and to appropriate local regulatory or health officials.

(b) Engineering Controls

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

(2) Control of Unit Operations

(A) Controls of unit operations of equivalent or superior effectiveness may be substituted for those specified in paragraphs (B) through (I) below.

(B) All fittings, hoses, tubing, pumps, valves, and associated equipment operated at positive pressure shall be sufficient to withstand 2½ times the maximum pressure normally encountered and shall be examined at least weekly for leaks and other signs of deterioration.

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

(D) Back siphoning by hoses used for filling vessels, tanks, or other containers with parathion, or for adding any other liquid if the container already contains parathion, shall not be permitted.

(E) 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 in order to prevent rupture of hoses, pipes, tubing, or pumps.

(F) All application equipment with 2 or more nozzles shall have the distribution manifold shielded to minimize operator exposure in the event of malfunction.

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

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

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

(3) Ventilation

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

(B) Exhaust ventilation systems discharging into outside air shall conform to 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 air-flow measurements, inspection of ductwork for leaks, and examination of the collecting element(s). These procedures shall be performed before manufacturing or formulating operations begin and at least twice monthly during manufacture or formulation.

(c) Storage

(1) All locations in which parathion is stored, or where access is not otherwise limited, shall be fenced and locked and shall be posted as specified in Section 3(b).

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

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

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

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

(6) Containers which are normally used for storage or preparation of food, feed, or drink shall not be used for storage of parathion.

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

(8) Outdoor storage facilities shall be

located at least 20 feet from any dwellings or populated area and shall be equipped with a sprinkler system, where feasible.

(d) Personal Hygiene

(1) The employer shall provide a changing area where street clothes may be stored free from contamination by parathion.

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

(3) The employer shall make extra clothes available at each work site for use when protective or personal clothing becomes contaminated with parathion.

(4) Employees occupationally exposed to parathion shall be required to wash hands and face with alkaline soap and water before eating, drinking, smoking, or using toilets.

(5) Employees occupationally exposed to parathion shall be required to take a 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 parathion spills shall be cleaned up as soon as possible. Continuous surveillance of spills shall be provided until decontamination is completed. Contaminated areas shall be roped off or access to them otherwise prevented. They shall also be posted.

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

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

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

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

(6) Unless otherwise provided by local, state, or federal regulation, clothing, rags, bags, or fiber drums heavily contaminated with parathion shall be incinerated with adequate precautions to prevent inhalation of potentially toxic fumes, vapors, or combustion products, or the materials shall be taken to a sanitary landfill and properly disposed of.

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

(8) Empty metal drums or containers contaminated with 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 parathion contamination.

(9) Whenever it is necessary for an employee to perform maintenance or repair work on parathion-contaminated equipment, such as a vessel, pump, valve, pipe, nozzle, etc, the equipment shall be decontaminated with a strong alkaline solution, or with an equivalent or superior decontaminating solution, before maintenance or repair is undertaken.

(10) Reusable clothing that has been worn during the work period shall be placed in a plastic bag or container and labeled with a suitable warning of possible contamination with parathion.

(f) Other Work Practices

(1) Employees handling parathion concentrates shall work in teams. In addition, regardless of the concentration of the material, all mixers, loaders, flaggers, and applicators must maintain periodic communication with a person capable of summoning emergency aid if needed.

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

(3) No aerial applicator may mix or load pesticides containing parathion in whole or in part, unless closed mixing or loading systems are used. This provision allows an aerial applicator to supervise mixing or loading operations involving open systems.

(4) Materials containing parathion shall not be used when testing mixing, loading, or application equipment for leaks, or when testing for clogged valves, lines, or strainers, or when equipment is calibrated.

(5) Dispersal equipment containing parathion may not be turned on outside the area to be treated. Except in an emergency, jettison or otherwise dumping of parathion from application, mixing, or loading vehicles shall be prohibited unless proper disposal procedures are followed.

(6) Employees piloting agricultural aircraft may not fly through the drift of an application, nor shall they start or continue an application if wind creates a drift hazard to themselves or others, nor shall they spray or dust over waterways, canals, buildings, dwellings, vehicles, or persons, including flaggers.

Section 7—Sanitation

(a) Food Facilities

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

(b) Smoking

Smoking shall be prohibited in areas where 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 Requirements

(a) Environmental Monitoring

(1) Each employer involved in the manufacture or formulation of parathion shall monitor environmental air levels of 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 parathion reveals that he is exposed at concentrations in excess of the recommended TWA environmental limit, control measures shall be initiated and the employee shall be notified of his exposure and of 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 parathion exposure area.

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

(b) Recordkeeping

(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. Each employee shall be allowed to obtain information on his or her own 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 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 Health, Education, and Welfare, of the Secretary of Labor, of the employer, and of the employee or former employee.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing occupational diseases arising from exposure to 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 workers from exposure to hazardous chemical and physical agents. Criteria for a recommended standard should enable management and labor to develop better engineering controls resulting in more healthful work environments and mere compliance with the recommended standard should not be used as a final goal.

In evaluating occupational hazards and setting priorities, it was determined that parathion is one of the chemicals of greatest immediate concern. Sporadic cases of occupational and accidental poisoning due to concentrated parathion and parathion and/or metabolite residues on fruits, vegetables, and foliage have been reported. Since the late 1940's, when parathion was introduced in the United States for use as an insecticide, an ever-increasing literature on the compound, its properties, and many aspects of its use has accumulated.

These criteria for a standard for parathion are part of a continuing series of criteria developed by NIOSH. The proposed standard applies only to those processes and operations involving the manufacture, processing, and use of parathion as applicable under the Occupational Safety and Health Act of 1970.

These criteria were developed to ensure that the standard based thereon would (1) protect employees against development of acute and chronic parathion poisoning, (2) be measurable by techniques that are available to industry and governmental agencies, and (3) be attainable with

existing technology. Although an environmental limit is recommended herein, because of the extensive use of parathion in agriculture, emphasis has been placed on proper work practices as a means of minimizing parathion exposure and on the appropriate biologic monitoring and medical surveillance of employees who work with parathion. Also, the recommended standard emphasizes the provision of sanitary facilities and the appraisal of all employees of the hazards of parathion and the importance of proper sanitary and work practices generally.

In addition to the obvious hazards attending exposure to concentrated parathion, more subtle problems are posed by the potential exposure of large numbers of agricultural workers to parathion residues on crops and in the agricultural workplace in general. Numerous documented instances of multiple "picker" poisonings exist but the factors involved in the causation of these incidents are only poorly understood. To protect workers from these hazards, the field reentry concept has been given much consideration during the period 1972-76. Reentry intervals define the time between application of the pesticide and entry of workers for any activity involving extensive contact with the crop. The protection of field workers from the potentially hazardous effects of parathion and parathion-metabolite residues on fruits, vegetables, and foliage through the establishment of safe reentry intervals has been intentionally omitted from this recommended standard because of standards promulgated and enforced by the Environmental Protection Agency (*Federal Register* 39:16888-91, May 10, 1974).

The recommended standard was not designed for the population-at-large and any extrapolation beyond general occupational exposures is not warranted.

The development of the recommended standard for occupational exposure to parathion has revealed deficiencies in the data base in the following areas: (1) epidemiologic studies of workers exposed to parathion for extended periods; (2) chronic animal exposure studies at low levels of parathion with emphasis on CNS effects; (3) animal experiments to determine the carcinogenic, mutagenic, and teratogenic potential of parathion for man; (4) the value of electromyography in assessing the toxic potential of parathion; and (5) improvement of the sampling method for personal

monitoring. A more complete discussion of these and several other gaps is presented in Chapter VII—Research Needs.

III. BIOLOGIC EFFECTS OF EXPOSURE

Parathion (O,O-diethyl O-p-nitrophenyl phosphorothioate) belongs to a family of organophosphorus (OP) compounds, members of which act directly or indirectly as cholinesterase (ChE) inhibitors. Direct inhibitors, such as paraoxon, are capable of reacting directly with the ChE enzymes thereby inactivating them. Parathion is called an indirect inhibitor because it must be converted in the environment or in vivo to the oxon (ie, active form) before it can effectively inhibit ChE's. Organophosphorus insecticide usage is increasing today as a result of the present restrictions against the use of DDT and related, persistent, chlorinated hydrocarbon insecticides.

Parathion is converted in the body in part to paraoxon, a strong inhibitor of the enzyme acetylcholinesterase.¹ Upon inhibition of this enzyme in the tissues, acetylcholine, the substance responsible for transmission of nerve impulses in much of the nervous system, accumulates, producing an initial overstimulation and subsequent blockage of nerve stimuli.¹

Extent of Exposure

In the United States during 1970, approximately 15,259,000 pounds of parathion were produced.² Technical grade material is formulated for insecticidal application usually as 15% and 25% wettable powders, dust concentrates (20% to 25%) and ready-to-use dry dust mixtures (1% to 10%), granules (2% to 25%), or emulsifiable concentrates (2-8 pounds/gallon).^{3,4} Parathion may be encountered as a relatively pure substance in the form of technical grade material, as a less-concentrated component of various formulations, such as described above, or as dilute sprays and dusts during field application. Even when parathion is contained in enclosed systems, potential exposures may occur from transfer of liquid, spillage, or from leaking equipment. Exposure may also occur during formulation, bagging operations, mixing, and application or by accidental or intentional contact with pesticidal preparations or incompletely emptied containers of formulations. Such accidental exposures have been particularly frequent among children less than 3 years old.

A number of occupations with potential exposure to parathion are listed in Table XVI-3.

Besides parathion, there are a number of other organophosphorus insecticides in use. In most cases, the newer compounds have a lower mam-

malian acute toxicity than parathion.⁵ Partly as a consequence of the increasing use of competing insecticides, the amount of parathion manufactured in this country dropped from a high figure of 20,000,000 pounds (estimated) in 1968 to 15,259,000 in 1970.²

Koelle¹ stated that parathion has probably been responsible for more cases of accidental poisoning and death than any other OP pesticide compound.

The magnitude of poisoning by parathion from occupational exposures is more difficult to assess than that from accidental poisonings. A relationship between occupational poisonings due to pesticides and all other poisonings for the State of California can be obtained from California Department of Public Health Reports.^{6,7} Under California law,⁶ each physician who attends an injured employee must file a report, the Doctors' First Report of Work Injury, with the Division of Labor Statistics and Research in the California Department of Industrial Relations (State of California Labor Code, 1967, Section 6407). The employer also files a report, the Employer's Report of Industrial Injury. By definition, work injury includes occupational disease. The physicians' reports of occupational disease are reviewed and subsequently published by the California Department of Public Health in statistical report form. Agricultural workers, exclusive of self-employed persons and unpaid family labor, are covered by the California Workmen's Compensation Law and thus come under the reporting system.

In California during 1970, a total of 33,085 cases of occupationally-related diseases from all causes were reported.⁷ Of these, 207 cases of systemic poisoning, or 0.63%, were due to OP pesticides and 55 (27%) were attributed to parathion.⁶ Sprayers, pickers, and truck and tractor drivers were the occupational groups most affected. The report does not identify formulators as a category of occupational exposure. Irrigators and loaders were also frequently involved in poisoning by agricultural chemicals. The data from California essentially agree with those reported by Hatcher and Wiseman⁸ and Tabershaw and Cooper,⁹ indicating that the greatest opportunities for occupational exposure to parathion exist during formulation and packaging operations, application equipment loading operations, and aerial and ground applications. In addition to the 55 reported cases of systemic parathion poisoning, 3 cases

complained of respiratory conditions, 3 of skin conditions, 3 of eye conditions, and 31 unspecified, for a total of 95 cases of occupational illness due to formulations of parathion.⁶ Of these 95 cases, 77 were in agriculture, 8 in manufacturing, 5 in transportation, communication, and utilities, 4 occurred in state and local government operations, and 1 in trade.

The report of Hatcher and Wiseman⁸ is an example of an effort to identify parathion poisoning in a heavily agricultural area and the resulting documentation of a large number of cases. In the lower Rio Grande Valley in Texas during 1968, 118 cases of OP pesticide poisoning were reported. Ninety of these, or 78.2%, involved exposure to parathion. Of the 118 cases of OP pesticide poisoning, 97 were the result of dermal exposure, 20 occurred by the respiratory route, and only one case, a suicide attempt, was by ingestion. These cases occurred during a year when parathion was used more extensively than before in an effort to overcome resistance by some of the major cotton pests. The authors concluded that the workmen occupationally exposed either did not know or failed to appreciate the increased hazards associated with dermal exposure to parathion, and used only the precautions they had used in previous years when handling methyl parathion alone. The majority of acute organophosphorus poisonings occurred in men employed in aerial application, almost 89.5% of those affected being ground personnel who assisted in loading the planes with spray materials and fuel, row flagging, loading, unloading and opening drums of undiluted material, or unloading and cleaning aircraft. No deaths resulted from the acute OP pesticide intoxications documented in this study.

Exposure of field workers to pesticide residues on the foliage of crops has recently become a matter of national concern (*Federal Register* 38:10715-17, May 1, 1973). During the years 1959-1963 in California, 369 cases of poisoning attributed to parathion residues were reported^{10,11} in field laborers involved in picking oranges, grapefruit, olives, and peaches. At least 3 severe episodes of OP insecticide residue poisoning in orchard workers occurred in California during 1970.¹² Each of the 3 orchards involved had been treated about 2 weeks prior to crew entry with one or more of a combination of ethion, Guthion, Delnav, or parathion. Fourteen of 35 crew members were hospitalized after picking oranges in a grove treated with parathion and Delnav nearly 5

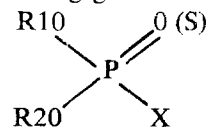
weeks and 4 months earlier, respectively. In another episode, 10 workers experienced nausea, vomiting, and diarrhea while working in an orange grove previously treated (5 weeks) with a mixture of parathion and malathion. Quinby and Lemmon¹³ reported parathion residue poisonings in California, Washington, and British Columbia.

Summaries of pertinent state pesticide regulations are presented in Appendices VI and VII.

NIOSH estimates that approximately 250,000 workers (including field workers exposed to residues) in the US are potentially exposed to parathion.

Historical Reports

According to Holmstedt¹⁴, the first indications that OP compounds might be highly toxic appeared during the early 1930's when Willy Lange and Gerda von Krueger experienced symptoms while synthesizing dimethyl and diethyl phosphorofluoridate. As early as 1934, Otto Bayer of the I. G. Farbenindustrie appointed Gerhard Schrader to investigate synthetic insecticides. By 1936, Schrader had turned his attention to organophosphorus compounds and, in 1937, he patented the following general formula for contact



insecticides.¹⁴ Parathion (E605) and paraoxon (E600) came out of Schrader's laboratory in 1944.¹⁴ Much of the information about Schrader's work was disseminated outside Germany at the end of World War II when British Intelligence published information about parathion in 1947 in the BIOS reports, as cited by Metcalf and March.¹⁵ Limited production for agricultural use was begun in this country in 1948.¹⁶ Cases of parathion poisoning were reported soon thereafter. In 1949, Grob et al¹⁷ reported that a man employed as a mixer of liquid parathion and clay powder had died after repeated exposures to the insecticide. The following year, Grob et al¹⁸ described the toxic effects of parathion in 32 men and 8 women following accidental exposures. Since that time, parathion has been responsible for many occupational poisonings as documented, for example, by the California Department of Public Health^{6,10,12} during the ensuing years.

Effects on Humans

Table III-3 summarizes the experimental and epidemiologic effects noted in humans exposed to

TABLE III-1

SIGNS AND SYMPTOMS ASSOCIATED WITH ACUTE AND SUBACUTE EXPOSURES TO PARATHION

Effector Organ	Sign or Symptom
1. 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 broncho-constriction; dyspnea; cough; increased bronchial secretion; pulmonary edema
(g) Pupils	Pinpoint (miosis) and nonreactive
(h) Ciliary body	Blurring of vision
(i) Bladder	Increased urinary frequency; involuntary urination
2. NICOTINIC manifestations	
(a) Striated muscle	Muscular twitching; fasciculation; cramping; weakness (including muscles of respiration)
(b) Sympathetic ganglia and adrenals	Pallor; tachycardia; elevation of blood pressure
3. CENTRAL NERVOUS SYSTEM 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 18,52

parathion. Evaluative or qualifying information on each study is included in the more complete description of the study as reported in the text.

(a) Physiology

The actions of such organophosphorus compounds as parathion depend upon the enzymes which they inhibit and the physiologic effects of such enzyme inhibition. These enzymes catalyze the hydrolysis of acetylcholine and other choline esters. In 1932, Stedman and his coworkers¹⁹ suggested the term "choline-esterase" (sic) for the

enzyme which is present in serum. Of the choline esters, the only one with demonstrated physiologic importance to man is acetylcholine, the substance which mediates the transmission of nerve impulses to the heart and to other parasympathetically innervated structures, including the iris, the salivary glands, the stomach and small intestine, the urinary bladder, the bronchial glands, and a few postganglionic sympathetic fibers, such as those to the eccrine sweat glands.¹ Acetylcholine has been shown to have a transmitter function also in 3 additional classes of nerves: the preganglionic fibers

of both the sympathetic and parasympathetic systems, motor nerves to skeletal muscles, and certain neurons within the central nervous system.¹

In man, there are two principal types of enzymes which hydrolyze choline esters: (1) acetylcholinesterase (AChE), or true cholinesterase, and (2) butyrylcholinesterase (BuChE), frequently called plasma cholinesterase, serum cholinesterase, or pseudocholinesterase.¹ Acetylcholinesterase occurs in neurons, at the neuromuscular junction, in erythrocytes, and in certain other tissues.¹ Practically all of the pharmacologic effects of the anti-cholinesterase agents, including those of parathion, are due to the inhibition of AChE, with the subsequent accumulation of endogenous acetylcholine.¹

Throughout the remainder of the document, the designation ChE is used interchangeably with the word cholinesterase. In all instances where ChE appears, it will be preceded or followed by either RBC, designating the erythrocyte enzyme, or plasma (or both), or blood, or whole blood in order to clearly indicate which cholinesterase(s) is/are being referred to. In a similar vein, the designation RBC is used interchangeably with erythrocyte.

BuChE is present in various types of glial or satellite cells of the central and peripheral nervous systems, as well as in the plasma, liver, and other organs.¹ It has no known physiologic function; inhibition of the plasma enzyme at most sites produces no apparent functional derangement.¹ Lehmann and Liddell²⁰ speculated that the plasma ChE may hydrolyze those cholinesters which inhibit acetylcholinesterase. These include propionylcholine and butyrylcholine, which can be formed *in vitro* by enzyme systems responsible for the synthesis of acetylcholine and may be produced also by bacterial action in the gut. There are a number of atypical plasma ChE's, discovered through an investigation of abnormal responses to the muscle relaxant, succinylcholine, which appear to be genetically controlled variants with differing abilities to hydrolyze acetylcholine and related compounds.^{20,21}

Parathion has only a slight direct inhibitory action on plasma and RBC ChE's but its active metabolite, paraoxon, is a potent inhibitor of these enzymes.²²⁻²⁵ The resultant phosphorylated enzyme is stable, so that hydrolysis leading to reactivation of the enzyme occurs slowly. Hydrolysis is limited, however, by another spontaneous reaction, aging, which leads to a stable phosphorylated RBC ChE, refractory to spontaneous or induced hydrolysis.¹

Aging of the phosphorylated enzyme has been attributed to a mono dealkylation of the phosphoryl or phosphonyl moiety, resulting in a change in the electronic charge of the phosphorus atom such that it can no longer be approached by the hydroxyl ion of water.²⁶

Regeneration of non-aged phosphorylated AChE is accelerated by nucleophilic reactivators, such as choline, pyridine, hydroxylamine, hydroxamic acids, and oximes.²⁷ In 1951, Wilson²⁸ reported that choline and hydroxylamine reactivated diethyl phosphorylated-AChE considerably faster than water alone. Childs et al²⁹ found that the oximes were generally superior to the hydroxamic acids in reactivating OP-inhibited ChE. Wilson³⁰⁻³² synthesized and tested several monoquaternary pyridine aldoximes. Subsequently,³³ pyridine-2-aldoxime (2-PAM; pralidoxime) methochloride was found to be highly effective in the reactivation of non-aged, inhibited RBC and neuroeffector ChE's.

(b) Absorption

Parathion is absorbed through the gastrointestinal tract,³⁴⁻³⁶ the respiratory tract,^{37,38} and the skin, the mucous membranes, and the eyes.^{11,16,39-41} Gleason et al⁴² pointed out that the response sequence and the interval between exposure and response are partly dependent upon the portal of entry. Respiratory tract symptoms usually appear first during a respiratory exposure⁴³ whereas the presenting symptoms are more likely to be gastrointestinal following ingestion.¹⁶ As shown by experimental results,⁵ parathion (equivalent dose basis) is less toxic by the dermal route than by ingestion. Holmstedt⁴³ speculated that this may be due to enzymes in the skin causing hydrolysis of parathion, much in the same way that paraoxon is detoxified partially during passage through the skin in man, rabbit, and cat as reported by Fredriksson et al.⁴⁴ However, the latter investigators⁴⁴ were unable to show that significant metabolism of parathion takes place in dermal tissue; it was absorbed in essentially unchanged form. Passage of parathion through human skin was shown to be relatively slow (0.001 $\mu\text{g}/\text{min}/\text{sq cm}$ *in vitro*),⁴⁵ and consequently a dermal exposure may result in a substantial as well as a prolonged period of absorption. However, although dermal absorption of parathion is a relatively slow process, the compound is neither irritant nor caustic in nature³⁹ and therefore provides no warning to the individual that his skin has been contaminated with parathion. Thus, dermal absorption leading to signs and symptoms of poisoning may occur without any awareness on the part of the exposed

individual. In actuality, dermal absorption has been shown to be a potentially greater hazard than respiratory absorption for parathion applicators.⁴⁶

In controlled studies, Durham et al⁴⁶ evaluated the comparative dermal and respiratory exposure of workers subjected to the mist from an airblast spray machine during parathion application in orchards. Three test subjects were about equally exposed to the parathion spray drift by transport in a vehicle following the spray machine at such a distance that the spray mist that came into contact with their bodies had to be fine enough to remain suspended in the air for a comparatively long period. The fine mist encountered approximated that to which the operator of the spray rig was exposed. One individual was completely covered with rubber and plastic clothing to prevent skin contamination. He wore no respirator and thus had a respiratory exposure. A second worker wore a respirator and breathed only noncontaminated air; however, he wore ordinary clothing and thus his exposure was dermal only. The third person had neither respiratory nor dermal protection, other than ordinary clothing. All three subjects wore absorbent pads to provide a measure of their surface exposures to airborne parathion. Analysis of the absorption pads worn by the subjects confirmed that all were subjected to parathion of the same order of magnitude (approximately 0.03 mg/sq in. for the 2 "protected" workers). However, total p-nitrophenol (PNP) excretion for the man wearing the rubber and plastic clothing (respiratory exposure only) was 0.088 mg; for the individual using the pure air supply (dermal exposure only), 0.666 mg; and for the man using no special protective equipment (both respiratory and dermal exposure), 0.433 mg. Since parathion has been shown by Fredriksson⁴⁴ not to be hydrolyzed or transformed into paraoxon by the skin of man, the use of urinary PNP excretion appears to be a valid procedure for the relative measurement of parathion absorption. The results show that dermal absorption exceeded that by the respiratory route by several times, clearly indicating the potential danger from dermal exposure to parathion.

Dermal absorption of parathion may be increased by the solvent used. Absorption of parathion from the skin of the forearm was approximately tripled by its application in the known irritant xylol above that measured when it was applied in acetone.⁴⁷

(c) Metabolism

The observation by Diggle and Gage²² that parathion in a pure state was a poor inhibitor of rat brain ChE in vitro led to the conclusion that

metabolic conversion was necessary. Incubation of parathion with liver slices did produce the active inhibitor, O,O-diethyl-O-p-nitrophenyl phosphate (paraoxon).^{24,48} Kubistova²⁴ demonstrated in vitro that enzymatic oxidation takes place also in the gut, lungs, kidneys, and suprarenal glands. Gardocki and Hazleton⁴⁹ found PNP to be the major nonphosphorus-containing end product of parathion metabolism in dogs, although traces of p-aminophenol were also found. PNP has been shown to be a major urinary metabolite of parathion in man.^{50,51}

(d) Acute Effects

The acute effects of parathion are due largely to its ability to inhibit ChE's throughout the body.¹ As indicated in the preceding section, inhibition of these enzymes in animals (including man) leads to the accumulation of endogenously produced acetylcholine, with the resultant signs and symptoms in man set forth in Table III-1.^{18,52} This table classifies man's response according to muscarinic, nicotinic, and central nervous system (CNS) responses. Muscarinic effects refer to the action of parathion on autonomic effector cells of the eyes, heart, lungs, stomach, blood vessels, and other organs.¹ Varying proportions of muscarinic receptors are also present on autonomic ganglion cells and on certain cortical and subcortical neurons.¹ The nicotinic actions of parathion refer to its effects (initial stimulation in high doses leading to subsequent blockade) on autonomic ganglion cells and the neuromuscular junction, actions comparable to those of nicotine.¹ Such a classification scheme is of some use in the rationale for treatment and diagnosis, since atropine, in the dosages normally used to treat parathion poisoning, blocks the muscarinic and CNS effects, but not the nicotinic effects.¹

The frequently observed delay in onset of symptoms of poisoning after exposure to parathion is attributed to the requirement that parathion be metabolized in the body to paraoxon.²⁵ However, commercial preparations of parathion have been reported²² to contain small amounts of the S-ethyl isomer which can produce localized effects at the site of contact. The sequence of symptoms depends on the route of entry of parathion preparations into the body and on their composition.^{16,43}

Appearance (signs of) of poisoning with dermal exposure to parathion is delayed, the onset being insidious after a latent period of one or more hours.^{9,17,52} Delayed absorption of parathion from material deposited on the skin or clothing can also occur over a period of several weeks or months. Kazen et al⁵³ found parathion on the hands of one

man 2 months after his last known contact with the insecticide. The authors found 38.8 μ g of parathion on the hands of another pesticide applicator 31 days after spraying. The delay of occurrence of systemic effects following dermal exposure to parathion may be attributable to two factors:

(1) the slow rate of absorption through the skin⁴⁵;

(2) contaminating paraoxon may be partially detoxified during passage through the skin.⁴⁴

Although the acute lethal dose for man is unknown, the results of animal experiments, as presented in the Animal Toxicity section, demonstrate the extreme toxicity of parathion to mammals.

Many occupational accidents involving parathion have occurred through the dermal route.^{6,8,9,18} Tabershaw and Cooper⁹ presented the case histories of several workers who developed signs and symptoms (eg, nausea, vomiting, weakness, blurring of vision) of OP insecticide poisoning while picking citrus fruits in orchards previously sprayed with parathion. In some cases, the insecticide had been applied as long as 25 days before worker entry, thus implicating the dermal route of exposure. However, it is difficult to rule out completely the possibility of concurrent respiratory and oral intake.

