TOXICOLOGICAL PROFILE FOR METHYL PARATHION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

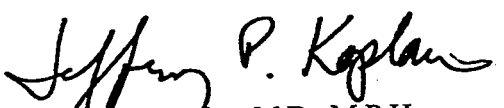
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Jeffrey P. Koplan, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepared toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by *type of health effect* (death, systemic, immunologic, reproductive), by *route of exposure*, and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 639-6357 ***Fax:*** (404) 639-6359
E-mail: atsdric@cdc.gov ***Internet:*** http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact*: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

*The National Institute of Environmental Health Sciences (*NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS(S):

Jewell D. Wilson, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Clement International Corporation

Joan Colman, Ph.D.
David Wohlers, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

Cheryl Sutton, Ph.D.
Syracuse Research Corporation, Arlington, VA

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for methyl parathion. The panel consisted of the following members:

1. Donald Morgan, M.D./Ph.D., Private Consultant, Cedar Rapids, Iowa;

2. Shane Que Hee, Ph.D., Department of Environmental Health Sciences, UCLA School of Public Health, Los Angeles, California;

3. Michael Utidjian, M.D., Private Consultant, Wayne, New Jersey.

These experts collectively have knowledge of methyl parathion's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about methyl parathion and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Methyl parathion has been found in at least 16 of the 1,585 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which methyl parathion is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to methyl parathion, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS METHYL PARATHION?

Methyl parathion is a pesticide that is used to kill insects on crops. Usually, it is sprayed on the crops. Methyl parathion comes in two forms: a pure form of white crystals and a technical-grade solution (brownish liquid), which contains methyl parathion (80%) and inactive ingredients in a solvent. The technical-grade methyl parathion smells like rotten eggs or garlic. Methyl parathion is a manufactured chemical, so it is found in the environment only as a result of its manufacture or use. Methyl parathion has been manufactured in the United States since 1952 and has been used to kill insects on many types of crops since this time. Because methyl

parathion can be dangerous to humans, the EPA has restricted how it can be used and applied. Methyl parathion must be sprayed on crops from the air or from the ground in certain ways to minimize the danger of being exposed, and only trained people are allowed to spray methyl parathion. Methyl parathion is no longer used on food crops commonly consumed by children, and the maximum amount of methyl parathion that can be present as a residue on specific crops is regulated (see Section 1.9). In these ways, exposure to methyl parathion can be controlled and accidental exposures can be prevented.

1.2 WHAT HAPPENS TO METHYL PARATHION WHEN IT ENTERS THE ENVIRONMENT?

Once methyl parathion is introduced into the environment from spraying on crops, droplets of methyl parathion in the air fall on soil, plants, or water. While most of the methyl parathion will stay in the areas where it is applied, some can move to areas away from where it was applied by rain, fog, and wind. Methyl parathion stays in the environment from a few days to several months. It is degraded to other chemical compounds by water, sunlight, and bacteria found in soil and water. On soil, methyl parathion sticks to the soil, and then is rapidly degraded by bacteria. It generally does not leach through the ground and end up in the groundwater. In water, methyl parathion breaks down quickly by the action of the water, bacteria in the water, and sunlight. In water and air, methyl parathion is broken down by sunlight to form a more toxic product called methyl paraoxon. If concentrated amounts of methyl parathion are present in soil, such as at landfills and hazardous waste sites, methyl parathion does not degrade as fast. For more information, see Chapters 4, 5, and 6.

1.3 HOW MIGHT I BE EXPOSED TO METHYL PARATHION?

Most people are not exposed to methyl parathion in the air they breathe or on things they touch, unless they live next to areas being sprayed. The people who are at the greatest risk of being exposed to methyl parathion are those who work with this chemical. These include farm workers, chemical sprayers, and people who work in factories that make methyl parathion. They are exposed to methyl parathion on things they touch where it can pass through their skin, or by

breathing it after it has been sprayed. Overexposure to methyl parathion may cause severe poisoning or death. Persons may be exposed to dangerous amounts if they go into fields too soon after spraying. The people most likely to be exposed to methyl parathion can be protected by wearing special clothing and breathing equipment and by staying out of sprayed fields for at least 2 days.

Individuals can also be exposed if they live near landfills where methyl parathion has been dumped or near water containing methyl parathion that washes off nearby land or that is accidentally spilled. The greatest amounts of methyl parathion are expected to be present near or on the farms where methyl parathion is used. After spraying, some methyl parathion can be transported by the wind or fog to areas away from where it is used, but the amounts present at these locations are not expected to be at dangerous levels. In 1988, one location in Mississippi had groundwater that contained 88 parts of methyl parathion per billion parts of water (ppb). More recent studies of water samples taken near where methyl parathion was sprayed indicate methyl parathion is not found in the groundwater. The risk of exposure to methyl parathion from drinking groundwater appears to be low, but the EPA is currently examining this issue. For more information, see Chapter 6.

Methyl parathion is approved only for use on crops. The maximum amount of methyl parathion residue allowed by the Food and Drug Administration (FDA) and EPA on crops used as food is 0.1–1 ppm. The FDA has monitored the food supply for pesticides for a number of years. FDA purchases many kinds of foods through Market Basket Surveys and analyzes them for residue levels of pesticides. These FDA studies allow scientists to estimate the daily intake of pesticides. Generally, the FDA monitoring studies conclude that the U.S. food supply contains only very small amounts of pesticides that are not a concern. However, there have been some reports of the illegal use of methyl parathion inside homes. For more information, see Section 1.7 and Chapter 6.

1.4 HOW CAN METHYL PARATHION ENTER AND LEAVE MY BODY?

Methyl parathion can enter your body if you eat food or drink water containing it; if you swim, bathe, or shower in contaminated water; if you touch recently sprayed plants or soil; if you touch contaminated soil near hazardous waste sites; or if you breathe air that contains methyl parathion, such as near factories or recently sprayed farm fields (or in recent accounts of the illegal use of methyl parathion, if you breathe air or touch contaminated surfaces inside homes where methyl parathion has been used to kill insects). By any means of exposure, methyl parathion goes into your body quickly and gets into your blood. From your bloodstream, methyl parathion goes to your liver, brain, and other organs. Your liver changes some of methyl parathion to a more harmful chemical called methyl paraoxon. Both methyl parathion and methyl paraoxon can bind to enzymes of your nerves within minutes or hours. Your liver breaks down methyl parathion and methyl paraoxon into less harmful substances. These less harmful substances leave your body in urine within hours or days. For more information, see Chapter 3.

1.5 HOW CAN METHYL PARATHION AFFECT MY HEALTH?

Methyl parathion interferes with the normal way that the nerves and brain function. Exposure to very high levels of methyl parathion for a short period in air or water may cause death, loss of consciousness, dizziness, confusion, headaches, difficult breathing, chest tightness, wheezing, vomiting, diarrhea, cramps, tremors, blurred vision, and sweating. Some people who have been exposed to substances similar to methyl parathion have experienced changes in mental state that lasted several months after exposure to high levels of these substances ended. If people are exposed to levels of methyl parathion below those that affect nerve function, few or no health problems seem to occur. There is no evidence that methyl parathion causes birth defects in humans or affects the ability of humans to produce children. There is also no proof that methyl parathion causes cancer in people who are regularly exposed, such as farmers and pesticide applicators.

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Animal studies show effects of methyl parathion similar to those seen in people. In addition, short-term high exposure of animals to methyl parathion caused decreased heart rate. This may be the result of methyl parathion's effects on the nerves that control the heart. Methyl parathion decreased the ability of animals to fight infections in some studies, but not in others. It is not known whether any of these effects occur in people. It is not known whether methyl parathion affects the ability of animals to reproduce. Studies in animals have not shown that methyl parathion causes cancer.

You can find more information on the health effects associated with exposure to methyl parathion in Chapters 2 and 3.

1.6 HOW CAN METHYL PARATHION AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

Children are likely to be exposed to methyl parathion in the same ways as adults, mainly by eating foods or drinking milk or water that contain residues of this chemical. Because of their smaller weight, children’s intake of methyl parathion per kilogram of body weight may be greater than that of adults. The FDA and EPA permit residues of pesticides to be present in crops used as food, and these amounts are considered to be safe. The EPA, however, has recently used stricter regulations and has canceled the use of methyl parathion on food crops

commonly eaten by children. As a result, the exposure of children to methyl parathion from foods will be very small.

Children are affected by methyl parathion in the same manner as adults. Exposure to high levels of methyl parathion, even for short periods, may result in changes in the nervous system, leading to headaches, dizziness, confusion, blurred vision, difficulty breathing, vomiting, diarrhea, loss of consciousness, and death (see also Section 1.5 for a more complete description of how methyl parathion affects human health). It is not known whether children are more sensitive to the effects of methyl parathion than adults. There is some indication that young rats may be more sensitive than adults to nervous system effects.

There is no evidence in humans that methyl parathion causes birth defects. Birth defects have not been seen when methyl parathion was given to animals by mouth, but minor birth defects did occur in one study in which high doses were injected into pregnant animals. It is not known whether these effects occur in people. It is unlikely that people would be exposed by breathing, touching, or eating as much methyl parathion as was injected in the animal studies.

Animal studies have also shown that methyl parathion can be transferred from a pregnant mother to the developing fetus. Methyl parathion caused changes in the behavior of young animals whose mothers were given methyl parathion during pregnancy, and this effect needs to be studied more. Methyl parathion has been detected in small amounts in breast milk, but only in a few localities in central Asia. Studies of mother animals fed methyl parathion show that methyl parathion can be transferred into their milk and their nursing newborn babies.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO METHYL PARATHION?

If your doctor finds that you have been exposed to significant amounts of methyl parathion, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

The only approved use of methyl parathion is on crops, including crops used as foods. Effective December 31, 1999, the EPA cancelled the use of methyl parathion on many kinds of crops used as foods because of a concern for exposure risks to children and to workers. This action will reduce the risks to families of methyl parathion exposure from food.

The general population is not likely to be exposed to large amounts of methyl parathion. The populations living in the areas where methyl parathion is used on crops, however, may be exposed to greater amounts of methyl parathion. Methyl parathion is often detected in foods and air samples collected where methyl parathion is used. People who live close to areas of methyl parathion use also may be exposed to larger amounts of methyl parathion, because small amounts of the pesticide will move from the place where it is used to nearby areas. These exposures may include such things as touching contaminated plants, breathing the mist formed from the sprayed chemical, drinking contaminated water, or eating recently sprayed fruits and vegetables. People who are most likely to receive the highest exposures are those who work in the factories that make methyl parathion, workers who spray it on crops, and farmers. Entry of methyl parathion into the body after contact with the skin is expected to be the major exposure pathway for those working in these operations. Breathing the mist containing methyl parathion may also occur.

Families can reduce the risk of exposure to methyl parathion in the soil, on plants, or in the air by staying away from fields that have been recently sprayed. If families wait at least 4–5 days before entering sprayed fields, then the amount of methyl parathion present in the air or on plants is expected to be small.

Families should also be aware that sometimes methyl parathion has been illegally sprayed inside the home to kill insects. Your children may be exposed to methyl parathion if an unqualified person applies pesticides containing it around your home. In some cases, the improper use of pesticides banned for use in homes has turned homes into hazardous waste sites. Make sure that any person you hire is licensed and, if appropriate, certified to apply pesticides. Your state licenses each person who is qualified to apply pesticides according to EPA standards and further certifies each person who is qualified to apply “restricted use” pesticides. Ask to see the license

and certification. Also ask for the brand name of the pesticide, a Material Safety Data Sheet (MSDS), the name of the product's active ingredient, and the EPA registration number. Ask whether EPA has designated the pesticide "for restricted use" and what the approved uses are. This information is important if you or your family react to the product. If you buy over-the-counter pesticides products to apply yourself, be sure the products are in unopened pesticide containers that are labeled and contain an EPA registration number. Carefully follow the instructions on the label. If you plan to spray inside, make sure the products are in unopened pesticide containers that are labeled and contain an EPA registration number. Carefully follow the instructions on the label. If you plan to spray inside, make sure the pesticide is intended for indoor use. If you feel sick after a pesticide has been used in your home, consult your doctor or local poison control center.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO METHYL PARATHION?

Several medical tests can determine whether you have been exposed to methyl parathion. The first medical test measures methyl parathion in your blood or measures 4-nitrophenol, which is a breakdown product of methyl parathion, in your urine. These tests are only reliable for about 24 hours after you are exposed because methyl parathion breaks down quickly and leaves your body. These tests cannot tell whether you will have harmful health effects or what those effects may be. The next medical test measures the levels of a substance called cholinesterase in your blood. If cholinesterase levels are less than half of what they should be and you have been exposed to methyl parathion, then you may get symptoms of poisoning. However, lower cholinesterase levels may also only indicate exposure and not necessarily harmful effects. The action of methyl parathion may cause lower cholinesterase levels in your red blood cells or your blood plasma. Such lowering, however, can also be caused by factors other than methyl parathion. For example, cholinesterase values may already be low in some people, because of heredity or disease. However, a lowering of cholinesterase levels can often show whether methyl parathion or similar compounds have acted on your nerves. Cholinesterase levels in red blood cells can stay low for more than a month after you have been exposed to methyl parathion or similar chemicals. For more information, see Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for methyl parathion include the following:

NIOSH recommends that a person not be exposed in the workplace to more than 0.2 mg/m^3 of methyl parathion for a 10-hour workday, 40-hour workweek.

According to EPA, the following levels of methyl parathion in drinking water are not expected to cause effects that are harmful to health: 0.3 mg/L for 1 or 10 days of exposure for children, 0.03 mg/L for longer term exposure for children, and 0.002 mg/L for lifetime exposure of adults.

It is illegal to use methyl parathion indoors. Methyl parathion is approved only for use on agricultural crops. In 1999, EPA canceled the use of methyl parathion on many food crops,

particularly those consumed by children, such as apples, peaches, pears, carrots, and peas, and also canceled nonfood uses such as ornamental plants and nursery stock uses. Methyl parathion use is still allowed on other crops eaten by people or by farm animals. A maximum of 0.1–1 ppm of methyl parathion is allowed in or on the other crops (fruits, vegetables, nuts, and grains) that may be eaten by people. For more information, see Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)
Fax: 1-404-498-0057

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 605-6000

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO METHYL PARATHION IN THE UNITED STATES

Methyl parathion is a broad-spectrum agricultural insecticide that is released to the environment primarily through spraying of the insecticide on a variety of agricultural products. Once methyl parathion is introduced to the environment, it is degraded by hydrolysis, photolysis, or by biodegradation from microorganisms found in most sediment, soils, and water. Methyl parathion is primarily confined to the application area, but some can be transported by rain, fog, and wind to other areas. Methyl parathion adsorbs to the soil and is relatively immobile. As a result, leaching into groundwater is not usually observed. Volatilization has been observed to occur from plants and soil post-application, with volatilization from plants being the faster of the two. Limited studies show that bioconcentration of methyl parathion does not occur to a significant extent; that which is accumulated in plants and animals is rapidly metabolized. Methyl parathion is not widely dispersed or persistent in the environment. Residue amounts of methyl parathion have been detected in air, water, fish, soil, and agricultural crops consumed as foods.

Methyl parathion is approved by the EPA only for use on agricultural crops. As a result, the general population is not likely to be exposed to large amounts of methyl parathion. Some exposure to residues of methyl parathion is possible, however, as many studies show that methyl parathion has been detected in foods and atmosphere samples. Populations living within or very near areas of heavy methyl parathion use would have an increased risk of exposure to large amounts of methyl parathion through dermal contact with contaminated plants, by inhalation of the mist formed from the applied insecticide, or by ingestion of water or food-borne residues. Those likely to receive the highest levels of exposure are those who are involved in the production, formulation, handling, and application of methyl parathion. Dermal contact appears to be the major route of exposure, while inhalation may also be an important route of exposure for those working in these operations.

The greatest potential for exposure of the general population to methyl parathion is by consumption of food containing residues from spray applications of the insecticide. In a 10-year study, methyl parathion was found at an average concentration of 0.0035 ppm in a few examples of ready-to-eat foods. Concentrations in the range of 0.05–2.0 ppm were reported in 0.5% of the samples of domestic and

imported foods and animal feeds in a 5-year analysis. Additional studies have reported concentrations of methyl parathion of 0.016–3.8 ppm in a small percentage of samples of various foods.

Residues in many foods should decrease because EPA has canceled many of the food crop uses of methyl parathion, including fruits and vegetables commonly eaten by children, some other vegetable uses, some feed uses, and all nonfood uses such as ornamental plants and nursery stock uses. Tolerances for methyl parathion on these foods and feed also have been canceled. This action was taken because of a concern for risks to children and workers. Some food and feed uses and tolerances are to be maintained.

In areas of agricultural methyl parathion usage, both outdoor and indoor air levels of methyl parathion of approximately 12 ng/m^3 have been measured, and household dust was found to contain 21 ppb of methyl parathion. Outdoor and indoor air concentrations of methyl parathion as high as 0.71 and 9.4 µg/m^3, respectively, have been measured at the homes of individuals employed as pesticide formulators.

Dermal exposure to methyl parathion is not likely to be a health concern to the general population, with the possible exception of individuals in the immediate vicinity of a field during application of the pesticide. Dermal exposure, however, is a major source of exposure for workers directly involved in the manufacture, application, and cleanup of the chemical, and for field workers. Laundry workers cleaning the clothing of such workers may also be exposed.

Children are expected to be exposed to methyl parathion by the same routes that affect adults. Small children are more likely to come into contact with methyl parathion residues that may be present in soil and dust both outside and inside the home, due to increased hand-to-mouth activity and playing habits. Methyl parathion has been detected in a few samples of breast milk, indicating potential for exposure of nursing infants. However, available data are not adequate for determination of the importance of this route of child exposure.

Populations residing near hazardous waste disposal sites may be subject to higher levels of methyl parathion in environmental media (i.e., air, groundwater, soil) than those experienced by the general population. Methyl parathion has been identified in at least 16 of the 1,585 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL). However, the number of sites evaluated for methyl parathion is not known. As more sites are evaluated, the number of sites where methyl parathion has been detected may increase.

See Chapter 6 for more detailed information regarding concentrations of methyl parathion in environmental media.

2.2 SUMMARY OF HEALTH EFFECTS

Methyl parathion is a highly toxic pesticide, and humans are susceptible to its acute toxic effects by various routes of exposure. Signs and symptoms of acute toxicity are typical of those induced by organophosphate insecticides as a group. Almost all systemic effects of methyl parathion are related to the action of this compound on the nervous system or are secondary to this primary action. Methyl parathion and its active metabolite, methyl paraoxon, exert their profound toxic effect by inhibiting the activity of acetylcholinesterase in the nervous system and at the motor end-plate. Hydrolysis of acetylcholine is inhibited and the neurotransmitter accumulates at its site of action, producing over-stimulation of cholinergic end organs. Information regarding effects in humans is limited to a few case reports of people acutely exposed to high levels of methyl parathion either by intentional ingestion or by multiple-route exposure from direct contact with spray material either in field applications or through illegal indoor spraying. Manifestations of acute poisoning are similar in humans and animals and include reduced cholinesterase levels in brain, erythrocytes, and plasma, clinical signs of neurological effects such as tremors and convulsions, and cardiac arrhythmia. Except for neuropsychiatric disorders reported in humans after chronic occupational exposure to organophosphates including methyl parathion, no chronic effects have been documented in humans. Effects in animals chronically exposed to methyl parathion include hematological and ocular changes. Available data regarding the genotoxicity of methyl parathion is inconclusive. Based on the lack of a carcinogenic effect in animals and the lack of evidence to indicate a strong genotoxic effect, methyl parathion does not appear to present a substantial carcinogenic risk to humans.

Neurological Effects. Clinical symptoms and signs of methyl parathion intoxication are typical of organophosphate poisoning. In mild or moderate cases, patients are alert and oriented; in severe cases, they can be confused and ataxic, with slurred speech. Headache, dizziness, and incoordination are common. Respiratory symptoms consist of chest tightness, a productive cough, and wheezing. Gastrointestinal symptoms are nausea, vomiting, diarrhea, and abdominal cramps. Findings considered characteristic of organophosphate intoxication are muscle fasciculations and miosis, although the latter sign is not always present. Severely intoxicated patients have extreme salivation, involuntary urination and defecation, sweating, lacrimation, bradycardia, and hypotension. Unconsciousness, respiratory arrest (due to depression of the respiratory center and paralysis of respiratory muscles), and death can result, the

latter from a combination of respiratory and cardiovascular failure. Marked depressions in erythrocyte and/or plasma cholinesterase levels are typically observed in individuals exhibiting clinical signs of organophosphate poisoning. Available data suggest that a rapid decline in cholinesterase levels may be more important than the degree of decline. Neurological signs and depressed cholinesterase levels have been observed in animals either acutely exposed to atmospheres containing 264 mg/m^3 of methyl parathion or administered single oral doses in the range of 4–8 mg/kg. Rats given single oral doses as low as 1.5 mg/kg exhibited significantly depressed plasma, erythrocyte, and brain cholinesterase within 30 minutes of dosing.

More subtle psychological symptoms have been reported after acute mild organophosphate intoxication. Psychological changes associated with dermal application of a potent organophosphate anticholinesterase (an unspecified military chemical) occurred in male volunteers who had no other clinical signs or symptoms of toxicity except nausea and vomiting. Psychological changes tended to occur when cholinesterase levels were depressed to 10–40% of controls. Changes were a state of altered awareness characterized by slowed intellectual and motor processes and difficulty in sustaining attention. Subjects felt slowed down, agitated, and confused. These changes may be a concern with exposure to other organophosphate insecticides, including methyl parathion.

Another condition that has been reported as a consequence of very high acute exposures to organophosphate insecticides is the intermediate syndrome. The onset occurs approximately 1–4 days after the acute cholinergic crisis has resolved. Clinical observations include acute respiratory insufficiency and muscular weakness, primarily of the neck flexors, proximal limb, and respiratory muscles, and motor cranial nerve palsies. Death may ensue from respiratory insufficiency. The syndrome is thought to result from prolonged acetylcholinesterase inhibition at the neuromuscular junction. The intermediate syndrome has been observed primarily in cases of exposure to fenthion, dimethoate, monocrotophos, and methamidophos, but also in one case of parathion ingestion, and in a few cases of ingestion and one of inhalation of a mixture of parathion and methyl parathion.