Hartwell et al³⁷ exposed human volunteers to vapor or particulates of parathion generated by either heating parathion dust or technical grade parathion or by spraying technical grade parathion into a chamber. No air sampling was performed. Urinary PNP excretion was determined from immediately prior to exposure until 40 hours after exposure. Both RBC and plasma ChE activities were determined. Neither the 2% dust heated to 82°F and 120°F nor the technical grade heated to 82°F and 105°F produced depressions exceeding 30% of preexposure values in either RBC or plasma ChE activity levels. Also, urinary PNP excretion was minimal in these exposures. However, a subject exposed to parathion accidentally heated to 150°F experienced signs of poisoning, a decline in RBC and plasma ChE activities to 2% and 12% of normal, respectively, and the excretion of large quantities of PNP (approximately 6 mg in 7 days).

In one Texas episode,⁸ a group of field workers entered a cotton field containing plants about 3½ feet tall approximately 12 hours after an aerial application of a mixture containing parathion and methyl parathion. After working around the dew-laden plants for 2½-3 hours, 23 of the workers

became ill, exhibiting signs and symptoms of organophosphorus insecticide poisoning. No indication of the dosage received was provided. Because of the extremely low vapor pressures of the pesticides,⁵⁴⁻⁵⁶ the time of entry into the treated field, the dew-laden nature of the foliage, and the necessity of worker-plant surface contact, these acute poisoning cases were probably due primarily to dermal absorption of the insecticides.

(e) Chronic Effects

Another hazard to workers relates to repeated exposures to small quantities of parathion, such that during a period of time the cumulative effect on tissue AChE may lead to toxic effects. Parathion itself, or its metabolic oxidation product paraoxon, does not cumulate to a significant degree in the body as evidenced by urinary PNP excretion.^{50,51} However, the effects of repeated small doses do become cumulative if replacement of AChE at its sites in tissues does not keep pace with the extent of inhibition of the enzyme.⁵⁷

In an effort to determine, on the basis of daily ingestion, the amount of parathion capable of producing minimal toxicity, Rider et al³⁴ exposed groups of five human volunteers to daily oral doses of either 3.0 mg, 4.5 mg, 6.0 mg, or 7.5 mg for periods approximating 30 consecutive days. Each group contained 2 control subjects who received only corn oil. The groups exposed to 3.0 mg and 4.5 mg showed no changes from baseline ChE levels. The group at the 6.0-mg level sustained a slight (unspecified) depression of plasma ChE. The effects of 7.5 mg/day were such that by day 16 the plasma ChE levels of 2 subjects had decreased to 50% and 52% of pretest levels, respectively, at which point administration of parathion was discontinued; by day 23, the plasma ChE activity of another test subject had dropped to 54% of his pretest level, at which point his participation in the study was ended. The remaining 2 subjects continued throughout the 35-day test period. Their lowest plasma ChE values were 86% and 78% of pretest values, respectively. The lowest RBC ChE activity levels obtained during the study for the 3 subjects to whom the administration of parathion was discontinued were 63%, 78%, and 86% of pretest levels, respectively. The 2 subjects who completed the test period experienced no significant reduction of RBC ChE activity. The plasma ChE was affected to a greater extent than the RBC ChE. The investigators considered that average depressions of the ChE activities in blood of 20-25% below control values were significant. The results demonstrated that the daily ingestion of 7.5 mg of parathion by man during 35 days led to a

significant reduction in blood ChE activities and thus constitutes an unsafe ingestion level. Because of the incompleteness of the data on the 6.0-mg daily dose, NIOSH concludes that only the 4.5-mg daily dose can be regarded as the maximum safe dose for parathion tested.

In another study, Edson³⁵ found that an oral dose of 7.2 mg parathion/day, 5 days/week, for 6 weeks produced a 33% decrease in whole blood ChE activity (16% and 37% for RBC and plasma ChE, respectively) in 4 adult female volunteers. This corresponded to a daily oral intake of 0.078 mg/kg. No significant effects on the activities of ChE's in blood were observed as a result of the daily oral ingestion by groups of 4 subjects of either sex of 0.6, 1.2, 2.4, or 4.8 mg of parathion for periods ranging from 25 to 70 days. The results showed that a safe no-effect daily oral dose of parathion in humans was smaller than 0.078 mg/kg and greater than 0.058 mg/kg.

In 1958, Rider et al³⁶ published the results of similar studies which demonstrated that the daily ingestion of 0.05 mg/kg/day of parathion by humans produced no significant decrease in plasma or RBC ChE activities and thus constituted a safe ingestion level.

Kay et al⁵⁸ studied the effects of exposure to parathion sprays on the ChE activities of the blood of Quebec apple-growers. Airborne parathion concentrations were determined, using impingers and fritted glass bubblers in series, both during and after spraying of 15% wettable powder (W/w) in concentrations of 0.75 to 1.5 lb/100 gal of water and dispersed at the rate of 300-400 gallons/acre. The orchards were sprayed from early May through June. Measurements were made in 4 orchards during approximately 4 weeks, beginning on May 28th. Both hand-held and mechanical sprayers were used. Air samples taken from the breathing zones of the operators ranged from 2 mg to 15 mg/m³ of air, reflecting downwind versus upwind (with heavy "blow back" and resultant high exposure) spraying. The sprayers were exposed for approximately 2 days at 10-day intervals during a 2-month period. Personal protective measures, such as coveralls, rubber boots, caps, and fabric mitts, were used by some workers. Respirators were indifferently used by approximately one-third of the group. Both RBC and plasma ChE activities were determined by a modified Michel technique. Blood samples were taken thrice during the spraying period and singly during the first and fourth months following the termination of exposure, for use as control values. Depression of RBC ChE activity at the end of exposure averaged 21% for all

sprayers, 27% for those reporting symptoms, and 17% for those reporting no symptoms, the difference between the depressions in the symptomatic and the symptom-free groups being insignificant. The results for plasma ChE, however, presented a different picture. In the group reporting symptoms, the plasma ChE activity was 20% lower than in the group reporting no symptoms. Using the average control value for all subjects determined approximately 3 months following exposure, the plasma enzyme activities in the groups reporting symptoms and no symptoms were depressed 22% and 3.5%, respectively. The authors reported that approximately one-half the exposed workers reported no symptoms of ill-health. The symptoms mentioned by the remaining half included nausea, headaches, and other non-specific symptoms on one or more occasions, with a few cases of confining illness of short duration. Two major points must be emphasized concerning these results. Firstly, the exposure to parathion was intermittent allowing time for partial return of blood ChE activity. Regeneration and replacement of enzyme activity between exposures undoubtedly account for the fact that depressions were not more severe in light of the magnitude of the airborne exposure to parathion. Secondly, little emphasis can be placed on the association between the occurrence of the reported non-specific symptoms and the levels of depression of RBC and plasma ChE activities due to the inability to calculate incidence rates from the data. Hayes et al⁵⁹ found that part-time OP insecticide applicators experienced nausea no more frequently than did controls (5% vs 4%) and headache less often (5% vs 19%).

CNS effects of chronic exposure to parathion and similar compounds have been reported.⁶⁰⁻⁶³ Gershon and Shaw⁶¹ reported the effects on the CNS of 16 workers "chronically exposed" to OP insecticides, including parathion. Of the 16 cases mentioned, only 4 case reports were presented by the authors. In one case involving parathion exposure, the individual exhibited severe depression, nightmares, impairment of concentration and memory, headache, and irritability. A schizophrenic reaction including auditory hallucinations was observed in a second parathion-exposed worker. Nausea and vomiting, muscle cramps, and dizziness also occurred in both. Parathion exposure levels were not reported. In both of these cases, after cessation of exposure for several months, these effects disappeared and the patients were feeling well. However, it must be emphasized that both of these cases involved expo-

sure to parathion and other ChE-inhibiting insecticides. Other investigators⁶⁴⁻⁶⁶ have presented reasons, and data, to doubt the conclusion of Gershon and Shaw that the psychoses studied by them were consequences of exposure to OP compounds.

Mixed exposures to pesticides are common in agriculture, a situation which complicates distinguishing definite, specific biologic responses to exposures to individual compounds. In a similar vein, Davignon et al⁶² reported on the chronic effects of insecticides, including parathion, in man. Signs of possible chronic intoxication due to insecticides were sought among 441 apple-growers. Because the growers had been exposed at various times to undetermined quantities of malathion, parathion, azinphosmethyl, carbophenothion, DDT, endrin, carbaryl, and other insecticides, the observed increased incidences of leukopenia and neurologic abnormalities, including weakening or loss of reflexes and disturbances in equilibrium, could not be attributed securely to parathion.

Durham et al,⁶³ in a study of 53 persons exposed to OP insecticides to determine whether or not mental effects may precede or take place in the complete absence of other more disabling signs or symptoms of OP poisoning, found no mental effects at levels where other clinical symptoms were not also present. In one case, an aircraft loader was exposed to undetermined amounts of parathion, tetraethylpyrophosphate, demeton, and mevinphos at various times for approximately 6 weeks. Sometime after the third week, he frequently became dizzy, noticed a slowing of his driving reactions, and complained of a loss of sense of timing. Prior to the appearance of these effects, his blood ChE activity was shown to be severely depressed (RBC and plasma ChE activities were reported as 0.10 and 0.27 Δ pH/hr, respectively). In addition, other more common signs of poisoning, such as muscular twitching (eyelids), nausea, and anorexia, had preceded the mental effects. Mental confusion and hallucinations occurred in another worker after 6 weeks of spraying trees with parathion using a hand-held sprayer. Headache, nausea, and paresthesia preceded the mental effects, which included confusion, hallucinations, and amnesia. None of the so-called mental effects persisted after termination of exposure.

There is an indication that electromyography (EMG) can detect changes in neuromuscular function in parathion-exposed workers who show no evident effect from their exposure.^{67,68} These

changes were present in test subjects exposed to a variety of pesticides even when there was no measurable decrease in blood ChE activity or adverse changes as indicated by routine physical examination.⁶⁷ EMG may prove to be a sensitive method to provide an early warning of exposure to parathion as well as other OP pesticides.

Some attention has been given to the possibility that parathion may produce the type of paralysis reported as a consequence of exposure to TOCP (tri-*o*-cresyl phosphate), DFP, and mipafox (N,N'-diisopropylphosphorodiamidic fluoride).⁶⁹ Bidstrup et al⁶⁹ stated that according to their observations the noted effects of mipafox closely resembled those of "ginger" paralysis caused by the drinking of extract of Jamaica ginger contaminated with TOCP. Although a case report⁷⁰ of suspected parathion-produced delayed paralysis was published in 1950, it does not clearly implicate parathion as a cause of permanent neuromuscular damage. Petry⁷⁰ reported that delayed polyneuritis developed in a worker who had sprayed a dilute solution of parathion within closed hothouses during a 4-week period. Subsequent to each of 10-12 applications, the man experienced nausea, an urge to vomit, and anorexia. Approximately 50 days following the last spraying, during which time he became ill with severe gastritis and was hospitalized, he noticed a feeling of tingling, numbness, and weakness in his legs which ultimately progressed to a permanent paralysis of the peroneus muscles. However, this appears to be an isolated human case and delayed adverse neuromuscular effects, such as paralysis, have not been shown to be a usual effect of parathion exposure, either acute or chronic.

The question of variability of individual susceptibility to parathion poisoning has not been studied fully. Experimental data⁷¹ indicate strongly that both plasma and RBC ChE may serve as "buffers", protecting functional AChE from inhibition by DFP. Although few in number, there are in the general population people who have a genetic plasma ChE variant^{20,21} which, in the heterozygous or abnormal homozygous state, may serve less well as a buffer than the normal enzyme. However, Tabershaw and Cooper⁹ in studying the case histories of 108 individuals poisoned by parathion or other OP pesticides found that 5 persons with the heterozygous variant were not more severely poisoned than those with the normal enzyme. People heterozygous for this variant occur in the normal population to the extent of 37/1,000, while the frequency of the atypical homozygote has been

estimated at 1/2820 of the population.²¹ Depression of liver function by hepatotoxic materials can result in lower plasma ChE.⁷² Low plasma levels are also seen in malnutrition, chronic debilitating disease, acute infectious disease, and anemia.⁷²⁻⁷⁴ Drugs which have been shown to decrease plasma ChE activity include physostigmine and related compounds,⁷⁵ Vitamin K,⁷² folic acid,⁷² tetraethylammonium chloride,⁷² quinine and a number of other antimalarial drugs,⁷⁶ morphine, codeine, and related analgesics.⁷⁷

The rate of return of plasma ChE activity to its normal value in man following depression by parathion has been shown to be approximately 3-4%/day.¹⁸ In a study of 18 subjects whose plasma and RBC ChE had been depressed by parathion, the plasma enzyme increased at an average rate of approximately 9% of normal activity during each of the first 3 days. This rate decreased to 5% by the fourth day and to 3% by the tenth day, after which it remained steady. During the first 3 days following depression, the RBC enzyme activity increased at an average rate of approximately 3.3% of normal activity. This rate diminished to between 1-2%/day by the fourth day and remained relatively constant thereafter (RBC ChE activity increased about 90% in 70 days).

Epidemiologic Studies

Epidemiologic studies of parathion-exposed worker populations have been directed at identifying the types of workers at greatest risk, the environmental conditions associated most frequently with poisoning, and the biologic results of prolonged exposure in an effort to determine whether or not chronic effects occur. One study⁵⁰ involving exposure to parathion indicated that mixing-plant personnel, commercial ground applicators, aircraft application workers, and orchard workers were the groups at greatest risk, while field men and warehousemen were at lesser risk.

In 1976, Maddy and Peoples⁷⁸ reported on occupational illnesses due to exposure to pesticides or their residues in California during 1973-75. Under the category of systemic illness the 5 occupations experiencing the greatest problems in those years were: (1) ground applicators—96 cases; (2) mixers and/or loaders—74 cases; (3) indoor workers exposed to pesticides—50 cases; (4) formulation plant workers—41 cases; and (5) firemen exposed to pesticide fires—37 cases. Field workers exposed to pesticide residues was the number 6 category, with 28 reported systemic illnesses.

The remaining 18 categories accounted for only 39% of the reported occupational illnesses due to pesticides. These data indicate the more hazardous occupations in the pesticide "industry." This report by Maddy and Peoples⁷⁸ encompasses all pesticides and is not specific to parathion.

In 1950, Brown and Bush⁷⁹ reported a study of workers in an industrial plant manufacturing both concentrated parathion and a dust formulation containing parathion. Air samples were taken at 8 locations throughout the plant; 2 samples were taken in the breathing zone of workers and the others were general atmosphere samples. Blood ChE (RBC and plasma) activity measurements were performed on 12 workers engaged in various jobs during a 6-month period. The concentration of parathion in the air varied from 0.1 to 0.8 mg/m³, with a mean exposure concentration of about 0.2-0.3 mg/m³. Details of times of sampling were not given. A greater than 30% depression in either or both plasma and RBC ChE activity was observed in 5 exposed workers from whom successive blood samples were taken during a 6-month production period. The authors reported that the plasma enzyme activity was depressed more than that of the RBC's. However, based on blood ChE activity levels measured 5 months following the cessation of parathion manufacture (ie, using these values as control levels) RBC enzyme activity was depressed to a greater extent than that of the plasma in these 5 workers during the exposure phase. Since the data do not allow for correlation of the ChE activity of whole blood with airborne concentrations of parathion on a precise basis, the only reasonable conclusion from the results is that continuous exposure to an airborne concentration of parathion above 0.2 mg/m³ can result in a reduction in blood ChE activity. The data do not identify a safe exposure level. No mention was made of percutaneous parathion absorption.

Arterberry and associates⁵⁰ used measurements of both blood ChE and urinary excretion of PNP to identify occupations with high exposures to parathion. These biologic indicators were used to determine the extent of exposure to parathion by workers performing a variety of jobs. The study groups included mixing plant personnel, commercial ground applicators, part-time ground applicators, aircraft application workers, workers in orchards (especially thinners), field men, warehousemen, miscellaneous workers, and residents living near orchards. Only the mixing plant workers showed a definite decrease in ChE activity within the blood, limited to ChE activity in the RBC's (36% decline). PNP excretion was greatest

in the commercial ground applicator group and decreased in the following order: part-time ground applicators, mixing plant personnel, aircraft application workers, and workers in orchards (especially thinners). The PNP excretion of the field men and warehousemen was less than half that of the orchard workers. The study demonstrated that mixing plant personnel, ground applicators (commercial and part-time), aircraft application workers, and orchard workers were the groups at greatest risk, while field men and warehousemen were at lesser risk.

Quinby and Lemmon¹³ called attention to the residue of parathion on the foliage of trees and vines as a source of poisoning. They investigated 11 episodes of group poisoning involving more than 70 persons from pesticide residues on the surfaces of plants. Illness was confirmed by low blood ChE values and relief of symptoms by atropine. One episode involving 16 cases occurred 33 days after spraying. Two days after the outbreak of poisoning, residue analysis showed that the leaves contained 8 ppm of parathion.

Milby and coworkers¹¹ studied an outbreak of parathion poisoning in 186 peach orchard workers. After elimination of the spraying-picking interval by matching workers in the various orchards on the basis of similar mean intervals, illness developed in orchards that received an average of 7.14 pounds/acre of parathion but did not develop in those that received an average of 4.99 pounds/acre. However, Milby et al,¹¹ utilizing breathing zone air samples and skin washes to measure the potential inhalation and dermal exposures, calculated that the maximal daily dose of parathion with which a worker could have come into contact was not in excess of 4 mg. This value was derived in the following manner: the ingestion

of 4 peaches/day with parathion residue levels of 125µg/peach; inhalation of 350µg parathion/day based on the highest breathing zone concentration found in the study, 35µg/m³, and a breathing rate of 10 m³/day; and a calculated daily dermal exposure of around 3,000µg based on multiplying the results of skin-rinse analyses by skin surface areas. They concluded that insufficient parathion was present on the surface of trees to produce illness in the orchard workers, and that some unmeasured, yet active anticholinesterase agent, probably paraoxon, also must have been present. Supporting this conclusion was the fact that one sample of leaves analyzed for paraoxon indicated the presence of 3.0 ppm paraoxon and 2.8 ppm parathion.

Animal Toxicity

Table III-4 summarizes animal data on the toxicity of parathion by various routes of administration. Evaluative or qualifying information on each study is included in the more complete description of the study as reported in the text.

(a) Acute Effects

LD50 data for various species are presented in Table III-2.

Because there is a significant sex difference in response to parathion in rats,^{5,80} separate values are provided for males and females. Such marked sex differences were not seen in other species.^{5,80,81}

(b) Subacute Studies

A cumulative toxic action of parathion in female rats was shown by DuBois et al.⁸⁰ After daily intraperitoneal doses of 3 mg/kg of parathion, none of 15 test animals survived more than five doses of the insecticide. Daily intraperitoneal doses of 1 and 2 mg/kg of parathion for 10 days resulted in 46% and 87% mortality, respectively. None of 5

TABLE III-2

LD50 VALUES OF PARATHION (mg/kg)

	IV [80]	IP [80]	Oral [5]	Dermal [5]
Rats				
Male	—	7	13	21
Female	—	4	3.6	6.8
Mice	—	9-10	—	—
Cats	3-5	—	—	—
Dogs	12-20	—	—	—

TABLE III-3

EFFECTS ON HUMANS FROM PARATHION EXPOSURE

Route(s) of Exposure	Number of Subjects Exposed	Exposure Concentration and Duration	Effects	Reference
Respiratory	1	2% parathion dust (PD) heated to 82°F for 30 min. on day 1; 2% PD heated to 120°F for 30 min. on days 2 and 3; 1 ml tech parathion (TP) heated to 82°F for 30 min. on day 6; 1 ml TP heated to 105°F for 30 min. on day 8; 1 ml TP heated to 120°F for 30 min. on days 10-12 (in all exposures breathing zone concentrations of parathion were unknown).	No signs or symptoms of parathion poisoning observed. At 82°F, lowest RBC ChE activity was 80% of pre-exposure value. Insignificant plasma ChE inhibition. No depression of ChE activities at 105°F. At 120°F, lowest RBC and plasma blood ChE activities were 63% and 66% of pre-exposure values, respectively.	[37]
"	1	First 3 exposures listed for above subject.	No signs or symptoms of parathion poisoning observed. At 82°F, lowest RBC ChE activity was 85% of pre-exposure value; insignificant inhibition of plasma ChE. At 120°F, lowest RBC and plasma ChE activities were 78% and 89% of preexposure values, respectively.	[37]
"	1	1 ml TP heated to 105-115°F for 30 min. on 4 consecutive days; 5 ml TP heated to 150°F for 10 min. on 5th day.	No clinical signs of poisoning either during or following the first 4 exposures; after 10 min. at 150°F (accidental), the subject developed unspecified signs of parathion poisoning.	[37]
Dermal and respiratory	1 female and 32 male adults (39 nonexposed controls)	A "few days" (unspecified) exposure during each 10-day spraying interval over a 2-month period to airborne concentrations of parathion ranging from 2 to 15 mg/cu m (during orchard-spraying operations).	Signs and symptoms, including headaches and nausea, were reported by about one-half of the exposed group. Average RBC and plasma ChE activities were 21% and 13% lower at the end of the spray period than they were about 4 months later. The plasma ChE activity in the group with symptoms was 20% lower than in the symptom-free group.	[58]
"	1 male	Exposed to a 1:10,000 spray of parathion 10-12 times during a 1-month period (during hot-house spraying operations).	Subject experienced nausea and vomiting several hours after each spraying; was hospitalized about 2 months later with gastritis. Ultimately developed polyneuritis in the legs.	[70]
"	12, plus 1 listed as being "not exposed"	Intermittent exposures to parathion at concentrations of 0.1-0.8 mg/cu m.	No signs or symptoms of parathion poisoning. Apparently significant depressions of both RBC and plasma ChE activities in some employees.	[79]
"	115*	Varied, but unknown (no air sampling performed).	36% decline (mean) in the RBC ChE activity in the blood of mixing-plant employees. No significant decline in the plasma ChE activity of either mixing-plant employees or any of the other exposure groups.	[50]

TABLE III-3 (CONTINUED)

Route(s) of Exposure	Number of Subjects Exposed	Exposure Concentration and Duration	Effects	Reference
Dermal	Not stated (cotton-field workers)	Entered the field about 12 hours after the aerial application of a mixture of methyl parathion and parathion; worked for 2.5-3 hours.	23 workers exhibited signs/symptoms of OP poisoning; 13 required hospitalization while 10 were successfully treated as outpatients.	[8]
Oral	5, plus 2 nonexposed controls	Subjects orally ingested capsules containing 3.0, 4.5, 6.0, or 7.5 mg parathion/day for approximately 30 days. Controls received corn oil only.	No significant inhibition of RBC or plasma ChE activities at 3.0 and 4.5 mg/day doses. "Slight" (unstated %) inhibition of plasma ChE at the 6.0 mg parathion/day dose. Plasma ChE activities were inhibited to 50% and 52% of pretest levels in 2 of 5 subjects receiving 7.5 mg parathion/day for 16 days. After 23 daily doses of 7.5 mg parathion, a third subject's plasma ChE activity was 54% of his normal value. Effects were less on the RBC activities of the exposed subjects. No signs/symptoms of poisoning were reported by the authors.	[34]
"	4 (males and females)	Subjects orally ingested 0.6, 1.2, 2.4, 4.8, or 7.2 mg parathion/day, 5 days/week for 25-70 days (4 adult females received the 7.2 mg/day doses).	Effects on blood ChE activities were observed only at the 7.2 mg/day dose: whole blood ChE activity declined to 67% of control activity after 6 weeks (RBC and plasma ChE activities at this time were 84% and 63% of control activities, respectively). No signs/symptoms of parathion poisoning were reported by the author.	[35]
"	8 (4 males and 4 females)	Subjects orally ingested 4 dose-levels of parathion for 12 weeks at 3 weeks/dose-level. The successive doses (capsules containing parathion in corn oil) were 0.003, 0.010, 0.025, and 0.050 mg/kg. 2 subjects received corn oil only.	No effects on RBC or plasma ChE at any dose level. No signs/symptoms of parathion poisoning were reported by the authors.	[36]

* 35 mixing-plant personnel, 2 commercial ground applicators, 44 part-time ground applicators, 4 aircraft application workers, 7 orchard workers, 3 fieldmen, warehousemen, and miscellaneous workers, and 20 residents near orchards.