Mental disturbances have been reported after organophosphate exposure. Neuropsychiatric symptoms occurred in two aerial applicators, one of whom used methyl parathion as well as other insecticides. One of these pilots had high levels of exposure to a mixture containing methyl parathion, toxaphene, and Dipterex® when his clothing became saturated when the tank of his aircraft accidentally overflowed. Several months after the accident, the subject complained of anxiety, dizziness, emotional lability, and frequent and severe disagreements with family members and associates. Similar observations had been

made among a group of 16 men who had worked with a variety of organophosphates over a number of years. Exposure was likely by both dermal and inhalation routes. During exposure, the men had periodic episodes of acute organophosphate toxicity: nausea, vomiting, excessive perspiration, muscle weakness, confusion, etc. When these men consulted psychiatrists or were admitted to mental hospitals, they had depressive or schizophrenic manifestations or major impairment of memory and concentration. These findings were attributed to the action of organophosphates on acetylcholinesterase in the central nervous system. Follow-up of the cases showed that these effects persisted for 6 months after exposure had ceased, but had disappeared by 12 months after exposure.

In animals, longer duration feeding studies have reported plasma, erythrocyte, and brain cholinesterase inhibition in dogs at 3.0 mg/kg/day for 13 weeks and in rats at 2.5 mg/kg/day for 2 years. Cholinergic signs were seen in the rats during the first few months. Electrophysiological effects were detected in the central nervous systems of male rats exposed to methyl parathion through gavage administration of 0.22 mg/kg/day to the dams on days 5–15 of gestation and days 2–28 of lactation, followed by direct administration of the same dose to the male pups for 8 weeks.

A serious neurological effect of some organophosphates and triarylphosphates, such as tri-*ortho*-cresyl-phosphate, is delayed neurotoxicity. Delayed neurotoxicity has been associated with inhibition of a neurotoxic esterase in nerve tissue. Axons in the spinal cord and peripheral nerves are targets for compound-induced damage. A classic screening test for such an effect is to administer the suspect chemical to atropinized chickens and to observe the animals for signs of leg weakness or paralysis. Methyl parathion does not appear to be a delayed neurotoxin, although studies in rats suggested that chronic oral exposure to 2.5 mg/kg/day methyl parathion may result in distal axonopathy, and intermediate oral exposure to 0.22 mg/kg/day may result in decreased nerve conduction velocity and increased refractory period.

Hematological Effects. No information was found regarding hematological effects in humans following exposure to methyl parathion. Repeated oral exposure to methyl parathion resulted in decreased mean corpuscular volume in one study and decreased hematocrit and erythrocyte count in another study in rats. Chronic ingestion of methyl parathion induced reduction of mean hemoglobin, hematocrit, and erythrocyte counts in rats.

Cardiovascular Effects. A number of cardiovascular lesions, such as acute myocardial degeneration and vascular degeneration, congestion, and hemorrhage, have been observed in individuals exposed to

fatal doses of methyl parathion. These effects may be secondary to neurological effects of methyl parathion on the central and peripheral nervous system and on heart contractility and vascular smooth muscle. Acute oral doses of methyl parathion, administered to rats in single doses $9.5 mg/kg, resulted in severe cardiac arrhythmias. Similar results were observed following dermal application of doses $34 mg/kg.

Developmental Effects. Adverse effects of methyl parathion on human fetal development have not been reported. Based on studies in animals, such effects appear to be possible if pregnant women were exposed during the first trimester to high concentrations of methyl parathion that resulted in significant depression of cholinesterase levels, particularly if concomitant signs and symptoms of organophosphate intoxication occur. Such an exposure scenario may occur with occupational exposure, exposure in homes or offices illegally sprayed with methyl parathion, or accidental exposure to methyl parathion, but is less likely as a result of low-level exposure.

The following studies in animals suggest that adverse effects on human fetal development could occur. Methyl parathion has been shown to transfer across the placenta of rats after oral exposure of pregnant females. Fetotoxicity and offspring with altered brain enzymes and impaired behavior have been reported in rats after oral or parenteral maternal administration of methyl parathion at doses that inhibited acetylcholinesterase activity and, in some studies, produced cholinergic signs in the dams. Pregnant female mice exposed to 60 mg/kg methyl parathion by the intraperitoneal route had a significant increase in fetuses with cleft palate compared to control litters. There was also a dose-related increase in fetal deaths. These observations suggest that developmental effects may occur in a susceptible population exposed to low doses of methyl parathion during pregnancy.

In addition, oral administration of methyl parathion at relatively low doses to male rats through the dams during gestation and lactation and then directly to the offspring until 12 weeks of age resulted in electro-physiological changes in the brain and peripheral nervous system, as described under neurological effects. These effects were seen at dose levels that did not cause cholinergic signs; cholinesterase activity was not monitored. Such effects were not seen in the same study when the period of administration was confined to gestation and lactation.

Ocular Effects. Pinpoint pupils (miosis) have been observed in individuals following acute exposure to methyl parathion. Electroretinographic changes have been reported in mice following intraperitoneal injection of 1.5 mg of methyl parathion. These changes were a direct effect of methyl parathion on

repolarization of retinal photoreceptors. Other data from animal studies indicate that oral exposure to methyl parathion may induce retinal degeneration and bilateral retinal atrophy. The relevance of the ocular effects noted in animals to humans is unknown.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

Although a number of studies have reported the effects of inhalation exposure to methyl parathion in humans, no inhalation MRLs were derived based on human data because of the lack of adequate quantitative exposure information. Animal data were also insufficient to support the derivation of an acute-, intermediate-, or chronic-duration inhalation MRL.

Oral MRLs

No acute oral MRL was derived for methyl parathion because data regarding the most sensitive effect that was observed after acute oral exposure are conflicting. Increased pup mortality and altered behavior occurred in offspring of rats exposed to 1 mg/kg/day methyl parathion during, but no effects on pup survival or on sensitive electrophysiological indices of neurotoxicity were seen at virtually the same dose, 0.88 mg/kg/day, in a similar developmental toxicity study.

- An MRL of 0.0007 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to methyl parathion.

An intermediate-duration oral MRL of 0.0007 mg/kg/day was derived for methyl parathion based on the observation of electrophysiological effects in the central and peripheral nervous systems of male rats exposed to methyl parathion through gavage administration of 0.22 mg/kg/day to the dams on days 5–15 of gestation and days 2–28 of lactation, followed by direct administration of the same dose to the male pups for 8 weeks. More marked effects occurred at the two higher doses, 0.44 and 0.88 mg/kg/day. The effects were dose-related, and were statistically significant at all three dose levels. The MRL was derived by dividing the LOAEL from this study (0.22 mg/kg/day) by an uncertainty factor of 300 (3 for a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

- An MRL of 0.0003 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to methyl parathion.

2. RELEVANCE TO PUBLIC HEALTH

A chronic-duration oral MRL of 0.0003 mg/kg/day was derived for methyl parathion based on the observation of reduced mean hematocrit and erythrocyte counts in rats fed methyl parathion in the diet for 2 years. Significantly decreased mean hematocrit and erythrocyte counts were observed at 24 months in males that consumed 0.25 and 2.5 mg/kg/day for 24 months; no effect on these end points in males was observed at 0.025 mg/kg/day. Significantly decreased mean hemoglobin, hematocrit, and erythrocyte counts were seen at 6–24 months in females that ingested 2.5 mg/kg/day, with no effect at 0.025–0.25 mg/kg/day. In the same study, significantly decreased plasma, erythrocyte, and brain cholinesterase activities, and abnormal gait, tremor, and peripheral neuropathy, were observed in the rats that consumed 2.5 mg/kg/day methyl parathion, but not in rats consuming the lower doses. The MRL was derived by dividing the NOAEL of 0.025 mg/kg/day for hematological effects in this study by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of methyl parathion. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not

the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (minimal risk levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for methyl parathion. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990c), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

Deaths following exposure to methyl parathion occurred in children (two sisters, aged 4 and 11 years). Exposure was by multiple routes including inhalation of methyl parathion that was sprayed inside a house from a solution containing 4% methyl parathion (1.25% methyl parathion was recommended by a manufacturer for field spraying). Thirteen days after spraying, the house air contained 0.041 mg/m^3, 7 times the concentration of methyl parathion found just outside. Drinking water, stored in open containers due to the lack of running water in the house, contained 0.138–0.275 mg/L of methyl parathion 12 days after spraying. Dermal exposure may also have been possible. All children in the household, including five surviving siblings, had depressed plasma and erythrocyte cholinesterase levels. Urinary 4-nitrophenol was detected in three children. Clinical signs and symptoms were typical of organophosphate toxicity, as described in Section 3.2.1.4, with respiratory arrest as the terminal event (Dean et al. 1984).

Death from a combination of inhalation and dermal exposures has been reported by Fazekas (1971) in four individuals who used methyl parathion (Wofatox) spray in a careless manner. These individuals were part of a larger series of 30 cases (20 men, 10 women) of fatal methyl parathion intoxication reported by Fazekas (1971). Since 26 of these fatalities followed oral exposure, this report is discussed in detail in Sections 3.2.2.1 and 3.2.2.2.

The LC_{50} values of methyl parathion have been established in rats. A 1-hour LC_{50} of 200 mg/m^3 and a 4-hour LC_{50} of 120 mg/m^3 for males were determined by Kimmerle and Lorke (1968). One-hour LC_{50} values of 257 mg/m^3 for male rats and 287 mg/m^3 for female rats were determined for 70–80% pure methyl parathion by EPA (1978e); the rats were exposed to aerosols of respirable size. Survivors of toxic doses recovered clinically by 10–14 days postexposure. Sex-related differences in acute mortality of rodents have also been observed after exposure to methyl parathion by other routes (Murphy and Dubois 1958).

The LC_{50} value for male rats for the acute-duration category is recorded in Table 3-1 and plotted in Figure 3-1.

Table 3-1. Levels of Significant Exposure to Methyl Parathion - Inhalation

Key to[a] figure	(strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat	1-4 hr once				120 M (LC_{50})	Kimmerle and Lorke 1968

[a]The number corresponds to entries in Figure 3-1.

hr = hour(s); LC_{50} = Lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; mg/m^3 = milligram per cubic meter; NOAEL = no-observable-adverse-effect level

Figure 3-1. Levels of Significant Exposure to Methyl Parathion - Inhalation

Acute (≤14 day)

3.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, hematological, musculoskeletal, or dermal effects in humans or animals after inhalation exposure to methyl parathion. Dean et al. (1984) reported that seven children exposed to methyl parathion by many routes exhibited pinpoint pupils, abdominal pain, and diarrhea. The respiratory, cardiovascular, hepatic, and renal effects reported by Fazekas (1971) that were found in humans acutely exposed to methyl parathion intoxication resulted from exposure by all three routes; however, the results did not distinguish between the routes.

Respiratory Effects. Pulmonary edema was reported in humans dying from acute methyl parathion (Wofatox) intoxication (Fazekas 1971). Edema was found in a man who died 2 hours after intoxication, and, in other cases, edema was found in others who died as long as 9 days after exposure. Broncho-constriction and hypersecretion of bronchial glands (bronchorrhea) are primary muscarinic effects of methyl parathion. The broncoconstriction, bronchorrhea, and bradycardia caused by methyl parathion are strongly conducive to pulmonary edema.

Rats exposed to a 1-hour LC_{50} of methyl parathion (see Section 3.2.1.1) had moderate pulmonary congestion, hemorrhage, and edema (EPA 1978e). While these lesions could represent an irritant effect of inhaled aerosols of methyl parathion, they also may be secondary to agonal death, meaning resulting from the death process, or to muscarinic effects as noted in the previous paragraph.

Cardiovascular Effects. Lesions in the heart and blood vessels have been reported in humans acutely intoxicated with methyl parathion (Wofatox) (Fazekas 1971) and are discussed in Section 3.2.2.2. However, many of these lesions may be secondary to the effects of methyl parathion on the conduction system of the heart, to other components ingested, or to therapeutic regimens that some of these patients received.

Thymic hemorrhage and congested cerebral blood vessels occurred in rats exposed to a 1-hour LC_{50} of methyl parathion described in Section 3.2.1.1 (EPA 1978e). These are probably nonspecific agonal lesions.

Hepatic Effects. Liver lesions were reported in humans dying of acute methyl parathion (Wofatox) intoxication (Fazekas 1971). See Section 3.2.2.2 for a description of these lesions. The hepatic effects

were nonspecific and were likely a reflection of systemic effects of hypoxia, stress, therapeutic agents, or a combination of all of these.

No studies were located regarding hepatic effects in animals after inhalation exposure to methyl parathion.

Renal Effects. Kidney lesions were reported in humans dying of acute methyl parathion (Wofatox) intoxication (Fazekas 1971). See Section 3.2.2.2 for a description of these lesions.

No studies were located regarding renal effects in animals after inhalation exposure to methyl parathion.

Ocular Effects. One study reported that seven children exposed to methyl parathion by inhalation, oral, and possibly dermal routes exhibited pinpoint pupils (miosis) (Dean et al. 1984). This effect is a consequence of the effects on the autonomic nervous system. No other studies were located regarding ocular effects in humans or animals after inhalation exposure to methyl parathion.

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to methyl parathion.

3.2.1.4 Neurological Effects

Neurological effects related to cholinesterase depression occurred in seven children acutely exposed to methyl parathion by inhalation as well as orally and dermally (Dean et al. 1984). The children were admitted to a local hospital with signs and symptoms of lethargy, increased salivation, increased respiratory secretions, and miosis. Two of the children were in respiratory arrest. Two children died within several days of each other. All of the children had depressed plasma and erythrocyte cholinesterase levels (Table 3-2). These effects are similar to those occurring in methyl parathion intoxication by other routes (see Sections 3.2.2.4 and 3.2.3.4). Three adults exposed in the same incident had normal plasma (apart from one female) and red blood cell cholinesterase, and urinary levels of 4-nitrophenol (0.46–12.7 ppm) as high as some of the ill children.

Table 3-2. Plasma and Erythrocyte Cholinesterase Levels in Children Intoxicated by Methyl Parathion[a]

Age/sex	Plasma cholinesterase (mU per mL per minute)[b]	Erythrocyte cholinesterase (ΔpH/hour)[c]
11 years/female (died)	No data	No data
9 years/male	1,023	0.15
8 years/male	987	0.10
6 years/female	1,707	0.10
5 years/female	964	0.10
4 years/female (died)	914	0.00
2 years/female	1,534	0.10

[a]Adapted from Dean et al. 1984
[b]Normal value: 2,450–4,850
[c]Normal value: 0.57–0.98

Δ = change; mU = milliunits; mL = milliliter

Male rats exposed to 264 mg/m^3 of methyl parathion by inhalation had 59% (range: 53–61%) inhibition of blood (a combination of erythrocyte and plasma) cholinesterase 1 hour after exposure (EPA 1978e). These animals had typical cholinergic signs of toxicity: salivation, exophthalmos, lacrimation, spontaneous defecation and urination, and muscle fasciculation. Values for controls were not provided. Death was not correlated to the degree of cholinesterase inhibition in whole blood.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after inhalation exposure to methyl parathion.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to methyl parathion.

3.2.1.7 Cancer

No studies were located regarding carcinogenic effects in humans or animals after inhalation exposure to methyl parathion.

3.2.2 Oral Exposure

3.2.2.1 Death

There have been a number of cases of human intoxication and death from oral exposure to methyl parathion.

Two of seven children who ingested methyl parathion in contaminated drinking water, and also were exposed by inhalation and possibly by dermal contact following spraying of methyl parathion inside a house, died (Dean et al. 1984). Additional details are provided in Section 3.2.1.1.

A 50-year-old white male died after intentional methyl parathion ingestion (Wofatox liquid) (Fazekas and Rengei 1964). The estimated dose of methyl parathion was 1,840 mg. Gross necropsy findings consisted

of congested cerebral meninges, brain edema, generalized visceral congestion, laryngeal and pulmonary edema, fatty liver, intense congestion of the esophageal mucosa, and petechial hemorrhages on the mucosa of the stomach and intestines. Histopathologic examination of tissues was not performed. The estimated dose of 1,840 mg methyl parathion corresponds to a bolus dose of 26 mg/kg. None of the reported autopsy findings are specific to organophosphate intoxication. A lethal oral dose of 307–660 mg has been reported for adults (Fazekas and Rengei 1964).

Thirty fatalities, 20 men and 10 women, resulted from acute exposure to methyl parathion (Wofatox) (Fazekas 1971). Patients ranged in age from 18 to 82 years. They died between 2 hours and 9 days after exposure to Wofatox. A number of these individuals received intensive therapy but died nonetheless. Of the 30 cases, 26 had intentionally ingested 50–300 g of Wofatox, while the rest had a combination of excessive dermal and inhalation exposure during spraying. Histological lesions were reported in liver, kidney, spleen, heart, brain, and vascular endothelium. Lesions were not categorized by exposure route. These lesions are described in Section 3.2.2.2 under the various organ systems and in Section 3.2.2.4 under neurological effects. Most of these lesions are not specific for methyl parathion in particular or organophosphates in general.

Numerous studies in experimental animals have established LD_{50} values for acute oral exposure to methyl parathion. In most of these studies, technical grade, purified methyl parathion, or an emulsion concentration (EC) formulation was administered by gavage in a vehicle such as propylene glycol. Species tested were rats (EPA 1978e; Gaines 1960; Miyamoto et al. 1963b; Sonnenschein et al. 1989b; Yamamoto et al. 1982), mice (El-Herrawie and El-Sayed 1986; Haley et al. 1975b; Metcalf and March 1953; Miyamoto et al. 1963b), and guinea pigs (Miyamoto et al. 1963b).

In rats, the LD_{50} for males tended to be lower, although not statistically significantly different, in comparison with that for females (EPA 1978e; Gaines 1960). In CD-1 mice, males had a significantly lower LD_{50} than did females (Haley et al. 1975b). Similar sex-related differences have been seen with some other thio-organophosphate pesticides and were attributed to more efficient conversion of these compounds to their active paraoxon metabolites in the liver of males (Murphy and DuBois 1958).

The LD_{50} values for methyl parathion were compared to those for methyl paraoxon, the active metabolite of methyl parathion, in rats, guinea pigs, and mice by Miyamoto et al. (1963b). Methyl paraoxon was 5.4 times more potent than methyl parathion in male rats, 5 times more potent in male guinea pigs, and 1.6 times more potent in mice.

In mice, heat-induced isomers of purified methyl parathion were less lethal than was purified methyl parathion alone (LD_{50} of >200 mg/kg for heat-induced isomers compared to 100–200 mg/kg for methyl parathion) (Metcalf and March 1953). Eighty-five percent of the sample was heat-isomerized, but the isomers were not precisely identified. Methyl parathion in an emulsifiable concentrate had greater acute (24 hours) oral lethality for male mice than it did in the technical or microencapsulated formulations. For microencapsulated methyl parathion, the toxicity of the supernatant increased over storage time from an LD_{50} value of 21.2 mg/kg before storage to 14.9 mg/kg at 2 months storage time, indicative of gradual release of methyl parathion from the capsules to the liquid during storage (El-Herrawie and El-Sayed 1986).

Clinical signs of acute oral toxicity of methyl parathion and methyl paraoxon were characterized by Miyamoto et al. (1963b) in rodents. Signs occurred within minutes after compound administration and consisted of dyspnea, twitching, clonic convulsions, salivation, chromodacryorrhea, and exophthalmos. The signs lasted for 30–60 minutes, at which time death usually occurred. However, guinea pigs tended to develop less severe signs, and deaths occurred up to 24 hours postdosing.

An 8-week dietary study of methyl parathion was performed by NCI (1979) in order to select doses for a chronic bioassay. F344 rats of both sexes (five animals/sex/group) received doses of 0, 0.5, 1, 1.5, 2, or 2.5 mg/kg/day. $B6C3F_1$ mice (five animals/sex/group) received doses of 0, 2.6, 5.2, 7.8, 10.4, 13, 16.2, 32.5, or 65 mg/kg/day. All male rats survived to study termination. One of five females fed 0.5, 1.5, and 2 mg/kg/day and two of five females fed 2.5 mg/kg/day died. In mice, significant mortality occurred at the two highest doses; all males died in the 32.5- and 65-mg/kg/day groups, as did all females in the 65-mg/kg/day group. Clinical signs in both sexes in the 32.5- and 65-mg/kg/day dosage groups were rough hair coat and arched back. The results suggest that male mice may be more susceptible than females to intermediate-duration exposure, in contrast to the acute lethality data for mice and to the results for rats in this intermediate-duration study.

All reliable lethal doses (LD_{50} values) for each species and for the acute- and intermediate-duration categories are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

Reductions in erythrocyte and plasma cholinesterase levels are considered biomarkers of neurological effects and not hematological effects as discussed in Sections 3.2.2.4 and 3.5.2.