TABLE III-4

RESULTS OF ANIMAL TOXICITY STUDIES OF PARATHION

Route of Administration	Species	Number	Results	Reference
Intraperitoneal injection: a) 3 mg/kg/day b) 2 mg/kg/day c) 1 mg/kg/day d) 0.5 mg/kg/day	Rats (female)	a) 15 b) 15 c) 24 d) 5	a) None survived more than 5 doses b) 87% mortality after 10 days c) 46% mortality after 10 days d) No deaths after 20 days of dosing	[80]
Oral: 1 mg/kg for 9 days, followed by 2 mg/kg for 2 days, followed by 5 mg/kg for 4 days	Rats (sex unstated)	Unreported	No alteration of conditioned behavior	[82]
Oral: a) 12 mg/kg b) 8 mg/kg c) 6 mg/kg d) 4 mg/kg	Mice	20/group for behavioral tests; 6/group for ChE determinations	a) Impaired performance on a passive- avoidance task; killed 40% of test mice b) Impaired performance; killed 19% of test mice c) Impaired performance; killed 10% of test mice d) Impaired performance	[83]
Subcutaneous injection: 1-4 mg/kg for 6 days	"	"	No effect on passive-avoidance learning; marked effects on brain AChE	[83]
Intraperitoneal injection: 4.5 mg/kg a) injected into animals fed a casein-free diet for 30 days or b) into animals fed a 15% casein diet for 30 days	Rats (female)	a) 12 b) 12	100% mortality 67% mortality	[86]
Subcutaneous injection: (administered in 3 successive doses "adequate to produce a severe cholinergic response")	Chickens	Unreported	No muscular weakness or paralysis observed	[88]
Intraperitoneal injection: a) 1 mg/kg/day and b) 1.3 mg/kg/day	Rats (female)	a) 13 b) 13	All treated rats exhibited signs of acute parathion poisoning (tremors, respira- tory difficulty, cyanosis). A progressive myopathy developed in rats receiving 1 and 1.3 mg/kg/day. Less than 5% of muscle fibers studied were affected.	[89]
Intraperitoneal injection: 1.0 and 1.5 mg/kg (animals killed at 2 or 5 hours after parathion injection)	Rats (male)	"4 or more"/ dose	Both doses produced similar depressions of brain and RBC ChE: 20-25% and slightly less than 50% inhibition, re- spectively. No gross signs of parathion poisoning were observed. At 2 hours after parathion injection, plasma levels of free corticosterone increased by 75%.	[91]
Oral: 1.3, 2.6, or 5.3 mg/kg/day for 5 days	Mice (male)	Unreported	No significant alteration in the metab- olism of androgens.	[92]

TABLE III-4 (CONTINUED)

Route of Administration	Species	Number	Results	Reference
Inhalation:				
a) 0.04-230.0 mg/cu m for 4 hours	a) Rats (male)	a) 34/group	a) LC50 = 84.0 mg/cu m RBC ChE50 = 5.4 mg/cu m Plasma ChE50 = 7.3 mg/cu m	[Edge-wood Arsenal study]
b) 0.015-37.1 mg/cu m for 4 hours	b) Dogs (male)	b) 4/group	b) LC50 = greater than 37.1 mg/cu m	
c) 0.01 mg/cu m 7 hours/day, 5 days/week, for 6 weeks	c) Rats (male)	c) 80/group	c) 1 rat died on the 1st day. RBC ChE activity decreased to 69% of normal during week 4.	
d) 0.10 mg/cu m 7 hours/day, 5 days/week, for 6 weeks	d) "	d) 80/group	d) No toxic signs were seen. RBC ChE activity decreased to 57% of normal after 1 week of exposure.	
e) 0.74 mg/cu m 7 hours/day, 5 days/week, for 6 weeks	e) "	e) 80/group	e) Animals developed congestion of the lungs. RBC ChE activity decreased to 58% of normal after 1 week of exposure. RBC ChE activity decreased to 16% of normal after 5 weeks of exposure.	
f) 0.001 mg/cu m 7 hours/day, 5 days/week, for 6 weeks	f) Dogs (male)	f) 6/group	f) No significant inhibition of either RBC or plasma ChE activities.	
g) 0.01 mg/cu m 7 hours/day, 5 days/week, for 6 weeks	g) "	g) "	g) RBC ChE activity decreased to 79% of normal after 2 weeks of exposure; 101% of normal at the end of the 6-week exposure period. After 6-weeks exposure, the plasma ChE activity was depressed to 58% of normal.	
h) 0.20 mg/cu m 7 hours/day, 5 days/week, for 6 weeks	h) "	h) "	h) RBC Che activity decreased to 54% of normal after 2 weeks of exposure; plasma ChE activity at this time was 26% of normal.	
Oral:				
a) 0.18-7.0 mg/kg (single doses)	a) Rats (male)	a) 10/group	a) RBC ChE50 = 2.6 mg/kg plasma ChE50 = 2.5 mg/kg	[Edge-wood Arsenal study]
b) 0.50, 1.26, 2.5, and 10.0 mg/kg (single doses)	b) Dogs (male)	b) 4/group	b) RBC ChE50 = 1.5 mg/kg plasma ChE50 = 1.7 mg/kg	
c) 0.25 mg/kg, 5 days/week, for 6 weeks	c) Rats (male)	c) 80/group	c) RBC and plasma ChE activities were inhibited to 46% and 52% of normal after 6 weeks of exposure.	
d) 0.10 mg/kg, 5 days/week, for 6 weeks	d) "	d) "	d) Lowest RBC ChE activity observed was 78% of normal after 4 weeks of exposure. Plasma ChE activity inhibited to 20% of normal after 2 weeks of exposure.	
e) 0.05 mg/kg, 5 days/week, for 6 weeks	e) "	e) "	e) No significant inhibition of RBC or plasma ChE activities.	
f) 0.50 mg/kg, 5 days/week, for 6 weeks	f) Dogs (male)	f) 6/group	f) RBC and plasma ChE activities were 42% and 15% of normal, respectively, after 6 weeks of exposure.	
g) 0.10 mg/kg, 5 days/week, for 6 weeks	g) "	g) "	g) RBC and plasma ChE activities were 80% and 61% of normal, respectively, after 6 weeks of exposure.	
h) 0.05 mg/kg, 5 days/week, for 6 weeks	h) "	h) "	h) RBC and plasma ChE activities were 83% and 54% of normal, respectively, after 6 weeks of exposure.	

TABLE III-4 (CONTINUED)

Route of Administration	Species	Number	Results	Reference
Intraperitoneal injection: a) 3.0 mg/kg, given as a single ip injection to pregnant rats on the 11th day after insemination b) 3.5 mg/kg, given as a single ip injection to pregnant rats on the 11th day after insemination	Rats (female)	a) 5 b) 5	a) Symptoms of poisoning in the dams. High incidence of resorptions and reduced fetal and placental weights. One edematous fetus out of 28. b) Symptoms of poisoning in the dams. High incidence of resorptions and reduced fetal and placental weights. No fetal malformations reported.	[97]
Subcutaneous injection: a) 2 mg/kg/day for 4 days b) 1.5 mg/kg/day for 4 days beginning on days 1, 7, or 13 of gestation c) 2.0 mg/kg/day for 4 days beginning on days 1, 7, or 13 of gestation.	Rats	a) 28 52 rats used in experiments b) and c)	a) Signs of parathion poisoning, including salivation, lacrimation, diarrhea, and tremors observed in test animals. 2 of 28 rats died after the 2nd injection. Severe depression of blood and brain AChE's. b) Signs of parathion poisoning in dams. Brain AChE activity of pups was normal but was depressed in the dams. No fetal resorptions were observed. c) Signs of parathion poisoning in dams. 4 rats died, 3 during the 3rd trimester. Brain AChE activity of pups was normal but was depressed in the dams. No fetal resorptions were observed.	[98]
Intraperitoneal injection: injected ip with single doses of 4, 8, 10, 11, or 12 mg/kg at varying times during gestation. Laparotomy performed on mice on the 19th day of gestation.	Mice (female)	Unreported	12 mg/kg administered on gestational days 12, 13, and 14 produced 90% incidence of deaths in utero. 12 mg/kg administered on gestational days 8, 9, and 10 produced 27% incidence of deaths in utero. Parathion significantly reduced fetal body weight.	[99]

female rats injected with 0.5 mg/kg/day died after 20 days of continuous dosing. The symptoms preceding death of the animals were similar to those observed in acutely poisoned rats. From these results the investigators concluded that "... continued exposure to sublethal doses of parathion results in subacute poisoning in rats and suggests the possibility of a cumulative action by parathion in other animals after continued exposure to the insecticide."

The effect of parathion on avoidance behavior in the rat was reported by Bignami and Gatti.⁸² Parathion was given orally to rats previously trained to give avoidance responses in fully automated shuttle-boxes. No modifications of behavior were observed during daily doses of 1 mg/kg of parathion given for 9 days, of 2 mg/kg given for 2 days, and of 5 mg/kg given for 4 days.

In 1973, Reiter et al⁸³ reported the effects of parathion on ChE activities and learning in mice.

A single-trial, passive-avoidance task was used to evaluate learning. Blood and brain ChE activities were determined. Mice used in the acute phase of the study were starved for 18 hours prior to oral administration by intubation of parathion (in polyethylene glycol) at a dose of 6 mg/kg. At least 20 animals in each group were used for the behavioral tests and at least 6 animals per group for the ChE determinations. This dose produced death in about 10% of the animals, usually within 15 minutes of administration. The animals died with typical signs of parathion poisoning: tremors, convulsions, and respiratory distress. Parathion was administered at various times prior to the learning trial and at various times prior to retesting. The maximum effect on performance, at a dose of 6 mg/kg, occurred when parathion was administered within the first hour before the learning trial; about 31% of the mice treated within this period remained on the platform during retesting.

Parathion in oral doses of 4 mg/kg, 8mg/kg, and 12 mg/kg was also administered to groups of mice 45 minutes prior to the learning trial. As in the case of the 6 mg/kg dose, these doses of parathion resulted in impairment of performance. However, the 8 mg/kg dose killed 19% of the mice while 12 mg/kg killed 40% of the animals tested. Thirty minutes after administration of an oral dose of 6 mg/kg of parathion, AChE and ChE activities in both blood and brain declined to 30-55% of controls. To determine the effects of subacute parathion treatment, mice were given daily sc injections of parathion for a period of 6 days in doses ranging from 1 to 4 mg/kg. This treatment had no effect on passive-avoidance learning. However, marked effects were seen on AChE and ChE activities in blood and brain. It is interesting to note that when measured 18 hours after the sixth sc injection, the 2 mg/kg dose produced the same degree of inhibition which was present ½ hour after the 6 mg/kg acute dose, namely, a 55% reduction in brain AChE, with no effect on learning.

The results indicated that acute exposure to high doses of parathion impaired passive-avoidance learning in mice and that maximal changes in ChE activity correlated closely with peak behavioral effects. Contrary to these results were those in mice exposed subacutely to parathion. No effects on learning were observed in mice injected subcutaneously with parathion for 6 days despite the fact that significant depressions in blood and brain ChE's occurred. The authors concluded that these animals were able to compensate for increased amounts of ACh at central synapses.

The possibility that potentiation may occur with combinations of two or more anticholinesterase agents has been discussed by DuBois.⁸⁴ Of particular interest has been the combination of EPN and malathion which causes potentiation of the acute toxicities of the components.⁸⁵ DuBois reported that parathion showed simple, additive acute toxicity with EPN, Dipterex, Systox, Co-Ral, and Di-Syston and less than simple, additive acute toxicity with malathion and Guthion. Potentiation of toxicity was not observed for parathion.

Other factors which may influence sensitivity to parathion include diet and preexposure levels of plasma and RBC ChE. In a study of the effects of diet, Casterline and Williams⁸⁶ found that low protein diets increased the susceptibility of rats to parathion. An intraperitoneal dose of 4.5 mg/kg resulted in 100% mortality in rats fed a casein-free diet for 30 days vs one of 67% in rats fed a 15% casein diet for a similar period. Casterline and

Williams found that single doses of parathion inhibited liver and brain AChE to a greater extent when animals were fed an essentially protein-free diet.

The importance of plasma ChE and RBC ChE in the protection of acetylcholinesterase at tissue sites was clearly demonstrated by Karczmar and Koppanyi.⁷¹ In one series of experiments, they infused groups of 10-18 atropinized dogs with either isotonic saline, Tyrodes' solution, glucose, or a 0.2% solution of ACh in saline. Plasma and RBC ChE's were measured manometrically before and after the infusions. The maximal hemodilution produced by the infusions (concentration of hemoglobin decreased by $26 \pm 6\%$) was accompanied by a decrease in the activities of the ChE's of the blood of $28 \pm 7\%$. When these dogs were given iv injections of standard doses of ACh and BCh (benzoylcholine), the pressor responses elicited in that way were about twice those obtained in the same dogs before the infusions. Reduction of the activities of the ChE's of the blood by dilution with the saline solutions was concluded to have enhanced the abilities of choline esters degradable by these enzymes to stimulate sympathetic ganglia and the adrenals.

In a second series of 34 experiments, normal dogs were transfused serially for up to 15 times with blood from heparinized, atropinized dogs that had been given iv doses of DFP (2.5 to 4.0 mg/kg) to inactivate the ChE's in their bloods. In this way, the bloods of the recipient dogs were diluted with respect to both RBC and plasma ChE's without any general hemodilution. In this series of experiments, a 40% decrease in the activities of the ChE's in the blood enhanced the pressor response to injected ACh but not that to injected methacholine (MCh). When additional transfusions had reduced activities of the ChE's of the blood to 10 to 15% of the normal values, the responses to both injected ACh and MCh were increased fourfold. At this time, iv injections of DFP (0.25 to 0.50 mg/kg) into these dogs enhanced still further the responses to injected BCh but not those to injected ACh, presumably by inhibiting all, or at least most, of the remaining BuChE in the blood and tissues of these dogs.

A third group of 15 atropinized dogs was given sufficient DFP to inhibit completely the ChE's of all tissues. The responses to injected ACh and BCh were increased. These animals were then transfused with blood from normal dogs to restore the activities of the ChE's of their bloods to approximately normal levels. Although the ganglionic AChE and the BuChE of the intestine were still in-

hibited in these dogs, the responses to injected ACh and BCh were similar to those recorded before the administration of DFP.

Eight control experiments were carried out in which both the donor and the recipient dogs were normal. The responses in the recipient dogs to injected ACh, BCh, MCh, nicotine, and epinephrine varied from the mean pre-transfusion magnitudes by less than 15% after a series of transfusions.

These experiments demonstrated apparently the ability of the ChE's of the blood to react with circulating cholinergic and anticholinesterase compounds and to reduce their impacts upon active sites of effector organs. Accordingly, plasma and RBC ChE's have been considered to have important buffer-like roles in protecting the AChE at neuroeffector junctions and other active sites from the inhibitory actions of parathion and other organophosphorus anticholinesterase compounds.

Recovery of an animal from parathion poisoning and its reestablishment of normal susceptibility to intoxication by OP compounds depend upon the reestablishment of normal activities of ChE's in blood and tissues. Although parathion is classified as an "irreversible" inhibitor of ChE, the reaction is reversible, at least initially.⁸⁷ Grob⁸⁷ demonstrated in vitro that the combination between parathion and ChE's from human plasma, RBC's, and brain was partially reversible during approximately the first 3 hours after addition of the compound to the enzyme, and irreversible after that time. DuBois et al⁸⁰ demonstrated that in rats acutely poisoned with 5 mg/kg of parathion brain ChE activity regenerated from an observed low of 5.8% after ½ hour to 97% of normal activity in 4 hours.

In animals, parathion has not been shown to exert toxic effects other than those related to inhibition of AChE. The ability of some OP compounds to produce persistent paralysis accompanied by toxic changes in distal axons and demyelination of the sheath of the damaged axon has focused a great deal of interest on the part of researchers in this effect. Barnes and Denz⁸⁸ found that neither parathion nor paraoxon produced a paralytic effect in chickens whereas TOCP, DFP, and mipafox did. Severe cholinergic responses but no demyelinating lesions were observed in chickens after 3 successive doses of parathion (amount unspecified). The chickens were observed for 3 weeks after the third dose.

In 1972, Kibler⁸⁹ reported that parathion-induced histologic evidence of skeletal muscle necrosis in rats. Thirteen Sprague-Dawley rats received daily ip injections of parathion at a dose of 1 mg/kg and 13 received 1.3 mg/kg. All in-

jected rats demonstrated several signs of acute parathion poisoning 20-30 minutes after each injection. These signs included tremors, respiratory difficulty with tachypnea and mild cyanosis, lethargy, and decreased responsiveness to sensory stimuli. These lessened in severity during the next 2-3 hours. Animals receiving both doses were sacrificed on days 1, 3, 5, 8, 10, 12, and 14 after the first injection. Six rats died as the result of parathion toxicity (the doses administered represented approximately 0.5-0.75 the LD50 for this species); 26 animals were killed by injection of pentobarbital sodium; then sections of their quadriceps, gastrocnemius, and soleus muscles were prepared and studied microscopically.

According to the author, the animals receiving 1 mg/kg of parathion/day developed a progressive myopathy which reached a peak on day 8, after which the number of new lesions diminished. Rats receiving 1.3 mg/kg/day developed large numbers of completely disrupted and phagocytized muscle fibers by the 3rd day. Although the appearance of new lesions progressed to day 5, their fibers did not continue to undergo degeneration and subsequent phagocytosis. Kibler reported that less than 5% of muscle fibers studied were affected and that this percentage "is far too small to produce clinical weakness." The effects observed were postulated by the author to be due to excessive ACh at the neuromuscular junction caused by inhibition of AChE. The doses of parathion administered were very large. No mention was made of demyelination of nerves, but the author may not have looked at nerves.

In 1975, Johnson⁹⁰ published a review article on neurotoxicity caused by organophosphorus esters. The study by Barnes and Denz⁸⁸ was referenced along with a later study by Johnson on the neurotoxicity of certain organophosphorus compounds, including paraoxon. Paraoxon did not produce ataxia. Johnson's paper provides an interesting discussion of the possible mechanism of delayed neurotoxicity.

The stress of exposure to parathion has been shown⁹¹ to result in increased plasma levels of free corticosterone (PFC) in rats. Murphy⁹¹ attributed this action of parathion to its stimulation of pituitary ACTH since depletion of adrenal ascorbic acid accompanied the increase in PFC. The 2 lowest doses of parathion tested (1.0 and 1.5 mg/kg) produced 20-25% inhibition of brain ChE and approximately 50% inhibition of RBC ChE. No gross signs of poisoning were observed in these animals. PFC levels increased by about 75% two hours after injection of parathion.

In 1974, Thomas⁹² reported on the effects of parathion and other pesticides on the mouse reproductive system. Parathion in daily oral doses of 1.3, 2.6, or 5.3 mg/kg was administered by gastric intubation for 5 days to male mice and effects on the reproductive system determined by measuring the uptake and subsequent metabolism of 1, 2-³H-testosterone by the prostate gland. The uptake of tritiated testosterone was not affected by pretreatment with parathion. Regardless of the dose of parathion, no changes in the pattern of radiosteroids were detected. Thomas concluded that parathion did not produce any significant changes upon the uptake and metabolism of androgens by sex accessory organs of the mouse.

(c) New Unpublished Research Data

Based on the limitations of the aforementioned data, the decision was made by NIOSH in late 1973 that extrapolation from the then existing data to a recommended safe environmental limit (ie, safe airborne concentration) for man could not be achieved with an acceptable degree of scientific reliability. In order to obtain additional information regarding the inhalation toxicity of parathion in experimental animals, and particularly inhalation-to-oral toxicity ratios, research was undertaken for the Institute by the Toxicology Division, Biomedical Laboratory, Edgewood Arsenal. The research described below was conducted during the period July 1974-December 1975, during which time the parathion criteria document was held in abeyance.

The research consisted of 2 parts: (1) acute inhalation and oral toxicity studies on rats and dogs; and (2) subacute inhalation and oral toxicity studies using the same 2 species. Purebred adult male beagle dogs and adult male Sprague-Dawley/Wistar strain rats were used in the experiments. The effects of the insecticide on both RBC and plasma ChE were used to calculate inhalation-to-oral toxicity ratios for rats and dogs.

These ratios were then used by NIOSH to determine a predicted safe environmental limit for man based on a known safe human ingestion dose (see Chapter V, Development of Standard).

Technical grade parathion of 99.3% purity was used in the inhalation and oral experiments. Chamber air samples collected during the inhalation phases of the work were analyzed to determine whether any paraoxon was present in the air being breathed by the animals. No paraoxon or any other more toxic derivative of parathion was detected in any samples. Particle diameters of the aerosols generated, as determined by use of a Rochester cascade impactor, were 1.0-2.0 microns.

RBC and plasma ChE activity levels were determined by an automated colorimetric procedure. Normal horse serum was analyzed periodically as a standard.

(1) Acute Inhalation Toxicity in Male Rats and Male Dogs

In acute inhalation toxicity tests, groups of 34 rats were exposed during 4 hours to concentrations of parathion ranging from 0.04 to 230.0 mg/m³ in a 1,000-liter dynamic flow chamber. Groups of 4 dogs were exposed to parathion for 4 hours at 5 concentrations ranging from 0.015 to 37.1 mg/m³. The LC50 for rats was estimated to be 84.0 mg/m³ while that for dogs was determined to be greater than 37.1 mg/m³ (the highest dose tested). The ChE50 for RBC ChE in the rat was 5.4 mg/m³ and that for plasma ChE was 7.3 mg/m³. In the experiment with dogs, the investigators were unable to estimate a ChE50 dose for this species because of the pronounced and inconsistent effects on blood ChE activity by the exposure concentrations used. No deaths occurred in dogs exposed to the aforementioned concentrations. However, blood ChE activities were significantly depressed by all exposure concentrations. These data seem rather remarkable because the lowest concentration produced nearly the same inhibitions of the activities of RBC and plasma ChE's as the largest concentration, and in close to the same times (1.5 days vs 1.0 day). The concentrations referred to above differed by a factor of more than 2,470 times, so that the Ct doses of parathion received by the groups of dogs exposed to the two extreme concentrations would be expected to differ by this same factor.

At the lowest exposure level for dogs, 0.015 mg/m³, the RBC and plasma ChE activities after 4-hour exposure were 62% and 18% of normal, respectively. Twenty hours after the termination of exposure the values were 49% and 14% of normal, respectively. Fourteen days after exposure the RBC and plasma ChE activity levels had risen to 58% and 75% of normal, respectively. The data are presented in Tables XVI-5 through XVI-8. Similar results were observed at airborne parathion concentrations of 0.15 mg/m³ and greater; the RBC and plasma ChE activities were significantly depressed.

Tremors, convulsions, respiratory difficulty, and excessive salivation were seen in rats exposed to parathion concentrations of 50 mg/m³ or greater. The EC50's for tremors and convulsions were estimated to be 73.7 mg/m³ and 110.6 mg/m³, respectively. At the lowest level tested, 26.1 mg/m³, occasional sneezing, diarrhea, urination (scrotal area

wet with urine), lethargy, and "wet dog shakes" were observed in test animals. The highest concentration that did not cause deaths was 35.0 mg/m³. A no-effect concentration was not determined for the rat in this series of exposures. At the end of the 4-hour exposure to parathion at a concentration of 0.04 mg/m³, the average RBC ChE activity of the exposed rats was 84% of normal.

(2) Subacute Inhalation Toxicity in Male Rats and Male Dogs

Groups of 80 male rats were exposed for 7 hours/day, 5 days/week for 6 weeks to aerosol concentrations of 0.01, 0.10, and 0.74 mg parathion/m³. Toxic signs were not seen in the rats exposed to the 0.01 and 0.10 mg/m³ concentrations of parathion except for 1 animal that died on the first day of exposure to 0.01 mg parathion/m³. Microscopic examination revealed congestion of the lungs with the highest parathion concentration used, 0.74 mg/m³. Two rats died, one on the 10th day of exposure and one on the 28th day of exposure. Both animals had congested lungs on gross examination. The lowest dose tested, 0.01 mg/m³, was estimated from the acute toxicity phase of the study to be a no-effect dose.

The average blood hematocrit value, 47.2 mg%, obtained from 9 exposed rats after the last exposure to parathion at a concentration of 0.74 mg/m³ was not significantly different from that obtained from 4 control animals. The exposed rats gained weight throughout the exposure and postexposure periods with all 3 parathion concentrations.

With the lowest exposure level, 0.01 mg/m³, the greatest effect of the parathion on RBC ChE occurred during week 4, when the activity decreased to 69% of normal. In contrast, the RBC ChE activity decreased to 57% and 58% of normal after one week of exposure to 0.10 and 0.74 mg parathion/m³, respectively. After 5 weeks' exposure to an airborne parathion concentration of 0.74 mg/m³ the RBC ChE activity had been lowered to 16% of normal. In almost all cases, the RBC ChE was inhibited to a greater extent than the plasma ChE. Of the 3 concentrations, 0.01 mg parathion/m³ produced the least inhibition of the ChE activity of either RBC's or plasma. The intermediate concentration, 0.10 mg parathion/m³, exerted a moderate inhibitory effect whereas the highest, 0.74 mg/m³, concentration produced marked inhibition. Table XVI-9 summarizes these data.

The results of the acute studies with dogs indicated that this species is more sensitive than rats to inhaled parathion, as shown by the effects on ChE activities in the blood of the dog. Ac-

ordingly, groups of 6 dogs were exposed to airborne parathion concentrations of 0.001, 0.01, and 0.20 mg/m³ for 7 hours/day, 5 days/week, for 6 weeks. RBC and plasma ChE activity determinations were made after 1 day and 1, 2, 3, 5, and 6 weeks of exposure to aerosols of parathion and at various times following cessation of exposure. The RBC and plasma ChE activity values are shown in Table XVI-10. With the 0.001 mg/m³ exposure concentration both the RBC and plasma ChE activities were not inhibited significantly during the 6-week exposure period and the 6-week postexposure period. Thus, the lowest exposure concentration constituted a safe level on the basis of inhibition of blood ChE's. After 2 weeks of exposure to 0.01 mg/m³, of parathion the RBC and plasma ChE activities were 79% and 70% of normal, respectively (average of 6 dogs). After a 6-week exposure to 0.01 mg/m³, the corresponding activities were 101% and 58%, respectively. With 0.20 mg parathion/m³, the effects on RBC and plasma ChE were great. After 2 weeks of exposure to this concentration, the RBC and plasma activities were 54% and 26% of normal, respectively. The RBC and plasma ChE activities decreased to 41% and 36% of normal, respectively, after 6 weeks of exposure; the RBC ChE activity did not return to normal until 4 weeks after termination of the exposure. All 3 parathion concentrations exerted greater inhibitory effects on the plasma enzyme than on that of the RBC's. Other than effects on blood ChE's, no toxic signs were observed in the dogs with any of the 3 exposure concentrations.

(3) Acute and Subacute Oral Toxicity in Male Rats and Male Dogs

Preliminary to subacute feeding studies, 50 adult male rats and 20 adult male dogs were used to determine the acute 24-hour LD50's following single oral doses of parathion in corn oil. These values were 6.85 (6.18-7.60) mg/kg and 8.27 (4.79-14.29) mg/kg for male rats and male dogs, respectively. The results indicate that parathion is approximately equitoxic when administered orally to these 2 species. Tables XVI-11 and XVI-12 list the dose levels administered, the percent of animals of each species responding at each level, the average percent inhibition of RBC and plasma ChE's, and the Bliss statistical analysis of the data.

Acute ChE50 values were also determined for male rats and male dogs. The dose range for groups of 10 rats was 0.18 to 7.0 mg/kg of parathion; 7 different doses in corn oil being used. Dogs in groups of 4 were given the following oral doses of parathion in corn oil: 0.50, 1.26, 2.5, and 10.0 mg/kg. In both species, blood samples for

ChE activity determinations were taken 24-hours postexposure.

For male rats the RBC and plasma ChE50 values were determined to be 2.6 (2.1-3.1) and 2.5 (2.1-3.0) mg/kg, respectively. In male beagle dogs, the ChE50 values for RBC and plasma were found to be 1.5 (1.1-2.1) and 1.7 (0.9-3.0) mg/kg, respectively. Like the LD50 data, the ChE50 values estimated for the 2 species indicate that orally administered parathion is approximately equitoxic in male rats and male beagle dogs. These data are presented in Tables XVI-13 through XVI-16.

Two hundred and forty rats received daily doses of 1 ml/kg of corn oil, 5 days/week, for 6 weeks and served as controls. Another 240 animals were divided into 3 groups of 80 rats each. These groups of rats received 1 ml/kg of corn oil containing parathion in concentrations of 0.25 mg/ml, 0.10 mg/ml, or 0.05 mg/ml. All rats were weighed daily on 5 days/week and dosed, presumably by stomach tube, on a ml/kg basis. With the highest dose, 10 control and 10 exposed rats were sacrificed for blood sampling at 1, 3, 4, 5, and 6 weeks during oral dosing, and at 1, 2, 4, and 6 weeks postexposure. With the 2 lowest doses, RBC and plasma ChE activities were determined at 1, 2, 4, and 6 weeks during exposure and at various times following the cessation of oral dosing until complete restoration of enzyme activity had occurred. The results of this study are given in Table XVI-17. The highest daily dose, 0.25 mg/kg of parathion inhibited about 54% of RBC ChE activity and about 48% of plasma activity by the end of the 6-week exposure period. No significant blood ChE inhibition resulted from the 0.05 mg/kg dose. The lowest RBC ChE activity observed at the intermediate dose of 0.10 mg/kg was 78% of normal (following the 4th week of exposure). Inhibition of plasma ChE was less marked in general than that of the RBC enzyme. Thus, the 2 lowest doses exerted no profound effects on either the RBC or the plasma ChE and can be considered safe oral doses for rats. None of the test animals exhibited toxic signs of parathion poisoning either during or after exposure. Weight gained by parathion-treated rats was not significantly different from that gained by the control animals.