Table 3-3. Levels of Significant Exposure to Methyl Parathion - Oral

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat	once (G)				12[b] M (LD_{50}) 18 F (LD_{50})	EPA 1978e
2	Rat	once (G)				14[b] M (LD_{50}) 24 F (LD_{50})	Gaines 1960
3	Rat	once (G)				24.5 M (LD_{50})	Miyamoto et al. 1963b
4	Rat	10 d 1x/d (G)				4 M (6/6 died)	Yamamoto et al. 1982
5	Mouse	once (G)				10.3 M (LD_{50} for EC formulation)	El-Herrawie and El-Sayed 1986
6	Mouse	once (G)				12.4 M (LD_{50} for technical formulation)	El-Herrawie and El-Sayed 1986
7	Mouse	once (G)				14.5[b] M (LD_{50}) 19.5 F (LD_{50})	Haley et al. 1975b
8	Mouse	once (NS)				100 (LD_{50})	Metcalf and March 1953
9	Mouse	once (G)				17 (LD_{50})	Miyamoto et al. 1963b

Table 3-3. Levels of Significant Exposure to Methyl Parathion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
10	Gn Pig	once (G)				417 M (LD_{50})	Miyamoto et al. 1963b
	Systemic						
11	Rat	once (GW)	Cardio			9.5 (cardiac abnormalities)	Galal et al. 1975
12	Rat	once (GO)	Hepatic		15.6 (hepatocellular damage)		Sonnenschein et al. 1989a, 1989b
	Neurological						
13	Rat	14 d 1x/d Gd6-19 (GO)				1.5 F (muscle fasciculations, tremors in dams)	Gupta et al. 1985
14	Rat (Wistar)	10 d 1 x/d Gd 6-15 (GO)		1.0 F		1.5 F (muscle fasciculations, tremors, convulsions in dams)	Kumar and Devi 1996
15	Rat	10 d 1x/d (GO)			1.3 M (44% decreased plasma and 25% decreased brain cholinesterase levels)		Yamamoto et al. 1982
16	Rat	once (GO)				5 M (convulsions)	Youssef et al. 1987

Table 3-3. Levels of Significant Exposure to Methyl Parathion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
Developmental							
17	Rat	9 d 1x/d Gd 7-15 (GO)				1 (impaired behavior; pup mortality)	Crowder et al. 1980
18	Rat (Wistar)	Gd 5-15 1x/d (G)		0.88 M			Desi et al. 1998
19	Rat	10-14 d 1x/d Gd6-15/19 (GO)			1 (decreased protein synthesis)		Gupta et al. 1984
20	Rat	14 d 1x/d Gd6-19 (GO)				1.5 (resorptions)	Gupta et al. 1985
21	Rat (Wistar)	10 d 1 x/d Gd 6-15 (GO)		1.0		1.5 (resorptions)	Kumar and Devi 1996

Table 3-3. Levels of Significant Exposure to Methyl Parathion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Death						
22	Rat	8 wk ad lib (F)				2.5 F (2/5 died)	NCI 1979
23	Mouse	8 wk ad lib (F)				32.5 M (5/5 died)	NCI 1979
	Systemic						
24	Rat (Wistar)	28 d 1x/d (GW)	Hemato	0.218 M	0.436 M (5% decrease in mean corpuscular volume)		Undeger et al. 2000
			Bd Wt	0.872 M			
25	Mouse (B6C3F1)	28 d 1 x/d (GO)	Hemato	6 F			Crittenden et al. 1998
26	Mouse	8 wk ad lib (F)	Gastro			32.5 (gastric hemorrhage)	NCI 1979
27	Mouse Kunming	15 d 1 x/d (GO)	Bd Wt	5.0			Tian et al. 1997

Table 3-3. Levels of Significant Exposure to Methyl Parathion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
28	Dog (Beagle)	13 wk (F)	Dermal	3.0 M			Daly 1989
			Ocular	3.0 M			
			Bd Wt	0.3 M	3.0 M (emaciation, dehydration in 2 of 8 dogs; 30% reduced body weight gain)		
Immunological/Lymphoreticular							
29	Rat	35 d 1x/d (G)			1.25 (97% decreased agglutinin titer)		Shtenberg and Dzhunusova 1968
30	Rat (Wistar)	28 d 1x/d (GW)		0.872 M			Undeger et al. 2000
31	Mouse Kunming	15 d 1 x/d (GO)		0.5	2.5 (36% increased T suppressor cell ratio)		Tian et al. 1997
Neurological							
32	Rat (Wistar)	13 wk Gd 5-15 Ld 2-28 Pd 28-84 1 x/d (GW)			0.22[c] M (electrophysiological effects in CNS and PNS)		Desi et al. 1998
33	Mouse (B6C3F1)	28 d 1 x/d (GO)		1 F	3 F (18% decreased brain AChE activity)		Crittenden et al. 1998

Table 3-3. Levels of Significant Exposure to Methyl Parathion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
34	Dog (Beagle)	13 wk (F)		0.30	3.0 (decreased plasma 53-59%, erythrocyte 20-23%, and brain 43-54% cholinesterase activity)		Daly 1989
	Developmental						
35	Rat (Wistar)	Gd 5-15 Ld 2-28 1x/d (G)		0.88 M			Desi et al. 1998
36	Rat (Wistar)	15 d 1x/d Gd 6-20 (IN)				1.0 (slightly impaired behavior)	Gupta et al. 1985

Table 3-3. Levels of Significant Exposure to Methyl Parathion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
CHRONIC EXPOSURE							
Systemic							
37	Rat	105 wk ad lib (F)	Resp	2			NCI 1979
			Cardio	2			
			Gastro	2			
			Hemato	2			
			Musc/skel	2			
			Hepatic	2			
			Renal	2			
			Dermal	2			
			Ocular	2			
			Bd Wt	2			

Table 3-3. Levels of Significant Exposure to Methyl Parathion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
38	Rat (Sprague-Dawley)	26 mo (males) 28 mo (females)	Cardio	0.25 F	2.5 F (increased heart to body weight ratio)		Suba 1984
		(F)	Hemato	0.025[d] M	0.25[b] M (decrease in mean hematocrit, and erythrocyte counts)		
				0.25 F	2.5 F (decreases in mean hemoglobin)		
			Dermal	0.25	2.5 (alopecia)		
			Ocular	0.25	2.5 (retinal degeneration and bilateral atrophy; sub capsular cataracts)		
			Bd Wt	0.25	2.5 (6% reduced body weight)		
			Other	0.25	2.5 (increased food consumption; ano-genital staining)		
39	Mouse (B6C3F1)	102 wk ad lib	Resp	16.2			NCI 1979
		(F)	Cardio	16.2			
			Gastro	16.2			
			Musc/skel	16.2			
			Hepatic	16.2			
			Renal	16.2			
			Dermal	16.2			
			Ocular	16.2			
			Bd Wt	16.2			

Table 3-3. Levels of Significant Exposure to Methyl Parathion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
40	Dog	1 yr (F)	Resp	0.3			Suba 1981
			Cardio	0.3			
			Gastro	0.3			
			Hemato	0.3			
			Musc/skel	0.3			
			Hepatic	0.3			
			Renal	0.3			
			Dermal	0.3			
			Ocular	0.3			
	Immunological/Lymphoreticular						
41	Dog	1 yr (F)		0.3			Suba 1981
	Neurological						
42	Rat (Sprague-Dawley)	26 mo (males) 28 mo (females) (F)		0.25 M	2.5 M (decreased plasma 67-88%, erythrocyte 9-20%, and brain 76-79% cholinesterase activity)	2.5 M (slight tremor, peripheral neuropathy)	Suba 1984

Table 3-3. Levels of Significant Exposure to Methyl Parathion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
	Reproductive						
43	Dog	1 yr (F)		0.3			Suba 1981

[a]The number corresponds to entries in Figure 3-2.
[b]Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[c]Used to derive an intermediate oral MRL of 0.0007 mg/kg/day; dose divided by an uncertainty factor of 300 (10 for extrapolation from animals to humans, 10 for human variability, and 3 for a minimal LOAEL).
[d]Used to derive a chronic oral MRL of 0.0003 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; d = day(s); F = female; (F) = feed; (G) = gavage; gastro = gastrointestinal;Gd = gestation day; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; (IN) = ingestion; Ld = lactation day; LD_{50} = Lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; mg/kg/day = milligram per kilogram per day; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; Pd = postnatal day; Resp = respiratory; wk = week(s); x = time; yr = year(s)

Figure 3-2. Levels of Significant Exposure to Methyl Parathion - Oral

Acute (≤14 days)

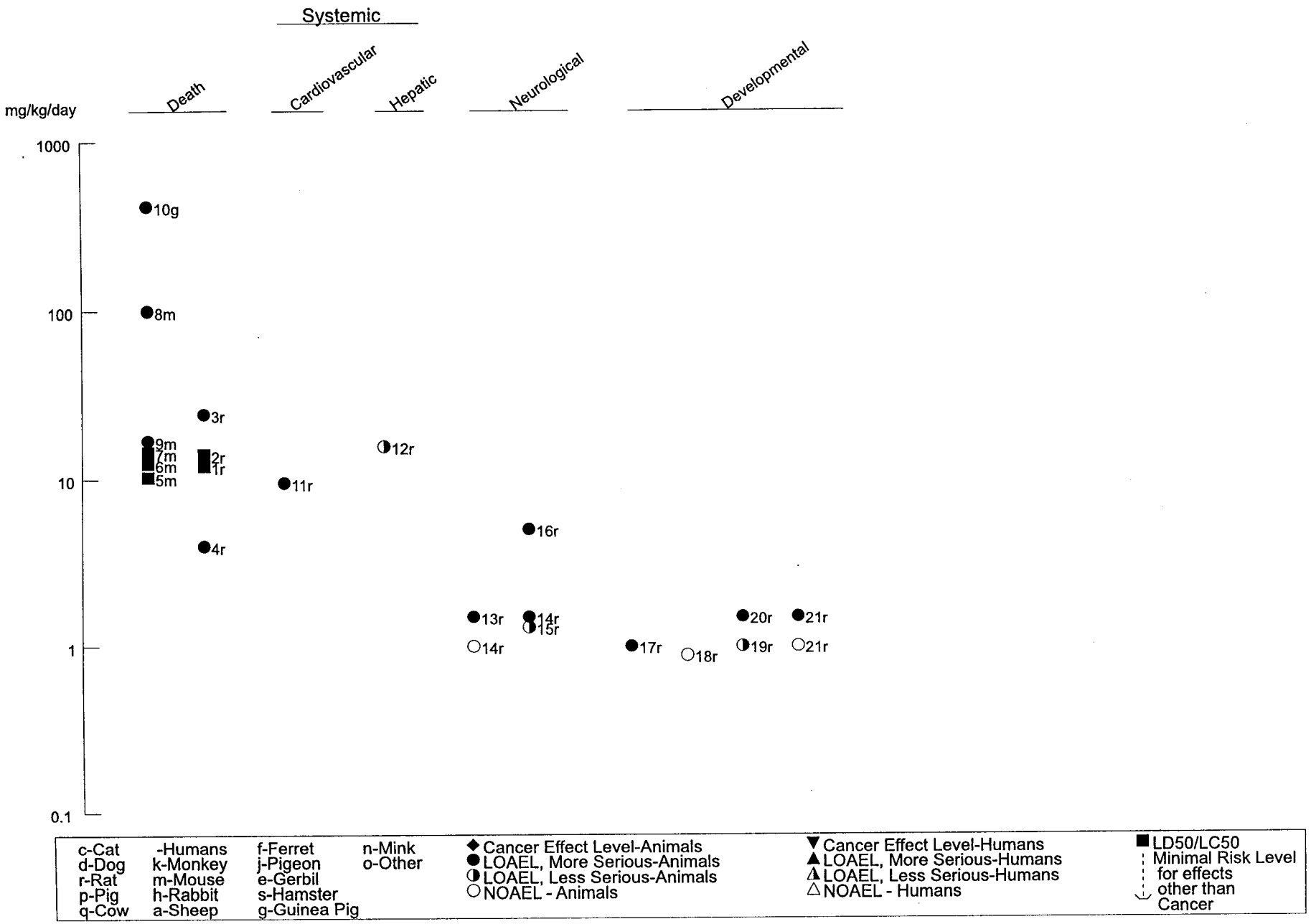


Figure 3-2. Levels of Significant Exposure to Methyl Parathion - Oral (*continued*)

Intermediate (15-364 days)

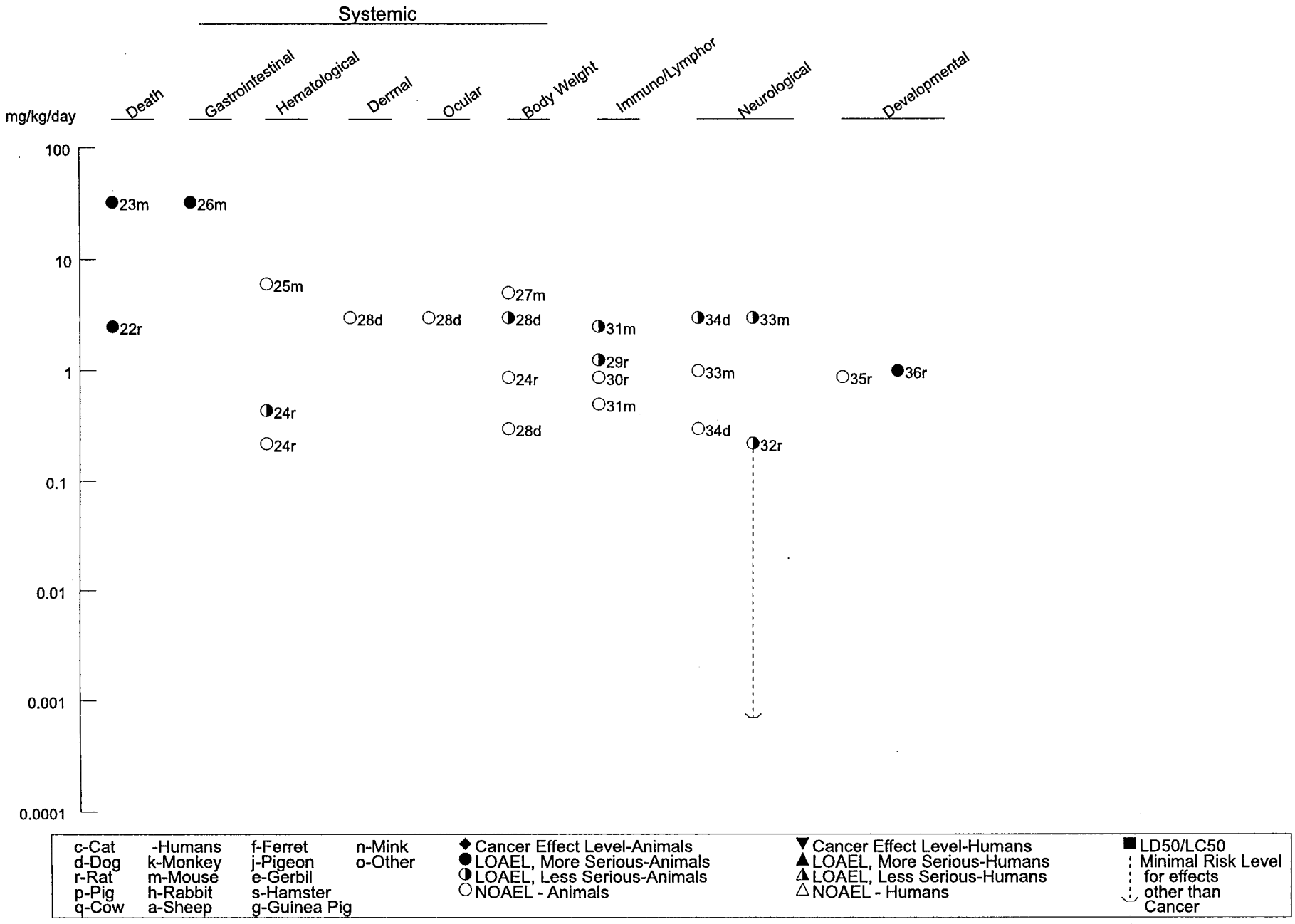
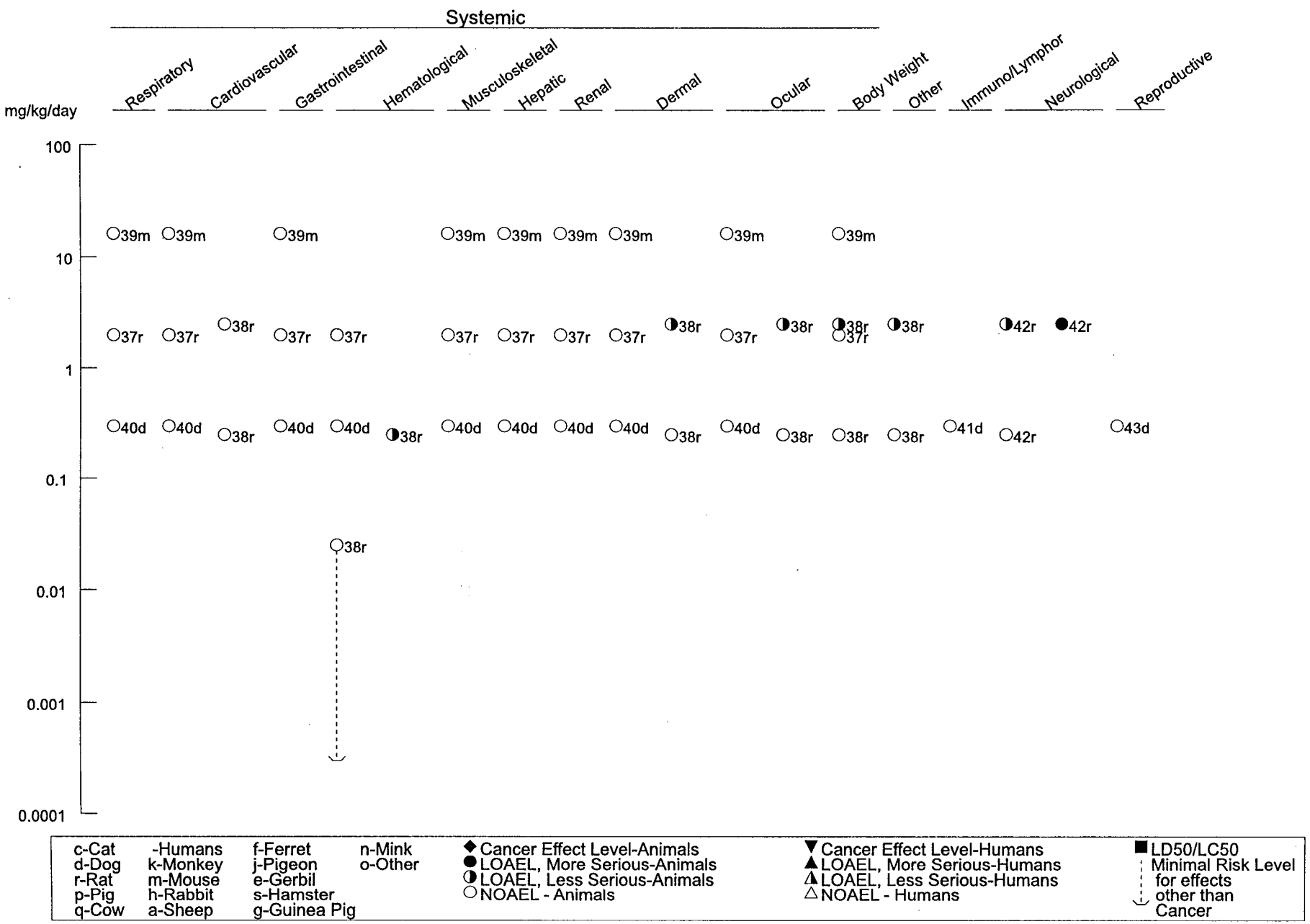


Figure 3-2. Levels of Significant Exposure to Methyl Parathion - Oral (*continued*)

Chronic (≥365 days)



The highest NOAEL and the reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-2.

Respiratory Effects. Pulmonary edema has been reported in humans who died of acute methyl parathion (Wofatox) intoxication (Fazekas 1971). Edema was found in a man who died 2 hours after intoxication and in others who died as long as 9 days after exposure. Bronchoconstriction and hyper-secretion of bronchial glands are primary muscarinic effects of methyl parathion. Pulmonary edema is not considered to be a primary effect of methyl parathion; it is considered to be secondary to the neurologic effects of this compound on the heart and vascular smooth muscle.

Routine gross and histopathological examinations revealed no treatment-related effects on the respiratory system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). Chronic dietary exposure to methyl parathion did not induce respiratory effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Cardiovascular Effects. Cardiovascular lesions were reported in some of the 30 cases of acute fatal intoxication by methyl parathion studied by Fazekas (1971). Patients who survived at least 20–24 hours had degeneration of the heart muscle with segmentation, fragmentation, and splitting of myofibers. Vascular lesions were congestion and multifocal hemorrhages in the central nervous system and in visceral organs. Patients surviving 28 hours to 9 days after intoxication (and receiving intensive therapy) had widespread swelling of vascular endothelium with areas of desquamation into vessel lumens. Blood vessel walls and perivascular spaces were edematous. However, many of these lesions may be secondary to the effects of methyl parathion on the conduction system of the heart, to other components ingested, or to therapeutic regimens that some of these patients received.

Rats exposed by gavage to 19 mg/kg (LD_{50} dose) or 9.5 mg/kg (half of the LD_{50} dose) of methyl parathion developed abnormalities in their heart rate and electrocardiograms (Galal et al. 1975). Bradycardia was observed in both groups 1 and 2 hours after oral introduction of the methyl parathion (85% reduction in rate in the LD_{50} group and 68% reduction in the one-half-LD_{50} group). Severe arrhythmia and electro-cardiographic abnormalities suggestive of myocardial ischemia also occurred. In comparison to malathion and carbaryl, methyl parathion produced the greatest cardiotoxic changes.

A significant increase in heart-to-body-weight ratio occurred in female rats exposed to 2.5 mg/kg/day methyl parathion in the diet for 2 years, but not in rats exposed to either 0.025 or 0.25 mg/kg/day methyl

parathion (Suba 1984). This effect did not have any complementary histopathology. Routine gross and histopathological examinations revealed no treatment-related effects on the cardiovascular system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). Chronic dietary exposure to methyl parathion did not induce cardiovascular effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Gastrointestinal Effects. Intense congestion of the esophageal mucosa and petechial hemorrhages in the stomach and intestine were reported in a patient who committed suicide by ingesting methyl parathion (Wofatox) (Fazekas and Rengei 1964). In a series of 30 cases of methyl parathion (Wofatox) fatalities, inflammation was present in the stomach and intestine at autopsy (Fazekas 1971). These victims died within 2 hours to 9 days after exposure, even after intensive therapy. All these gastro-intestinal findings are nonspecific and cannot be attributed to a primary effect of methyl parathion.

In an 8-week study to establish doses for a chronic dietary bioassay of methyl parathion, B6C3F_1 mice received dietary methyl parathion at levels of 0, 2.6, 5.2, 7.8, 10.4, 13, 16.3, 32.5, and 65 mg/kg/day. Gastric hemorrhage was present at necropsy in five of five males receiving 32.5 mg/kg/day and in three of five males and five of five females receiving 65 mg/kg/day (NCI 1979). This finding was correlated with mortality (see Section 3.2.2.1). Routine gross and histopathological examinations revealed no treatment-related effects on the gastrointestinal system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). Chronic dietary exposure to methyl parathion did not induce gastrointestinal effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to methyl parathion.