In a similar manner, the effects of orally administered parathion on the RBC and plasma ChE's of dogs were determined. Twenty-four adult male beagle dogs in groups of 6 each were dosed orally 5 days/week for 6 weeks with one of 4 concentrations of parathion in corn oil: 0.00, 0.05, 0.10, or, 0.50 mg/kg. All dogs were weighed

weekly. Blood samples for ChE determinations were taken at 1, 2, 4, and 6 weeks during exposure and at 1, 2, 4, and 6 weeks postexposure, if required.

The effects on the blood ChE's of the dog by these daily doses of parathion are presented in Table XVI-18. The 0.50 mg/kg dose produced after 6 weeks about 58% inhibition of RBC ChE and about 85% inhibition of the plasma enzyme.

With respect to the RBC ChE activity, the 0.10 mg/kg and 0.05 mg/kg dose levels produced approximately equivalent results. With 0.10 mg/kg of parathion, the RBC activity was 80% of normal after 6 weeks of exposure and with the 0.05 mg/kg dose, 83%. However, the plasma ChE activity was inhibited to a significantly greater extent by the daily dose of 0.1 mg/kg of parathion than by the lower dose. No toxic signs were observed in any of the test or control dogs during or after exposure to these oral doses of parathion. There was no significant effect on body weight in any of the exposed animals. The only conclusion from these results is that a daily dose of 0.05 mg/kg may not produce any deleterious inhibition of the ChE's of the blood of the dog during 6 weeks and that the 2 highest doses probably are not safe for repeated daily oral ingestion.

Experiments were performed also to determine the rates of recovery of the RBC and plasma ChE activities in male rats and dogs. A total of 60 rats and 4 dogs were administered single oral doses of parathion in corn oil of 2.8 mg/kg and 2.5 mg/kg, respectively. Twenty control rats received corn oil alone. No mention was made by the investigators of control dogs. Rats were bled at 4 hours and 1, 2, 3, 7, and 14 days postexposure; dogs were bled at 1, 11, 15, 29, and 36 days postexposure. The rates of recovery for both RBC and plasma ChE activities agree with those reported previously in the criteria document. The RBC ChE activity recovered at the following rates: 1.7%/day and 1.6%/day for male rats and male dogs, respectively. For rats, the plasma ChE activity returned at a rate of 3.1%/day whereas in dogs the rate was 5.5%/day. The results are presented in Tables XVI-19 and XVI-20.

Carcinogenicity, Mutagenicity, Teratogenicity

Malformations in the embryonic skeleton of the Japanese quail by parathion have been reported by Lutz-Ostertag et al.⁹³ and by Meiniel et al.⁹⁴ These workers either injected eggs with a 0.1% solution of parathion or immersed the eggs in a 2% solution of parathion-in-acetone for 30 seconds. The dose received by the embryos cannot be calculated

but must have been very high. All embryos from eggs treated with parathion by immersion showed abnormalities, principally localized in the cervical region. Malformations of the axial skeleton and reductions in the length of the spine were common. Similar results from studies on hen and quail eggs were published by Meiniel in 1973.⁹⁵

Khera and Bedok⁹⁶ obtained similar results in chick and duck embryos. They injected 1 mg of parathion (presumably in propylene glycol) into the yolk sac of preincubated or 4-day-incubated chick eggs and 4-day-incubated duck eggs. Control eggs of both species were injected with sterile propylene glycol. Parathion treatment resulted in characteristically tortuous and shortened vertebral columns composed of abnormal vertebral bodies (fused neural arches).

Kimbrough and Gaines⁹⁷ reported the effects of parathion on the rat fetus. Intraperitoneal injections of parathion in dams in doses of 3.0 and 3.5 mg/kg caused a high incidence of resorptions and reduced the weights of the fetuses and placentas. With the higher dose, one edematous fetus was observed out of a total of 28. However, the investigators emphasized that only those doses of parathion that produced toxic symptoms in the dams affected the fetus.

Talens and Woolley⁹⁸ reported the effects of exposure to parathion during gestation on development in the rat. Female rats were subcutaneously injected with 2 mg/kg of parathion for 4 days and then killed at various intervals for determination of blood and brain AChE activities. Cholinergic signs of poisoning, including salivation, lacrimation, diarrhea, and tremors were observed in the test animals; 2 of 28 animals died after the second injection. Twenty-six hours after the last injection, the AChE activities in the neocortex, brain stem, remaining brain, and blood were 21%, 40%, 19%, and 49% of control activities, respectively. To determine effects on development, pregnant rats were injected subcutaneously with 1.5 or 2.0 mg/kg parathion daily for 4 days beginning on day 1, 7, or 13 of gestation. Signs of poisoning were seen in the dams (most severe when administered during the third trimester). Four of 52 rats injected with the highest dose died, 3 during the third trimester. In surprising contrast to the effects in the dams, the brain AChE activity of the pups at birth was normal in all treated groups. At birth, the average litter size of the parathion-treated dams did not differ from that of controls. Thus, fetal resorption did not occur, in contrast to the results previously reported by Kimbrough and Gaines.⁹⁷ Average birth weights of pups born to

dams injected with parathion during the latter third of pregnancy were significantly lower than those of controls. By the second week, body weights were normal in pups from all treated groups. The authors' statement that the slower body growth and later development may be attributable to poor maternal behavior appears reasonable in light of the fact that brain AChE activity was normal in the pups at birth and also to their observations that the parathion-treated dams appeared to pay less attention to their pups than unpoisoned mothers.

In 1975, Harbison⁹⁹ reported the results of his study on parathion-induced toxicity during prenatal development in mice. Mice were injected ip with parathion at doses of 4, 8, 10, 11, or 12 mg/kg. Control mice were injected with corn oil. Laparotomy was performed on pregnant mice on gestational day 19. At this time, the number and positions of live, dead, and resorbed fetuses were noted and then fetuses were removed and weighed. The greatest effects were observed when parathion was injected during gestational days 12, 13, and 14. During this period, a dose of 12 mg/kg killed 90% of the fetuses, while the same dose was lethal to 27% of the fetuses in utero during gestational days 8, 9, and 10, the period of early organogenesis. A dose of 12 mg/kg was not lethal to the maternal animal. The body weights of surviving fetuses were significantly reduced by parathion treatment. As in the case of resorptions, a gestational period susceptibility was observed; the developing organism appeared to be more susceptible to parathion-induced reduction in body weight during late organogenesis or the fetal maturation period. Data were also presented showing that phenobarbital greatly protected the developing fetus from the effects of ip-injected parathion.

Weis and Weis¹⁰⁰ subjected fertilized killifish (*fundulus heterclitus*) eggs to parathion at concentrations of 1 and 10 ppm. The insecticide was dissolved in acetone and added to dishes containing the eggs at the 8-16 cell stage, in filtered sea water. When controls had reached the 19-20 cell growth stage, embryos in 1 ppm parathion were in stage 17-18 while those in 10 ppm were in stage 17. Sixty-four percent of eggs exposed to 10 ppm of parathion successfully formed axes vs 93% in controls. After 3 days in parathion, 10-12 embryos were removed from the 1- and 10-ppm dishes, washed, and placed in clean sea water. Fifty percent of the group exposed to 10 ppm parathion developed a thin feebly-beating tube with rudimentary chambers stretching between the yolk and the embryo, instead of a normal heart. The authors

stated that other tissues and spontaneous movement were normal. The concentrations of parathion did not produce death in the embryos. Because of the species used and the nature of the exposure, it is impossible to extrapolate these results to man.

In 1973, Mohn¹⁰¹ reported on the mutagenic potential of parathion and other insecticides. The induction of 5-methyltryptophan (5-MT) resistant mutations in *Escherichia coli* by parathion was evaluated. A concentration of 20 µg 5-MT/ml was used and the inoculum contained 300,000-500,000 cells/ml. Cultures with a low spontaneous mutation frequency were used. The test system was subjected to 0.043 M parathion with no increased mutagenic activity observed; the number of 5-MT resistant mutations did not differ significantly from the spontaneous value.

In a 1975 review article dealing with mutagenesis by pesticides, Fahrig¹⁰² compared the results of 4 studies with parathion. One of the mutagenicity studies was his own, which was published in 1973 and is described above.¹⁰¹ Two of the 4 studies were apparently not published and are referenced in Fahrig's review as personal communications. The fourth study was performed by the author but the data had not been published. Results in the 3 unpublished studies were obtained using the following procedures: (1) spot test for back-mutations to prototrophy in the 2 auxotrophic strains, a 21 and a 742, of *S. marcescens* and for forward mutations to galactose prototrophy in the phenotypic galactose-negative Gal RS strain of *E. coli*; (2) a liquid holding test for forward mutations to streptomycin resistance in *E. coli*; and (3) a liquid holding test for mitotic gene conversion at the *ade2* and *trp5* loci of *S. cerevisiae*. Fahrig reported that parathion was negative in all test systems.

No papers have been found reporting the production of carcinomas or other malignancies by parathion. However, parathion is presently undergoing carcinogenesis bioassay by the National Cancer Institute. (H Kraybill, written communication, March 1976) Male Osborne-Mendel rats have been fed parathion (ad libitum) for 18 months in their diets at concentrations of 30 and 60 ppm. Females of the same species and strain were fed parathion in their diets at 20 and 40 ppm for the same length of time. Male and female mice (*B₆C₃F₁* strain) were fed 80 and 160 ppm parathion in their diets for 16 months. The observation periods for rats and mice were 6 months and 5 months, respectively. Although a preliminary report was anticipated during the Fall of 1975,

it did not materialize. Results of the carcinogenesis bioassay of parathion have not been made available to NIOSH as of July 1, 1976. When the bioassays are completed and the results made available to NIOSH, appropriate action will be taken.

The data presented in this section relating to the testing of parathion for carcinogenic, mutagenic, and teratogenic activity in various mammalian and nonmammalian species indicate that the compound is not active in these respects. It is concluded that parathion is unlikely to produce mutations, terata, or cancer in humans.

Correlation of Exposure and Effect

Evaluation of the literature pertaining to the effects of overexposure to parathion indicates that parathion is absorbable after inhalation,^{37,38} ingestion,³⁴⁻³⁶ and impingement on conjunctival, cutaneous, or mucous membranes,^{11,16,39-41} and induces either subclinical (ie, depression of blood ChE activity) or toxic (ie, signs/symptoms of parathion poisoning) effects, or both, depending on the amount absorbed. It is probable that the high solubility of parathion in lipid media influences its absorption through the skin and its distribution in the body. Parathion is converted in vivo and oxidized in the air to paraoxon²²⁻²⁵ which then reacts with, and inhibits the activity of, ChE enzyme throughout the body.¹ When the ChE activity of tissues is inhibited to a certain degree, resulting in a disruption of normal enzyme function, a local condition of excess concentration of acetylcholine results. The signs and symptoms of parathion poisoning arise from the totality of these individual local effects.¹ The signs and symptoms most frequently seen in parathion poisoning are presented in Table III-1.

Effects of parathion due to actions other than inhibition of AChE are not proved. Karczmar and Koppanyi⁷¹ demonstrated that both RBC and plasma ChE's may serve as "buffers," protecting neuroeffector ChE's from inhibition by parathion. Experiments^{81,91,103} have shown that in animals poisoned with parathion, the blood ChE's are depressed along with tissue ChE's. Similar results in humans have been reported^{17,18}; a decrease in the activities of the blood ChE's reflects concomitant, but not necessarily proportional, reductions in tissue ChE's. Grob et al¹⁸ made a comparison of the ChE activities of various tissues of two subjects who died after exposure to parathion with the average ChE activities of 8 subjects who had received no exposure to parathion or any other anti-ChE agent and who had no disease of the CNS, liver, kidneys, or blood-forming organs. In

the 2 parathion-poisoned individuals, the percentage of control ChE activities for various tissues were: plasma—2.5%, RBC's—16.5%, liver—60%, kidney—88% (one patient), cerebral cortex—26.5%, thalamus—52%, cerebellum—52.5%, pons—41%, and medulla—39%. Both patients developed marked signs/symptoms of parathion poisoning prior to death. The blood ChE's and the urinary excretion of PNP are the only well-demonstrated and practical measures, from the viewpoint of a compliance standard, of subclinical parathion exposure presently available. Chronic occupational exposures to parathion are typified by repeated absorption of amounts of parathion which in single doses would not produce signs/symptoms of poisoning. However, the effect of repetition during a sufficiently long period of high enough doses is to progressively inhibit tissue acetylcholinesterase to the point where decreased enzyme function results in the development of signs/symptoms of poisoning.⁸⁰ Neither parathion nor its metabolites cumulate in the body.^{50,51,104} However, the effects of parathion on ChE's may be cumulative depending on the rate of enzyme inhibition. Grob et al¹⁸ demonstrated in humans that after inhibition by parathion, RBC ChE activity returned at an average daily rate of 1-2% while the plasma ChE activity returned at the average rate of 3-4%/day. If the daily inhibition of blood enzymes exceeds the daily recovery of ChE activity, there will ultimately be a progressive decrease in tissue enzyme activity to a level where signs/symptoms of poisoning will probably occur. Thus, monitoring of the RBC and plasma ChE activities serves as an indicator of what is happening to tissue ChE activity levels. A review of the data presented^{18,34,35,39,87,103} reveals that both plasma and RBC ChE activity may be depressed simultaneously upon exposure to parathion, with the plasma enzyme inhibited to a greater extent (ie, preferentially inhibited). Thus, plasma ChE activity is usually depressed more promptly and extensively and recovers more rapidly than RBC ChE activity when parathion is

administered in uniform oral daily doses. Accordingly, if RBC ChE activity rather than plasma ChE activity were being monitored on a fixed routine it might provide a better warning that excessive absorption of parathion was occurring than would be provided by monitoring of plasma ChE activity. In the situation where absorption of parathion occurs on each of several serial days and then ends a few days before a preset monitoring time, plasma ChE activity could return to normal before the blood sample was collected whereas the RBC ChE activity would be more likely to remain depressed.

For this reason, selection of RBC ChE activity for routine biologic monitoring of blood to detect exposure to parathion seems appropriate. Determining both plasma and RBC ChE activities would not significantly increase the likelihood of detecting progressive inhibition of tissue ChE above that provided by monitoring RBC enzyme activity alone.

In summary, progressive depression of tissue ChE activity to a dangerous extent is believed to be preventable by a biologic monitoring program involving measurement of the activity of RBC ChE. Thus, by preventing a chronic but sustained progressive depression of this blood enzyme, poisoning by parathion may be prevented. However, it is highly unlikely that infrequent blood ChE monitoring can prevent the occurrence of acute poisoning caused by a relatively massive exposure with a resultant precipitous decline in both the blood and the tissue ChE's. In cases of serious overexposures to parathion, such as by contamination of a large area of skin by spills or splashes of concentrate material, it is recommended that both the RBC and the plasma ChE's be measured, because the latter type of ChE is more sensitive to inhibition by single large doses of parathion than the RBC ChE, the latter retaining still its value as an indicator of cumulative absorption of parathion during a relatively long period of time.

IV. ENVIRONMENTAL AND BIOLOGIC METHODOLOGIES

Measurements of atmospheric concentrations of parathion within the work areas of pesticidal manufacturing and formulation plants and during application of parathion-containing pesticides in agricultural operations provide an indication of the airborne levels of parathion encountered by workers in these operations. Various experiments have also been conducted in order to determine the extent of dermal exposure to parathion during similar operations. The results of such studies define the need to wear proper protective clothing and equipment during potentially hazardous operations to prevent the occurrence of poisoning by parathion. Recommended environmental controls and work practices are essential for the control of occupational parathion exposure.

Brown and Bush⁷⁹ measured airborne parathion concentrations at several locations in and near a parathion-manufacturing and -formulating plant. Concentrations of the toxicant ranged from 0.1 to 0.8 mg/m³. As mentioned previously, plant workers experienced significant declines in their blood ChE activities. No mention was made of engineering controls.

Several reports dealing with airborne concentrations of parathion in fields and orchards following spray application have appeared.^{58,105-111} In 1951, Stearns et al¹⁰⁵ applied a spray mixture containing 4 lb of 15% wettable parathion and 10 lb of wettable sulfur/100 gal to a 16-acre grove of grapefruit trees at a rate of 1,173 gal/acre. Air sampling was carried out during the spraying operation and at 24-hour intervals for the next 3 days, then at 48-hour intervals for 6 days. A final air sample was collected 19 days after application. A breathing zone sample taken during application analyzed at 0.03 ppm (0.36 mg/m³) of parathion. On the following 3 days, the maximum airborne concentration found was 0.005 ppm (0.06 mg/m³). Seven days after application, parathion could not be detected in the orchard air.

Batchelor and Walker¹⁰⁶ analyzed air samples from fruit orchards sprayed with parathion and DDT at average single application rates of 1.8 and 10.1 lb/acre, respectively. The material was applied by either high-pressure hand spray equipment, air-blast equipment, or aircraft. In addition, the authors determined airborne parathion concentrations during pesticide mixing/loading of both the high-pressure hand sprayer and the air-blast sprayer in a mixing plant and in a warehouse. The

results indicated that the application of parathion is considerably less hazardous than its mixing and loading into application equipment, especially in orchard operations. Application by high-pressure hand sprayers resulted in slightly higher atmospheric concentrations of parathion than were brought about by use of either air-blast ground rigs or aircraft application equipment. The mean airborne concentrations resulting from these three methods of application were 0.09, 0.03, and 0.05 mg/m³, respectively. In contrast, mean airborne concentrations for mixing/loading operations involving ordinary water-wettable powder (WWP), antidusting WWP, and liquid concentrates were 2.15, 0.37, and 0.02 mg/m³, respectively. By utilizing filter pads attached to various parts of the operator's body and clothing (shoulders, forearms, thighs, back of neck, and chest), estimates of the potential dermal exposure were made. Similar estimates of the potential respiratory exposure were made by measuring the parathion absorbed onto filter pads contained in respirators worn by the subjects. The dermal parathion exposure of spray operators was found to average 12.8 and 21.5 mg/sq ft/hr in high-pressure spraying and air-blast spraying, respectively. The calculated average daily dermal exposure of the workers engaged in either high-pressure hand spraying or air-blast spraying was 7.7 versus 0.02 mg/kg for respiratory exposure (using the respirator pad technique). The respirator pad technique gave values that were approximately 3-5 times as great as those calculated on the basis of the airborne samples. However, Durham and Wolfe¹¹² suggested that both techniques provide the same value when the data are adjusted to reflect their demonstrated ratio of impinged to inhaled toxicant. The results indicate the relative magnitudes of exposures during mixing-loading and application of parathion by the dermal and the respiratory routes, and the need for protective clothing and equipment.

By sampling within a few feet of the spray operator's breathing zone, airborne parathion concentrations ranging from 2.0 to 15.0 mg/m³ were measured by Kay and associates⁵⁸ during the application of 15% wettable powder in the concentration of 0.75 to 1.5 lb/100 gal of water and dispersed at the rate of 300-400 gal/acre. High concentrations occurred primarily when spraying during windy conditions. Workers exposed to these concentrations of parathion experienced declines

in blood ChE activities. Air samples were also collected while workers added 15% parathion wettable powder to spray tanks. Parathion concentrations derived from two tests in which the dust cloud rose to the operator's breathing zone were 16 and 26 mg/m³. During the application of 0.75 lb of 15% parathion wettable powder and 10 lb of sulfur in 100 gal of water (a low-concentration mixture) to apple trees, Kay et al⁵⁸ measured 14.0 mg/m³ of parathion in the breathing zone air of the operator. The following day, the airborne concentration of parathion was diminished to 0.09 mg/m³ and approximately 3 weeks later it was measured at 0.03 mg/m³.

Jegier¹⁰⁷ reported on the health hazards to tractor operators from insecticide spraying of crops. Air samples were collected at the tractor operators' breathing zone and the results of the analyses for parathion were used to calculate respiratory exposures. Filter pads attached to double-unit respirators and to the forehead and wrists of observers riding beside the tractor drivers were used to calculate respiratory (a second method) and dermal exposures. Parathion was applied to apples as a spray in concentrations of 0.4-4.0 lb of 15% wettable powder/100 gal of water. The air concentrations of parathion ranged from 0.05 to 0.26 mg/m³ with a mean of 0.15 mg/m³ (10 samples). Jegier estimated a mean respiratory exposure of 0.03 mg/hour (range of 0.01-0.05 mg/hour) from analyses of the filter pads. Calculation of respiratory exposure based on the air sampling results and a lung ventilation rate of 444 liters/hour provided an estimated respiratory exposure to parathion of 0.07 mg/hour. The mean dermal exposure was estimated at 2.4 mg/hour (range of 0.7-5.8 mg/hour).

Using similar absorption pad techniques to measure the potential respiratory and dermal exposure of workers spraying parathion on vegetable crops with hand knapsack-misters, Simpson and Beck¹⁰⁸ estimated the daily (8 hours) dermal and respiratory exposures at 72.8 mg and 2.32 mg, respectively. A study of the blood ChE activity of the sprayers indicated that 30% of those tested had decreased levels. The investigators did not specify what level of enzyme depression they regarded as significant; however, they stated that workers with activities less than 60% of their preexposure values were removed from exposure. All samples collected in the operator's breathing zone by midjet impingers contained parathion in excess of 0.1 mg/m³.

Wolfe et al¹⁰⁹ studied the exposure to parathion of orchard spraymen operating low-volume spray

rigs and compared it with that of spraymen using high-volume sprayers. Parathion was applied to fruit trees in the low-volume spray in 8-12 times the concentration of the high-volume mixture (0.24-0.36% vs 0.03% parathion). Both the potential dermal and respiratory exposures were calculated by attaching absorbent cellulose pads to various parts of the worker's body or clothing and by placing filter pads in special single- or double-unit respirators designed to prevent direct impingement of spray droplets onto the respirator pads. The total dermal exposure was calculated on the basis of the exposed person wearing a short-sleeved, open-necked shirt, no gloves or hat, with his clothing providing complete protection of the areas covered. Since drenching sprays can wet the worker's clothing, dermal absorption can occur through nonimpervious clothing; however, the dermal exposure values calculated by Wolfe et al¹⁰⁹ on the basis of minimal protective clothing would tend to provide work practice recommendations on the conservative side. The amount of parathion drawn into the respirator with sufficient velocity to reach the absorbent pad was considered to represent respiratory exposure. The calculated potential dermal exposure for operators of low-volume spray equipment was 27.9 mg/hour as compared to 19.4 mg/hour with high-volume (ie, dilute spray) equipment. The authors¹⁰⁹ attributed the difference to an observed greater parathion contamination of the hands of the spraymen working with the low-volume spray. Potential respiratory exposure for low-volume spraying was 0.055 mg/hour, or about 2.7 times that estimated for operators of conventional high-volume machines (0.020 mg/hour).

Samples of spray mist were taken during and after spraying operations with parathion in a study¹¹⁰ of orchard workers in Quebec. Parathion was applied as a spray (a fine mist) composed of 1.5-4 lb of 15% wettable powder/1,000 lb of water to apple trees. During the spraying operations, air samples were taken in the tractor-drivers' breathing zones using fritted-glass bubblers containing alcohol. Both air residual and leaf residue analyses were performed subsequent to application. For sprays containing 3-4 lb of parathion 15% wettable powder/1,000 lb of water, applied at the rate of 0.12-0.15 lb (of 15% wettable powder) for each tree, average spray concentrations in the operators' breathing zones ranged from 0.29 to 0.52 mg/m³ of air. Under near-windless conditions, the investigators found an airborne parathion concentration of 0.12 mg/m³ in the orchard 1 hour after spraying. Parathion was not detected in the

orchard air after 1 hour of completing spraying in winds of 3-4 mph.

Braid et al¹¹¹ assessed the potential exposure from drifting parathion dust by taking samples of the airborne dust and of vegetation at distances up to 400 feet from the dusting machine. One percent parathion dust was applied at a rate of 40 lb/acre from a tractor-drawn duster which dispersed the material at a height of approximately 2 feet above ground. The air was sampled at a height of 4 ft above ground, corresponding to the average breathing zone height of people working in the field, using electrostatic precipitators. Thirty-nine cubic feet of air was sampled in each of five 13-minute dusting trials. Airborne dust loads were determined at distances of 50, 100, 200, 300, and 400 feet from the application equipment. Average wind speed during the 5 trials was 6.6 mph. The airborne parathion concentrations at downwind distances of 50, 100, 200, 300, and 400 feet were 3.0, 0.85, 0.22, 0.07, and 0.03 mg/m³, respectively.

From the results of these studies, it is evident that dermal exposure to parathion is significant and actually constitutes a greater potential hazard than respiratory exposures in most occupational situations.

General room ventilation is needed in parathion-manufacturing and formulating areas. In addition, exhaust systems are needed at loaders, blenders, mills, kettles, packaging equipment, and all other possible sources of vapor, spray, or dust containing parathion. Liquid and dust exhaust systems must be so designed that neither the workers nor other human and animal life in the surrounding area are at risk. Dust exhaust systems should be vented through a dust collector and organic vapor absorber, so that air vented to the atmosphere is adequately scrubbed.³ Detailed information on the design and installation of exhaust systems for vapor and dusts of parathion should be sought from competent sources, such as ventilation engineers or industrial hygienists.

Air Sampling Methods

The sampling of air for parathion is complicated by the fact that it may exist in vapor or particulate (ie, aerosolized liquid or dust) form. Thus sampling devices must be versatile in their ability to trap all the physical states of airborne parathion. The most widely used pesticide air sampling devices include: Greenburg-Smith or midget impingers^{58,106, 108,112-118}, bubblers or scrubbers (fritted glass absorbers)^{58,114,116,119,120}, glass fiber filters^{118,121} or cellulose filter pads^{106-109, 112,113,118,120}, gauze pads

^{112,113}, and packed adsorbent columns, such as alumina.^{112,122} Nylon chiffon screens have also been used.¹²³ Each device has its advantages and disadvantages, summarized by Miles et al¹¹⁸ as follows: “. . . packed columns are very efficient for trapping vapors, but recovery of the sample is frequently difficult; the filter systems permit the collection of large volumes of air in short periods of time, but their efficiency for vapors is low and unknown losses of particulate and aerosol samples occur during the sampling period; the scrubbers are good for aerosols and vapors, but the sampling rate is slow and the use of sintered glass precludes the collection of particles; and cold traps are of limited value in field work in view of the maintenance problem. Midget and Greenburg-Smith type impingers seem to offer a compromise in that they can be operated at a reasonably fast rate, they are very efficient for collection of particulate matter, and with proper selection of solvent they can collect aerosols and vapors efficiently.”

Durham and Wolfe,¹¹² in their review of sampling methods for human respiratory exposure to pesticides, stated that the midget impinger has been reported to duplicate “reasonably well” the spectrum of particle sizes picked up by the nostrils in breathing. They further stated that the Greenburg-Smith impinger has the advantage of sampling large volumes of air in a given time, thus improving sensitivity where the concentration of pesticide is low or the exposure time is brief. Using a 4-hour sampling time for the Greenburg-Smith impinger, Miles et al¹¹⁸ reported a sensitivity of 2.0 ng/m³ of parathion in air, or 1/25,000th the airborne concentration permitted in the proposed environmental standard.

Because of the low air sampling rate inherent in the midget impinger,¹¹⁷ sensitivity for similar sampling times is less than for the Greenburg-Smith impinger though still very high. However, the size of the midget impinger imparts greater adaptability to the air sampling procedure without sacrificing precision. The midget impinger appears to be the recommended collection device of choice for obtaining parathion-containing air samples. However, neither the sampling efficiency nor the overall precision of the sampling and analytical method are known. (RH Hill, Jr, written communication, March 1976) In addition, the Environmental Protection Agency has withdrawn this sampling method (ie, midget impinger using purified ethylene glycol) from its pesticide sampling and analysis manual since “a controversy concerning the reliability of the data” has arisen from using the method. (RH Hill, Jr, written communication,

March 1976) Despite this, the impinger is presently the best available sampling device for parathion in air. Since parathion may occur in air as vapor, liquid droplets, or as an adsorbed film on solid particles, it is essential that the impinger be operated at a flow rate which will efficiently collect all forms of airborne parathion. Appendix I gives details of the sampling and air flow calibration procedures to be followed when using this method. Other air sampling methods which can be shown to be equivalent, or superior, in efficiency to the impinger method may be used.

Parathion Analysis

The first step in all the analytical methods considered here is the removal of the pesticide and other compounds of interest from the substrate or trapping medium. Filters and solid adsorbents are amenable to solvent extraction or desorption. The extraction solvent must be compatible with subsequent analytical procedures unless the solvent is to be removed in the procedure. The contents of impingers or bubblers using nonvolatile solvents must be partitioned into an immiscible, volatile solvent. For example, parathion collected in ethylene glycol is extracted from it with a light hydrocarbon, preferably hexane.

The variety of techniques available for assay of parathion-containing materials covers the gamut of testing procedures from titration to the more complex instrumental methods. Several techniques are applicable to the analysis of large amounts of parathion, such as are found in the technical material or its formulations. Analysis of trace amounts of chemicals presents problems in sensitivity and specificity which can be overcome only with certain instrumental methods. The spectrophotometric methods can be used to analyze parathion directly or to assay it after derivatization.

The residue method most commonly used before the development of a gas chromatographic detector specific for phosphorus was that of Averell and Norris.¹²⁴ In this method, the nitro group of the parathion is reduced to an amino group with zinc and hydrochloric acid. The amino group is then diazotized with nitrite and coupled with N-(1-naphthyl)-ethylenediamine dihydrochloride. The resulting dye has a deep magenta color, absorbing at 555 nm. The light absorption of the colored derivative is measured at 555 nm and is compared to a standard curve for quantitation.

The spectrophotometric method of Gage¹²⁵ is a modification of the Averell-Norris method. Although it was developed as an assay method for

technical parathion and formulations, it is applicable to trace analysis where relatively high concentrations of PNP or the S-ethyl isomer of parathion (O,S-diethyl-O-p-nitrophenyl phosphorothioate) are present.

Parathion, itself, has a moderate absorption maximum in the near ultraviolet spectrum at 274 nm; Hirt and Gisclard¹¹⁶ utilized this property for direct analysis of the insecticide in air sampling devices. The solution from a bubbler or midget impinger is diluted to a known volume, the absorbance of the parathion being measured spectrophotometrically.

Range and sensitivity of the spectrophotometric methods are limited by two factors, the absorbance of the material analyzed and the sensitivity of the instrument used to perform the analysis. They also suffer from a variety of interferences. Many compounds absorb light in the near ultraviolet region, especially aromatic compounds; therefore, the Hirt and Gisclard¹¹⁶ method is especially susceptible to interferences. Compounds that absorb in the visible spectrum are less common and would not normally be expected to appear in air sampling devices and, as such, do not represent a problem in the Averell-Norris¹²⁴ method. However, aromatic nitro or amino compounds can potentially behave like parathion by forming a dye in the color development procedure, which may absorb at the same wavelength and thus interfere. Isomers of parathion, its oxon, and p-nitrophenol are especially likely to give high parathion assays in the Averell-Norris method which is not specific for parathion.

Of the spectrophotometric methods, that of Gage¹²⁵ is the only one to have any specificity for any of the isomers of parathion; however, none of them estimates paraoxon separately from parathion, it is either lost by hydrolysis or is read as parathion. There is no UV-visible spectrophotometric scheme of analysis for the separate determination (ie, limit of detection) of paraoxon in the presence of parathion.

In 1964, the thermionic emission or alkali flame ionization detector (AFID) was introduced by Giuffrida¹²⁶; in 1966, Brody and Chaney¹²⁷ introduced the flame photometric detector (FPD). Both detectors are modifications of the universal flame ionization detector and are highly specific for phosphorus. Since the development of the phosphorus-specific detectors, the preferred method for the analysis of parathion has been gas liquid chromatography (GLC) for the following reasons: GLC offers the advantage over the spectrophotometric methods of superior specificity in

that it separates the components of the sample under scrutiny before the compound is quantitized; that is, the instrumental signal from the gas chromatograph, as it is recorded, has a higher probability of arising from a true response to the compound being assayed than that from a spectrophotometer. Thus, GLC offers simultaneous qualitative and quantitative analysis. For parathion collected in air sampling devices, analysis should be straightforward and should require no elaborate cleanup steps.¹²⁸ Analysis follows direct extraction of filters or vapor adsorbent and concentration of the extracting solvent to an appropriate volume.

A pertinent problem in trace analysis of a pesticide is the choice of a detector system. As mentioned above, two widely used phosphorus-specific detectors have been developed for pesticide residue analysis, the FPD and the AFID.^{126,127} The FPD has much less stringent requirements than the AFID for detector gas flow control and, thereby, requires less time for maintenance and adjustment of the detector. The FPD also maintains a more stable response during a period of time than the AFID and requires less frequent injection of standards for proper calibration. In addition, the AFID is responsive to organic compounds containing chlorine, nitrogen, and sometimes sulfur, though to a lesser degree than to phosphorus when the instrument is tuned properly. Therefore, the FPD is considered to be superior to AFID.

Great sensitivity is also a major advantage of the GLC-phosphorus specific detector method of analysis. Averell and Norris¹²⁴ reported that 20 μg of parathion in the final 50-ml aliquot represented the sensitivity of their method. Because of great differences in extinction coefficients, the Averell-Norris method is inherently a thousand times more sensitive than the method of Hirt and Gisclard.¹¹⁶ In contrast, Guiffrida¹²⁶ detected 0.024 μg of parathion using GLC with AFID. For normal analytical work, a convenient working range for AFID is between 50-1,000 picograms (pg)/injection volume. GLC with FPD was reported¹²⁷ to be sensitive to 250 pg of parathion using a 526-nm filter; the response was linear from 6 ppb to 60 ppm.

The precision of GLC analysis depends largely on several factors. Syringe-handling technique is very important for the small volumes of samples used with the phosphorus-specific detectors. Injections are commonly made against 20-40 psi of carrier gas pressure, and a worn syringe or injection-port septum can cause serious sample loss. Use of a solvent-flush technique usually increases the reproducibility of sample analyses. Instrument sta-

bility is another factor in precision. A dirty detector, especially with the AFID, a bad column, or a faulty electrometer or recorder will cause loss of sensitivity and erratic responses. Overall precisions of $\pm 5\%$ are not uncommon. Factors affecting accuracy are extraction efficiency, interferences, instrument stability, and frequent use of standards. Integration of the areas of various peaks is a critical step in deriving numbers related to sample composition; it is the conversion of the record produced by the detector from analog to digital form.

All the methods for estimation of parathion discussed in this document, photometric, spectrophotometric, and GLC, quantitate their responses to unknown quantities of the insecticide by comparing them with standard curves. The standards used are originally weighed out and brought to known concentrations by serial dilutions and, as such, are secondary gravimetric standards. Thus, all the methods yield values that are in units of weight of parathion, so that the estimates obtained by different methods are comparable directly.

Air monitoring should produce samples relatively free of interferences when analyzed with a gas chromatograph equipped with a specific detector of phosphorus. Any organophosphorus compound that survives pyrolysis will be detected, but only those having a retention time close to that of parathion will interfere. Large quantities of organic material will increase background noise for the FPD, thereby reducing the accuracy of the method. In summary, GLC with FPD offers the following advantages over the photometric and spectrophotometric methods:

- (1) Less subject to interferences from contaminants.
- (2) Specific for parathion.
- (3) Greater sensitivity.
- (4) Greater precision and accuracy. The GLC with FPD method is therefore recommended.

Plasma and RBC ChE Analysis

As the identification of the various ChE enzymes developed, the determination of the catalytic ability of enzymes in tissue by various methods was performed to determine the effects of various inhibitors on tissue enzyme activities.

The early methods of determination of ChE activities used principally acetylcholine as a substrate and measured the release of H⁺ ions as the esters were hydrolyzed. This change has been measured manometrically,^{129,130} by change in an acid-base indicator,^{131,132} and by electrometric pH measurement.¹³³

Manometric methods for analysis of ChE's have been found to be among the most precise but have the inherent drawbacks of time-consuming manipulations and procedures. These methods have been used for both RBC and plasma ChE assays.¹³⁴⁻¹³⁶

Methods using a change of indicator color have been successfully used with serum ChE samples,¹³² but are not applicable to hemolyzed RBC samples or plasma because of the turbidity of such solutions. Unless dialysis membranes are used,¹³⁷ the analytical precision decreases because of the turbidity.^{132,138} The principle of this method has led to several useful field screening methods. Such field methods have poor precision, $\pm 25\%$, but this degree of precision is not inappropriate for screening methods.¹³⁷⁻¹⁴⁴

The electrometric method of Michel¹³³ was developed primarily to decrease the time required for analysis and has been found to be well-suited for determinations of both RBC and plasma ChE activities. This method has been widely used in the measurement of RBC and plasma ChE in men exposed to OP ChE-inhibitors. In fact, the ΔpH method has been the one used in most of the reported determinations of normal human RBC and plasma ChE values.¹³⁴ Additionally, the best established normal values for humans were determined¹⁴⁵ using the original ΔpH method of Michel.¹³³ The studies by Vorhaus and Kark¹⁴⁶ of changes in serum ChE activities due to disease also used the original ΔpH method of Michel.

Variations of the original Michel method have been proposed to make the method more convenient. Procedures have been proposed using capillary blood sampling methods rather than those involving venipuncture,¹⁴⁷ automated systems,¹⁴⁸ less analysis time,¹⁴⁹ and a single measurement of pH.¹⁵⁰ The method of Wolfsie and Winter¹⁴⁷ has the advantage of not requiring samples as large as those of the original Michel method, without any apparent loss of precision.¹⁵¹

The production of acid has also been monitored by continuously adding base to maintain a constant pH as hydrolysis occurs. Such methods are referred to as pH-stat methods.^{152,153} The pH-stat methods have not been reported in surveys and case studies of OP poisoning as often as the ΔpH methods. Equipment required is more difficult to operate and maintain than the relatively simple equipment of the ΔpH methods. The pH-stat method was found by Crane et al¹⁵¹ to be less precise (1.70% relative standard deviation) than the ΔpH method (1.45% relative standard deviation), and to exhibit a high degree of interlabora-

tory variation. The pH-stat method employs a titration at constant pH. Although the activity of ChE enzymes has been observed to be pH-dependent, the small change in pH observed in the ΔpH methods has a comparatively small and correctible effect on the activity of ChE. Thus, the pH-stat method does not have a significant advantage in this regard; it does have the advantage that a 5-minute titration is usually sufficient for estimating the ChE activity of a sample. Furthermore, normal human values are less well established with this method than with that of Michel.^{134,154}

Other methods have been used to determine the rate of hydrolysis of various substrates by enzyme-containing biologic samples. This has been done by estimating the amount of unreacted ACh after a period of incubation with a source of ChE¹⁵⁵⁻¹⁵⁷ and by measuring the release of thiocholine from acetylthiocholine by ChE's.^{158,159,160,161} The methods for the determination of unreacted ACh have been used primarily with serum samples and have not been used frequently in this determination after OP exposures. The method of Hestrin, which appears to be the standard method for serum ChE,^{162,163} has been used in establishing normal values,¹⁵⁴ and has precision comparable with the ΔpH method.¹³⁶ The method has apparently not been used for determining ChE in plasma or RBC's, presumably because of the turbidity of such solutions. The method can be used under a great variety of experimental conditions, however, including wide ranges of pH's, substrate concentrations, enzyme concentrations, and buffer solutions.¹³⁶ A method which can accommodate variable conditions does not necessarily gain an advantage from this fact, however, because such variations usually are not encountered in the routine analysis of human ChE's.

The methods which estimate ChE by determining the amount of hydrolyzed acetylthiocholine have been used for several years since they were first developed by Koelle and Friedenwald¹⁵⁹ for histochemical determinations. Methods have been developed using several reagents which form colors with the thiocholine present after hydrolysis of acetylthiocholine.^{158,161,164} Determinations of ChE's in plasma, serum, RBC's, and other tissues were possible using the method of Ellman et al,¹⁶⁴ but there are possibilities of interferences by icteric or hemolytic plasma. This method has been adapted for use with an automatic analyzer and is thus useful for the routine analysis of large numbers of samples. Normal activities of human ChE's with these methods have not been reported extensively.¹³⁴ The precision of these colorimetric

methods is not as great as that of the ΔpH methods,^{164,165} and there are some additional characteristics which may detract from their suitability for routine analysis. Among these are the fact that the substrate concentration is too low for the determination of plasma ChE,¹⁶⁵ and that auto-oxidation of thiocholine is possible¹⁶⁵; there is also some disagreement over the relative specificities of acetylcholine and acetylthiocholine.^{159,160,164}

Several other laboratory methods have been devised, such as the amperometric method described by Einsel et al¹⁶⁶ and the radioassay methods of Winteringham and Disney,^{167,168} and Potter.¹⁶⁹ A gas chromatographic method was developed by Cranmer and Peoples¹⁷⁰ and an acetylcholine-ion-selective electrode was developed by Baum.¹⁷¹ These alternate methods have not received widespread acceptance and have not been well documented in the open literature. The principal reasons are that these methods require more expertise than the colorimetric and ΔpH methods. Equipment used in these methods is more specialized and expensive than that used in manual colorimetric and ΔpH methods. A comparison of normal values of activity for RBC ChE in humans by the Wolfsie and Winter¹⁴⁷ method and the original method of Michel used by Rider et al,¹⁴⁵ shows similar values for mean activity of RBC ChE. Wolfsie and Winter¹⁴⁷ found a mean of 0.861 $\Delta\text{pH}/\text{hour}$ with a standard deviation of 0.091. Rider et al¹⁴⁵ found a mean of 0.766 $\Delta\text{pH}/\text{hour}$ with a standard deviation of 0.081. Rider et al explained the difference between the mean RBC ChE activity that they determined and that of Wolfsie and Winter on the basis of probable contamination of red cells by plasma in the last two authors' work, since the RBC's were not washed during that study. Witter¹⁶⁵ suggested that the difference may have been due to increased packing of RBC's in the Wolfsie and Winter study. Also, this difference in means may be due, in part, to the fact that the same persons were not tested in the two studies. In establishing their mean, Rider et al¹⁴⁵ sampled 400 men, whereas Wolfsie and Winter sampled 255 men. The two groups of subjects were small enough to allow the discrepancy in mean values without necessarily concluding that the RBC's were contaminated, especially in view of the ranges and standard deviations in the studies. The ranges determined by Wolfsie and Winter and by Rider et al were 0.554-1.252 $\Delta\text{pH}/\text{hr}$ and 0.58-0.95 $\Delta\text{pH}/\text{hr}$, respectively. The range of ChE activities of the group of subjects studied by Rider and his associates fell within the range for the group of Wolfsie and Winter.

Clearly, there is much overlap of the distributions of normal ChE activities in the two studies, and the difference in means should not be given undue significance in these comparatively small samplings from the entire population.

The standard deviations for chemical analyses of ChE's by the methods of Wolfsie and Winter¹⁴⁷ and Rider et al,¹⁴⁵ 0.03 $\Delta\text{pH}/\text{hr}$, are small in comparison to the interindividual variations observed.¹⁴⁵ They are included in the overall standard deviation reported.

The means of the normal populations by these two " ΔpH " methods^{145,147} are closer for plasma ChE activity than for RBC ChE activity. The means of the plasma ChE activities of the 2 groups of normal subjects were found by Wolfsie and Winter¹⁴⁷ and Rider et al¹⁴⁵ to be 0.912 and 0.953 $\Delta\text{pH}/\text{hr}$, respectively, and the standard deviations were 0.11 and 0.19, respectively. The ranges for plasma ChE in normal humans of Wolfsie and Winter and Rider et al were 0.408-1.652 $\Delta\text{pH}/\text{hr}$ and 0.52-1.39 $\Delta\text{pH}/\text{hr}$, respectively, indicating again that the group of normal subjects used by Rider et al had plasma ChE activities included within the range determined by Wolfsie and Winter.

Based upon the consideration of means, standard deviations, and ranges, the conclusion can be made with a high degree of reliability that there is not an appreciable difference in either the normal values determined in the 2 studies or the analytical methods used in them.

In studies of serum ChE activities in various groups, different normal values have been found for men and women.¹⁵⁴ In the largest study reported,¹⁴⁵ the mean of the female plasma ChE was found to be lower than the plasma ChE of men. The female/male ratio of 0.86 found by Rider et al¹⁴⁵ was representative of those found in several other studies reported by Wetstone and LaMotta.¹⁵⁴

Based on the foregoing, the biochemical assay method of Michel¹³³ has been selected as the method of analysis to be recommended because it has been the most popular, is the most widely documented, and is unsurpassed in precision. The laboratory equipment necessary is standard, relatively inexpensive, and simple to use. Although the method is not automated, it does provide small laboratories with the capability to analyze many samples without excessive expense. Normal values using this method are based upon the largest extant survey of a nonexposed population. (Table XI-2) The micromodification of the sampling method used in the original Michel method,

described by Wolfsie and Winter,¹⁴⁷ used in conjunction with the original biochemical assay method of Michel will provide sufficient precision in analysis without excessively great bloodletting.^{148.172}

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

Parathion appeared in both the tentative Threshold Limit Value and established value lists of the American Conference of Governmental Industrial Hygienists (ACGIH) in 1954,¹⁷³ with a suggested TLV of 0.1 mg/m³.

Documentation for the ACGIH value¹⁷⁴ was published in 1962. The TLV of 0.1 mg/m³ was primarily based on conclusions drawn from the studies of Kay et al⁵⁸ and Brown and Bush.⁷⁹ Kay et al⁵⁸ measured airborne parathion levels ranging from 2 to 15 mg/m³ in the breathing zones of workers engaged in orchard spraying. At the end of a 2-month spraying period, during which time the workers were intermittently exposed, the blood ChE levels of the sprayers were decreased about 25% below control values. The average daily exposure was estimated¹⁷⁴ by the Committee on Threshold Limit Values to be not more than 2.0 mg/m³ even though the range of measured airborne parathion levels was 2-15 mg/m³. Brown and Bush⁷⁹ measured airborne parathion levels ranging from 0.1 to 0.8 mg/m³ in a manufacturing/formulating plant in which workers showed decreased RBC and plasma ChE activities. The TLV documentation states,¹⁷⁴ "Based on these calculations, 2 mg/m³ would appear to be an excessive exposure. From the work of Brown and Bush, 0.5 mg appears excessive. It is concluded that the figure of 0.1 mg/m³ provides the best estimate for a threshold limit from available data."

In the 1966 Documentation of Threshold Limit Values,¹⁷⁵ the results of various animal feeding studies were reported. In addition, the results of Edson's study³⁵ involving the daily oral ingestion of parathion by human volunteers were presented; "doses of 1.47 mg/man/day produced no effect in volunteers, while a dosage of 5.46 produced moderate depression of blood cholinesterase."¹⁷⁵ The TLV was believed to be sufficiently low to prevent significant depression of blood ChE activity provided that contamination of the skin was prevented.

The data of Arterberry et al⁵⁰ showing a slight depression in blood ChE activity at a urinary PNP excretion of about 2 mg/liter in workers repeatedly exposed to parathion was included in the Third Edition (1971) of the Documentation of the Threshold Limit Values.¹⁷⁶ The recommended TLV remained at 0.1 mg/m³.

A federal ambient air (ie, workplace) standard for parathion of 0.1 mg/m³, with a warning concerning skin absorption, has been promulgated by the Occupational Safety and Health Administration under the authority of the Occupational Safety and Health Act of 1970 (29 CFR Part 1910.93 published in the *Federal Register* 39:23542, June 27, 1974). This standard is based upon the recommendation of the ACGIH. The use of the word skin following parathion in the federal standard is intended to suggest appropriate measures for the prevention of cutaneous absorption so that the ambient air limit is not invalidated. There are no state environmental limits more restrictive than the federal.

Permissible levels of toxic substances in the work environment for a number of countries in addition to the US have been published by the Joint ILO/WHO Committee on Occupational Health.¹⁷⁷ Finland, the Federal Republic of Germany, Japan, Rumania, and Yugoslavia all have occupational exposure standards of 0.1 mg/m³, while Bulgaria, Hungary, and the USSR adopted 0.05 mg/m³ as a maximal acceptable concentration (MAC). In the USSR, MAC's are defined as ". . . absolute limits that should not be exceeded during any part of the working day, regardless of lower concentrations that may have existed during any of its period. They are set at a value which will not produce, in any of the persons exposed, any deviation from normal, or any disease which can be detected by the most modern research methods available."¹⁷⁷ Smelyanskiy and Ulanova,¹⁷⁸ in a paper dealing with Russian MAC's, stated that methods for investigating CNS function and higher nervous activity, biochemical and delicate morphologic and histologic techniques, and the use of both conditioned and unconditioned reflexes, among others, are of value in detecting early manifestations of chronic toxicity of workplace substances.

Basis for the Recommended Environmental Standard

The characteristic signs and symptoms of parathion poisoning, discussed in Chapter III and listed in Table III-1, are due to cholinergic stimulation resulting from inhibition of the activity of neuroeffector and other tissue ChE's.¹ There is

evidence from experiments with DFP⁷¹ that RBC and plasma ChE's serve as "buffers" protecting the more vital tissue ChE's from inhibition. Karczmar and Koppanyi⁷¹ demonstrated in animals with a normal amount of neuroeffector ChE that lowered activities of plasma and RBC ChE's increased responses to ACh, BCh, and DFP. They were able to demonstrate also that, in animals in which the tissue ChE's had been reduced to near zero, the infusion of ChE-rich blood probably did not restore activity at the neuroeffector sites. In such animals, however, responsiveness to injected ACh was nearly the same as that of control animals.

The absorption and subsequent metabolic conversion²³⁻²⁵ of parathion by the body reduce the ChE activities in central, peripheral, and autonomic nerve tissues, RBC's, and blood plasma.¹⁸ Grob et al¹⁸ demonstrated that the blood ChE's are depressed along with tissue ChE's in humans poisoned by parathion. Other investigators have shown^{8,9,11,13, 17,18,34,35,61} significant depressions of both RBC and plasma ChE's in workers exposed to parathion but not exhibiting signs and symptoms of parathion poisoning as well as in those exposed and exhibiting signs and symptoms of poisoning.

In addition to blood ChE determinations, estimation of metabolites such as urinary PNP as a measure of human exposure to parathion has been proposed.^{37,46,51,104,179} Determinations of blood and urine alkyl phosphates have been suggested also.¹⁸⁰⁻¹⁸² In 1970, Wolfe et al⁵¹ reported that PNP excretion levels correlated well with exposure to parathion. The average peak excretion level occurred 8.7 hours after exposure; the levels of PNP were insignificant 48 hours after exposure. Thus, it is important to obtain urine samples soon after exposure. Arterberry et al⁵⁰ concluded in 1961 that PNP excretion is not a reliable measure of the severity of poisoning. In agreeing with the conclusion of Arterberry et al, Wolfe et al⁵¹ stated that PNP was a more sensitive measure of exposure than were blood cholinesterase levels though the latter seemed to correlate better with occurrence of poisoning than did PNP excretion. As a hypothetical example, following an exposure to parathion sufficient to depress the RBC and plasma ChE's to 60% of their preexposure values, PNP will be excreted in the urine. In order to determine the extent of this exposure, the urine would have to be collected within approximately 9 hours of exposure.⁵¹ About 2 days later, the urinary PNP excretion would have ended⁵¹ whereas the blood ChE's would still be depressed from normal.¹⁸ Subsequent significant exposures would

produce the same effects, with further depression in blood ChE's and urinary excretion of PNP. Thus, the likelihood of detecting continuing parathion absorption with resultant ChE depression through a routine biologic monitoring program is greater by estimation of blood ChE's than of urinary PNP. Cholinesterase activity levels appear to be better indicators of OP exposure since the regeneration/replacement rates are slow enough¹⁸ to integrate the exposure effectively and allow practical sampling frequencies. In addition, workers engaged in formulation, mixing, and application of parathion are likely to be simultaneously exposed to other ChE-inhibiting insecticides, such as mevinphos, monocrotophos, TEPP, azinphosmethyl, and others, which do not result in urinary excretion of PNP. In cases of exposure to mixed anticholinesterase pesticides, urinary monitoring of PNP levels would not necessarily provide warning of additional inhibition of blood ChE's. Workers exposed to parathion alone are the exception rather than the rule.

The metabolism and hydrolysis of OP pesticides in mammals result in the excretion in urine of a variety of alkyl phosphates.^{181,182} Shafik et al¹⁸² fed parathion to rats at 1/10 the LD₅₀ for this species and recovered both O,O-diethyl phosphate (DEP) and O,O-diethyl thiophosphate (DETP) in the urine. The total DEP and DETP excreted in the urine accounted for 30-40% of the parathion initially fed. Their results suggested that the DEP arose from the action of hydrolytic enzyme(s) on paraoxon, a metabolite of parathion. Excretion of these metabolites remained relatively constant during exposure and dropped rapidly to zero upon cessation of feeding. Blood and urine alkyl phosphate (ie, phosphates, thiophosphates, and dithiophosphates) determinations are presently undergoing additional research and evaluation; they show great promise for the future as diagnostic procedures.

Electromyography (EMG)^{67,68} has been used to measure the effects of mixed pesticide exposure (organochlorine and organophosphorus pesticides) on the neuromuscular system. No studies showing altered electromyographic response in workers exposed to parathion alone have been published.

Neither the alkyl phosphate metabolite method nor the EMG technique is currently acceptable since the test results cannot be satisfactorily quantitatively related to either the extent of exposure or the hazard to the worker.

Thus, because RBC ChE activity levels provide an acceptable means of correlating the extent of exposure with the immediate effect, and because

these levels are relevant to mixtures of ChE-inhibiting pesticides and allow for practical sampling frequencies, routine biologic monitoring of the RBC ChE and monitoring of both RBC and plasma ChE's in emergency exposure situations are recommended for the prevention of adverse health consequences in parathion-exposed workers.