Total leukocyte and differential cell counts were not affected in female mice given 6 mg/kg/day of methyl parathion by gavage for 28 days (Crittenden et al. 1998). In male rats administered methyl parathion by gavage at doses of 0.218, 0.436, or 0.872 mg/kg/day for 28 days, the two highest dose groups exhibited dose-related significant decreases in mean corpuscular volume. No significant dose-related changes were seen in red blood cell count or absolute and differential white blood cell counts (Undeger et al. 2000). An additional intermediate-duration study in rats reported anemia (decreased hematocrit and erythrocyte count) and slight leukocytosis with neutropenia and lymphocytosis following treatment with an undetermined dose of methyl parathion, but higher than 0.37 mg/kg/day (Galal et al. 1977); this study is not presented in Table 3-2. Mean hemoglobin, hematocrit, and erythrocyte counts were significantly

reduced in female rats at 6–24 months of exposure to 2.5 mg/kg/day methyl parathion, which was given in the diet for 2 years (Suba 1984). Mean hematocrit and erythrocyte counts were significantly reduced in males at 24 months of exposure to either 0.25 or 2.5 mg/kg/day methyl parathion. These effects did not occur in rats exposed to 0.025 mg/kg/day methyl parathion. A NOAEL of 0.025 mg/kg/day was identified from these data. Based on this value, a chronic oral MRL of .0003 mg/kg/day was calculated as described in the footnote in Table 3-3. No treatment-related effects were noted following routine hematological testing in dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to methyl parathion.

Routine gross and histopathological examinations revealed no treatment-related effects on the musculoskeletal system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). Chronic dietary exposure to methyl parathion did not induce musculoskeletal effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Hepatic Effects. Liver lesions have been reported in humans acutely intoxicated by methyl parathion formulation (Wolfatox) (Fazekas 1971; Fazekas and Rengei 1964). These studies are discussed in detail in Section 3.2.2.1. Liver lesions were hepatocellular swelling, degeneration, and fatty change. Intoxicated patients surviving for 28 hours to 9 days had hepatocytes free in central or hepatic veins; this finding was described as mobilization of liver cells. The role of methyl parathion in the induction of all of these lesions is unclear.

Rats were given one or two LD_{50} doses of methyl parathion, spaced 14 days apart (Sonnenschein et al. 1989b). Male rats had elevated serum alanine aminotransferase indicative of hepatocellular damage. The enzyme levels returned to normal within 48 hours after exposure. Serum levels of tyrosine aminotransferase, an enzyme induced in liver by glucocorticoids, also increased. Liver lesions were more severe after the second dose of methyl parathion. They consisted of single cell necrosis of hepatocytes, hepatocellular swelling, binucleate hepatocytes, rare fatty vacuolization of hepatocytes, and Kupffer cell proliferation (Sonnenschein et al. 1989a). These changes may be secondary, stress-related findings rather than direct toxic effects of methyl parathion.

Routine gross and histopathological examinations revealed no treatment-related effects on the hepatic system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). Chronic dietary exposure to methyl parathion did not induce hepatic effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Renal Effects. Acute nephrosis has been reported in humans after acute, lethal intoxication (Fazekas 1971) by methyl parathion (Wofatox). This may be a secondary effect of hypoxia related to the neurologic effects of methyl parathion on vascular smooth muscle and on the electrical conduction system of the heart. It could also be related to therapeutic efforts.

Routine gross and histopathological examinations revealed no treatment-related effects on the renal system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). Chronic dietary exposure to methyl parathion did not induce renal effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to methyl parathion.

Routine gross and histopathological examinations revealed no treatment-related dermal effects on dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981).

There was an increased incidence of alopecia in female rats treated for 2 years with 2.5 mg/kg/day methyl parathion compared to either vehicle controls, high-dose males, or rats treated with either 0.025 or 0.25 mg/kg/day methyl parathion (Suba 1984). Chronic dietary exposure to methyl parathion did not induce dermal effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Ocular Effects. One study reported that seven children exposed to methyl parathion by inhalation, oral, and possibly dermal routes exhibited pinpoint pupils (miosis) (Dean et al. 1984). This effect is a consequence of the effects on the parasympathetic nervous system. No other studies were located regarding ocular effects in humans after oral exposure to methyl parathion.

There were no treatment-related effects on retinal function and no morphological effects on the eyes of dogs that were exposed to 0.03, 0.30, or 3.00 mg/kg/day methyl parathion for 13 weeks and allowed 4 weeks of no exposure to recover (Daly 1989).

Routine gross and histopathological examinations revealed no treatment-related effects on the ocular systems of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981).

Female rats exposed to 2.5 mg/kg/day methyl parathion exhibited retinal degeneration, which was noted at 24 and 28 months but not at 3 or 12 months of a 2-year treatment (Suba 1984). Posterior subcapsular cataracts also occurred in the high-dose females and may be related to retinal degeneration. These data are limited because the incidence of the effects was not reported with respect to controls or other treated groups and the statistical significance was not determined. The incidence of bilateral retinal atrophy was significantly greater in female rats that were chronically exposed to 2.5 mg/kg/day methyl parathion than in vehicle controls (Suba 1984). This effect was not significant in rats exposed to either 0.025 or 0.25 mg/kg/day methyl parathion. Chronic dietary exposure to methyl parathion did not induce ocular effects in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Body Weight Effects. No effect on body weight was seen in mice administered 5 mg/kg/day of methyl parathion by gavage for 15 days (Tian et al. 1997). Body weight gain in male rats was not affected by oral (gavage) administration of methyl parathion at 0.872 mg/kg/day for 28 days (Undeger et al. 2000). No effect on body weight gain was seen in male rats whose dams were administered 0.88 mg/kg/day during days 5–15 of gestation and from day 2 after delivery through weaning of the pups, which were then continued on the same doses for 8 weeks (Desi et al. 1998). Emaciation and dehydration were noted in two of eight male dogs treated with 3.00 mg/kg/day methyl parathion for 13 weeks in the diet, but not in dogs treated with either 0.03 or 0.30 m7g/kg/day methyl parathion (Daly 1989). These effects were reported to be due to treatment with methyl parathion, although the statistical significance of the effects was not determined. Also, male dogs treated with 3.00 mg/kg/day methyl parathion had a 30% decrease in body weight gain compared to controls. The other treatment groups did not exhibit this effect. There were no significant effects on mean body weights in any of the treatment groups.

Male and female rats exposed to 2.5 mg/kg/day methyl parathion in the diet for 2 years had statistically significant reduced body weights when compared to vehicle controls (Suba 1984). This effect was not consistent throughout the study and did not occur in rats exposed to either 0.025 or 0.25 mg/kg/day methyl parathion. Mean food consumption values were significantly elevated in male rats but only within the first 13 weeks of the 2-year exposure to 2.5 mg/kg/day methyl parathion (Suba 1984). Females exposed to 2.5 mg/kg/day methyl parathion had significantly reduced food intake values during the first 2 weeks of exposure, but intake was significantly elevated from week 3 to termination. Effects on food

consumption did not occur in rats exposed to 0.025 or 0.25 mg/kg/day methyl parathion. There were no treatment-related effects on body weight or food intake in dogs that were exposed to either 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). Also, no such effects were noted following chronic dietary exposure to methyl parathion in mice fed 16.2 mg/kg/day or rats fed 2 mg/kg/day (NCI 1979).

Other Systemic Effects. Female rats, but not males, treated with 2.5 mg/kg/day methyl parathion had greater frequency of yellow ano-genital staining than the control females or females treated with either 0.025 or 0.25 mg/kg/day methyl parathion (Suba 1984).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to methyl parathion.

An increased ratio of T suppressor cells to T helper cells was seen in mice given 2.5 and 5.0 mg/kg/day of methyl parathion for 15 days; the spleen to body weight ratio was increased at 5 mg/kg/day (Tian et al. 1997). No other immunological or lymphoreticular end points were measured.

In female mice administered methyl parathion by gavage at doses of 1, 3, or 6 mg/kg/day for 28 days or 6 mg/kg/day for 7, 14, 21, or 28 days, natural killer cell activity was increased at 1 and 3 mg/kg/day (but not at 6 mg/kg/day at any duration) (Crittenden et al. 1998). Peritoneal macrophage activity was increased at all three doses, and cytotoxic T lymphocyte activity was not affected. Spleen cellularity (but not spleen weight) was increased at 7–21 days, but decreased at 28 days in mice receiving 6 mg/kg/day. The number of splenic plaque-forming cells following *in vitro* challenge with sheep red blood cells was decreased at all three doses of methyl parathion, in a dose-related manner. No decrease in antibody production was seen, however, when the mice were immunized with sheep red blood cells *in vivo* during methyl parathion treatment. Resistance to melanoma cells and to group b streptococci was not affected by methyl parathion. The results, taken together, do not indicate a serious decrement in immune function at these doses, which produced no overt cholinergic signs.

There was a suggestion of dose-related immunosuppressive effects in rabbits fed methyl parathion in the diet at 0.04, 0.16, 0.57, and 1.48 mg/kg/day for 4 weeks. These effects consisted of decreased numbers of plasma cells in popliteal lymph nodes (at all doses compared to controls), decreased numbers of germinal

centers in splenic white pulp, and atrophy of thymic cortical tissue (only at 0.57 mg/kg/day) (Street and Sharma 1975). Humoral immunity to NIISI typhoid vaccine was inhibited in rats given 1.25 mg/kg/day methyl parathion. This effect was noted when vaccination occurred prior to or during the 35–50-day period of exposure to methyl parathion (Shtenberg and Dzhunusova 1968).

The effects on the immune system may be related to stress (glucocorticoid) rather than a direct effect of methyl parathion, although a stress-related effect is more likely for neurotoxic doses (Kunimatsu et al. 1996).

No significant changes in immune function parameters (IgM-plaque forming cells assay, delayed-type hypersensitivity reaction) were observed in rats administered methyl parathion by gavage at doses of 0.218, 0.436, or 0.872 mg/kg/day for 28 days (Undeger et al. 2000). Routine gross and histopathological examinations revealed no treatment-related effects on the immune system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981).

The reliable LOAEL values for immunological effects in rats for the intermediate-duration category and the highest NOAEL in dogs for the chronic-duration category are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

Neurological effects related to cholinesterase depression occurred in seven children acutely exposed to methyl parathion by inhalation as well as orally and dermally (Dean et al. 1984). See Section 3.2.1.4 for additional details.

Neurologic signs and symptoms developed in 26 humans after intentional lethal intoxication by methyl parathion (Wofatox) via the oral route (Fazekas 1971). A number of the patients studied had considerable reduction (values not specified) in plasma cholinesterase activity. Typical signs and symptoms of intoxication by methyl parathion or other organophosphates are described in Section 3.5. Reductions in erythrocyte or plasma cholinesterase levels did not occur after two male university faculty volunteers ingested 2 mg/day of methyl parathion for 5 days and again 1–8 weeks later ingested 4 mg/day for 5 days (Rodnitzky et al. 1978). Neurobehavioral changes, as measured by a battery of tests, also did not occur. The subjects' predosing test values were the only controls for this study.

Neurologic signs did not occur over a 30-day period in male prisoner volunteers in California who ingested daily doses of methyl parathion ranging from 1.0 to 19 mg. There were no uniform changes in plasma or erythrocyte cholinesterase levels at any of these doses (Rider et al. 1969). By increasing concentrations of methyl parathion administered to the same experimental population and using the same protocol, a dose that inhibited cholinesterase values was established. These additional studies were published nearly 20 years ago in abstract form only; therefore, they are not discussed in this section.

Neurologic signs occurred in animals following oral exposure to methyl parathion at doses that caused reductions in erythrocyte, brain, and/or plasma cholinesterase levels. Male rats receiving 5 mg/kg orally by gavage developed cholinergic signs 7 minutes after dosing, with convulsions beginning within 16 minutes. Plasma cholinesterase was reduced to 43.6% of control levels (Youssef et al. 1987). Rats given methyl parathion by gavage at doses of 4 or 8 mg/kg/day developed cholinergic signs, and all rats died within 4 days. A single oral dose of 13 mg/kg or repeated doses of 1.3 mg/kg/day for 10 days induced significant inhibition of plasma and brain cholinesterase levels, with brain levels being 43% of the control value after the single dose and 56% of the control value after the repeated lower doses (Yamamoto et al. 1982).

When methyl parathion was given orally to rats at doses of 1.5 mg/kg and to guinea pigs at 50 mg/kg, plasma, erythrocyte, and brain cholinesterase activity was maximally inhibited within 30 minutes after administration. In rodents of both species that died after acute intoxication, brain cholinesterase levels decreased to 20% of control values and often to 5–7% (Miyamoto et al. 1963b). The species difference in susceptibility to orally administered methyl parathion is noted in Section 3.2.2.1.

Following acute oral toxicity from dosages ranging from 14 to 80 mg/kg, laboratory rats had earlier recovery of brain acetylcholinesterase levels than did feral cotton rats. Similar results were seen in a comparison of laboratory mice to feral mice (Roberts et al. 1988).

No cholinergic signs were seen in mice administered 6 mg/kg/day for 7–28 days (Crittenden et al. 1998). Brain acetylcholinesterase was significantly decreased at 3 and 6 (but not 1) mg/kg/day, and plasma cholinesterase was significantly decreased at 6 mg/kg/day.

Pregnant rats given methyl parathion orally at 1.5 mg/kg/day from day 6 to day 15 or 19 of gestation had cholinergic effects (Gupta et al. 1984). These effects were not seen at 1 mg/kg/day. Similarly, pregnant rats given methyl parathion orally at 1.5 mg/kg/day from day 6 through day 20 of gestation had

cholinergic signs, but those given 1 mg/kg/day did not (Gupta et al. 1985). At both dose levels, the dams had significant and dose-related depression of brain acetylcholinesterase activity and nondose-related decreases in brain muscarinic receptors. Effects in the fetuses and offspring are discussed in Section 3.2.2.5.

A study of three pesticides, administered separately, reported electrophysiological effects in male rats treated with methyl parathion through gavage administration to their dams during days 5–15 of gestation and days 2–28 of lactation at doses of 0.22, 0.44, or 0.88 mg/kg/day, followed by direct treatment of the male offspring in the same manner for 8 weeks, from weaning through 11–12 weeks of age. Dose-related changes on electrocorticograms of the somatosensory, visual, and auditory centers, on evoked potentials, and on tail nerve conduction velocity and refractory period were observed (Desi et al. 1998). The results were stated to be significantly different from controls at all three dose levels, but results specifically for methyl parathion were shown only for the electrocorticogram of the somatosensory area. No overt signs of toxicity were seen in the offspring. A minimal LOAEL of 0.22 mg/kg/day was identified from these experiments in which the rats were treated starting in the prenatal period and continuing though 12 weeks of age. Based on this value, an intermediate oral MRL of .0007 mg/kg/day was calculated as described in the footnote in Table 3-3.

In the same study (Desi et al. 1998), no significant effects on these end points were seen in male rats exposed to methyl parathion only through the treatment of their dams during gestation or gestation and lactation; these results are presented in Section 3.2.2.6.

Dogs receiving 0.12, 0.5, or 1.2 mg/kg/day methyl parathion in their diet for 12 weeks had reduced erythrocyte cholinesterase levels: 65% of baseline values for the 0.5-mg/kg/day group and 60% of baseline values for the 1.2-mg/kg/day group (Williams et al. 1959). Cholinesterase values in dogs fed 0.12 mg/kg/day in the diet did not differ significantly from controls. Over an 8-week postexposure period, the erythrocyte cholinesterase levels in dogs in the two highest dose groups recovered approximately 1% per day. Study limitations included the use of only two dogs (one of each sex) per dose group, use of dogs from unspecified sources, no discussion of clinical signs (if any), and no correlation of reduced cholinesterase values with general effects on the dogs' health.

A dose-response relationship was noted in dogs exposed to 0.03, 0.3, or 3.0 mg/kg/day methyl parathion in the diet for 13 weeks (Daly 1989). Significant reductions in erythrocyte cholinesterase activity (20–23%) and cholinesterase activity in the pons and cerebellum of the brain (43–54%) occurred in dogs

that were given 3.0 mg/kg/day methyl parathion for 13 weeks. There were no effects on either erythrocyte or brain cholinesterase activities in dogs that were given either 0.03 or 0.3 mg/kg/day methyl parathion. Significant reductions (53–59%) in plasma cholinesterase also occurred in the high-dose females. This latter effect was observed in both low- and high-dose males, but not in males at the mid dose. Thus, the results in the low-dose males do not appear to be treatment related. There were no effects on cholinesterase activity in any of the exposure groups following a 30-day postexposure recovery period.

Routine gross and histopathological examinations revealed no treatment-related effects on the nervous system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981). In addition, there were no treatment-related effects on cholinesterase activity in plasma, red blood cells, or brains in dogs under these exposure conditions. These data are in agreement with the NOAEL established above for dogs exposed to these levels for 13 weeks.

Slight tremor was noted during the first 3 weeks to 4 months of treatment in male and female rats that were exposed to 2.5 mg/kg/day methyl parathion for 2 years; however, this effect subsided as exposure continued (Suba 1984). This effect was not noted in rats exposed to either 0.025 or 0.25 mg/kg/day methyl parathion. Abnormal gait was consistently observed in 2–14 out of 60 of the high-dose female rats from week 19 to termination and in 1 high-dose male, but only at the beginning of the second year of exposure. In addition, one female exposed to 0.25 mg/kg/day exhibited this effect from week 77 until termination. This effect did not occur in the controls or the low-dose exposure group. The data are limited for each of these effects because statistical significance was not determined. Peripheral neuropathy of the proximal and distal sciatic nerve in male and female rats was found to be related to chronic exposure to 2.5 mg/kg/day methyl parathion but not to 0.025 or 0.25 mg/kg/day methyl parathion (Suba 1984). Methyl parathion did not induce histopathological effects in the brain or spinal cord of treated animals. The pathology data are limited because statistical significance was not determined.

Mean plasma, erythrocyte, and brain cholinesterase activities were significantly reduced by 67–88%, 9–20%, and 76–79%, respectively, in rats of both sexes following 2-year exposures to 2.5 mg/kg/day methyl parathion (Suba 1984). This effect did not occur in rats exposed to either 0.025 or 0.25 mg/kg/day methyl parathion.

All reliable LOAEL values for neurological effects in rats for the acute-duration category, the highest NOAEL and all reliable LOAEL values in dogs for the intermediate-duration category, and the highest

NOAEL and all reliable LOAEL values in dogs and rats for the chronic-duration category are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to methyl parathion.

Methyl parathion has not been shown to be toxic to male germ cells in mice exposed to the chemical in the diet or drinking water in three studies discussed in Section 3.2.2.7. An additional study, also discussed in Section 3.2.2.7, reported significantly increased numbers of abnormal sperm in male mice administered methyl parathion by gavage at relatively high doses. Routine gross and histopathological examinations revealed no treatment-related effects on the reproductive system of dogs exposed to 0.03, 0.1, or 0.3 mg/kg/day methyl parathion in the diet for 1 year (Suba 1981).

The highest NOAEL value in dogs for reproductive effects for the chronic-duration category is recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental toxicity in humans after oral exposure to methyl parathion.

Placental transfer of methyl parathion was demonstrated following oral administration to pregnant rats 1–3 days before parturition (Ackermann and Engst 1970).

In a study of the effects of methyl parathion on protein synthesis, rats were given 1 mg/kg/day of methyl parathion in a small amount of peanut butter (eaten within 2 minutes) or 1.5 mg/kg methyl parathion by gavage in peanut oil starting on day 6 of gestation and continuing through day 15 or 19. These exposures inhibited incorporation of ^{14}C valine into protein in maternal, placental, and fetal tissues (Gupta et al. 1984). A dose-related inhibition was observed in maternal brain, viscera, placenta, and whole embryos in rats on day 15 and in fetal brain and viscera on day 19. The inhibitory effect of methyl parathion on protein synthesis was greater on day 19 than on day 15 of gestation and was more pronounced in fetal than in maternal tissues. No signs of maternal toxicity were seen at 1 mg/kg/day. Signs of cholinergic stimulation, including muscle fasciculation, tremors, and mild clonic convulsions, were seen in some of

the dams at 1.5 mg/kg/day, maternal body weight gains were slightly but significantly depressed, and resorptions were increased. No gross structural abnormalities were found in the fetuses. This study is limited in that it did not adequately examine whether reduction in protein synthesis during the prenatal period would cause adverse effects in the offspring. The purity of the compound was also not reported.

In a follow-up study, pregnant rats were given 1 or 1.5 mg/kg/day of methyl parathion on days 6–20 of gestation (Gupta et al. 1985) in the same manner as in the previous study. Exposure to 1 mg/kg/day caused significant but small and transient reductions in maternal and fetal brain acetylcholinesterase activity, an increase in maternal but not fetal brain choline acetyltransferase activity, and a decease in maternal but not fetal muscarinic receptors. No visible signs of maternal or fetal toxicity were observed. Exposure to 1.5 mg/kg/day, on the other hand, significantly reduced acetylcholinesterase activity and increased choline acetyltransferase activity in the maternal brain and in all fetal brain regions at various stages during development. Muscarinic receptors were decreased in maternal but not fetal brains. Signs of cholinergic stimulation were seen in some of the dams. A slight but significant reduction in maternal weight gain and an increased incidence of fetal resorptions were also observed at 1.5 mg/kg/day. No gross structural abnormalities or changes in brain morphology were found in the fetuses. Impairment of behavior (decreased latency for cage emergence, reduction in accommodated locomotor activity, impairment of operant behavior) was found in 2–6-month-old offspring of rat dams fed methyl parathion at 1 mg/kg/day in peanut butter, but not in offspring of those administered 1.5 mg/kg/day in oil by gavage. The observed differences may have been caused by the differences in method and vehicle of administration, or potential nonlinearity in the dose-response for behavioral effects. Several other behavioral end points, measured in the offspring at various times from 1 day to 6 months of age, were not affected at either dose level.

Similar results for rats were reported by Crowder et al. (1980). Oral administration of 1 mg/kg/day of methyl parathion (99.9% purity) in corn oil on days 7–15 of gestation resulted in increased mortality in pups, relative to controls. Significant difference from controls in a maze transfer test was observed in pups from the treated group. However, use of a single-dose level precluded the assessment of dose-response, and several other behavioral end points were not affected. Furthermore, no information was presented regarding body weights or signs of toxicity in the treated dams.

Gavage administration of 1.5 mg/kg/day of methyl parathion to rats on days 6–15 of gestation resulted in increased resorptions, decreased fetal body weight, and hemorrhagic spots in the brain ventricles and skin

of the upper body of some of the fetuses (Kumar and Devi 1996). The data for hemorrhagic spots in the brain and skin were presented and analyzed for statistical significance as percent affected fetuses/total fetuses in dose group rather than percent per litter. Maternal toxicity (cholinergic signs and slight but significant depression of body weight gain) and significantly decreased placental weight and amniotic fluid weight were seen at 1.5 mg/kg/day.

In a study of three pesticides, the 11–12-week-old male offspring of rat dams administered methyl parathion at 0.22, 0.44, or 0.88 mg/kg/day on days 5–15 of gestation by gavage in an aqueous vehicle had no statistically significant changes in electrocorticograms, evoked potentials, or tail nerve conduction velocity or refractory period (Desi et al. 1998). A similar lack of significant effect was seen in male offspring of dams treated in the same manner during gestation and from the second day after delivery until weaning of the offspring at 4 weeks of age. There were slight trends in these indices, consistent in direction with the results obtained when treatment of the offspring was continued after weaning (see next paragraph). The electrocorticograms and evoked potentials studied by Desi et al. (1998) are more sensitive than the behavioral end points studied by Gupta et al. (1984, 1985) and Crowder et al. (1980), the doses were similar (0.88 mg/kg/day versus 1 mg/kg/day), and the period between dosing and testing was similar. The above findings by Desi et al. (1998), therefore, do not corroborate the findings in the other two studies. Whether the exposure vehicle contributed to the different outcomes is uncertain.

In the male offspring whose treatment was continued through 11–12 weeks of age, however, dose-related effects were seen on all the above end points, and these effects were significantly different from controls at all three dose levels (Desi et al. 1998) (see also Section 3.2.2.4). The study did not determine the critical period (if any) and duration of exposure for these neurological effects. A limitation of this study is that results specifically for methyl parathion were shown only for the somatosensory electrocorticogram; the other results for this chemical were stated in the text, but not shown.

No dose-response relationship can be established for the developmental toxicity of methyl parathion from the available database. All reliable LOAEL values in rats for developmental effects for the acute- and intermediate-duration categories are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located regarding carcinogenic effects in humans after oral exposure to methyl parathion.

There are two studies that describe negative carcinogenesis of methyl parathion administered orally to rodents. Methyl parathion was given in the diet to F344 rats and B6C3F_1 mice for 105 weeks (NCI 1979). Methyl parathion dosages were as follows: 0, 1, and 2 mg/kg/day for rats; 0, 8, and 16.2 mg/kg/day for female mice; and time-weighted average of 4.5 and 9.7 mg/kg/day for male mice. Time-weighted averages were used for male mice because methyl parathion dosages had to be adjusted downward after week 37 due to decreased mean body weight gain. A comprehensive set of tissues was examined by microscopy and gross necropsy. Study limitations included matched control groups for both species that were smaller (n=20) than methyl parathion dosage groups (n=50), dose adjustments during the study, and a significant increase in mortality in high-dose female rats (only 46% survived to study termination compared to 82% survival of low-dose females and 95% survival of control females). There were no lesions associated with the increased mortality. Under conditions of the bioassay, methyl parathion was not carcinogenic in rats or mice of either sex. Also, there were no noncancer systemic effects associated with methyl parathion exposure in rats or mice. In the second study, no treatment-related benign or malignant neoplasms were observed in rats following 2-year exposures to either 0.025, 0.25, or 2.5 mg/kg/day methyl parathion in the diet (Suba 1984).

3.2.3 Dermal Exposure

3.2.3.1 Death

Death in humans related to a combination of inhalation and dermal exposure was discussed in Sections 3.2.1.1 and 3.2.2.1.

LD_{50} values for the dermal route of exposure to methyl parathion have been established in acute studies for rats: 67 mg/kg for males and females (Gaines 1960), 110 mg/kg for males, and 120 mg/kg for females (EPA 1978e). The LD_{50} in male mice exposed by dermal application of methyl parathion to their hind feet (rather than shaved backs) was 1,200 mg/kg (Skinner and Kilgore 1982a). The mice were muzzled to prevent oral exposure from grooming.

The reliable LD_{50} values for rats and mice for the acute-duration category are recorded in Table 3-4.

Table 3-4. Levels of Significant Exposure to Methyl Parathion - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
				Less serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE							
Death							
Rat	once				67	(LD_{50})	Gaines 1960
Mouse	once				1200 M	(LD_{50})	Skinner and Kilgore 1982a
Systemic							
Rat	once	Cardio			67	(bradycardia; arrhythmia myocardial ischemia; complex heart block)	Galal et al. 1975

Cardio = cardiovascular; LD_{50} = Lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; mg/kg/day = milligram per kilogram per day; NOAEL = no-observable-adverse-effect level

3.2.3.2 Systemic Effects

No studies were located in humans or animals regarding respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects after dermal exposure to methyl parathion.

Cardiovascular Effects. No studies were located in humans regarding cardiovascular effects after dermal exposure to methyl parathion. Rats exposed dermally to the LD_{50} of 67 mg of methyl parathion/kg or to a one-half-LD_{50} dose developed abnormalities in their heart rate and electrocardiograms (Galal et al. 1975). Bradycardia occurred by 1 hour after dosing with a severe effect at 2 hours after dosing (91% reduction in rate in the LD_{50} group and 70% reduction in rate in the one-half-LD_{50} group). Arrhythmia and electrocardiographic abnormalities were pronounced in rats receiving the dermal LD_{50} dose of methyl parathion.

Dermal Effects. Based on a skin patch test, allergic (contact) dermatitis to methyl parathion occurred in a farmer (Lisi et al. 1987).

No studies were located regarding dermal effects in animals after dermal exposure to methyl parathion.

3.2.3.3 Immunological and Lymphoreticular Effects

A single case report of skin allergy to methyl parathion has been reported in humans (Lisi et al. 1987). Also see Section 3.2.3.2.

No studies were located regarding immunological effects in animals after dermal exposure to methyl parathion.

3.2.3.4 Neurological Effects

Mental disturbances, manifested as psychiatric sequelae, have been reported after exposure to organophosphates, including methyl parathion. Neuropsychiatric symptoms occurred in two aerial applicators, one of whom used methyl parathion as well as other insecticides, including chlorinated insecticides. One of these pilots had high levels of exposure to methyl parathion, toxaphene, and Dipterex® with saturation of his clothing when the tank of his aircraft accidentally overflowed (Dille and Smith 1964). Several

months after the accident, the subject complained of dizziness, anxiety, emotional lability, frequent and severe disagreements with family and associates, and inability to perform familiar tasks.

Erythrocyte cholinesterase levels were monitored in two men exposed dermally to methyl parathion after entering a cotton field that had been sprayed with this pesticide (Nemec et al. 1968). The field was entered on two separate occasions: twice within 2 hours after an ultra-low-volume spraying and a third time within 24 hours after spraying. Dermal methyl parathion residues 2 hours after spraying were 2–10 mg on the arms; dermal residues 24 hours after spraying were 0.16–0.35 mg on the arms. The exposed individuals did not have signs of cholinergic toxicity, but erythrocyte cholinesterase levels after the third exposure were 60–65% of preexposure levels.

Mice that were exposed dermally to residues of methyl parathion in emulsifiable concentrate on foliage, and were muzzled to prevent oral intake, developed inhibition of plasma cholinesterase and erythrocyte cholinesterase after two 10-hour exposures (Skinner and Kilgore 1982b). For the organophosphate pesticides tested in this study, cholinergic signs generally were seen in mice with cholinesterase inhibition >50%; results for this end point were not broken down by pesticide.

In male mice in the dermal LD_{50} study described under lethality, the ED_{50} values (doses at which adverse effects were observed in 50% of the treated animals) for plasma and red blood cell (RBC) cholinesterase inhibition in survivors were 950 and 550 mg/kg, respectively, compared to a dermal LD_{50} of 1,200 mg/kg (Skinner and Kilgore 1982a). The hind feet of the mice were exposed to the pesticide, and the mice were muzzled to prevent oral exposure from grooming. Because these ED_{50} values were obtained in surviving mice in a 24-hour LD_{50} study, they were based on a resistant population, and are not considered suitable for inclusion in the LSE tables and figures.

3.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans and animals after dermal exposure to methyl parathion.

3.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans and animals after dermal exposure to methyl parathion.

3.2.3.7 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to methyl parathion.

3.2.4 Other Routes of Exposure

Ocular effects consisting of electroretinographic changes occurred in mice exposed by the intraperitoneal route to an LD_{50} dose or a dose equal to half of an LD_{50} dose of methyl parathion (Carricaburu et al. 1980). These changes were a direct effect of methyl parathion on repolarization of retinal photo-receptors. Rats, injected intraperitoneally with methyl parathion, developed cholinergic signs at dosage levels as low as 1.0 mg/kg/day for 7 days (Hasan and Khan 1985; Khan and Hasan 1988). Exposed rats had alterations in brain structural components with an increase in brain lipid, phospholipid, and cholesterol content in various portions of the brain (Hasan and Khan 1985) and depletion of gangliosides and glycogen (Khan and Hasan 1988). Lipid peroxidation was increased in the cerebrum but inhibited in the hindbrain (Hasan and Khan 1985). These changes in brain structural components suggest another type of toxic change induced by methyl parathion in the nervous system that could also be responsible for some of the acute and chronic neurologic effects seen in humans. Whether such effects could occur in humans exposed to low levels of methyl parathion that did not produce overt toxicity is unknown. Assays for estrogenic activity of intraperitoneally injected methyl parathion in hemi-ovariectomized rats indicated some interference with compensatory ovarian hypertrophy, but a lack of typical estrogenic activity (Asmathbanu and Kaliwal 1997; Dhondup and Kaliwal 1997). Fetotoxicity and offspring with altered brain enzymes and impaired behavior have been reported in rats after oral or parenteral maternal administration of methyl parathion at doses that inhibited acetylcholinesterase activity and, in some studies, produced cholinergic signs in the dams (Crowder et al. 1980; Fish 1966; Gupta et al. 1985; Tanimura et al. 1967). Pregnant female mice exposed to 60 mg/kg methyl parathion by the intraperitoneal route had significantly increased incidences of fetuses with cleft palate and dose-related increases in fetal deaths, compared to control litters (Tanimura et al. 1967). Significant increases in abnormal sperm morphology were seen in mice following intraperitoneal injection of methyl parathion at a dose level of 6 mg/kg (Pagulayan et al. 1994).

3.3 GENOTOXICITY

In a case-control study of pesticide factory workers in Brazil exposed to methyl parathion and formulating solvents, the incidence of chromosomal aberrations in lymphocytes was investigated (De Cassia Stocco et al. 1982). Though dichlorodiphenyltrichloroethane (DDT) was coformulated with methyl parathion, blood DDT levels in the methyl parathion-examined workers and "nonexposed" workers were not significantly different. These workers were presumably exposed to methyl parathion via both inhalation and dermal routes; however, a dose level was not reported. The exposed workers showed blood cholinesterase depressions between 50 and 75%. However, the baseline blood cholinesterase levels in nonexposed workers were not reported. No increases in the percentage of lymphocytes with chromosome breaks were found in 15 of these workers who were exposed to methyl parathion from 1 week to up to 7 years as compared with controls. The controls consisted of 13 men who had not been occupationally exposed to any chemical and were of comparable age and socioeconomic level. This study is limited because of concomitant exposure to formulating solvents, the recent history of exposure for the workers was not reported, the selection of the control group was not described adequately, and the sample size was limited.

Chromosome aberrations were detected in lymphocytes of individuals acutely intoxicated by methyl parathion by the inhalation route (Van Bao et al. 1974). Blood samples were taken 3–6 days after exposure and again at 30 and 380 days. A temporary but significant ($p<0.05$) increase was noted in the frequency of stable chromosomal aberrations in the exposed individuals. The study limitations include small sample size, absence of a control group, lack of quantification of exposure levels, and a possible concomitant exposure to other substances via the dermal route.

No studies were located regarding genotoxic effects in animals after inhalation exposure to methyl parathion.

The lymphocytes from 31 patients exposed to various organophosphate pesticides were examined for chromosomal aberrations (Van Bao et al. 1974). Five of the patients were exposed to methyl parathion only. Blood samples were taken 3–6 days after exposure and again at 30 and 180 days. A significant ($p<0.05$) increase was noted in the frequency of stable chromosomal aberrations in acutely intoxicated persons (although such cells are eventually lost from the cell population). Two of the methyl parathion-exposed persons had taken large doses orally in suicide attempts. The study limitations include small sample size, absence of a control group, lack of quantification of exposure levels, and possible

concomitant exposure to other substances via the dermal route. Although the study did not quantify the exposure levels, the results suggest that methyl parathion can exert direct genotoxic effects on chromosomes.

In a similar study, the lymphocytes from five patients who ingested methyl parathion (Wofatox) in suicide attempts were examined for aneuploidy, chromatid aberrations, and chromosome aberrations (Czeizel 1994). No significant differences from the 15 control patients were seen in these end points. The controls were patients who had undergone appendicitis or hernia surgery, and were matched for sex, age, and socioeconomic status with a larger set of 31 pesticide poisoning cases, of which the methyl parathion cases were a subset. Limitations of this study include the small number of methyl parathion cases, and the use of appendicitis and other surgery patients as controls.

Methyl parathion administered to male mice in the diet or drinking water did not increase the incidence of resorption of fetuses in mated dams (Degraeve et al. 1985; Waters et al. 1982). In mice, dietary exposure to the maximum tolerated dose, and one-half and one-quarter of the maximum tolerated doses failed to produce preimplantation embryo loss from the resultant matings with untreated females (Waters et al. 1982). However, no specific details regarding the actual doses administered were provided by the authors. The findings of these two studies were also supported by the absence of a dominant-lethal effect in mice receiving 0.026 mg/kg/day of methyl parathion in drinking water for 7 weeks (Degraeve et al. 1984a). This result suggests that methyl parathion is not toxic to male mouse germ cells. However, relatively high levels of methyl parathion can result in changes in sperm morphology. Male mice, orally exposed (gavage) to doses in the range of 9.375–75 mg/kg, exhibited dose-related significantly increased percentages of abnormal sperm at all doses (Mathew et al. 1992). Significant increases in abnormal sperm morphology were also seen in mice following intraperitoneal injection of 6 mg /kg, but not 1.3 mg/kg (Pagulayan et al. 1994). Of two studies in *Drosophila melanogaster*, one (Tripathy et al. 1987) showed mutagenic effects in somatic and germ cell lines and induction of sex-linked recessive lethals, whereas the other one (Waters et al. 1982) provided negative results.

Methyl parathion has been tested in numerous genotoxicity assays using prokaryotic and eukaryotic systems with both positive and negative results. Results of these studies are summarized in Tables 3-5 and 3-6.

When methyl parathion was tested in *Salmonella typhimurium*, contradictory results were reported with or without using metabolic activation (Rashid and Mumma 1984; Shigaeva and Savitskaya 1981; Waters

Table 3-5. Genotoxicity of Methyl Parathion *In Vivo*

Species (test system)	End point	Results	Reference
Eukaryotic organisms:			
Drosophila melanogaster/males	Recessive lethal	–	Waters et al. 1982
D. melanogaster/dietary exposure	Recessive lethal somatic mutation	+	Tripathy et al. 1987
Mammalian cells:			
Rat bone marrow/intraperitoneal injection	Induction of micronuclei	+	Grover and Malhi 1985
Mouse/oral exposure; diet or drinking water	Dominant lethal	–	Degraeve et al. 1985; Waters et al. 1982
Mouse/oral exposure; drinking water	Chromosomal aberrations	–	Degraeve et al. 1985
Mouse/intraperitoneal administration	Chromosomal aberrations	–	Huang 1973
Mouse/oral exposure; gavage	Sperm shape abnormalities	+	Mathew et al. 1992
Human lymphocytes/dermal and inhalation exposure	Chromosomal aberrations	–	De Cassia Stocco et al. 1982
Human lymphocytes/oral exposure	Chromosomal aberrations	+	Van Bao et al. 1974
Human lymphocytes/oral exposure	Chromosomal aberrations	–	Czeizel 1994

– = negative result; + = positive result; (+) = weakly positive result

Table 3-6. Genotoxicity of Methyl Parathion *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Bacteria:				
Salmonella typhimurium/plate incorporation	Reverse mutation	–	–	Waters et al. 1982
		+	–	Rashid and Mumma 1984
		No data	+	Shigaeva and Savitskaya 1981
Escherichia coli/WP2;plate incorporation	Reverse mutation	–	–	Dean 1972; Waters et al. 1982
E. coli/K-12 COIE/plasmid DNA	DNA damage	No data	+	Griffin and Hill 1978
E. coli/plate incorporation	5-Methyltryptophan resistance	No data	+	Mohn 1973
Eukaryotic organisms:				
Yeast:				
Saccharomyces cerevisiae (D7)/plate incorporation	Reverse mutation	–	–	Waters et al. 1982
S. cerevisiae (D3)/plate incorporation	Mitotic recombination	No data	+	Waters et al. 1982
S. cerevisiae (D7)/spot test	Gene conversion	–	–	Waters et al. 1982
S. typhimurium	DNA damage	No data	+	Rashid and Mumma 1984
Mammalian cells:				
Chinese hamster ovary	Sister chromatid exchange	+	–	Waters et al. 1982
Chinese hamster V79	Sister chromatid exchange	No data	+	Chen et al. 1981
Human lymphoid cells/LAZ-007	Sister chromatid exchange	No data	+	Sobti et al. 1982
Human lymphocytes	Sister chromatid exchange	No data	+	Chen et al. 1981; Gomez-Arroyo et al. 1987
Burkitt lymphoma/835M	Sister chromatid exchange	No data	+	Chen et al. 1981
Human lymphocytes	Chromosomal aberrations	No data	+	Kumar et al. 1993

Table 3-6. Genotoxicity of Methyl Parathion *In Vitro (continued)*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Human hematopoietic cells/RPMI 1788, 7191; B411-4	Chromosomal damage	No data	–	Degraeve et al. 1985; Huang 1973
Human lung fibroblasts	Unscheduled DNA synthesis	–	–	Waters et al. 1982

– = negative result; + = positive result; DNA = deoxyribonucleic acid

et al. 1982). However, it tested negative in *Saccharomyces cerevisiae* strain D7 for both reverse mutation and gene conversion (Waters et al. 1982) and in *Escherichia coli* WP 2 for reverse mutation (Dean 1972). Methyl parathion treatment resulted in a negative response for reverse mutation (Waters et al. 1982) but a positive response for 5-methyl tryptophan resistance assay (Mohn 1973) in *E. coli*. Positive results were also reported for mitotic recombination in *S. cerevisiae* D3 (Waters et al. 1982) and for deoxyribonucleic acid (DNA) damage in *S. typhimurium* (Rashid and Mumma 1984) and *E. coli* (Griffin and Hill 1978). Methyl parathion gave a negative response for unscheduled DNA synthesis in cultured human lung fibroblasts (Waters et al. 1982).

Results of methyl parathion assays involving effects on chromosomes have also been contradictory. For sister chromatid exchange, Waters et al. (1982) reported a positive response in Chinese hamster ovary cells only in the presence of metabolic activation system, while methyl parathion tested positive without a metabolic activation system in Chinese hamster V79 cells (Chen et al. 1981), cultured normal human lymphoid cells (Chen et al. 1981; Gomez-Arroyo et al. 1987; Sobti et al. 1982), and Burkitt's lymphoma cells (Chen et al. 1981). Chen et al. (1981) found a significant dose-related increase in sister chromatid exchange in both hamster and human cultured cells, but dose-related cell cycle delays were less pronounced in human cell lines than in V79 cells. Negative results were obtained for chromosomal aberrations in human lymphocytes without a metabolic activation system (Kumar et al. 1993).

Induction of micronuclei has been reported in bone marrow cells of rats injected intraperitoneally with methyl parathion (Grover and Malhi 1985). Although negative results were obtained for chromosomal aberrations in mouse cells and human hematopoietic cells (Degraeve et al. 1984a; Huang 1973), contradictory results were reported in human lymphocytes following exposure of humans to methyl parathion (Czeizel 1994; De Cassia Stocco et al. 1982; Van Bao et al. 1974). Exposure to other compounds complicates interpretation. In the dominant lethal assay, no increase in the incidence of pre- or postimplantation fetal lethality was found in the litters of male mice following oral exposure (Degraeve et al. 1985; Jorgensen et al. 1976; Waters et al. 1982), but an assay for sperm shape abnormalities yielded positive results at relative high oral doses (Mathew et al. 1992). Thus, the available evidence is inconclusive, and no determination regarding the potential genotoxic risks of methyl parathion exposure for humans can be made.

3.4 TOXICOKINETICS

Methyl parathion can be readily absorbed by humans following inhalation, oral, or dermal exposure, although quantitative data are lacking. Studies in animals indicate that oral absorption following single doses can amount to 80% of the administered dose within a few days of dosing. A single dermal study in rats also suggested almost complete absorption of an applied dose within a 96-hour period. No data are available regarding pulmonary absorption of methyl parathion in animals. Methyl parathion was found to be widely distributed in organs and tissues of rats following dermal exposure, but first-pass metabolism greatly limits its distribution following oral absorption. Methyl parathion has been detected in human breast milk and studies in animals have shown that it can cross the placenta and be transferred to the fetus. Methyl parathion is rapidly and extensively metabolized, mainly in the liver, to polar substances that are quickly excreted in the urine. Oxidative desulfuration by microsomal oxidases transforms methyl parathion into the neurotoxic, active metabolite, methyl paraoxon; the specific isozyme involved in this reaction has not been identified. Other reactions including oxidation, hydrolysis, dearylation, and dealkylation detoxify methyl parathion. A major detoxification pathway is enzymatic hydrolysis of methyl paraoxon to dimethyl phosphate and 4-nitrophenol. These metabolites are eliminated primarily in the urine in humans, rats, and mice.

3.4.1 Absorption

Often, absorption occurs by multiple routes in humans. Dean et al. (1984) reported deaths and toxic effects as well as lowered blood cholinesterase levels and excretion of urinary 4-nitrophenol in several children who were exposed by inhalation, oral, and possibly dermal routes after the spraying of methyl parathion in a house. In the same incident (Dean et al. 1984), absorption was indicated in adults who also excreted 4-nitrophenol in the urine, though at lower levels than some of the children, and in the absence of other evidence of methyl parathion exposure. In this study, the potential for age-related differences in absorption rates could not be assessed because exposure levels were not known and the children may have been more highly exposed than the adults. Health effects from multiple routes are discussed in detail in Section 3.2.

3.4.1.1 Inhalation Exposure

No studies were located regarding absorption in humans and animals after inhalation exposure to methyl parathion. However, it can be concluded that pulmonary absorption occurred in humans as evidenced by

toxic systemic effects found in humans dying after acute inhalation exposure to methyl parathion (Fazekas 1971).