There are daily variations, both in the plasma and RBC ChE activities of normal, healthy persons who are unexposed to ChE-inhibiting OP pesticides, including parathion.^{58,135,154,172} Fryer et al¹⁷² determined the probable daily variations of plasma and RBC ChE activities for a normal, healthy individual using a micromodification of the Michel method. In this study of 17 volunteers from a university staff with no known exposure to OP insecticides, the normal daily variation from the group mean in both plasma and RBC ChE's was determined. Five consecutive daily samples were taken from each volunteer except one; in that case, there was a one-day gap in the series. For RBC ChE activity, the range was $\pm 23\%$ from the group mean; for plasma, the range was $\pm 37\%$. The day-to-day variation within individuals for RBC and plasma ChE activities was $\pm 5\%$ and $\pm 9\%$, respectively, for the group as a whole. Individual maximal variations were $\pm 13\%$ and $\pm 23\%$ for RBC and plasma ChE activities, respectively. The authors¹⁷² did not indicate race, age, or sex differences in the volunteer group. It must be noted, however, that any extrapolation of these data to a larger group must consider the possible changes in variation that may occur because of these factors. Rider et al¹⁴⁵ have shown that the plasma ChE levels are higher in men than in women and increase slightly with age. In men, the increase was $0.002 \pm 0.001 \Delta pH/\text{hour}/\text{year}$ of age and twice that in women. The authors did not find significant differences in RBC ChE with age or sex. On the other hand, Vorhaus and Kark¹⁴⁶ could not find a difference in plasma enzyme activity that could be correlated with age, sex, weight, or height. They did not evaluate differences in RBC ChE.

Reinhold et al¹³⁸ also found plasma ChE activity higher in men than in women. They noted also differences between blacks and whites in both men and women. The group mean of 0.926 for the serum ChE activity of white men was significantly higher than the observed group means of 0.814 and 0.768 for black men and women, respectively. In this study, 130 white men, 46 black men, 70 white women, and 28 black women were compared.

In addition to changes in blood ChE activities due to sex, race, and age, serum ChE activities

have been reported⁷²⁻⁷⁴ to be depressed in persons afflicted with liver disease, anemia, acute infectious and chronic debilitating diseases, and malnutrition. Drugs such as caffeine and related xanthine compounds,¹⁸³ chloroquine and other antimalarial drugs,⁷⁶ chloroform,¹⁸⁴ ether,¹⁸⁴ narcotic analgesics such as morphine and codeine,⁷⁷ and thiamine¹⁸⁵ have been shown to depress the activity of serum ChE. A few drugs have been reported to depress RBC ChE activity, including quinine,⁷⁶ other antimalarial drugs,⁷⁶ and echothiophate.¹⁸⁶

Fryer et al¹⁷² analyzed the day-to-day variations in the ChE's of the blood of 17 unexposed subjects during 5 days and concluded that 95% of normal people would have day-to-day variations of not more than 0.171 $\Delta pH/\text{hr}$ in RBC ChE and not more than 0.351 $\Delta pH/\text{hr}$ in plasma ChE. Applying these criteria to a group of 89 agricultural workers who had not knowingly been exposed to OP compounds for at least three months, they found, with 95% confidence, that there were 3 true positive reports, 12 false positive reports, and no false negative reports of decreased RBC ChE, and one false negative report and no positive report of decrease plasma ChE. The authors pointed out that a knowledge of preexposure ChE activities is necessary for any degree of accuracy in determining whether a particular individual's ChE's have been altered, but that their tolerance limits may be useful in interpreting measurements of ChE activities in blood samples submitted at random from the field.

The two populations differed somewhat in mean age: 30 years for the unexposed group and 38 years for the group of agricultural workers. Fryer et al did not give any further identification of the test populations by sex or race or give any indication of other possible exposures that might have affected blood ChE levels except that they ruled out recent known exposure to OP insecticides.

The most striking, and perhaps the most significant, difference between the handling of the blood samples from the two groups was that those from the agricultural workers were not refrigerated for about 6 hours after their collection and during that time were subjected to some agitation. The finding that the unexposed individuals had a higher mean RCB ChE activity and a lower mean plasma ChE activity than the agricultural workers could mean that their blood samples underwent slight hemolysis during transport to the laboratory. Such an effect could contribute to the false negative reports of decreased RBC ChE but would not increase the ChE activity of the plasma sufficiently to explain the excess activity there in the group of agricul-

tural workers. Some other factor seems to be involved, therefore, in generating the differences between the two groups.

Even though the effect of these limitations cannot be assessed, the estimates by Fryer et al¹⁷² of normal daily variations in plasma (9%) and RBC (5%) ChE activities among individuals are in approximate agreement with those determined by Callaway et al¹³⁵ and Wetstone and LaMotta.¹⁵⁴ Callaway et al¹³⁵ found that the daily variations in the plasma and RBC ChE activities of normal, healthy men were 8.5% and 6.6%, respectively. Wetstone and LaMotta¹⁵⁴ reported that the overall intra-individual variation in serum ChE activity for 82 subjects tested 373 times during a 1- to 250-week interval was 8.4%. In 1975, Sidell and Kaminskis¹⁸⁷ reported on the temporal variability of human ChE. Twenty-two subjects were studied during a 1-year period. The coefficients of variation for plasma ChE activity were reported to be about 6% for both males and females. In agreement with previous investigators, the authors found that the activity of the RBC ChE was more constant; the average coefficient of variation was 2.1% for males and 3.1% for females.

Based on the aforementioned experimental evidence, depressions in plasma and RBC ChE activities less than 36% and 22%, respectively, from mean normal values can be due to normal daily variations. Another important consideration in selecting a particular percentage level of blood ChE depression for both worker protection and compliance purposes is the correlation between blood ChE activity depression and the appearance of signs and symptoms of parathion poisoning. The level of depression to be tolerated must be such that it will demonstrate that an exposure to parathion has occurred before the worker actually becomes ill and allows immediate steps to be taken to correct the situation leading to the exposure. It is important also that the worker not be removed from his job unnecessarily, so that a warning level of RBC ChE depression and an action level, at which the worker must be removed from potential exposure, seem desirable.

In general, the literature indicates^{11,18,34,35,37,38,52,79} that normally only at depressions of plasma and RBC ChE activities considerably greater than 30% do signs and symptoms of systemic parathion poisoning appear in individuals. Certain degrees of depression of blood ChE activities are not accompanied by a significant prevalence of local or systemic effects.

In the study by Brown and Bush,⁷⁹ exposure to parathion of 5 of 12 workers in a manufactur-

ing/formulating plant resulted in average depressions of plasma of 34% and RBC ChE activities of 61%, without the appearance of signs and symptoms of poisoning.

Rider et al³⁴ observed depressions in plasma ChE of 50%, 52%, and 54% in 3 subjects receiving daily oral doses of 7.5 mg parathion for approximately 30 days without signs and symptoms of poisoning. In these same individuals, the lowest RBC ChE activity levels observed during the study were 63%, 78%, and 86% of pretest levels (ie, depressions of 14-37%).

In 4 female volunteers receiving 7.2 mg parathion/day orally, the plasma and RBC ChE activities declined to 84% and 63%, respectively, of control activity after 6 weeks of exposure.³⁵ Neither signs nor symptoms of poisoning occurred in these subjects.

Hartwell and associates³⁷ observed no signs or symptoms of poisoning in a volunteer exposed for 30-minute periods on each of 4 consecutive days to vapors of heated parathion when the RBC and plasma ChE activities were depressed 30% and 53%, respectively. However, signs of parathion poisoning appeared in the subject 10 minutes after the parathion was mistakenly heated to 150 F; a subsequent determination of blood ChE activity levels indicated that RBC and plasma ChE were depressed 98% and 83%, respectively.

Plasma and RBC ChE activity levels were depressed 98.6% and 93.3% respectively, from normal, in a 15-year-old girl suffering from parathion poisoning.³² Prior to blood ChE activity determinations, she exhibited the following signs of parathion poisoning: shallow and irregular respiration, constricted pupils, low systolic blood pressure, inspiratory rales in all lung fields, muscle fasciculations in the limbs, and bronchopharyngeal secretions, among others.

Grob et al¹⁸ studied the effects of parathion on 40 men and women who had been exposed to the compound on one or more days during the month preceding the appearance of symptoms. Only 5 of the 40 (12.5%) poisoned individuals experienced any "warning" symptoms, including intermittent nausea, vomiting, giddiness, weakness, drowsiness, and twitching of the eyelids, prior to the day on which severe signs and symptoms appeared. The average period of exposure was 8 hours/day for 12 days. Six men died, 2 men and 2 women experienced severe but not fatal symptoms, and 24 men and 6 women had mild to moderate symptoms. Four patients who survived despite severe symptoms and 2 who died had plasma and RBC ChE depressions (compared to normal values) of

95% or greater and 78-89% (average 86%), respectively. These values averaged 90% and 78%, respectively, in 6 other subjects with symptoms of moderate degree.

Hartwell and Hayes³⁸ reported the case of a pilot who became ill with mild poisoning after applying both dust and liquid forms of parathion intermittently for several days; his RBC and plasma ChE activities were depressed 48% and 44% from normal, respectively, measured on the day of onset of illness. RBC and plasma ChE activities were depressed 34% and 28%, respectively, in a second pilot engaged in crop-dusting who complained of excessive sweating and a mildly upset stomach.

In a group of 4 workers exposed to parathion residues during apple thinning, in whom signs and symptoms of parathion poisoning occurred, RBC and plasma ChE activity depressions ranged from 61-66% and 71-83%, respectively.¹¹ The enzyme activities were measured by the Michel method 2 days following the onset of symptoms (percent depressions were calculated using the mean values for the Michel method determined by Rider et al).¹⁴⁵ Nausea, vomiting, sweating, weakness, shortness of breath, headache, giddiness, and twitching of the eyelids were seen in these workers.

Important conclusions can be evolved from the preceding discussion: (1) there may be day-to-day variations in both the RBC and plasma ChE's of normal, healthy individuals,^{58,135,154,172} and (2) signs and symptoms of chronic systemic parathion poisoning usually do not appear in humans until these enzyme activities are depressed by about 50% below normal levels.^{11,18,34,35, 37,38,52,79} Even greater depressions of the ChE's of the blood may be incurred without the appearance of signs or symptoms of poisoning by parathion.

In many cases, individual worker preexposure blood ChE activity values will not be available, thereby necessitating the use of mean values determined for normal populations. Because of the fact that both the individual preexposure and group mean activity levels will be used as the situation warrants, it would be arbitrary to set an allowable level of blood ChE depression based solely on the variation calculated for 95% of the population at a 95% confidence level, namely, approximately 22% and 36% for RBC and plasma ChE, respectively. Therefore, in the case of RBC ChE, a depression exceeding 30% of the worker's baseline value will be considered as indicating excessive exposure to parathion. Only the RBC ChE is recommended for routine monitoring for the following reasons. Although the results of studies^{18,34,81,103} involving animals and human volunteers have shown that

plasma ChE is inhibited more promptly and to a greater extent than the RBC enzyme in individuals initially exposed to parathion. The rate of return of inhibited plasma ChE exceeds that of the RBC enzyme so that, during a period of consistent but moderate exposure, the ChE activity of plasma may actually be greater than that of the RBC's.¹⁸ Grob et al,¹⁸ in their study of 18 workers poisoned by parathion found that plasma ChE increased at an average rate of approximately 9% of normal activity during each of the first 3 days following termination of exposure, while the RBC ChE activity increased at an average daily rate of approximately 3%. However, averaged over the entire period of recovery, the rates of return approximated 1-2%/day and 3-4%/day for RBC and plasma ChE's, respectively. Thus, under certain exposure situations, the plasma ChE activity could return to normal while the RBC ChE activity remained depressed. For this reason, it is more likely that excessive absorption of parathion resulting from relatively low-level repeated exposure can be detected by routinely monitoring for RBC ChE activity. In addition, the plasma enzyme is subject to greater normal daily variation than the RBC ChE, approximately 9% versus 5%, respectively.¹⁷² Previously, we have pointed out that the plasma ChE can be lowered in individuals with liver disease, anemia, debilitating disease, or malnutrition; drugs such as quinine,⁷⁶ morphine, and codeine⁷⁷ also depress the plasma ChE activity. Thus, monitoring plasma ChE activity increases the likelihood of false positive results. On the other hand, the RBC ChE has not been shown to be affected by such diseases; a depression in the RBC ChE activity exceeding normal variation in parathion-exposed workers is almost certainly due to the effects of the insecticide. A similar reduction in the activity of the plasma enzyme is considerably less certain to be due to exposure to parathion. Therefore, routine monitoring of RBC ChE will provide a better estimate of exposure to parathion. However, an RBC ChE monitoring program based on a preset sampling frequency should be effective in detecting the slow development of systemic parathion poisoning due to progressive inhibition of the activity of AChE at various sites throughout the body; it is intended to warn of excessive parathion absorption in a situation involving long-term, low-level exposure. Routine RBC ChE monitoring will not, in all likelihood, provide a warning of impending poisoning from massive exposures, resulting in precipitous declines in both the blood and tissue ChE's, such as in the case of inhalation exposure to high concentrations of parathion dust

or aerosol or dermal exposure to spills, sprays, or splashes of concentrated material on the skin or clothing. Also, since relatively nonsevere signs and symptoms of cholinergic stimulation can occur as the result of localized effects of parathion exposure, a biologic monitoring program based on the activity levels of the blood ChE's may not prevent or warn of the development of such signs and symptoms under certain exposure conditions. For example, miosis and blurred vision can result from direct exposure of the eyes to parathion, local fasciculations can occur in the immediate area of absorption of parathion from the surface of the skin, and bronchial secretions can result from respiratory exposure, all in the absence of significant effects on the blood ChE's. Good work practices and the use of personal protective clothing and equipment will best serve to protect workers from such effects, particularly those resulting from accidental spills, sprays, or splashes. Also, since the plasma ChE is inhibited more readily than the RBC ChE^{18,34,87,103} under acute exposure conditions, the plasma ChE activity may decline precipitously in massive exposure situations while the RBC enzyme at first is relatively uninhibited. Therefore, in cases of known or suspected parathion overexposure (ie, exposure to either airborne concentrations exceeding the environmental limit or to spills or splashes, etc), both the RBC and plasma ChE activities should be determined.

Kay et al⁵⁸ demonstrated that workers engaged intermittently in the ground spraying of parathion experienced significant seasonal declines in blood ChE activities. They found no significant difference in the RBC ChE activity levels between sprayers reporting symptoms of parathion overexposure and those apparently symptom-free. However, the plasma ChE activity was 20% lower in the group with symptoms of parathion overexposure than in those not complaining of symptoms. The sprayers were exposed for a few days during each 10-day interval over a 2-month period. Airborne parathion concentrations collected in the operators' breathing zone ranged from 2.0 to 15.0 mg/m³. Erythrocyte and plasma ChE activities were determined both during and subsequent to spraying in order to establish normal activity levels. These results of intermittent exposure demonstrate the hazard involved in a continuous exposure to airborne concentrations of parathion in the range of 2.0 to 15.0 mg/m³. Concomitant dermal exposure, which is significant in the application of parathion,⁴⁶ compounds the hazard.

The only reported study of parathion exposure

in industry in which both air samples indicating significant exposure and RBC and plasma ChE monitoring showing biologic response were obtained is the often-cited work of Brown and Bush.⁷⁹ Thirteen workers in a plant manufacturing concentrated parathion and dusts of varying concentration were studied. Twelve of the 13 workers were exposed to airborne concentrations of parathion ranging from 0.1 to 0.8 mg/m³ (0.1 mg/m³ being the lower limit of detectability) as determined using sintered glass absorbers, midget impingers, and Greenburg-Smith impingers. Six general location and 6 worker breathing zone air samples were collected. The average airborne parathion concentration for 8 sampling sites was 0.2-0.3 mg/m³. Because of rotation of plant personnel, the workers were only intermittently in contact with parathion-contaminated air. Both plasma and RBC ChE activity levels were determined during a 10-month period; however, preexposure control values had been obtained for only 6 of the 12 parathion-exposed workers. A maximum of 3 blood samples was collected during a 5-month exposure period; control values for the other exposed workers were determined from blood samples collected 5 months after the end of exposure. Five of the 6 workers with preexposure ChE activities experienced the following depression of plasma and RBC ChE activities, respectively: 22% and 73%, 7% and 42%, 46% and 63%, 52% and 60%, 41% and 66%. The reductions in plasma and RBC ChE activities averaged 34% and 61%, respectively. An engineer in the plant, the sixth worker for whom baseline blood ChE values were available, experienced no significant decline in blood ChE activities. Several other workers for whom no preexposure ChE activities had been obtained appear to have exhibited significant depressions in blood ChE activities. The results of this study indicate that continuous exposure to airborne parathion in a concentration range of 0.1-0.8 mg/m³ may pose a hazard to the health of workers. However, the data do not provide firm evidence of what airborne concentration of parathion, if any, in this range constitutes a safe exposure. The results obtained by Brown and Bush⁷⁹ can be used only to indicate a suspected unsafe continuous exposure level to airborne parathion, namely, the average value obtained for the 8 sampling sites, or approximately 0.25 mg/m³.

In the absence of additional published data similar to that of Brown and Bush⁷⁹ upon which an environmental standard for parathion can be directly based, an indirect estimate based on extrapolation from a demonstrated safe daily oral

dose in humans must be made.

Rider et al³⁴ administered parathion to human volunteers at dosages of 3.0, 4.5, 6.0, and 7.5 mg/day. Each phase of the study was conducted on groups of 7 subjects, 5 of whom served as test subjects and 2 as controls. The study was divided into three periods: (1) a pretest period of approximately 30 days during which normal plasma and RBC ChE activities were determined; (2) an approximately 30-day test period during which parathion was taken orally by the subjects; and (3) a post-test period. Plasma and RBC ChE activities were measured twice each week throughout each phase. None of the subjects receiving the two lowest daily dosages, 3.0 and 4.5 mg, exhibited significant depressions in either plasma or RBC ChE activities. The investigators reported a slight but unspecified depression in plasma ChE activity in the group receiving 6.0 mg/day. Significant depressions in blood ChE activities occurred in the group receiving 7.5 mg parathion/day. Sixteen days after the start of dosing the plasma ChE activities of 2 of the 5 subjects were 50% and 52% of pretest levels, at which time administration of parathion to them was discontinued. On day 23, a third subject had a plasma ChE activity equal to 54% of his pretest level and parathion exposure was terminated. Subjects 4 and 5 completed a 35-day dosing period during which time plasma ChE activities of 78% and 86% of normal were the lowest observed. In the 3 subjects in whom the administration of parathion was discontinued because of significant plasma ChE depressions, the lowest RBC ChE activities observed were 63%, 78%, and 86% of the pretest values. No significant reduction in the RBC ChE activity occurred in the remaining 2 subjects. No signs or symptoms of parathion poisoning were reported. The results of this experiment demonstrated that the daily oral ingestion of 7.5 mg of parathion by humans resulted in a progressive and substantial depression in the activity of the blood ChE's, particularly the plasma enzyme, and thus constituted an unsafe oral exposure. In addition, the oral ingestion of 4.5 mg of parathion/day was shown to be a safe dose for man, exerting neither progressive depression of blood ChE activities nor clinical signs of illness in the subjects. Insufficient information was provided by the authors to determine the results of oral intake of 6.0 mg parathion/day.

In a similar manner, Edson³⁵ determined the effects of prolonged administration of small daily doses of parathion in man. Human volunteers were given parathion 5 days/week, for 25- to 70-day periods, at various dose levels. Whole blood, RBC,

and plasma ChE activities were measured at various times. Daily ingestion of 0.6, 1.2, 2.4, and 4.8 mg parathion by human volunteers resulted in no significant effects on whole blood ChE activity. However, in 4 women receiving 7.2 mg parathion daily, 5 days/week, whole blood ChE activity declined to 67% of control activity after 6 weeks. At this time, RBC and plasma ChE activities were 84% and 63% of control levels, respectively. Within 28 days of withdrawal of parathion, whole blood ChE was restored to approximately 87% of control activity. Thus, the daily oral intake of 4.8 mg of parathion was shown to be safe for humans based on response of the blood ChE activity. The maximum daily no-effect level was estimated by the authors to be 0.05 mg/kg.

Rider et al³⁶ administered parathion, in capsules, to human volunteers in daily doses of 0.003, 0.010, 0.025, and 0.050 mg/kg. The study consisted of four successive 3-week treatment periods within a 12-week span during which 8 of 10 subjects were given the 4 doses of parathion. Baseline blood ChE activities were measured during a 3-week pretreatment period; weekly measurements were made during the periods of daily dosing. No significant depressions in either plasma or RBC ChE activities resulted from any of the 4 dosages of parathion. No adverse effects were observed in any of the volunteers.

Thus, the results of studies conducted by Rider et al^{34,36} and Edson³⁵ demonstrate that parathion can be ingested by humans in a daily dose of 0.05 mg/kg without signs or symptoms of parathion poisoning and significant inhibitory effect on the blood ChE activities.

As a first step in calculating a no-effect (based on blood ChE activity response) respiratory dose from a safe oral dose, the assumption must be made that all parathion inhaled, particulate as well as vapor, is retained in the respiratory system and subsequently absorbed. Although such an assumption is not supported by the accumulated scientific evidence, it is necessary in order to account for all possible exposure situations. Also, calculations of the environmental limit based on 100% retention and absorption of inhaled parathion, in vapor and particulate form, provide the greatest possible margin of safety for employees exposed to this extremely toxic insecticide. An approximation of the ratio of respiratory toxicity to oral toxicity of parathion in humans is essential to the determination of a safe respiratory dose. As discussed previously, the human respiratory parathion exposure study of Hartwell et al³⁷ cannot be used in determining this ratio because the amounts of parathion

inhaled by the subjects were not determined by air sampling procedures but rather by extrapolation from the amount of PNP excreted in the urine. The results of other studies^{105,108} in which both airborne parathion concentrations and blood ChE activities were measured are also inadequate for determining this ratio. Thus, to determine the respiratory-to-oral toxicity ratio for parathion in man, an extrapolation must be made from experimental animal data. The LCt50 (20-minute exposure) in mice was found to be about 3,800 mg min/m³, according to a written communication from BP McNamara in October 1973. Using a ventilation rate of 0.023 liter/min and an average weight per mouse of 19.8 g,¹⁸⁸ this corresponds to an LD50 (inhalation) of 4.4 mg/kg. The oral LD50 of parathion in mice has been reported in the range of 18.5-20.0 mg/kg.¹⁸⁹⁻¹⁹¹ Thus, the ratio of respiratory to oral lethality of parathion in mice was about 0.23 to 1, or, in other words, parathion in these studies, under the existing experimental conditions, was approximately 4-5 times more lethal by inhalation than by ingestion.

As stated previously in Chapter III, it is not scientifically sound to extrapolate from minimal inhalation data in mice to a safe inhalation exposure concentration (ie, environmental limit) in man. Accordingly, the Toxicology Division, Edgewood Arsenal, Md, undertook studies of the inhalation and oral toxicities of parathion for rats and dogs. A thorough discussion of the study and results are presented in Chapter III and Appendix XV.

Groups of 34 rats were exposed for 4 hours to parathion in aerosol form at 13 concentrations ranging from 0.04 mg/m³ to 35.0 mg/m³. The RBC ChE50 and plasma ChE50 values, with 95% confidence limits, were calculated to be 5.43 mg/m³ (range 4.2-7.03) and 7.28 mg/m³ (range 5.24-10.12), respectively. The RBC and plasma ChE50 values for adult male rats exposed acutely by the oral route were 2.58 mg/kg (range 2.12-3.14) and 2.55 mg/kg (range 2.12-3.05), respectively. The approximate average weight of the rats used in these experiments was 250 g. For white rats of this weight, the average ventilation rate has been reported to be about 0.10 l/min. Thus, based on inhalation and oral RBC ChE50 values for the rat, parathion appears to be approximately 5 times more effective by the inhalation route than by ingestion in adult male rats. The corresponding value for plasma ChE was found to be approximately 3.6.

Because of the pronounced effects observed on blood ChE's at the airborne concentrations of parathion used, acute (ie, 4-hour exposures) in-

halation ChE50 values for RBC's and plasma were not obtained for dogs. However, in the acute oral studies, groups of 4 dogs were exposed to 7 dose levels of parathion ranging from 0.5 to 10.0 mg/kg. The RBC ChE50 was determined to be 1.50 mg/kg (range 1.06-2.12) while the plasma ChE50 was found to be 1.67 mg/kg (range 0.94-2.96). The RBC and plasma ChE50 values for adult male beagle dogs do not appear to be significantly different from the corresponding values for male rats. Likewise, the oral LD50 for dogs determined in these experiments, 8.27 mg/kg, is not greatly different from the oral LD50 of 6.85 mg/kg determined for rats. The data strongly suggest that parathion is approximately equitoxic to both species. Thus, because of the close agreement between the results obtained from the acute oral studies in male rats and male dogs, particularly the ChE50 determinations, the assumption is made, as a first approximation, that parathion is about 4 to 5 times more effective by inhalation than by ingestion in inhibiting RBC and plasma ChE of dogs. Some confirmation for this assumption is found in Tables XVI-5 and XVI-15. If a curve is drawn through the inhibition of RBC ChE produced by exposure to the 5 concentrations stated in Table XVI-5, it is seen that the 64% inhibition caused by an oral dose of 2.5 mg/kg (Table XVI-15) is reproduced approximately by a 4-hour exposure to a concentration of 23 mg/m³. If these dogs weighed 12 kg (no weights are stated), they would be expected to breathe about 0.356 m³ of air during the 4-hour exposure period. This would give an inhaled amount of 8.2 mg of parathion (0.68 mg/kg) with the assumption of 100% retention. The ratio of the oral dose to the estimated inhaled dose is then 2.5/0.68, or 3.7.

Because of the extreme mammalian toxicity of parathion and the number of illnesses and deaths associated with its use in agriculture,^{6-8,10,11,13} it is essential to provide the highest safety factor indicated by the experimental data. Therefore, for the purpose of establishing a safe inhalation exposure concentration (ie, environmental limit) in man, an inhalation-to-oral toxicity ratio of 5 is indicated.

The no-effect respiratory dose (Dr) of parathion accumulated during a 10-hour workday is defined as

$$Dr = 10 \times V_p \times Ca$$

where:

V_p = pulmonary ventilation rate of an average worker in m³/hr

Ca = mean airborne concentration of parathion in mg/m³.

Based on the demonstrated³⁴⁻³⁶ safe daily oral parathion dose for humans of 3.5 mg, calculated on an average-man weight of 70 kg, the no-effect respiratory dose is estimated to be 0.7 mg/10-hour working day. As stated previously, no-effect exposure levels are based on insignificant depression of either the plasma or RBC ChE's from exposure to parathion.