3.4.1.2 Oral Exposure

Absorption following acute oral exposure is indicated in a study in which four volunteers received methyl parathion once a day with food for 5 consecutive days (Morgan et al. 1977). Urine was collected for 24 hours after each dose and for 2 days after the last dosing day. The average 24-hour excretions of the metabolites 4-nitrophenol and dimethyl phosphate following each dose accounted for 27 and 12% of the ingested dose, respectively. The highest rate of excretion for 4-nitrophenol occurred during the first 4 hours after dosing, and for dimethyl phosphate, occurred during in the interval from 4 to 8 hours after dosing. These results indicate rapid absorption.

Rapid and efficient absorption in animals follows oral administration of methyl parathion (Braeckman et al. 1983; Hollingworth et al. 1967). Oral absorption was 77 and 79% in two dogs receiving 3 mg/kg of ^{35}S-labeled methyl parathion by gavage (Braeckman et al. 1983). This conclusion was based on a comparison of the 6-day urinary excretion of radioactivity after gavage administration versus intravenous injection. In mice, 80% of the radioactivity from a gavage dose of 3 mg/kg of ^{32}P-labelled methyl parathion was recovered as radiolabeled metabolites in the urine, and up to 10% was recovered in the feces at 72 hours (Hollingworth et al. 1967). Estimates of fecal excretion were considered unreliable. Therefore, based on 80% recovery in the urine, it can be concluded that at least 80% of the dose was absorbed following oral administration of methyl parathion. Approximately 75% of the urinary excretion occurred within the first 12 hours. Furthermore, decreased cholinesterase activity (Ceron et al. 1995; Miyamoto et al. 1963b) and detection of methyl parathion urinary metabolites (Chang et al. 1997; Youssef et al. 1987) after oral doses of methyl parathion provide indirect evidence of absorption in animals.

The data presented above suggest that methyl parathion would be absorbed by humans following ingestion of food and drinking water contaminated with methyl parathion. However, no data are available on the rate and extent of absorption in humans.

3.4.1.3 Dermal Exposure

Epidemiological studies indicate that absorption of methyl parathion occurs in humans following acute dermal exposure (Nemec et al. 1968; Ware et al. 1973, 1974, 1975). On two separate occasions, two entomologists were in a field for 5 minutes, 2 hours after it was sprayed with methyl parathion; 2–10 mg methyl parathion was measured on the skin of both arms (Nemec et al. 1968). A third exposure occurred 24 hours after spraying the field; levels of methyl parathion on the skin of the arms ranged from 0.163 to 0.351 mg methyl parathion. Blood cholinesterase levels after the three exposures were 60% of pre-exposure levels in these subjects, which suggests that absorption had occurred (Nemec et al. 1968). Two volunteers entered treated cotton fields for 30-minute periods at 0, 12, 24, 48, and 72 hours postexposure (Ware et al. 1973). Twenty-four hours after exposure, 0.027 and 0.032 mg/L methyl parathion were detected in the serum. The skin was considered to be the major route of exposure in this study (Ware et al. 1973). In five subjects, the amount of methyl parathion on the hands averaged 1.7 mg following 5 hours of exposure in fields that had been sprayed with methyl parathion 12 hours earlier (Ware et al. 1975). The amount of methyl parathion averaged 2.2 mg on the arms, 0.4 mg on the torso, 0.03 mg on the legs, 10.6 mg on the shirts, and 40.0 mg on the pants. The serum contained 70–227 ppb of methyl parathion 3–7 hours after the 5-hour exposure compared with 0–4 ppb at 24 hours. Serum levels were highest immediately after exposure (0.156 mg/L); after 48 hours, cumulative levels of urinary 4-nitrophenol varied between 1.1–23 mg.

Although the extent of absorption was not measured, the above evidence suggests that absorption in humans occurs rapidly following dermal exposure to commercial pesticide formulations of methyl parathion.

In a study of pregnant rats exposed to 10 mg/kg of radiolabeled methyl parathion (in acetone) that was applied to the back of the neck (unoccluded), approximately half of the dose was absorbed within 1 hour postapplication, and 95% was absorbed within 96 hours. Skin disappearance rate constants of 0.35 $hour^{-1}$ and 0.03 $hour^{-1}$ were estimated, and corresponded to half-lives of 2 and 22 hours, respectively (Abu-Quare et al. 2000). Although animals were housed individually, the possibility of some degree of oral absorption could not be discounted. Additional evidence of dermal absorption comes from the finding of inhibition of plasma cholinesterase activity in mice following dermal exposure to methyl parathion (Skinner and Kilgore 1982b).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals after inhalation exposure to methyl parathion. Although cases of inhalation exposure have been reported, there were no data that provided detailed information on the distribution of methyl parathion residues in various tissues.

3.4.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to methyl parathion.

Following a single gavage administration of 20 mg/kg methyl parathion, the highest serum concentration reported in dogs ranged from 0.13 to 0.96 µg/mL 3–9 hours postexposure (Braeckman et al. 1983). The low systemic availability of methyl parathion following oral gavage in dogs was suggested to be the result of hepatic first-pass metabolism (Braeckman et al. 1983).

Placental transfer of methyl parathion was demonstrated following oral administration to pregnant rats 1–3 days before parturition (Ackermann and Engst 1970). Thirty minutes after administration, methyl parathion was found in fetal brain, liver, and muscle, and in the placenta and maternal liver, suggesting its rapid distribution. The fetal liver concentration of methyl parathion was nearly 2-fold that of the maternal liver and approximately half of the concentration found in the placenta. Small amounts of methyl paraoxon, the oxidative metabolite of methyl parathion, were found in fetal brain, liver, and muscle, but could not be detected in maternal liver or placental tissue. Although the source of exposure was not determined, methyl parathion was detected in breast milk of 8/90 women tested in 5 of 10 regions of central Asia (Lederman 1996). Methyl parathion was not detected in the breast milk of mothers tested in the other 5 regions (Lederman 1996) or in breast milk of 11 Italians tested for the presence of a number of pesticides, including methyl parathion (Roggi et al. 1991). A study of a mixture of pesticides (methyl parathion, lindane, and permethrin) in rats reported that methyl parathion was present in higher concentrations in the dams' milk and in the pups' blood than in the dams' blood following oral exposure of the dams on lactation days 1–14 (Golubchikov 1991; Goncharuk et al. 1990). Confidence in these findings is low because descriptions of the methods and results were cursory.

The available data are insufficient to determine the pattern or extent of distribution in human tissues after oral exposure to this compound.

3.4.2.3 Dermal Exposure

There is limited information available regarding the distribution of methyl parathion after dermal exposure in humans. Two subjects, dermally exposed to methyl parathion, had 2.74 and 1.23 mg on their hands. Twenty-four hours after exposure, the serum levels were 0.027 and 0.032 mg/L, respectively (Ware et al. 1973). Twelve hours after cotton fields were sprayed, five men entered the treated fields for 5 hours. An average of 1.7 mg methyl parathion was detected on their hands. Serum concentrations averaged 0.156 mg/L in these subjects after 3 hours of exposure. Levels decreased to 0.1 and 0.002 mg/L at 2 and 24 hours postexposure, respectively (Ware et al. 1975). Although 0.5 mg methyl parathion was detected on the hands of four subjects, none was found in the serum (Ware et al. 1974). No information on the tissue distribution of methyl parathion in humans was found.

Following single dermal applications of 10 mg/kg of radiolabeled methyl parathion to pregnant rats, methyl parathion was found to be widely distributed to all major tissues and organs. Concentrations were highest in plasma and kidney, maximum levels measured 2 hours postapplication. Peak levels in liver, brain, fetus, and placenta, were measured 2 to 10 hours later, at which times the highest concentration of methyl parathion was in the fetus (Abu-Quare et al. 2000).

3.4.2.4 Other Routes of Exposure

Distribution of methyl parathion was rapid when it was administered intravenously to rats (3 and 15 mg/kg) and guinea pigs (20 and 40 mg/kg) (Miyamoto 1964). Levels were highest in the brain, liver, lungs, kidneys, and heart of these animals at 2.5 minutes postexposure (Miyamoto 1964). The levels of a metabolite, methyl paraoxon, were highest in the lungs and liver of guinea pigs, and in the liver of rats. However, it should be noted that the protein-bound oxygen analog was not measured in the study. Serum methyl parathion levels were highest in dogs immediately following intravenous exposure (Braeckman et al. 1980). The serum concentrations declined rapidly, followed by a slower clearance, beginning at 5 hours postexposure, for doses of 3, 10, or 30 mg/kg methyl parathion. Intraperitoneal injection of methyl parathion in pregnant rats has resulted in fetal toxicity, expressed in reduced fetal brain cholinesterase levels; this is another indication that methyl parathion and/or its toxic metabolite can cross the placental barrier (Fish 1966).

The protein binding of methyl parathion *in vitro* was 93% in dog serum and 94% in human serum (Braeckman et al. 1983). The protein binding of methyl parathion in a solution of human albumin that approximated the concentration of albumin in human serum also was 94%, suggesting that albumin is the main binding protein for methyl parathion in serum. Albumin probably acts as a transport protein, because although the degree of protein binding in serum is high, a high volume of distribution has been determined for methyl parathion in the dog (Braeckman et al. 1980, 1983).

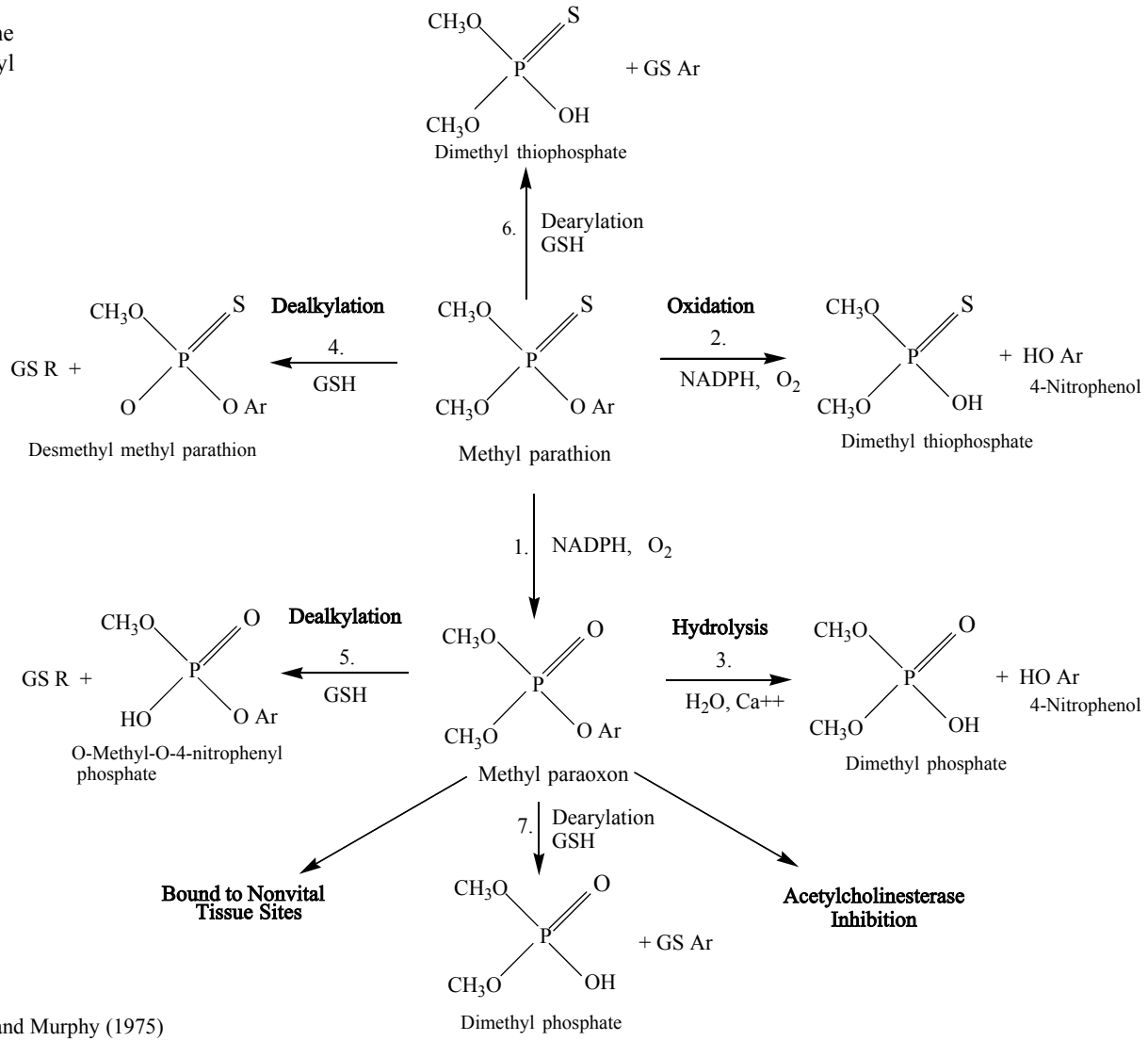
3.4.3 Metabolism

Methyl parathion is a phosphorothioate, which refers to the organophosphate compounds that contain the P=S substructure (Nakatsugawa et al. 1968). The metabolism of methyl parathion has been well studied *in vitro* using rat, mouse, rabbit, guinea pig, and human liver homogenates (Benke and Murphy 1975; Hollingworth et al. 1973; Nakatsugawa et al. 1968; Neal and DuBois 1965) and *in situ* using intact rat livers (Zhang and Sultatos 1991). Metabolism has also been studied *in vivo* using pregnant rats exposed by dermal application of radiolabeled methyl parathion (Abu-Qare et al. 2000). No metabolism studies were conducted by the inhalation route. The low systemic availability of methyl parathion after oral administration in dogs, and the high hepatic extraction ratios after intravenous administration, suggest first-pass metabolism by the liver (Braeckman et al. 1983). The proposed metabolic pathway based on the results of *in vitro* studies is shown in Figure 3-3 (Benke and Murphy 1975). This compound can be activated (oxidative desulfuration) to its toxic metabolite, methyl paraoxon, *in vitro* using mouse liver homogenates (Benke et al. 1974) and *in situ* (Zhang and Sultatos 1991) in rats (see reaction 1 in Figure 3-3). Methyl paraoxon has been found in liver and brain of rats following dermal exposure to methyl parathion (Abu-Qare et al. 2000). This intermediate oxygen analog is more potent than the parent compound in inhibiting cholinesterase enzyme activity and causing the neurotoxic effects of methyl parathion (Benke et al. 1974). This oxidative reaction requires microsomal oxidases, NADPH, and oxygen (Benke et al. 1974; Hollingworth et al. 1973; Nakatsugawa et al. 1968).

The detoxification of methyl parathion may occur through any of several metabolic processes (i.e., oxidation, hydrolysis, dearylation, and dealkylation) (Benke and Murphy 1975; Benke et al. 1974; Hollingworth et al. 1973; Nakatsugawa et al. 1968; Neal and DuBois 1965). A major detoxification pathway is enzymatic hydrolysis of the toxic metabolite, methyl paraoxon to dimethyl phosphate and 4-nitrophenol (reaction 3 in Figure 3-3) (Benke and Murphy 1975; Benke et al. 1974). In humans, rats, and mice, these nontoxic metabolites are eliminated primarily in the urine (Hollingworth et al. 1973; Morgan et al. 1977; Plapp and Casida 1958). Another detoxifying pathway (reaction 2) is the oxidation

Figure 3-3. Proposed Metabolic Pathways of Methyl Parathion

GSH = Glutathione
Ar = p-Nitrophenyl



*Adapted from Benke and Murphy (1975)
The numbered reactions (1-7) are reference numbers for pathways discussed in the text.

of the aryl group in the parent compound to produce dimethyl thiophosphate and 4-nitrophenol. The reaction occurs only in the presence of NADPH (Nakatsugawa et al. 1968) and has been studied in liver homogenates of rats, rabbits, mice, and guinea pigs (Benke et al. 1974; Nakatsugawa et al. 1968; Neal and Dubois 1965). Radiolabeled 4-nitrophenol has been detected in the liver of rats following dermal exposure to radiolabeled methyl parathion (Abu-Qare et al. 2000). Dimethyl thiophosphate has been detected in the urine of rats treated with methyl parathion (Plapp and Casida 1958). The 4-nitrophenol can be glucuronidated to form 4-nitrophenol glucuronide (Zhang and Sultatos 1991).

In vitro studies indicate that detoxification of methyl parathion and methyl paraoxon can occur by glutathione-dependent alkyltransferase and aryltransferase (Benke and Murphy 1975; Benke et al. 1974). Glutathione (GSH) alkyltransferase converts methyl parathion to desmethyl methyl parathion (reaction 4 in Figure 3-3), and methyl paraoxon to O-methyl-O-4-nitrophenol phosphate (reaction 5 in Figure 3-3). Glutathione aryltransferase produces dimethyl thiophosphate from methyl parathion (reaction 6 in Figure 3-3), and dimethyl phosphate from methyl paraoxon (reaction 7 in Figure 3-3) (Benke and Murphy 1975). The addition of glutathione in liver homogenates increases the disappearance of methyl parathion and methyl paraoxon in mice (Benke et al. 1974). Pretreatment with dimethyl maleate, which reduces glutathione levels, potentiated toxicity in mice (Mirer et al. 1977), but not in female rats (Chambers et al. 1994). Zhang and Sultatos (1991) did not detect methyl parathion-related glutathione conjugates in the effluent or bile of rat livers perfused *in situ* with 20–80 µM solutions of methyl parathion. Although the Mirer et al. (1977) study indicates that glutathione conjugation might be involved in detoxification of methyl parathion in mice, it should be noted that near lethal concentrations of methyl parathion were used in the intraperitoneal studies, and *in vitro* studies employed exposure levels higher than those likely to be encountered in sublethal *in vivo* toxicity studies. Glutathione-dependent metabolism of methyl parathion, therefore, may not be a significant detoxification pathway *in vivo* at sublethal toxic concentrations in which access to glutathione *S*-transferases might be concentration limited (Huang and Sultatos 1993).

Methyl paraoxon may also be made unavailable by binding to noncritical tissue and plasma constituents (Benke and Murphy 1975), including cholinesterase (Parkinson 1996). In addition, the parent compound is bound to albumin, in serum, as discussed previously in Section 3.4.2.4, but this binding does not appear to limit the availability of methyl parathion to the tissues, indicating that it is reversible. Tissue binding appears to be more important than serum binding (Braeckman et al. 1980, 1983).

The relative rates of activation and detoxification of methyl paraoxon within the liver determine whether net activation or detoxification will occur (Sultatos 1987). Sex-differences have been observed in acute

LD_{50} values for methyl parathion (see Section 3.2.2.1). The lower LD_{50} values in male (compared to female) rats may possibly be attributed to enhanced activation of thio-organophosphate pesticides in the liver of male rats as reported by Murphy and DuBois (1958). Acute intraperitoneal LD_{50} values in male and female rats increase with increasing postpartum age, up to approximately 35–40 days for males and 60 days for females (Benke and Murphy 1975). It has also been found that the metabolism of methyl parathion is affected by the age of rats (Benke and Murphy 1975). The age-related ratios of oxidative deactivation (reaction 2 in Figure 3-3) to oxidative activation (reaction 1) of methyl parathion correlated with the LD_{50} values better than did either measure alone. In addition, age-related increases in hydrolysis (reaction 3), glutathione-dependent dealkylation and dearylation (reactions 5 and 7), and tissue binding of methyl paraoxon correlated with the increase in LD_{50} values (Benke and Murphy 1975), indicating that detoxification pathways for methyl parathion may be more effective in 60-day-old rats than in younger ones (Benke and Murphy 1975). However, at present, mechanisms relating to increased susceptibility of immature rats relative to adults are not fully understood.

3.4.4 Elimination and Excretion

4-Nitrophenol and 4-nitrophenol glucuronide are excreted in urine. The studies of urinary excretion of methyl parathion metabolites, including those reported in this section, generally hydrolyze the glucuronide prior to analysis and report the resulting total 4-nitrophenol values.

3.4.4.1 Inhalation Exposure

Most of the toxic effects caused by methyl parathion resulted from exposure by multiple routes, especially for workers in sprayed fields or formulating facilities, or people in homes. Dean et al. (1984) reported deaths and toxic effects in several children as well as lowered blood cholinesterase levels and excretion of urinary 4-nitrophenol (adults showing no adverse effects also excreted 4-nitrophenol). Health effects from multiple routes have been discussed in detail in Section 3.2.

No studies were located regarding excretion in animals after inhalation exposure to methyl parathion.

3.4.4.2 Oral Exposure

Limited information was available regarding excretion in humans after oral exposure to methyl parathion. During 5 days of exposure of four subjects to 2 or 4 mg of methyl parathion once daily in food (0.028 or

0.057 mg/kg/day), the average 24-hour excretions of the metabolites dimethyl phosphate and 4-nitrophenol accounted for 27 and 12% of the administered dose, respectively (Morgan et al. 1977). An average of 60 and 86% of the total urinary excretion of 4-nitrophenol had been eliminated at 4 and 8 hours, respectively, after ingestion of each dose. Thus, the highest recoveries of 4-nitrophenol occurred during the first 4 hours after exposure. Dimethyl phosphate was excreted mainly during the interval from 4 to 8 hours after exposure (Morgan et al. 1977). However, there was a low and variable recovery of alkyl phosphate metabolites from spiked urine samples (Morgan et al. 1977). Nevertheless, the available data suggest that methyl parathion metabolites are rapidly excreted in humans following oral exposure.

Urinary excretion of metabolites of methyl parathion is rapid and efficient in animals (Braeckman et al. 1983; Hollingworth et al. 1967). In mice, 70–80% of the ^{32}P activity was excreted in the urine within 72 hours after an acute exposure to radiolabeled methyl parathion (Hollingworth et al. 1967). Excretion in the feces represented, at most, 10% of the total radioactivity recovered. Dimethyl phosphate was the major metabolite in mice (Hollingworth et al. 1973). At 24 hours, urinary excretion of dimethyl phosphate was 53 and 31.9% of the activity for 3- and 17-mg/kg doses, respectively (Hollingworth et al. 1973). In rats, urinary dimethyl thiophosphate accounted for 27% of the dose of radioactivity from 2 mg/kg of methyl parathion 24 hours after oral administration. In two dogs, the cumulative radioactivity in the urine 6 days after exposure was 63 and 78% of the 3 mg/kg oral dose (Braeckman et al. 1983). Single oral (gavage) doses of 1.4–7.0 mg methyl parathion/kg, administered to rats, were followed by 24-hour excretion of 2.8–22.0 µg 4-nitrophenol/mL urine with a linear correlation (Chang et al. 1997).

The available evidence suggests that excretion of methyl parathion metabolites in humans and animals following acute oral exposure is essentially the same and occurs rapidly. Excretion occurs primarily via the urine. Methyl parathion can also be excreted in breast milk, although it has been detected only in a limited number of samples from women of central Asia, for which exposure data were not available (Lederman 1996) (see also Section 3.4.2.2). A study in rats also reported excretion of methyl parathion in the milk (Golubchikov 1991; Goncharuk et al. 1990).

3.4.4.3 Dermal Exposure

Only two studies were available that reported detection of a metabolite of methyl parathion in the urine of persons dermally exposed to methyl parathion (Ware et al. 1974, 1975). Four subjects were exposed for 5 hours to a methyl parathion formulation in a field that had been sprayed 24 hours prior to exposure (Ware et al. 1974). At 48 hours, an average of 0.5 mg 4-nitrophenol was found in the urine, but

4-nitrophenol recoveries were low and variable. In a later study using a different analytical method, an average of 1.98 mg 4-nitrophenol was measured in the urine of five men exposed for 5 hours (Ware et al. 1975). The absorption, distribution, and excretion of methyl parathion were evident from these studies. Air levels in the Ware et al. (1975) study averaged 12.6 ng/m^3, with an average respiratory dose of 75 ng for the 5-hour exposure. Dislodgeable residues on the skin just after spraying (at a level of 1 lb active ingredient/acre) ranged from 3.5 to 24 mg, and after 12 hours, they were 2.1–16 mg.

In a study of pregnant rats that were exposed to radiolabeled methyl parathion by single dermal application, half-life elimination rate constants for various tissues ranged from 0.04 to 0.07 $hour^{-1}$, highest values noted in plasma, kidneys, and fetus. Of the applied radioactivity, 14% was recovered in the urine in the first hour postapplication. By the end of the 96-hour study, 91% of the applied dose had been recovered in the urine. Fecal excretion accounted for only 3% of the administered dose (Abu-Qare et al. 2000).

3.4.4.4 Other Routes of Exposure

The elimination of methyl parathion following intravenous injection is rapid in dogs (Braeckman et al. 1980, 1983). Two dogs received 3 mg/kg ^{35}S-methyl parathion intravenously. Urinary excretion was 80–96% of the dose of radioactivity within the 6 hours following injection. Measurement of plasma concentrations of radioactivity before and after passage through the liver indicated high hepatic extraction (Braeckman et al. 1983). Thus, similar elimination data were obtained for both the intravenous and oral routes of exposure. The mean terminal half-life for elimination of a 10-mg/kg intravenous dose of methyl parathion was determined through modeling of the data to be 7.2 hours (Braeckman et al. 1980).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

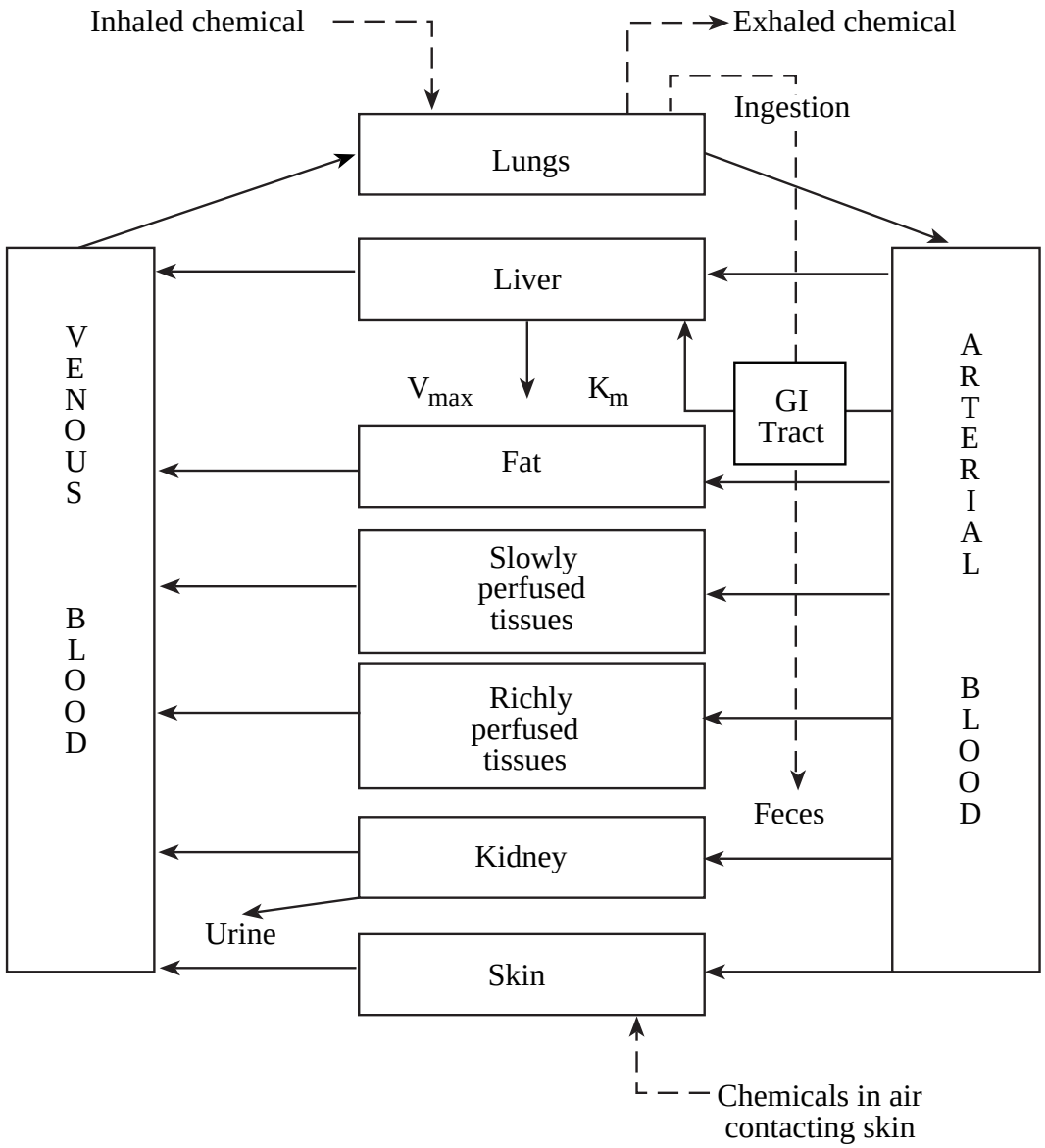
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

No PBPK models were identified for methyl parathion.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Based on the rapid appearance of clinical signs and cholinesterase inhibition, methyl parathion appears to be readily absorbed by humans and animals following inhalation, oral, and dermal exposure. Following oral administration of methyl parathion to animals, the extent of absorption was at least 77–80% (Braeckman et al. 1983; Hollingworth et al. 1967). No studies were located regarding the extent of absorption following inhalation and dermal exposure, or the mechanism of absorption.

Data from a single study in dogs suggest that hepatic first-pass metabolism may limit systemic availability of the parent compound following oral exposure (Braeckman et al. 1983). Placental transfer of methyl parathion was demonstrated in pregnant rats 1–3 days before parturition. Thirty minutes after administration, both methyl parathion and methyl paraoxon were found in fetal brain, liver, and muscle; methyl parathion, but not methyl paraoxon, was detected in placenta and maternal liver (Ackermann and Engst 1970). Methyl parathion binds reversibly to serum albumin, but is readily distributed to the tissues (Braeckman et al. 1980, 1983).

Methyl parathion is activated by desulfuration to its toxic metabolite, methyl paraoxon, by microsomal oxidases (cytochrome P-450) (Benke and Murphy 1975; Benke et al. 1974; Hollingworth et al. 1973; Nakatsugawa et al. 1968). The specific isozyme(s) that catalyze this reaction for the phosphorothioate esters, such as parathion and methyl parathion, do not appear to have been identified. Detoxification can occur through a number of pathways, including oxidation and removal of the aryl group from the parent compound, also mediated by microsomal oxidases (P-450 isozyme not known) (Benke and Murphy 1975; Benke et al. 1974; Nakatsugawa et al. 1968). Additional detoxification pathways include glutathione-mediated dearylation of the parent compound, and hydrolysis or glutathione-mediated dealkylation or dearylation of methyl paraoxon (Benke and Murphy 1975; Benke et al. 1974). The importance of the glutathione-mediated pathways *in vivo*, however, is unclear (Chambers et al. 1994; Huang and Sultatos 1993; Zhang and Sultatos 1991). An additional inactivating mechanism may be binding to tissue and plasma constituents (Benke and Murphy 1975), including plasma cholinesterase (Parkinson 1996), making methyl parathion unavailable.

3.5.2 Mechanisms of Toxicity

Almost all systemic effects of methyl parathion are related to the action of this compound on the nervous system or are secondary to this primary action. It is therefore necessary to preface a description of the mechanisms of toxicity of methyl parathion with a brief discussion of the nervous system and neurohumoral transmitters (excerpted from Lefkowitz et al. 1996).

Neurohumoral transmitters are chemicals that facilitate the transmission of nerve impulses across nerve synapses and neuroeffector junctions. Acetylcholine is a neurohumoral transmitter that is present in the peripheral autonomic nervous system, in the somatic motor nervous system, and in some portions of the central nervous system.

The autonomic nervous system is also called the involuntary nervous system; nerve fibers innervate heart, blood vessels, glands, various visceral organs, and smooth muscles. The autonomic nervous system is further divided into the parasympathetic and sympathetic systems. Both systems are involved in regulating the internal environment of the body and act in a contrasting manner. In general, the parasympathetic system is responsible for the maintenance of normal visceral organ functions including digestion and voiding; the sympathetic system has connections to the adrenal medulla and is geared for the body's "fight or flight" mechanisms. In the autonomic system, acetylcholine is a neurohumoral transmitter for all of the first set of neurons in this system (preganglionic fibers), for all of the second set of parasympathetic fibers (postganglionic fibers), and for a few postganglionic sympathetic fibers. These are all termed cholinergic fibers.

The somatic motor nervous system or voluntary nervous system consists of nerve fibers that innervate skeletal muscle motor end-plates.

Following release of acetylcholine at a nerve synapse or at a neuromuscular junction, the transmitter is rapidly hydrolyzed (within less than a millisecond) by an enzyme called acetylcholinesterase. This enzyme is present in high concentrations in cholinergic neurons and is localized at skeletal muscle end-plates. Acetylcholinesterase is a highly efficient enzyme capable of hydrolyzing $6x10^5$ acetylcholine molecules per molecule of enzyme per minute (Taylor 1996).

Acetylcholinesterase contained in erythrocytes is identical to that found in the nervous system. Its function within erythrocytes may be to control permeability of the cell membrane, to an extent.

Functional neurological changes due to acute organophosphate exposure generally correlate with acetylcholinesterase inhibition in erythrocytes (Wills 1972).

There is a second type of cholinesterase called butyrylcholinesterase, pseudocholinesterase, or cholinesterase. This enzyme is present in some nonneural cells in the central and peripheral nervous systems as well as in plasma and serum, the liver, and other organs. Its physiologic function is not known, but is hypothesized to be the hydrolysis of esters ingested from plants (Lefkowitz et al. 1996). Plasma cholinesterases are also inhibited by organophosphate compounds through irreversible binding; this binding can act as a detoxification mechanism as it affords some protection to acetylcholinesterase in the nervous system (Parkinson 1996; Taylor 1996).

Methyl parathion and other organophosphates and their active metabolites exert their profound toxic effect by inhibiting the activity of acetylcholinesterase in the nervous system and at the motor end-plate. The active metabolite of methyl parathion, methyl paraoxon, inactivates acetylcholinesterase by phosphorylating the active site of the enzyme. The initial binding is somewhat reversible over a period of several hours, but over the following 24–48 hours, a process called “aging” occurs, resulting in the formation of a more stable covalent bond. Aging results from the removal of one of the alkyl side-chains of the phosphate group, leaving a hydroxyl group. This change prevents regeneration of the active enzyme, possibly by causing a conformational change that prevents the access of water for dephosphorylation, and represents an irreversible inhibition of the enzyme. Activity is regained only through the synthesis of new enzyme. Hydrolysis of acetylcholine is inhibited and the neurotransmitter accumulates at its site of action, producing overstimulation of cholinergic end organs, as described below (Proctor et al. 1988; Sultatos 1994; Taylor 1996).

Clinical signs and symptoms of toxicity are related to the overstimulation of muscarinic, nicotinic, and central nervous system receptors in the nervous system. Muscarinic receptors are those activated by the alkaloid drug muscarine. These receptors are under the control of the parasympathetic nervous system, and their hyperactivity results in respiratory and gastrointestinal dysfunction, incontinence, salivation, bradycardia, miosis, and sweating. Nicotinic receptors are those activated by nicotine. Hyperactivity of these receptors results in muscle fasciculations; even greater stimulation results in blockade and muscle paralysis (Lefkowitz et al. 1996; Tafuri and Roberts 1987). Hyperactivity of central nervous system receptors results in the frank neurological signs of confusion, ataxia, dizziness, incoordination, and slurred speech, which are manifestations of acute intoxication. Muscarine and nicotine are not

physiological stimulants, but rather are exogenous drugs that have been used experimentally to differentiate between the two types of receptors in the cholinergic system.

The phenomenon of tolerance is well recognized in humans and other animal species after repeated exposure by various routes to sublethal doses of organophosphates (Costa et al. 1982). Typical cholinergic signs will occur after the initial exposure to an organophosphate; signs then diminish or disappear with continued dosing at the same level. A hypothetical mechanism for tolerance is down-regulation, or decrease in the number of active muscarinic cholinergic receptors. Tolerance appears to be an adaptive response to organophosphate exposure.

The mechanisms for the observed decrease in susceptibility of rats to the lethality of methyl parathion with increasing age may be age-related changes in metabolism. The deactivating pathways appear to increase, relative to the activating pathway, with increasing age from 1 to 60 days of age, leading to the hypothesis that detoxification pathways may be more effective in adult rats than in younger ones (Benke and Murphy 1975). These conclusions are based on the correlations of *in vitro* metabolism data with LD_{50} values; additional detail is provided in Section 3.3.3.

In addition to effects mediated through glucocorticoid secretion (stress-related), a hypothetical mechanism for direct immunotoxicity of organophosphates is the inhibition of esterases and stabilization of the lysosomal membrane of lymphocytes, thus blocking release of lymphokines (Sharma and Reddy 1987).

3.5.3 Animal-to-Human Extrapolations

Rigorous within-study comparisons of the toxicokinetics and health effects of methyl parathion in humans and experimental animals are generally not available, but across-study comparisons suggest that the kinetics and effects tend to be similar across species, with the following exception. The chicken, a test animal in studies of delayed neurotoxicity, is considered to be a good indicator species for delayed neurotoxicity. Treatment of chickens with methyl parathion did not cause signs of delayed neurotoxicity (Gaines 1969). Studies in rats, however, have indicated that intermediate or intermediate-to-chronic exposure to methyl parathion may result in decrements in nerve conduction (Desi et al. 1998) and in distal axonopathy (Suba 1984). The potential for methyl parathion to cause delayed neurotoxicity, and the relevance to humans of the negative findings in chickens versus the positive findings in rats, is unclear. This effect has not been observed in humans exposed to methyl parathion.

3.6 ENDOCRINE DISRUPTION

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

For methyl parathion, most of the information on health effects in humans is derived from cases of acute exposure to relatively high concentrations of the pesticide. Such reports have not addressed the issue of the potential endocrine-disrupting capacity of methyl parathion in humans. An added complication in determining whether methyl parathion has endocrine-disrupting capabilities in humans is the fact that humans are seldom exposed to a single pesticide.

Studies in experimental animals have evaluated a wide array of relevant end points and the results have been mixed. For example, methyl parathion was not toxic to male germ cells from mice administered the test material in the diet or drinking water at up to the maximum tolerated dose (not specified) (Degraeve et al. 1985; Waters et al. 1982), but a later study showed that doses between 9.4 and 75 mg methyl parathion/kg increased the percentages of abnormal sperm cells in a dose-related manner (Mathew et al. 1992). Repeated exposure of pregnant rats to an oral methyl parathion dose of 1.5 mg/kg, a dose that caused frank neurotoxicity, resulted in increased fetal resorptions (Gupta et al. 1984, 1985). Similar exposure of pregnant rats to 1 mg/kg/day of methyl parathion resulted in alterations in some behavioral end points in their offspring, evaluated at 2–6 months old (Gupta et al. 1985), suggesting that exposure *in*

utero may lead to persistent effects; however, whether this may have been caused by an endocrine-disrupting mechanism cannot be determined. Similar results had been reported earlier by Crowder et al. (1980) following gavage administration of 1 mg/kg/day to pregnant rats.

Intraperitoneal administration of a dose of 60 mg methyl parathion/kg to pregnant mice resulted in increased incidence of cleft palate in the fetuses and fetal deaths (Tanimura et al. 1967). In a more recent study, gavage administration of 1.5 mg methyl parathion/kg/day to rats on days 6–15 of gestation resulted in increased resorptions, decreased fetal body weight, and hemorrhagic spots in the brain ventricles and skin of the upper body of some of the fetuses (Kumar and Devi 1996). This dose level, however, also caused maternal toxicity expressed as cholinergic signs and depressed body weight gain.

Decreased ovarian weight gain and inhibition of compensatory ovarian hypertrophy was observed in hemi-ovariectomized rats injected intraperitoneally with methyl parathion for 15 days at 5 mg/kg/day, in comparison with hemi-ovariectomized controls (Asmathbanu and Kaliwal 1997; Dhondup and Kaliwal 1997). A decrease in the number of healthy follicles, no change in the number of atretic follicles, increase in duration of diestrus, decrease in the number of estrous cycles, and decrease in uterine weight also occurred in the methyl parathion-treated rats. Body weight gain was not decreased by methyl parathion, indicating that the effects were not due to nutritional deficiency. The effects of methyl parathion were not fully consistent with those of chlorinated pesticides that have estrogenic activity because methyl parathion did not increase follicular atresia, estrus duration, or uterine weight.

Collectively, the findings in experimental animals are insufficient to categorize methyl parathion as an endocrine-disrupting chemical.

The potential endocrine-disrupting capacity of methyl parathion in wildlife has also been examined, and results of some recent studies are summarized below.

Exposure of two species of freshwater fish to 0.106 ppb of a commercial formulation containing 50% methyl parathion increased serum levels of T3 and reduced T4 (Bhattacharya 1993). This effect was attributed to inhibition of acetylcholinesterase activity in the fish brain, but no direct evidence was presented. Similar treatment of freshwater perch for 35 days resulted in decreased release of progesterone from the ovaries (Bhattacharya and Mondal 1997). Also, treatment of freshwater perch for up to 90 days with methyl parathion induced a decrease in the gonadosomatic index (not defined) after day 15 of

exposure and in profiles of 17β-estradiol in serum and ovary that differed considerably from those in control animals over the exposure period (Choudhury et al. 1993).

Exposure of male and female Japanese quail to 3, 12, or 48 ppm methyl parathion in the diet for 6 weeks throughout the laying period resulted in reduced number of eggs laid and in increased percentage of cracked eggs at the highest exposure level (Solecki et al. 1996). The highest exposure level also resulted in decreased plasma cholinesterase, whereas brain cholinesterase was reduced at all exposure levels. Neither fertility nor hatchability were affected by treatment. Oral treatment of wild passerine birds (*Lonchura malabarica*) with up to 200 µg methyl parathion/kg resulted in a significant reduction in testes weight at $100 µg/kg after 10 days of treatment (Maitra and Sarkar 1996). However, a single dose of 50 µg/kg induced a significant decrease in the number of tubules containing healthy germ cells; the frequency and severity of this effect was dose-related and related to exposure duration. The authors also reported that effect on tubular germ cells was negatively correlated with acetylcholinesterase activity in the testes and brain and suggested that cholinergic activity may play a role in the influence of methyl parathion on gametogenic activities in the testes. Alternatively, they noted that brain cholinergic activity may also play a role through regulation of gonadotrophic secretion.

In addition to *in vivo* tests, *in vitro* assays have been developed to test for hormone-mimicking properties of chemicals. These tests include cell proliferation assays and gene expression assays in mammalian cells and yeast. Although easy to conduct, these assays can yield both false negatives and false positives; for this reason, it is preferable to perform both *in vivo* and *in vitro* assays before classifying a chemical as to its endocrine-disrupting capacity. Limited information exists in this regard for methyl parathion. Methyl parathion exhibited very weak estrogenic properties (>10,000 times less potent than 17β-estradiol) in a yeast system expressing rainbow trout estrogen receptor (Petit et al. 1997). However, methyl parathion had an estrogenic potency similar to 17β-estradiol in a test in trout hepatocyte aggregate cultures that express the estrogen receptor (Petit et al. 1997). The structurally-related organophosphate pesticide, parathion, did not show estrogenic properties in breast cancer estrogen-sensitive MCF-7 cells (Soto et al. 1995).

In summary, while there is information on effects of methyl parathion that could be considered as endocrine-mediated, the less than optimal quality of the many of the studies do not allow for firm conclusions. Further research is needed to clarify whether methyl parathion may act as an endocrine disruptor.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient

tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Present information indicates a potential for age-related differences in susceptibility to methyl parathion. However, data are limited in both human and animal studies.

Acute exposure (via inhalation, dermal, and/or oral exposure routes) to methyl parathion has resulted in typical symptoms of organophosphate poisoning including depressed plasma and erythrocyte cholinesterase levels, altered function of nervous, cardiac, pulmonary, and gastrointestinal systems, and death in adults (Fazekas 1971; Fazekas and Rengei 1964) and children (Dean et al. 1984), indicating similarity in targets of toxicity from exposure to methyl parathion (see Section 3.5 for a more complete description of organophosphate poisoning). Toxicity in the nervous system is elicited by inhibition of the enzyme, acetylcholinesterase, which helps to control the level of the neurotransmitter acetylcholine. Lower levels of acetylcholinesterase result in effectively higher concentrations of acetylcholine and hyperactivity within the nervous system.