Table XVI-4 gives minute volumes applicable to metabolic levels ranging from sleep to maximum work. Based on these data, a reasonable inhalatory minute volume for a 10-hour exposure is 25 liters/min or 1.5 m³/hour. This 25 liters/min is an approximately median value between light and medium work. Based on the spectrum of work activity observed in various manufacturing operations, in formulation, and in mixing and application involving parathion exposures, an average pulmonary ventilation rate of 25 liters/min should encompass the workers' respiratory exposure to parathion in vapor, aerosol, and dust form. The equation thus reduces to

$$Ca = \frac{0.7}{10 \times 1.5} = 0.05 \text{ mg/cu m}$$

In summary, the human no-effect concentration of airborne parathion based on 100% retention and subsequent absorption of inhaled material for a 10-hour workday, 5-day workweek, is estimated to be 0.05 mg/m³.

Male rats subjected to parathion aerosol (average particle diameter of 1-2 microns) in a concentration of 0.10 mg/m³ of parathion for 7 hours/day, 5 days/week, for 6 weeks in the Edgewood Arsenal study experienced no signs of poisoning at any time during the exposure or postexposure periods. As seen in Table XV-8 the RBC and plasma ChE activities after 5 weeks' of exposure were 67% and 92% of normal activities (determined from the activities in unexposed control animals), respectively. Exposure of male rats to parathion aerosol in a concentration of 0.01 mg/m³ for the same period of time exerted no significant effects on blood ChE's. On the other hand, significant inhibition of both RBC and plasma ChE's occurred as the result of inhalation exposure of male rats to 0.74 mg parathion/m³ of air breathed.

In adult male dogs exposed to parathion aerosol 7-hours/day, 5-days/week, for 6 weeks, the following results were obtained: a concentration of 0.001 mg/m³ produced no significant inhibition of either RBC or plasma ChE's; one of 0.01 mg/m³ also produced no significant inhibition of RBC ChE during the 6-week exposure period; but the plasma

ChE activity was depressed to 58% of normal after 6 weeks' exposure. No signs of overt parathion poisoning were observed in any test animal; significant inhibition of both RBC and plasma ChE's occurred as the result of exposure to airborne parathion in a concentration of 0.20 mg/m³. Two weeks' exposure to this concentration resulted in RBC and plasma ChE activities of 54% and 26% of normal values, respectively. After 6 weeks' exposure to 0.20 mg/m³ of parathion, the corresponding values were 41% and 36%, respectively.

The results of these chronic exposure studies with male rats and dogs indicate that continuous exposure via inhalation to a concentration of parathion of 0.10 mg/m³ in aerosol form results in significant inhibition of the blood ChE's. These data suggest that the environmental limit of 0.05 mg parathion/m³, derived from inhalation-to-oral toxicity ratios in mice, rats, and dogs, and recommended as safe for employees exposed to parathion, is appropriate.

It may be argued that, on the basis of the results of Rider et al.,³⁴ 4.5 mg represents a safe continuous daily oral dose of parathion rather than 3.5 mg. However, since the weights of the subjects were not given, unlike Edson's study,³⁵ 4.5 mg cannot be stated unequivocally to be a safe dose for the average (ie, 70 kg) man. A daily oral dose of 3.5 mg has been shown, in 3 separate studies,³⁴⁻³⁶ to produce no signs or symptoms of parathion poisoning and no significant depression in either RBC or plasma ChE activity levels—a no-effect exposure level. Another major factor favoring a conservative approach in estimating a safe working lifetime exposure to parathion for up to 10 hours/day, 5 days/week—the likelihood of simultaneous absorption through more than one avenue of entrance into the body (skin and gastrointestinal tract, for example) of this toxic insecticide. As stated previously, it is extremely important to emphasize that the greatest danger to employees from exposure to parathion, under most conditions, is from SKIN CONTACT. Because of non-respiratory hazards, such as those resulting primarily from skin contact and absorption, it is recommended that appropriate work practices and protective measures be required regardless of the airborne concentration of parathion. For this reason, "occupational exposure to parathion" has been defined as employment in any area in which parathion or materials containing parathion, alone or in combination with other substances, is produced, packaged, processed, mixed, blended, handled, stored in large quantities, or applied.

VI. WORK PRACTICES

Work practices are important for the control of exposures to parathion. This is particularly true because parathion is absorbed through the intact skin, mucous membranes, and eyes, as discussed in Chapter III. Therefore, every effort must be made to avoid contamination of the skin via direct spills, splashes, or spray/dust, and indirectly via contaminated clothing or other materials. Should such contamination occur, it is essential that the worker involved be taken immediately to an uncontaminated area and the contaminated clothing or equipment removed from the body, the skin and hair thoroughly and quickly washed with water (and preferably soap) or with other suitable decontaminating solution, a physician contacted, and the exposed worker placed under observation for at least 24 hours. Contaminated clothing and other articles should be appropriately labeled and safely stored until they can be washed or destroyed. The provision for basic sanitary facilities and their use is essential in minimizing dermal exposures to parathion as reflected in the recommendations in Chapter I, Section 7.

To protect against contamination by direct spills, it is recommended that workers handling parathion wear adequate protective clothing including impervious gloves, coveralls (covering entire body) or rubber aprons, impervious footwear, and a protective head covering. It is important that personnel such as shippers and warehousemen handling nonleaking sealed containers of parathion, such as drums, wear full-body coveralls and impervious gloves. The routine maintenance of this protective clothing and equipment, usually by daily washing, is essential. Hydrogen peroxide or hypochlorous acid (dilute) should be available to decontaminate badly contaminated clothing before its subjection to laundering.

Workers engaged in the formulation of parathion and in the mixing and loading of parathion solutions and dusts into application equipment may be exposed to relatively large amounts of concentrated parathion. In these situations, the likelihood of skin contamination through spills and splashes may be great depending on the protective clothing and equipment and engineering controls being used. In addition, because of the processes involved, fairly large concentrations of airborne parathion, primarily in particulate form (ie, droplets or dusts containing adsorbed parathion), may be generated. Airborne concen-

trations of parathion were found to range from 0.25 to 0.4 mg/m³ in the breathing zone of workers filling 50-lb cartons with parathion dust in the study by Brown and Bush.⁷⁹ Airborne parathion concentrations measured during mixing and loading of water-wettable powder were reported to average 2.15 mg/m³ in a mixing plant surveyed by Batchelor and Walker.¹⁰⁶ Air monitoring was conducted by Kay et al⁵⁸ while workers added 15% parathion wettable powder to spray tanks. A mean airborne parathion concentration of 21 mg/m³ was found. Such exposures are normally of short duration; however, the level of exposure may be high enough to constitute a significant hazard. Where adequate vapor and dust exhaust systems are not feasible, such as in certain field situations, workers engaged in mixing or loading of parathion in liquid or powder (dust) form must wear a suitable respiratory protective device.

Direct contamination is also possible during spray operations. The results of studies conducted by Batchelor and Walker,¹⁰⁶ Jegier,¹⁰⁷ and Simpson and Beck¹⁰⁸ showed that respiratory exposures of spraymen ranged from 0.03-0.26 mg/m³ in air-blast spraying of orchards and fields to greater than 0.1 mg/m³ during use of hand knapsack sprayers on tomatoes. Kay et al⁵⁸ in their study of Quebec apple orchards measured airborne parathion concentrations ranging from 2 to 15 mg/m³ during the use of either hand-type or mechanical-rocker type sprayers. High-pressure hand sprayers have generated 0.09 mg/m³ levels of airborne parathion.¹⁰⁶ The spraying of concentrated parathion resulted in air levels ranging from 0.29 to 0.52 mg/m³ and a calculated respiratory exposure of 0.055 mg/hour according to Braid et al¹¹⁰ and Wolfe et al.¹⁰⁹ These results when compared to the estimated workplace environmental limit of 0.05 mg/m³ demonstrate that applicators may need respiratory protection under certain situations. In addition, results of several of these studies¹⁰⁶⁻¹⁰⁹ indicate substantial simultaneous dermal exposures. Therefore, under the specified conditions (see Chapter I, Section 4), respirators or masks approved for toxic dusts and organic vapors may have to be worn in addition to protective clothing, such as coveralls (covering entire body) or waterproof rainsuits, impervious gloves, impervious footwear, goggles, and a waterproof head covering. Waterproof or repellent parkas may be used to protect the head and neck simultaneously.

Pesticide drift is a common occurrence during the aerial application of parathion and other insecticides. Based on the results of studies conducted during the period 1961-69, Ware et al¹⁹² concluded that aerially applied insecticides in Arizona apparently deposited less than 50% on-target during the normal period of use of insecticides. Many factors, including droplet size in the spray cloud, wind speed, and the altitude of aircraft during application, play an important part in pesticide drift. During these studies, Ware et al found that wind-speed changed from less than 1 to 5.6 miles/hour. In 1972, Ware¹⁹³ reported that pesticide dusts deposited 9 times as much material on a field of alfalfa 0.5 mile from target as aerosolized emulsion preparations of the same pesticides sprayed from the same height and under similar wind conditions. The smaller particle size of the dusts resulted in a larger airborne time, which led directly to greater drift.

Braid et al¹¹¹ reported airborne parathion concentrations of 3.0, 0.85, 0.22, 0.07, and 0.03 mg/m³, measured at downwind distances of 50, 100, 200, 300, and 400 feet, respectively, during the application of 1% parathion dust. Thus, at a distance of 300 feet from the application rig, the airborne concentration exceeded the recommended air standard.

To prevent spray contamination of other workers due to drift, it is recommended that spraying not take place when excessive drift onto adjacent property is likely. Workers, except flagmen, must be removed from areas, particularly the one to be sprayed, where contamination is likely because of either fallout or spraydrift. However, care must be taken to ensure that flagmen do not receive a direct application of the spray. In addition, exposed flagging personnel should wear coveralls or waterproof rainsuits, impervious gloves, and a protective head covering. All flagmen should also be provided with a respirator approved for use against toxic dusts and organic vapors and with goggles.

The recommendation that the work environment be maintained free of unattended equipment, clothing, refuse, or natural materials contaminated with parathion reflects the experience in agriculture, in particular, of the dangers inherent to parathion contamination. Ganelin et al¹⁹⁴ reported several cases of poisoning from contact with contaminated equipment. In one case, a worker became ill about 2 hours after washing an aircraft previously used for applications of organophosphorus pesticides. A second worker suffered a similar exposure but, in this case, the aircraft had already been washed once since the last

application of parathion. A third illness occurred after a pilot had dismantled the hopper of his aircraft for maintenance. In this last case, although parathion had been applied previously in large quantities from this aircraft, only magnesium chlorate had been used for 2 weeks preceding the illness.

Although further cases illustrating the occupational hazards of a parathion-contaminated environment are easily found, it must be mentioned that such contamination may present a serious accidental hazard to children. Eitzman and Wolfson¹⁹⁵ reported the deaths of 30 children in Florida during the period 1959 to 1964 due to accidental parathion poisoning. Although the majority of these deaths resulted from ingestion, dermal absorption was implicated in 8 cases. One boy and his sister died and another brother became seriously ill after playing on a swing made from a cloth-filled burlap sack found later to be heavily contaminated with parathion. Two other poisonings occurred in older children and were occupationally related.

These incidents illustrate the potential hazards posed by parathion as an environmental contaminant if not properly handled, stored, and disposed of, to workers and their families. The case for the employee education requirements recommended in Chapter I, Section 6, rests primarily on experience and common sense. These requirements are currently common practice in many agricultural operations.

Fires and large-scale accidental spills of parathion in industrial areas or while in transport present obvious hazards. It is standard operating procedure to have plans for these eventualities in dealing with any toxic substance. In particular, in any emergency situation, it is essential to inform emergency control personnel of their potential exposure. To minimize the hazard to these groups and to workers routinely exposed to concentrated parathion, the labeling requirements in Chapter I, Section 3, are recommended, as are the several reporting and advisory requirements in Chapter I, Section 6.

In the industrial workplace, the procedures for exerting proper control over exposures to parathion are relatively standardized and do not require further elaboration other than to reiterate the obvious need for the provision and use of clean clothing daily, showers at the end of a work shift, and the use of appropriate sanitary practices.

In agriculture, the problems are much more complex because the site of use of the chemical is not fixed and access to the workplace cannot be

reliably restricted. Moreover, supervision of employees is more difficult, with resulting uncertainty in ensuring that appropriate work practices are followed. The last problem area demonstrates the importance of employee education.

The recommendations regarding employee education in Chapter I, Section 6, are quite general; in practice, however, the proper instruction must be quite specific. There are myriad details associated with the use and cleaning of goggles and respirators and with the appropriate emergency procedures to be used in the event of parathion spills or fires. Such details are covered in various pesticide safety manuals,^{3,196} which contain the

type of material that must be made generally available to employees exposed to parathion.

It is the employer's responsibility to be informed himself of the appropriate work practices and safety procedures and to make certain that employees know, understand, and practice those precautions appropriate to their own operations. Also, it must be made very clear to all employees that parathion is a highly toxic compound and that the various safety rules are based on long-standing experience and common sense. It cannot be overemphasized that proper employee education and attendant supervision are essential in minimizing the occupational hazards posed by parathion.

VII. RESEARCH NEEDS

Despite its decreasing usage, relatively large quantities of parathion are currently being manufactured, formulated, mixed, and applied to various crops in the United States. Accordingly, the following research is recommended in order to add to our existing knowledge of parathion:

(1) Animal experiments to determine whether or not permanent effects on the central nervous system occur as the result of chronic low-level exposure. Well-designed and controlled behavioral studies should be undertaken as a major part of the attempt to better define the effects of parathion on the central nervous system.

(2) Animal experiments to determine the mutagenic, teratogenic, and carcinogenic potentials of parathion in realistic doses.

(3) Electromyographic testing of human subjects exposed to parathion to determine particularly whether low concentrations of the insecticide produce adverse effects on the neurologic system.

(4) Studies to determine whether parathion exerts any toxicity by a mechanism, or mechanisms, other than inhibition of tissue ChE.

(5) Additional studies to more clearly define the environmental factors responsible for

the demonstrated conversion of parathion deposited on surfaces to other toxic substances.

(6) An epidemiologic study of a worker population exposed to parathion for a long period of time. In the event that an adequate cohort of workers exposed to parathion cannot be identified, a retrospective morbidity and mortality study of a worker population exposed to parathion and other ChE-inhibiting organophosphorus pesticides would be of great use in determining the long-term effects, if any, of these compounds.

(7) A program to develop more effective and satisfactory protective clothing for employees working with parathion as well as other pesticides (eg, cool, lightweight, and impervious to parathion).

(8) Studies to develop an accurate and precise solid sampling system for airborne parathion. In addition, the recommended impinger device should be thoroughly evaluated in order to determine its sampling efficiency and the overall precision of the recommended sampling and analytical method.

(9) A research effort to develop an improved biologic test method to supersede blood ChE determinations.

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APPENDICES

IX. APPENDIX I

SAMPLING AND CALIBRATION PROCEDURES

The sampling method recommended is based on those described by Miles et al,¹¹⁸ and the *NIOSH Manual of Analytical Methods*.¹⁹⁷ As stated previously in Chapter IV, the sampling efficiency and the overall precision of the recommended sampling and analytical method are unknown. 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 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 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. A prefilter unit consisting of the filter media and cassette filter holder can be used if needed.

(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 analysis. Consequently, the only ethylene glycol suitable is that which has been preextracted and found to be free of interfering substances by gas-liquid chromatography using 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 $\pm 5\%$ during the sampling period. The sampling pump must be capable of operating at a pressure drop of 1 inch of mercury while providing the designated flow rate of 1-2 liters/min. The flowrate of the pump must be calibrated and this calibration checked periodically to ensure that it has not changed.

(4) An integrating volume meter such as a dry-test or wet-test meter.

(5) Thermometer

(6) Manometer

(7) Stopwatch

(8) Filter cassette with glass-fiber filter, 8μ , 37 mm.

(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 upon 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, an absorption tube, 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. The inside of the soapbubble meter is then moistened by immersing the buret into 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 liters/min.

(5) A soapbubble is started up the buret, and the time required for 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 to be 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 in-

dividual 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 standard, as specified in Chapter I, Section 1(a), may be detected accurately by the recommended analytical method. An air sample of 25-50 liters should be collected. 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 hard, nonreactive stopper (preferably Teflon). Do not seal with rubber. The impinger is placed upright in a carrying case, with care taken to prevent losses due to spillage or evaporation. The trapped parathion is extracted into hexane and analyzed as described in Appendix II. Other collection methods shown to be equivalent or superior may be used. If shipment of the impingers with the stems is preferred, the outlets of the stems should be sealed with paraffin sheet or other nonrubber covers, and the ground glass joints should be sealed (ie, taped) to secure the tops tightly. A "blank" impinger should be handled as the other samples (fill, seal, and transport) except that no air is sampled through this impinger. Where a prefilter has been used, the filter cassettes are capped and placed in an appropriate cassette shipping container. One filter disc should be handled like the other samples (seal and transport) except that no air is drawn through it. This is labeled as a blank.

X. APPENDIX II

ANALYTICAL METHOD FOR PARATHION

The gas-liquid chromatographic method presented in the *NIOSH Manual of Analytical Methods*¹⁹⁷ is recommended for analysis of parathion in air. NIOSH classifies the method as Class C (tentative), which is described as a method in wide use and which has been adopted as a standard method or recommended by another government agency or one of several professional agencies.

Principle of Method

Parathion in workplace air is trapped in ethylene glycol contained in a midjet impinger. The ethylene glycol solution is diluted with water and extracted with hexane. The resulting solution of parathion in hexane is concentrated and subjected to gas-liquid chromatographic 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 parathion. For a 50-liter air sample carried through the following procedure to solution in 1 ml of hexane, 2 μ l of which is injected into the gas chromatograph, the range of workplace air concentrations over which analysis is linear is 5-250 μ g/m³. These limits can be lowered or raised by changing (1) the volume of air sampled, (2) the volume of the final hexane solution, or (3) the size of the aliquot injected into the gas chromatograph.

Interferences

Phosphorus compounds having retention times close to that of 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 be somewhat expensive for 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, 60-ml and 125-ml with Teflon stopcock.
- (d) Beakers, 100-ml.
- (e) Funnels, 65- or 75-mm (diameter at top).
- (f) Glass wool (preextracted with hexane).
- (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- μ l and 100- μ l.
 - (m) Transfer pipets, volumetric.
 - (n) Gas chromatograph, with attendant equipment, including a phosphorus flame photometric detector. The following modification is suggested for operation of the GC with flame photometric detection and is generally applicable to any GC. A switching valve should be interfaced between the gas chromatographic column and the detector. The valve, which is heated with a 432-watt 2 1/2" x 24" insulated heating tape, permits interchange of column effluent and nitrogen purge. The nitrogen purge flow rate is adjusted to equal the flow from the gas chromatographic column so that when an interchange of flows is made for the purpose of venting solvent, no change is observed in the recorder baseline. This arrangement avoids extinguishing the flame when sample injections are made.
 - (o) Gas chromatography column constructed from 6 ft x 4 mm inside diameter borosilicate glass (silanized) packed with one of the following:
 - (1) 10% DC-200 (12,500 cst) on 80-100 mesh Gas Chrom Q.

(2) 15% QF-1 (10,000 cst)/ 10% DC-200 (12,500 cst) on 80-100 mesh Gas Chrom Q.

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

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

Columns 1 and 2 are conditioned by heating 2-4 days at 240-250°C under nitrogen flowing at 60 ml/min, then primed by repeated injections of standard 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/min. Column 4 is conditioned for at least 3 days at 245°C under nitrogen flowing at 60 ml/min. A column of 10% Carbowax 20M on 80-100 mesh silanized support (2 in x 4 mm inside diameter 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/min. The 10% Carbowax 20M column is subsequently removed.

Reagents

(a) Ethylene glycol, interference-free (pesticide quality).

(b) Hexane, interference-free (pesticide quality).

(c) Distilled water, interference-free.

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

(e) Anhydrous sodium sulfate.

(f) 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 and glassware sizes specified below apply to a sample in 20 ml of ethylene glycol and must be scaled proportionately for different volumes.) 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 3 times with 12-ml portions of hexane (total of 36 ml).

(c) Extract the combined hexane extracts 2 times with 10-ml portions of distilled water.

(d) 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 3 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 2 more 2-ml portions of hexane.

(e) Set the Kuderna-Danish assembly in a boiling water bath and concentrate the extract to about 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 about 0.5 ml. Rinse down the wall of the tube with hexane, delivered from a 100- μ l syringe, diluting the extract to exactly 1.0 ml, and stir.

(f) Inject a 2- μ l aliquot of the hexane solution into the gas chromatograph and obtain a chromatogram. The chromatographic conditions are:

Column temperature	220 C for columns 1 and 2 210 C for column 3 200 C for column 4
Injection port temperature	225 C
Detector temperature	200 C
Transfer line temperature	235 C
Switching valve temperature	235 C
Carrier gas (nitrogen) flow	120 ml/min for columns 1 and 2; 60 ml/min for column 3; and 75 ml/min for column 4.

The retention times (relative to parathion) at these conditions for parathion, related analytes, and some interfering organophosphorus pesticides are tabulated Table X-1.

The solvent-flush sample injection technique is recommended. Duplicate injections should be made. The hexane, which precedes the parathion should be vented according to (n) under Apparatus so that the detector flame is not extinguished. The conditions of the run should be such that no parathion is lost during the venting process.

(g) By comparison to standard curves for parathion, average of the area under the parathion peak is converted to the amount in ng of parathion seen by the detector. Paraoxon, if present in the sample, can be quantitated by comparison of its peak area with a standard curve for paraoxon.

TABLE X-1
RETENTION TIMES — PARATHION AND
OTHER COMPOUNDS OF INTEREST

OP Compound	Column 1	Column 2	Column 3	Column 4
Parathion	1.00 (4.4 min)	1.00 (8 min)	1.00 (3.4 min)	1.00
Paraoxon	0.77	1.13	1.23	1.17
Methyl parathion	0.73	0.78	1.18	0.76
Methyl paraoxon	0.56	0.88	1.41	0.90
Amino parathion	1.04	0.78		
Dursban	1.00			
Fenthion	0.97			
Ruelene		1.01		
Phosphamidon				1.12

Adapted from *NIOSH Manual of Analytical Methods* [197].

Calibration and Standards

(a) Prepare at least 3 standard solutions in the concentration range 100-10,000 ng/ml from a stock solution of parathion in hexane.

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

(c) Plot the amount in ng of 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 amount in ng of parathion present in the sample:

$$\text{Sample weight of parathion (ng)} = \text{ng}(0) \times \frac{\text{Solution volume}}{\text{Injection volume}}$$

where:

ng(0) = nanograms of parathion determined

from calibration curve based on peak area responses

Solution = volume in μl of the final hexane volume solution (usually 1 ml)

Injection = volume in μl of the aliquot of the volume 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 and 760 mmHg

V = volume of air in liters as measured

P = barometric pressure in mmHg

T = temperature of air in degrees Celsius

(c) The concentration of parathion can be expressed in ng/liter or $\mu\text{g}/\text{m}^3$:

$$(u) \text{ g/cu m} = \text{ng/liter}$$

or

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

XI. APPENDIX III

METHOD FOR BIOCHEMICAL DETERMINATION OF BLOOD CHOLINESTERASES

The method of Wolfsie and Winter,¹⁴⁷ a micromodification of the Michel method,¹³³ is recommended for the measurement of cholinesterase activity.

Reagents

All reagents should be at least ACS reagent grade.

(a) Buffer Solution I (for erythrocytes)

For 1 liter of buffer, dissolve 4.1236 g 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; 28.0 ml of 0.1 N hydrochloric acid is added while shaking the solution, and the flask is brought to volume with distilled water. The pH of Buffer I should be 8.10 at 25°C.

(b) Buffer Solution II (for plasma)

For 1 liter of buffer, dissolve 1.2371 g 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 of Buffer II should be 8.00 at 25°C.

The pH of the buffer solutions will decrease over a period of several weeks. The pH should be checked before using and, if it has dropped more than 0.03 pH units, it should be discarded and a fresh solution made.

(c) Acetylcholine Substrate (for erythrocytes)

This is 0.11 M acetylcholine chloride (2.000 g in 100 ml of distilled water).

(d) Acetylcholine Substrate (for plasma)

This is 0.165 M acetylcholine chloride (3.000 g in 100 ml of distilled water).

A few drops of toluene are added to each acetylcholine substrate solution as a preservative, and the solutions are refrigerated when not in use. The acetylcholine solutions should not be retained for more than 1 week.

(e) Saponin Solution

This is 0.010% saponin (100 mg in 1,000 ml of distilled water). This solution should be made fresh as needed.

Apparatus

- (a) Centrifuge capable of 3,500 rpm and holding capillary sample tubes.
- (b) A pH meter, calibrated to 0.01 pH units.
- (c) 0.02 ml Sahli-type hemoglobin pipet.
- (d) Constant-temperature bath, 25°C.
- (e) 100- and 1,000-ml volumetric flasks.
- (f) Heparinized capillary tubes.
- (g) A Bunsen burner.

Sampling, 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 $\frac{3}{4}$ 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 in order to guard against the initiation of the clotting process before the blood contacts the heparin lining in 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. 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 ampul 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 solution in a microbeaker, and rinse the pipet well (3 times) into the solution. Glass vials, 1 inch (2.5 cm) deep by $\frac{3}{4}$ 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 discharged into 1.0 ml of distilled water, the Sahli pipet being rinsed into the solution (3 times) as with the erythrocytes.

Erythrocyte Cholinesterase Assay

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

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

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

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

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

Note: The buffer solution I 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 milliliter of buffer solution II.

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

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

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

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

Calculations

The final units derived from this assay are ΔpH/hour:

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

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 XI-1.¹³³ Average baseline values of erythrocyte and plasma cholinesterase activity determined by this method for healthy nonexposed men and women are given in Table XI-2.^{145,147} The value for average RBC ChE activity for men is drawn from Wolfsie and Winter.¹⁴⁷ The value for women is obtained by multiplying the average RBC ChE activity figure for men¹⁴⁷ by the ratio of mean ΔpH/hr for women to mean ΔpH/hr for men derived from the data of Rider et al.¹⁴⁵ The use of the data of Wolfsie and Winter¹⁴⁷ allows for the increased packing and possible contamination of RBC's by plasma ChE. Plasma ChE values were selected from Rider et al,¹⁴⁵ since their larger data base probably provides a closer approximation of the true population mean of normal values for plasma ChE activity. For the same reason, their data provide the most reliable women/men ratio for RBC ChE activities.

TABLE XI-1
CORRECTION FACTORS
FOR USE IN EQUATION FOR Δ pH/HR

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	0.02	1.00
7.0	0.00	1.00	0.01	1.00
6.8	0.00	0.99	0.01	1.00
6.6	0.00	0.97	0.01	1.01
6.4	0.00	0.97	0.01	1.02
6.2	0.00	0.97	0.01	1.04
6.0	0.00	0.99	0.01	1.09

Adapted from Michel [133].

TABLE XI-2
MEAN BASELINE VALUES
OF ERYTHROCYTE AND
PLASMA CHOLINESTERASE IN MEN
AND WOMEN [Δ pH/HR]

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

Adapted from Rider et al [145] and Wolfsie and Winter [147].

TABLE XI-3
NORMAL VALUES FOR CIRCULATING CHOLINESTERASES
IN HEALTHY NONEXPOSED PERSONS*

Subjects	Erythrocyte Cholinesterase Activity (Δ pH/hr)			Plasma Cholinesterase Activity (Δ 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	Rider et al** [145]
400 women	0.56- 0.94	0.750	0.082	0.38- 1.25	0.817	0.187	
255 men	0.554- 1.252	0.861	0.091	0.408- 1.652	0.912	0.112	Wolfsie & Winter*** [147]
120 men & women	—	—	—	0.58- 1.37	0.94	0.16	Vorhaus and Kark [146]
20 men	—	—	—	—	0.95	0.24	Fremont-Smith et al [200]
20 women	—	—	—	—	0.78	0.12	

* All analyses performed by method of Michel. [133]

** Ranges, means, and standard deviations in this study are estimates based on data extrapolated to age 40; ranges reflect elimination of highest 1% and lowest 1% of values.

*** Analytic method modified for smaller blood sample.

XII. APPENDIX IV

DIAGNOSIS AND MEDICAL MANAGEMENT OF PARATHION POISONING

The text appearing immediately below is adapted in large part from a publication entitled *Prevention and Management of Organophosphate Poisoning*. This material, 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 1971.²⁰¹

(a) Diagnosis

A diagnosis of parathion intoxication is based primarily on a definite history of exposure to the material usually 6 hours or less before onset of illness plus clinical evidence of diffuse parasympathetic stimulation. Laboratory verification is based on depression of plasma and RBC ChE to a level substantially (50% or more) below preexposure values determined according to the recommended standard. Monitoring of RBC ChE activity levels, as specified in the recommended standard, is intended to prevent the development of poisoning by removing the exposed worker from the toxic environment at a point prior to the development of signs and symptoms. In actual practice, the ChE test is often of value as a confirmatory, rather than a diagnostic, procedure. In treating patients with moderate to severe parathion poisoning, the clinician should act on his clinical impression and on the history of exposure rather than wait for laboratory confirmation of ChE activity depression.

Initial signs and symptoms of parathion intoxication are usually giddiness, sometimes accompanied by headache, constriction of the pupils (miosis), and tightness in the chest. Nausea, vomiting, sweating, blurred vision, weakness, diarrhea, abdominal cramps, and pallor may follow. In moderate to severe cases of intoxication, signs and symptoms may also include dyspnea, salivation, lacrimation, muscular twitchings, convulsions, cyanosis, shock and cardiac arrhythmias, coma, and possibly death. Greatly increased salivary and bronchial secretions are common. 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.

(b) Treatment

Treatment of parathion 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 cases, weakness of the muscles of respiration may necessitate the use of positive pressure artificial respiration. Careful attention must be paid to removal of secretions and to maintenance of a patent airway. Anticonvulsants, such as trimethadione and sodium thiopental, may be necessary. The critical point is that respiration must be maintained since death usually results from respiratory failure (usually accompanied by a secondary cardiovascular component) due to weakness of the muscles of respiration and to accumulation of excessive secretions in the upper respiratory tract. If therapy is to be effective, it must be instituted with the least possible delay. To relieve the symptoms of excess parasympathetic stimulation, large (heroic) doses of atropine are usually required.

For adults, as much as 2-4 mg (1/30 g to 1/15 g) should be administered by intravenous or intramuscular injection every 5-10 minutes until signs of atropinization appear: dry, flushed skin; tachycardia as high as 140 beats/minute; dilation of the pupils. Obviously, caution must be exercised in administering these amounts of atropine. No generalization of the amount necessary is possible; the dose is administered according to the patient's condition. As much as 50 mg may be required the first day. A mild degree of atropinization should be maintained as long as symptoms are in evidence.

Although atropine remains the drug of choice, particularly if the treatment must be continued for more than a day or two, pralidoxime (Protopam; 2-PAM) chloride is a commercially available antidote which complements atropine and hastens the reactivation of parathion-inhibited ChE's. For adults moderately to severely poisoned by parathion, pralidoxime chloride should be used along with atropine, injected intravenously as an initial dose of 1 g at a rate not in excess of 500 mg/minute. If weakness is not relieved or if it recurs after 20 minutes, the dose may be repeated. After an overwhelming inhalation, skin exposure, or ingestion of parathion, the doses may be doubled. For children, the usual dose is 25-50 mg/kg of body weight. Treatment with pralidoxime chloride will be most effective if given within 24

hours after poisoning. (Its usefulness after 36-48 hours is questionable.) Together, the 2 antidotes, atropine and pralidoxime chloride, are more effective in treating parathion poisoning than is either one alone. Morphine and other respiratory depressant drugs, theophylline and aminophylline, are specifically contraindicated because they accentuate symptoms.

It is of great importance to decontaminate the patient. The stomach should be lavaged and a saline cathartic administered if parathion has been ingested. However, nothing should ever be given by mouth to an unconscious person. Contaminated clothing should be removed at once and the skin and hair should be washed with generous amounts of water (and preferably soap) or other suitable decontaminating solution. Cleansing may be 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 hair. The patient should be attended and monitored continuously for a minimum of 24 hours, since serious and sometimes fatal relapses have occurred because of continuing absorption of the insecticide or dissipation of the effects of the antidote.

(c) First-Aid Measures

Industrial handbooks discussing the use of various OP compounds typically include a section on first aid.

General signs and symptoms of parathion poisoning are headache, blurred vision, weakness, nausea and vomiting, cramps, looseness of the bowels, and pain or tightness in the chest. Signs and symptoms may also include sweating, pinpoint pupils (even when in the shade), drooling, watering eyes, difficulty in breathing, and convulsions.

If the above warning signs and symptoms are definitely observed and parathion poisoning is

suspected, the following measures should be put into effect immediately:

(1) If the patient is not breathing, start artificial respiration.

(2) In all cases of suspected parathion poisoning, call a physician at once.

(3) If parathion has been swallowed, induce vomiting by sticking a finger into the throat, by giving warm salt water (one tablespoonful of salt to a glass of water), or by giving soapy water. Repeat until vomit fluid is clear. Make the victim drink plenty of water or milk, if available; however, **NEVER GIVE ANYTHING BY MOUTH TO AN UNCONSCIOUS PERSON.**

(4) If the patient has been poisoned by contact with the insecticide, move him away from the possibility of any further exposure. If parathion has been spilled or splashed onto the clothes or skin, remove clothing immediately and wash the skin thoroughly with water (and preferably soap) or other suitable decontaminating solution; use copious amounts of water/decontaminating solution in rinsing. If splashed into the eyes, wash continuously with copious amounts of water for at least 15 minutes. Care should be taken to prevent contamination of the skin and clothing of those providing first aid.

(5) Keep the patient lying down, quiet, and warm. Take him to the nearest source of medical care if not available at the scene of poisoning.

(6) Try to find out the names of all pesticides (including the names of their active ingredients) with which the patient has been working or with which he has been contaminated and tell the physician. Take a label from the container (or a clean, labeled container) to the physician along with any other available literature describing the products involved.

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, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

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

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor relative to the density of air (air=1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water=1); percent volatiles (indicated whether by weight or volume) at 70 degrees Fahrenheit (21.1 degrees Celsius); evaporation rate for liquids or sublimable solids, relative to the evaporation rate of 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 rate 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, local sweating and muscular fibrillation.

Eye Contact—constriction of iris; poor vision in dim light; scleral injection.

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

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

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances such as water, direct sunlight, steel or copper piping, acids, alkalis, etc. "Hazardous Decomposition Products" shall in-

clude those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

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

(h) Section VIII. Special Protection Information

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

(i) Section IX. Special Precautions

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

(j) Signature and Filing

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

The MSDS shall be filed in a location readily accessible to workers potentially exposed to the hazardous material. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work prac-

tices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.

--

MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION		
MANUFACTURER'S NAME	REGULAR TELEPHONE NO. EMERGENCY TELEPHONE NO.	
ADDRESS		
TRADE NAME		
SYNONYMS		
II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA
III PHYSICAL DATA		
BOILING POINT (760 MM HG)		MELTING POINT
SPECIFIC GRAVITY (H ₂ O=1)		VAPOR PRESSURE
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H ₂ O % 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 PERTINENT CALIFORNIA STATE PESTICIDE REGULATIONS, 1974

Under the California regulations,²⁰² 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, parathion is considered a Category 1 pesticide. This supervision includes preexposure baseline ChE determinations and periodic biologic monitoring of RBC and plasma ChE 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 depression of plasma ChE to 50% of the preexposure baseline or RBC ChE to 40% of the preexposure baseline. Both ChE activities must return to within 20% of the preexposure baseline before the employee can resume exposure to organophosphates or carbamates. Whenever a ChE test indicates a depression of 30% or more, a retest is required. Laboratories performing ChE assays must be approved by the California State Department of Health.

Closed mixing and loading systems are required²⁰² to prevent exposure to concentrates caused by spills in the course of pouring. Ground and aerial application tanks must have an external means for determining the internal liquid level, or the filler hose must have an automatic shut-off 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 training previously, employers must instruct employees²⁰² 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. 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."²⁰² To prevent the simple masking of symptoms, atropine may not be taken by an employee except under direction of a physician.

Neither pilots of agricultural aircraft nor employees under the age of 18²⁰² are permitted to mix or load pesticides in Category 1 or 2 unless closed mixing or loading systems are used. 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 flaggers²⁰² handling pesticides in Category 1 or 2 who work for more than 30 hours in any 30-day period. Contaminated equipment or work clothing may not be taken home by employees. In addition, minimum amounts of water are required at work sites, along with soap and towels, for routine or emergency washing.

Mixers, loaders, applicators, and flaggers handling Category 1 or 2 pesticides²⁰² must be provided daily by the employer with clean outer clothing. Contaminated clothing must be immediately removed. 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 blood ChE test-

ing intervals.²⁰³ The table (XIV-1) was provided in a letter to physicians with the caveat 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	Days of 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 ChE tests by 1 week for this group. Adapted from Kahn [203].

XV. APPENDIX VII

SUMMARY OF PERTINENT STATE (EXCLUDING CALIFORNIA) PESTICIDE REGULATIONS

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

In most of the administrative units, the responsible authority is a governmental department, most commonly the Department of Agriculture or its equivalent. Departments of Environmental Protection or Conservation are designated as the responsible authorities in several administrative units. Other governmental entities (Department of Natural Resources, Department of Health, State Clinics, and Director of Regulatory and Public Service Programs of Clemson University) appear occasionally as responsible authorities. Thirty-nine administrative units provide for Pesticide Boards, Councils, or Committees. In most cases, these administrative units have advisory capacities only,

but in a few administrative units they are made the responsible governmental authorities to control the use of pesticides and to license or certify custom or private applicators of pesticides.

In 22 administrative units other than California, the law gives to the responsible authority the power to require reports of illness due to accidental exposure to pesticides. 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, Virgin Islands, and Washington. This power generally has been available for only a short time in the administrative units other than California, where it has existed since the passage of the Injurious Materials Law in 1949. California has, therefore, a particularly extensive, but not necessarily complete, inventory of illnesses due to 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 licenses or certifications requires full reporting of pesticide usage during the previous period of licensing or certification. A number of the other administrative units do have a means for obtaining approximations of such information through requiring use or purchase permits for pesticides. Maine, New Hampshire, and Rhode Island have this mechanism as a check on the required reporting of use of pesticides.

XVI. TABLES

TABLE XVI-1

PHYSICAL PROPERTIES OF TECHNICAL GRADE PARATHION

Chemical names	Phosphorothiotic acid, 0,0-diethyl 0-(P-nitrophenyl) ester, 0,0-diethyl 0-p-nitrophenyl phosphorothioate, 0,0-diethyl 0-(4-nitrophenyl) thio-phosphate, diethyl p-nitrophenyl thionophosphate
Common names	Parathion or ethyl parathion
Form and color	Liquid, straw-yellow or amber
Odor	Pungent, garlic-like
Molecular weight	291.3
Molecular formula	C ₁₀ H ₁₄ N ₀₅ PS
Boiling point	375 C at 760 mmHg
Melting point (freezing point)	6.1 C
Vapor pressure	0.003 mmHg at 24 C
Specific gravity	1.27 at 25 C
Viscosity	15.30 cp at 25 C
Solubility	Parathion is miscible with acetone, alcohol, benzene, CCl ₄ , CHCl ₃ , ethyl acetate, o-dichloro-benzene, toluene, xylene. Parathion is slightly soluble in kerosene, petroleum ether, other paraffinic solvents. Parathion is relatively insoluble (very slightly soluble) in water — 24 (n) g/ml at 25 C.
Conversion factors	1 ppm = 11.9 mg/cu m (25 C; 760 mg Hg) 1 mg/cu m = 0.084 ppm

Adapted from [3, 54, 56, 198].

TABLE XVI-2

SYNONYMS, INCLUDING TRADE NAMES, FOR PARATHION

AAT	Niran
AATP	Nitrostigmine
Alkron	Niuif-100
Alleron	Nourithion
American Cyanamid 3422	Oleofos 20
Bladan F	Oleoparathion
Corothion	Orthophos
Corthione	PAC
Danthion	Paramar 50
Diethylparathion	Paraphos
DNTP	Parathion-ethyl
E605	Parawet
Ecatox	Pestos Plus
Ekatox	Pethion
Ent (5,108	Phoskil

Ethyl parathion	Phosphemol
Etilon	Phosphenol
Folidol	Phosphostigmine
Fosferno	RB
Fosfex	Rhodiatox
Fosfive	SNP
Fosova	Stabilized ethyl parathion
Fostern	Sulphos
Genithion	T-47
Kolphos	Tiofos
Kypthion	Thiophos
Lirothion	Thiophos 3422
Metacide	Tox 47
Murfos	Vapophos

Adapted from the *Registry of Toxic Effects of Chemical Substances* [204].

TABLE XVI-3

OCCUPATIONS WITH POTENTIAL EXPOSURE TO PARATHION

Aerial application personnel	Flaggers
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 (formulators, "swampers")
Drum reconditioning personnel	Refuse haulers
Dump personnel	Tractor tank loaders
Field checkers	Truck loaders
Field workers (exposed to "residues" on fruits, vegetables, foliage, etc.)	Warehouse personnel

TABLE XVI-4

PULMONARY VENTILATION RATES FOR VARIOUS WORK LEVELS

Metabolic Level	Minute Volume (liters)
Sleep	6.0
Rest	9.3
Light work	19.7
Medium work	29.2
Medium heavy work	40
Heavy work	59.5
Maximum work	132.0

Derived from [199].

TABLE XVI-5

**ERYTHROCYTE (RBC) AND PLASMA CHOLINESTERASE
INHIBITION IN DOGS FOLLOWING 4-HOUR INHALATION
EXPOSURES TO PARATHION**

Parathion Concentration (mg/cu m*)	Ct (mg min/ cu m)	Toxic Signs	Cholinesterase, % of normal (avg of 4 dogs)			Mortality (24-hour)
			Time	RBC	Plasma	
37.1*	8912		4 hours	73	20	0/4
			24 hours	45	8	
			48 hours	78	16	
			7 days	65	38	
			14 days	85	76	
8.93	2143	Lacrimation occurred in 1 of 4 dogs	4 hours	64	14	0/4
			24 hours	42	7	
			48 hours	37	7	
			7 days	27	21	
			14 days	37	32	
3.42	821.0		4 hours	71	23	0/4
			24 hours	44	13	
			48 hours	39	4	
			7 days	19	9	
			14 days	24	30	
0.145	34.8		4 hours	70	40	0/4
			24 hours	56	20	
			48 hours	57	17	
			7 days	57	28	
			14 days	60	37	
0.015	3.672		4 hours	62	18	0/4
			24 hours	49	14	
			48 hours	44	15	
			7 days	72	35	
			14 days	58	75	

* Average of 2 chamber samples collected at 1 and 2 hours.

TABLE XVI-6

**PROBIT ANALYSIS OF ERYTHROCYTE (RBC) CHOLINESTERASE
INHIBITION IN RATS FOLLOWING 4-HOUR INHALATION
EXPOSURES TO PARATHION**

Parathion Dose (mg/cu m)	Percent RBC Cholinesterase Inhibition (34 rats)	Bliss Statistical Analysis			
		Cholinesterase Inhibition, %	Dose (mg/cu m)	95% Confidence Limits Lower	Upper
0.04	7	16	0.38	0.17	0.83
0.21	8	50	5.43	4.20	7.03
0.24	28	84	78.20	26.43	231.34
0.83	17				
0.91	8				
1.21	11				
2.17	30				
2.27	60				
12.8	58				
19.1	69				
26.1	85				
31.4	80				
35.0	68				

Probit Y = 4.369 + .859 Log X

Blood sampled 24 hours postexposure.

TABLE XVI-7

**PROBIT ANALYSIS OF PLASMA CHOLINESTERASE
INHIBITION IN RATS FOLLOWING 4-HOUR INHALATION
EXPOSURES TO PARATHION**

Parathion Dose (mg/cu m)	Percent Plasma Cholinesterase Inhibition (34 rats)	Bliss Statistical Analysis			
		Cholinesterase Inhibition, %	Dose (mg/cu m)	95% Confidence Limits Lower	Upper
0.04	0	16	0.51	0.51	1.18
0.21	0	50	7.28	5.24	10.12
0.24	24	84	103.85	27.23	396.05
0.83	37				
0.91	12				
1.21	0				
2.17	28				
2.27	58				
12.8	69				
19.1	52				
26.1	58				
31.4	77				
35.0	74				

Probit Y = 4.257 + .862 Log X

Blood sampled 24 hours postexposure.

TABLE XVI-8

ERYTHROCYTE (RBC) AND PLASMA CHOLINESTERASE ACTIVITY IN RATS EXPOSED BY INHALATION TO PARATHION AEROSOLS FOR 4 HOURS

Parathion Concentration* (mg/cu m)	Percent Cholinesterase Activity from Start of Exposure									
	4 Hours		24 Hours		48 Hours		168 Hours		336 Hours	
	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma
0.04	84	100	93	100	91	100	91	100	83	100
0.21	67	81	92	100	100	100	98	100	70	100
0.24	100	80	73	76	86	80	100	76	74	67
0.83	66	63	83	63	66	76	74	90	85	69
0.91	100	88	92	88	81	68	88	81	77	74
1.21	100	100	89	100	79	100	80	100	95	100
2.17	84	65	70	72	69	69	74	74	78	71
2.27	56	52	40	42	72	68	78	81	53	50
12.8	66	48	42	31	46	44	60	73	61	67
19.1	43	47	31	48	18	59	49	60	78	78
26.1	24	33	15	42	42	38	46	64	58	58
31.4	42	40	20	23	19	27	57	67	74	63
35.0	44	24	32	26	27	28	49	61	60	77

* 34 rats exposed/concentration level.

TABLE XVI-9

ERYTHROCYTE (RBC) AND PLASMA CHOLINESTERASE ACTIVITY IN MALE RATS EXPOSED BY INHALATION TO PARATHION AEROSOLS FOR 7 HOURS/DAY, 5 DAYS/WEEK, FOR 6 WEEKS

Parathion Concentration (mg/cu m)	Percent Cholinesterase Activity from Start of Exposure											
	1st Week		2nd Week		3rd Week		4th Week		5th Week		6th Week	
	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma
0.01	88	96	93	100	—	—	69	97	70	77	97	99
0.10	57	99	60	66	—	—	65	79	67	92	Exposure terminated	
0.74	58	68	50	67	24	23	33	21	16	34	26	40
Percent Cholinesterase Activity — Postexposure Period												
0.01	82	97	84	127	—	—	94	99	—	—	119	141
0.10	61	116	76	133	82	119	—	—	81	113	—	—
0.74	44	113	—	—	65	100	—	—	—	—	88	117

TABLE XVI-10

**ERYTHROCYTE (RBC) AND PLASMA CHOLINESTERASE ACTIVITY
IN MALE DOGS EXPOSED BY INHALATION TO PARATHION
AEROSOLS FOR 7 HOURS/DAY, 5 DAYS/WEEK, FOR 6 WEEKS**

Parathion Concentration (mg/cu m)	Percent Cholinesterase Activity from Start of Exposure													
	Day 1		1st Week		2nd Week		3rd Week		4th Week		5th Week		6th Week	
	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma
0.001	101	88	135	88	129	96	106	95	—	—	135	102	135	91
0.01	124	113	106	92	79	70	86	72	—	—	97	72	101	58
0.20	89	46	75	41	54	26	74	35	—	—	57	53	41	36
	Percent Cholinesterase Activity — Postexposure Period													
0.001	—	—	95	99	95	79	—	—	86	97	90	131	98	103
0.01	—	—	98	91	104	91	—	—	—	—	—	—	—	—
0.20	—	—	77	72	61	94	—	—	86	115	84	134	79	112

TABLE XVI-11

**RAT 24-HOUR LD50 FOLLOWING ORAL ADMINISTRATION
OF PARATHION IN CORN OIL**

Parathion Dose (mg/kg)	Percent Mortality (10 rats/dose)	Bliss Statistical Analysis (95% Confidence Limits)			
		Percent Mortality	Dose (mg/kg)	Lower Limit	Upper Limit
10.0	100	16	5.72	5.01	6.53
7.9	80	50	6.85	6.18	7.60
6.3	20	84	8.21	7.17	9.40
5.0	10				
4.0	0				

TABLE XVI-12

**DOG 24-HOUR LD50 FOLLOWING ORAL ADMINISTRATION
OF PARATHION IN CORN OIL**

Parathion Dose (mg/kg)	Percent Mortality (4 dogs/dose)	Bliss Statistical Analysis (95% Confidence Limits)			
		Percent Mortality	Dose (mg/kg)	Lower Limit	Upper Limit
20.0	100	16	4.42	1.29	15.07
15.8	75	50	8.27	4.79	14.29
10.0	50	84	15.50	6.61	36.34
6.3	50				
2.5	0				

TABLE XVI-13

**RAT ACUTE ERYTHROCYTE (RBC) ChE50
FOLLOWING ORAL ADMINISTRATION OF PARATHION**

Parathion Dose (mg/kg)	Percent RBC Cholinesterase Inhibition (10 rats/dose)	Bliss Statistical Analysis (95% Confidence Limits)			
		Percent Inhibition	Dose (mg/kg)	Lower Limit	Upper Limit
0.18	8	16	0.410	0.318	0.527
0.35	13	50	2.579	2.117	3.141
0.70	27	84	16.236	11.716	22.499
1.40	32				
2.80	52				
5.60	70				
7.00	69				

TABLE XVI-14

**RAT ACUTE PLASMA ChE50
FOLLOWING ORAL ADMINISTRATION OF PARATHION**

Parathion Dose (mg/kg)	Percent Plasma Cholinesterase Inhibition (10 rats/dose)	Bliss Statistical Analysis (95% Confidence Limits)			
		Percent Inhibition	Dose (mg/kg)	Lower Limit	Upper Limit
0.18	0	16	0.622	0.416	0.930
0.35	9	50	2.546	2.123	3.054
0.70	23	84	10.424	5.813	18.692
1.40	45				
2.80	34				
5.60	78				
7.00	75				

TABLE XVI-15

**DOG ACUTE ERYTHROCYTE (RBC) ChE50
FOLLOWING ORAL ADMINISTRATION OF PARATHION**

Parathion Dose (mg/kg)	Percent RBC Cholinesterase Inhibition (4 dogs/dose)	Bliss Statistical Analysis (95% Confidence Limits)			
		Percent Inhibition	Dose (mg/kg)	Lower Limit	Upper Limit
10.0	73	16	0.114	0.032	0.412
2.50	64	50	1.497	1.060	2.115
1.26	50	84	19.619	6.620	58.141
0.50	29				

TABLE XVI-16

**DOG ACUTE PLASMA ChE50
FOLLOWING ORAL ADMINISTRATION OF PARATHION**

Parathion Dose (mg/kg)	Percent Plasma Cholinesterase Inhibition (4 dogs/dose)	Bliss Statistical Analysis (95% Confidence Limits)			
		Percent Inhibition	Dose (mg/kg)	Lower Limit	Upper Limit
10.0	65	16	0.020	0.000	0.893
2.50	59	50	1.670	0.942	2.960
1.26	40	84	141.422	4.061	4,294.465
0.50	42				

TABLE XVI-17

**ERYTHROCYTE (RBC) AND PLASMA CHOLINESTERASE ACTIVITY IN MALE RATS
DOSED ORALLY WITH PARATHION 5 DAYS/WEEK FOR 6 WEEKS**

Daily Dose (mg/kg)	Percent Cholinesterase Activity from Start of Exposure											
	1st Week		2nd Week		3rd Week		4th Week		5th Week		6th Week	
	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma
0.05	85	98	95	127	—	—	119	133	—	—	115	156
0.10	87	106	79	20	—	—	78	94	—	—	81	115
0.25	74	103	—	—	66	106	44	115	57	54	46	52
	Percent Cholinesterase Activity — Postexposure Period											
0.05	85	96	—	—	—	—	—	—	—	—	—	—
0.10	119	109	141	117	—	—	72	103	—	—	—	—
0.25	44	76	69	101	—	—	68	106	—	—	159	119

TABLE XVI-18

**ERYTHROCYTE (RBC) AND PLASMA CHOLINESTERASE ACTIVITY IN MALE DOGS
DOSED ORALLY WITH PARATHION 5 DAYS/WEEK FOR 6 WEEKS**

Daily Dose (mg/kg)	Percent Cholinesterase Activity from Start of Exposure											
	1st Week		2nd Week		3rd Week		4th Week		5th Week		6th Week	
	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma	RBC	Plasma
0.05	82	44	105	68	—	—	101	87	—	—	83	54
0.10	73	24	86	32	—	—	81	44	—	—	80	61
0.50	74	22	65	37	—	—	51	80	—	—	42	15
	Percent Cholinesterase Activity — Postexposure Period											
0.05	70	74	95	92	—	—	101	99	—	—	—	—
0.10	77	165	90	94	—	—	91	90	—	—	—	—
0.50	50	70	49	90	—	—	68	93	—	—	67	74

TABLE XVI-19

**ERYTHROCYTE (RBC) AND PLASMA CHOLINESTERASE ACTIVITY
RECOVERY IN MALE RATS FOLLOWING A SINGLE ORAL DOSE
(2.8 mg/kg) OF PARATHION**

Time (Postexposure) Hours	Percent Residual Cholinesterase Activity	
	RBC	Plasma
4	44	35
24	45	49
48	56	52
72	51	85
168	60	70
336	67	89

TABLE XVI-20

**ERYTHROCYTE (RBC) AND PLASMA CHOLINESTERASE ACTIVITY
RECOVERY IN MALE DOGS FOLLOWING A SINGLE ORAL DOSE
(2.5 mg/kg) OF PARATHION**

Time (Postexposure) Hours	Percent Residual Cholinesterase Activity	
	RBC	Plasma
24	36	41
264	53	78
360	58	85
696	67	117
864	89	112

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