Acetylcholine, acetylcholinesterase, and butyrylcholinesterase are involved in the development of the nervous system (Brimijoin and Koeninsberger 1999; Layer 1990; Layer and Willbold 1994); some of this development is not complete until adulthood. Therefore, toxic chemicals acting on these substances could cause deleterious developmental effects in addition to the typical physiological effects already discussed.

Limited information regarding potential for age-related differences in susceptibility to methyl parathion in humans was reported by Dean et al. (1984). Seven children (ranging in age from 2 to 11 years) and three adults were exposed to unknown concentrations of methyl parathion sprayed illegally inside a house at a concentration of 4% (>3 times the recommended concentration for field applications). The children

exhibited typical signs of organophosphate poisoning; two of them (4 and 11 years of age) died of respiratory arrest. Although the adults did not exhibit typical overt signs of methyl parathion poisoning, urinary levels of a methyl parathion metabolite (4-nitrophenol) were as high in the adults as in some of the children exhibiting toxic effects. The potential for age-related susceptibility could not be clearly assessed since critical information on individual exposure levels and routes was lacking.

The only other information regarding the potential for age-related differences in susceptibility to methyl parathion came from a study by Garcia-Lopez and Monteoliva (1988). The investigators showed increasing mean erythrocyte acetylcholinesterase activity levels with increasing age range, starting at birth (in 10-year increments and >60 years of age) in both males and females. However, it is not known whether increased erythrocyte acetylcholinesterase activity indicates a decreased susceptibility to methyl parathion toxicity.

Age-related differences in LD_{50} values for methyl parathion administered intraperitoneally have been shown in rats, with perinates being most susceptible and LD_{50} values increasing with age through adults (Benke and Murphy 1975; Kimmerle and Lorke 1968). The greatest change in LD_{50} values occurred in pups between 1 and 12–13 days old (Benke and Murphy 1975). While no significant age-related differences were noted in the *in vitro* inhibition of cholinesterase in brain homogenates treated with methyl paraoxon, *in vitro* metabolic studies of methyl parathion provide some evidence that age-related variation in a number of metabolic reactions might account, in part, for observed age-related changes in lethality. This age-related evidence includes positive correlations between changes in LD_{50} values for methyl parathion and ratios of oxidative deactivation (reaction 2 in Figure 3-3) to oxidative activation (reaction 1) of methyl parathion, as well as increases in hydrolysis (reaction 3), glutathion-dependent dealkylation and dearylation (reactions 5 and 7), and tissue binding of methyl paraoxon (Benke and Murphy 1975). The decreased susceptibility to methyl parathion toxicity (i.e., increased LD_{50} values) with increasing age was attributed to more effective detoxification in older rats relative to younger ones (Benke and Murphy 1975). However, *in vivo* studies have yet to confirm this hypothesis, and it is not known whether age-related differences in detoxification rates would play a role in low-level acute or chronic exposure scenarios.

Pope et al. (1991) found that 7-day-old Sprague-Dawley rat pups were approximately twice as sensitive as 80–100-day-old adults to single subcutaneous doses of methyl parathion; the highest nonlethal dose 7.8 mg/kg for the neonates and 18.0 mg/kg for adults. Initially, both neonates and adults exhibited similarly reduced brain acetylcholinesterase activity levels (approximately 10% that of controls);

however, recovery of cholinesterase activity was more rapid in neonates (approximately 75% at 4 days posttreatment compared to only 30% in adults). In a subsequent study, Pope and Chakraborti (1992) showed that these age-related effects also occurred in a dose-related manner. Using daily subcutaneous dosing for 14 days, Liu et al. (1999) found that brain acetylcholinesterase activity was inhibited to a significantly greater extent in neonatal than in adult rats during dosing with 1.5 mg/kg/day, but that 8 days after termination of exposure, there was little or no difference. The difference was diminished at a higher dose of 3 mg/kg/day, and recovery of activity was higher in the neonates after 8 days post-exposure. Two other animal studies reported age-related responses to methyl parathion exposure by the oral route. Kumar and Desiraju (1992) found no statistically significant difference in the magnitude of brain acetylcholinesterase inhibition in 15-day-old Wistar rat pups and 90-day-old adults (approximately 47 and 60%, respectively) following single oral (gavage) doses of 1 mg/kg.

Placental transfer of methyl parathion was demonstrated in pregnant rats after oral administration of 11.1 mg methyl parathion/kg body weight (Ackermann and Engst 1970). Following sacrifice 30 minutes posttreatment, maternal liver and placenta were found to contain measurable amounts of methyl parathion, but not methyl paraoxon. Fetal brain, liver, and muscle tissues contained methyl parathion concentrations up to approximately 2.5 times that of the maternal liver. Similarly, placental transfer was demonstrated in pregnant rats following dermal application of 10 mg methyl parathion/kg (Abu-Qare et al. 2000). By 4 hours postadministration, the highest concentration of methyl parathion was found in fetal tissue; the concentration in placental tissue was about as high as that of the maternal liver. Fish (1966) gave supporting evidence for placental transfer of methyl parathion and/or its toxic metabolites by demonstrating that brain cholinesterase activity was reduced in fetal rats following intraperitoneal injections of the pregnant dams with maternally-toxic doses of methyl parathion. Methyl parathion was found in breast milk in a limited number of samples from women of central Asia, for which exposure data were not available (Lederman 1996) (see also Section 3.4.2.2). This indicates that methyl parathion might be transferred from contaminated mother to nursing infant. No information was locating regarding the presence of methyl parathion metabolites in breast milk. A study of a mixture of pesticides (methyl parathion, lindane, and permethrin) in rats reported that following oral exposure of the dams on lactation days 1–14, methyl parathion was present in higher concentrations in their milk and in the pups' blood than in the dams' blood (Golubchikov 1991; Goncharuk et al. 1990). Confidence in this study is low because descriptions of the methods and results were cursory.

It is not presently known what phase I enzymes metabolize methyl parathion, and consequently, whether metabolism differs between children and human adults. There is some suggestive evidence for age-related differences in metabolism of methyl parathion in rats (Benke and Murphy 1975).

Tanimura et al. (1967) reported increased incidences of cleft palate and mortality in fetuses of pregnant mice injected intraperitoneally with 60 mg methyl parathion/kg. Significantly reduced maternal and fetal brain acetylcholinesterase activity, increased resorptions (Gupta et al. 1985), and dose-related reductions in net maternal and fetal protein synthesis (Gupta et al. 1984) were noted following oral exposure of pregnant rats to methyl parathion during gestation. Crowder et al. (1980) reported increased mortality in rat pups (relative to controls) following oral administration of methyl parathion to pregnant dams during gestation and a significant difference in maze transfer tests between treatment and control groups. Kumar and Devi (1996) also reported treatment-related maternal and fetal effects in rats following oral administration of methyl parathion to dams during gestation. However, there were no reports of age-related differences in susceptibility to methyl parathion in any of these studies.

Dose-related changes on electrocorticograms and on nerve conduction velocity and refractory period were reported in rats that were exposed to methyl parathion via treatment of the dams during gestation and lactation, and then orally at dose levels of 0.22, 0.44, or 0.88 mg/kg/day for 8 more weeks of postnatal development to the age of 12 weeks (Desi et al. 1998). These effects were not seen in 12-week-old rats following exposure only during gestation and lactation or gestation alone. No overt toxic signs were seen in dams or offspring.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and

interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to methyl parathion are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by methyl parathion are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Methyl Parathion

The most specific biomarker of exposure to methyl parathion is the presence of the compound in serum or tissue. This is an especially good biomarker for detection shortly after acute exposure. For example, methyl parathion levels were detected in the sera of five men who were exposed for 5 hours in a cotton field 12 hours after it was sprayed with methyl parathion. The route of exposure was dermal, through unprotected hands. Serum levels averaged 156 ppb after 3 hours of the 5-hour exposure, and averaged 101.4 and 2.4 ppb at 7 and 24 hours postexposure, respectively (Ware et al. 1975).

These results are supported by studies in animals in which methyl parathion was detected 30–155 minutes after exposure (oral, dermal, inhalation, or intravenous routes) in plasma and liver (Abu-Qare et al. 2000; EPA 1978e). Due to extensive and rapid metabolism of methyl parathion (see Section 3.3), measurable levels are not expected to persist in tissue or serum for prolonged periods after exposure.

Urine of exposed humans can also be monitored for two metabolites of methyl parathion: 4-nitrophenol (measured after hydrolysis of the glucuronide, Section 3.3.4) and dimethyl phosphate. After ingestion of 2 or 4 mg of methyl parathion, maximum urinary excretion occurred as follows: 4-nitrophenol within 4 hours, and dimethyl phosphate between 4 and 8 hours. Metabolites were not detected in urine on the second day after exposure (Morgan et al. 1977). Metabolites, such as 4-nitrophenol, have also been detected in stomach contents, urine, and tissues of humans committing suicide by ingestion of methyl parathion (Fazekas 1971). These metabolites are not, however, specific for methyl parathion. The metabolite 4-nitrophenol can also occur as a breakdown product of other organophosphate insecticides such as parathion as well as some nonorganophosphate compounds, while alkylphosphates are metabolic end-products of most organophosphates (Davies and Peterson 1997; Morgan et al. 1977).

Urinary 4-nitrophenol was detected in intoxicated children and clinically normal adults in a household where there had been exposure to methyl parathion (Dean et al. 1984).

Associations between urinary 4-nitrophenol and indoor residential air and surface-wipe concentrations of methyl parathion have been studied in 142 residents of 64 contaminated homes in Lorain, Ohio (Esteban et al. 1996). The homes were contaminated through illegal spraying. A mathematic model was developed to evaluate the association between residential contamination and urinary 4-nitrophenol. There were significant positive correlations between air concentration and urinary 4-nitrophenol, and between maximum surface-wipe concentrations and urinary 4-nitrophenol. The final model includes the following variables: number of days between spraying and sample collection, air and maximum surface wipe concentration, and age, and could be used to predict urinary 4-nitrophenol.

3.8.2 Biomarkers Used to Characterize Effects Caused by Methyl Parathion

Diagnosis of organophosphate poisoning (including methyl parathion) can be confirmed by evaluation of serum (plasma) cholinesterase and erythrocyte cholinesterase. However, cholinesterase inhibition is not specific for organophosphates. For example, carbamate insecticides also result in cholinesterase inhibition, which is usually transitory. Erythrocyte cholinesterase measurement is a specific test for

acetylcholinesterase inhibition since it is found in both the peripheral and central nervous systems. However, measurement is complicated by the fact that normal erythrocyte cholinesterase values encompass a broad range in the human population (Midtling et al. 1985; Tafuri and Roberts 1987). Serum cholinesterase (pseudocholinesterase) is a more sensitive but less specific indicator of organophosphate toxicity since the levels may also be suppressed due to genetic factors and to a variety of conditions and diseases (Henry 1984; Tafuri and Roberts 1987). Acetylcholinesterase activity recovers as a result of the synthesis of new enzyme and recovery generally occurs at a rate of approximately 1% per day. However, the symptoms of methyl parathion poisoning usually resolve more rapidly. Therefore, even if they are symptom-free, persons poisoned by methyl parathion may have lowered cholinesterase levels for a month after exposure and should avoid re-exposure for several weeks (Proctor et al. 1988). Also, normal values may have interlaboratory variation (NIOSH 1976). Several field tests for measuring erythrocyte acetylcholinesterase and plasma cholinesterase are available (Wills 1972). Baseline data are often collected for workers, but these data would not be available for environmentally exposed people. Sequential determinations of cholinesterase levels from individuals probably exposed to methyl parathion could be an alternative method of determining cholinesterase inhibition (Midtling et al. 1985). In interpreting results, it should be noted that there are both age- and gender-related differences in normal erythrocyte and plasma cholinesterase levels in humans (Garcia-Lopez and Monteoliva 1988; Wills 1972). See Sections 3.7 and 3.10 for additional information on these age- and gender-related differences.

A classification of organophosphate poisoning has been proposed by Tafuri and Roberts (1987) modified from Namba et al. (1971). Clinical signs and symptoms of intoxication may occur when serum cholinesterase levels drop to below 50% of the normal value. Mild poisoning, with the patient still ambulatory, may occur when serum cholinesterase levels are 20–50% of normal; moderate poisoning with inability to walk with levels 10–20% of normal; and severe poisoning with respiratory distress and unconsciousness with serum cholinesterase levels <10% of normal.

Following exposure of humans to organophosphates, but not specifically methyl parathion, restoration of plasma cholinesterase occurs more rapidly than does restoration of erythrocyte cholinesterase (Grob et al. 1950; Midtling et al. 1985). These findings are supported by studies of methyl parathion in animals. Erythrocyte cholinesterase levels are representative of acetylcholinesterase levels in the nervous system, and, therefore, may be a more accurate biomarker of the neurological effects of chronic low level exposure of humans to methyl parathion (Midtling et al. 1985; NIOSH 1976).

3.9 INTERACTIONS WITH OTHER CHEMICALS

Emergency therapy of acute organophosphate (including methyl parathion) intoxication in humans and other mammals relies on the antagonistic interactions of several drugs. Atropine serves as a potent antidote by blocking the action of acetylcholine at muscarinic nerve receptors and, therefore, lessens clinical signs related to parasympathetic stimulation caused by the inactivation of acetylcholinesterase by methyl parathion. 2-Pyridine aldoxime methiodide (2-PAM) reverses the effect of cholinergic nicotinic stimulation such as at the motor nerve junctions with the end-plates of skeletal muscle fibers. This treatment ameliorates signs and symptoms of skeletal muscle fasciculation, muscle weakness, and life-threatening paralysis of respiratory muscles. 2-PAM is able to reactivate phosphorylated cholinesterase if the drug is administered within 24–36 hours of acute methyl parathion intoxication. After that time, irreversible changes in the phosphorylated enzyme occur, and 2-PAM is ineffective as an antidote (Tafuri and Roberts 1987).

Compounds that affect activities of hepatic microsomal enzymes can antagonize the effects of methyl parathion, presumably by decreasing metabolism of methyl parathion to methyl paraoxon or enhancing degradation to relatively nontoxic metabolites. For example, pretreatment with phenobarbital protected rats from methyl parathion's cholinergic effects (Murphy 1980) and reduced inhibition of acetyl-cholinesterase activity in the rat brain (Tvede et al. 1989). Phenobarbital pretreatment prevented lethality from methyl parathion in mice compared to saline-pretreated controls (Sultatos 1987). Pretreatment of rats with two other pesticides, chlordecone or mirex, also reduced inhibition of brain acetylcholinesterase activity in rats dosed with methyl parathion (2.5 mg/kg intraperitoneally), while pretreatment with the herbicide linuron decreased acetylcholine brain levels below those found with methyl parathion treatment alone (Tvede et al. 1989).

Cimetidine, an H_2 antagonist used therapeutically in patients with ulcers, inhibits activity of hepatic microsomal enzymes. When rats or mice were pretreated with cimetidine, dose-related lethality of methyl parathion was reduced, and cholinergic signs of toxicity were delayed. Simultaneous administration with methyl parathion did not reduce toxicity (Joshi and Thornburg 1986).

Piperonyl butoxide, a common potentiator of insecticide effects that inhibits microsomal enzymes, antagonized the toxic effects of methyl parathion in mice (Mirer et al. 1977).

Gentamicin is a broad spectrum aminoglycoside antibiotic, and rifamycin is an antituberculosis drug. Pretreatment of rats with these agents protected them against toxic effects of a single oral dose of methyl parathion. Plasma cholinesterase and liver carboxylesterase levels were higher in pretreated than untreated rats challenged with methyl parathion. Pretreated rats had significantly decreased methyl paraoxon levels in liver and skeletal muscles while 4-nitrophenol levels were increased in the urine, indicative of enhanced detoxification (Youssef et al. 1987).

Acetaminophen, which depletes hepatic glutathione, does not potentiate the toxicity of methyl parathion in mice. A possible mechanism of action may be competition between acetaminophen and methyl parathion for mixed function oxidases and subsequent prevention of activation of methyl parathion to methyl paraoxon (Costa and Murphy 1984). Diethyl maleate, an agent that depletes cytosolic glutathione and is not an enzyme inducer, potentiates toxicity of methyl parathion in mice (Mirer et al. 1977).

Permethrin, a pyrethrin pesticide, decreased the inhibition of brain cholinesterase activity by methyl parathion, but methyl parathion decreased the LD_{50} of permethrin when the two pesticides were simultaneously administered to rats (Ortiz et al. 1995). The potentiation of permethrin lethality may be due to the inhibition by methyl parathion of carboxylesterase, which metabolizes permethrin.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to methyl parathion than will most persons exposed to the same level of methyl parathion in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of methyl parathion, or compromised function of organs affected by methyl parathion. Populations who are at greater risk due to their unusually high exposure to methyl parathion are discussed in Section 6.7 Populations With Potentially High Exposures.

Unusually susceptible populations are those groups of individuals who respond more quickly or at lower exposure levels than the general population to the toxic effects of methyl parathion. These responses may be genetic in origin or may be due to differences in development or life style factors such as nutrition or behavior, or due to preexisting disease states.

People who should not work with organophosphate insecticides are those with organic central nervous system disease, mental disorders, epilepsy, pronounced endocrine disorders, respiratory conditions, cardiovascular diseases, circulatory disorders, gastroenteric diseases, liver or kidney disease, and chronic conjunctivitis and keratitis (Medved and Kagan 1983).

Individuals with hereditary low plasma cholinesterase levels (Kalow 1956; Lehman and Ryan 1956) and those with paroxysmal nocturnal hemoglobinuria, which is related to abnormally low levels of erythrocyte acetylcholinesterase (Auditore and Hartmann 1959), would have increased susceptibility to the effects of anticholinesterase agents such as methyl parathion. Repeated measurements of plasma cholinesterase activity (in the absence of organophosphate exposure) can be used to identify individuals with genetically determined low plasma cholinesterase.

Women have exhibited significantly decreased plasma cholinesterase levels (De Peyster et al. 1994; Evans and Wroe 1980; Evans et al. 1988; Howard et al. 1978; Sanz et al. 1991; Venkataraman et al. 1990) and significantly increased erythrocyte acetylcholinesterase levels (De Peyster et al. 1994; Sanz et al. 1991; Venkataraman et al. 1990) during pregnancy. It is not known whether these differences might make pregnant women more susceptible to methyl parathion toxicity.

Several studies in animals suggest that age may affect susceptibility to methyl parathion toxicity, and that children may be more susceptible than adults, but the data are limited. (See Section 3.7 for more information on Children's susceptibility.) A study in humans showed that mean erythrocyte acetyl-cholinesterase activity levels increase with increasing age from birth through old age in both sexes (Garcia-Lopez ad Monteoliva 1988), but it is not known whether increased erythrocyte acetyl-cholinesterase activity indicates decreased susceptibility to methyl parathion.

Male rodents have been shown to be more susceptible to acute toxic effects of methyl parathion than females (EPA 1978e; Murphy and Dubois 1958).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to methyl parathion. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to methyl parathion. When specific exposures have occurred, poison control centers and medical toxicologists should be

consulted for medical advice. The following texts provide specific information about treatment following exposures to methyl parathion:

Aaron CK, Howland, MA. 1998. Insecticides: Organophosphates and carbamates. In: Goldfrank LR, Flomenbaum NE, Lewin NA, et al., eds. Goldfrank's toxicologic emergencies. Stamford, CT: Appleton & Lange, 1429–1449.

Bronstein AC, Currance PL, eds. 1988. Emergency care for hazardous materials exposure. St. Louis, MO: CV Mosby Company, 66, 199–200.

Ellenhorn MJ. 1997. Pesticides: Insecticides. In: Ellenhorn's medical toxicology: Diagnosis and treatment of human poisoning. Baltimore, MD: Williams & Wilkins, 1614–1631.

EPA. 1989b. Recognition and management of pesticide poisonings. 4th ed. Washington, DC: U.S. Environmental Protection Agency. Health Effects Division. Office of Pesticide Programs. EPA 540/9-88-001.

3.11.1 Reducing Peak Absorption Following Exposure

Procedures that have been used to reduce absorption of methyl parathion include the following. In inhalation and dermal exposures, the exposed person is first removed from the source of exposure. Dermal absorption is then reduced by washing the skin and hair with mild soap or detergent and copious amounts of water. If immediately available, a mild hypochlorite (bleach) solution can be used on the skin (*not* in the eyes); the chlorine radical deactivates organophosphate agents. Care is taken to avoid abrading the skin as methyl parathion may be more rapidly absorbed through cuts, cracks, or abrasions in the skin (Aaron and Howland 1998). Ocular absorption is limited by irrigating the eyes with copious amounts of normal saline or lactated Ringer's solution, or, if these solutions are not available, water (Aaron and Howland 1998; Stutz and Janusz 1988). After acute oral exposures to high doses, absorption from the gastrointestinal tract is limited by gastric lavage followed by administration of activated charcoal to absorb residual methyl parathion present in the gut. Emesis with ipecac has been discouraged because coma or seizures may develop rapidly in acute high-dose situations (Aaron and Howland 1998). In low-dose situations, where swallowing is not impaired and a good gag reflex and no drooling exist, absorption of methyl parathion from the gastrointestinal tract may be limited by drinking water to dilute the contents of the gastrointestinal tract (Bronstein and Currance 1988), but this procedure will expose a larger area of absorptive surface to the toxicant.

3.11.2 Reducing Body Burden

No information was located regarding methods for reducing body burden of methyl parathion.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Methyl parathion produces its toxic effects by inhibiting acetylcholinesterase. This results in excess acetylcholine at the synapses and neuroeffector junctions. Treatment of methyl parathion poisoning is directed toward reducing the effects of the excess acetylcholine and reactivating acetylcholinesterase. Atropine may be given to block muscarinic cholinergic receptors and limit the action of acetylcholine at this class of receptors. In cases of moderately severe poisoning, a state of atropinization (tachycardia, flushing, dry mouth, dilated pupils) is maintained for extended periods (Aaron and Howland 1998; Ellenhorn 1997; Proctor et al. 1988). Pralidoxime (2-PAM) acts to reactivate acetylcholinesterase and is given in conjunction with atropine therapy. It is most effective if administered shortly after exposure to methyl parathion because the inhibited acetylcholinesterase molecule becomes resistant to reactivation (aging) within several hours (24–36 hours). Therapy with 2-PAM is continued for at least 18 hours (Aaron and Howland 1998; Ellenhorn 1997; EPA 1989b). However, prophylactic administration of atropine and/or 2-PAM prior to organophosphate exposure is not recommended (EPA 1989b). The intermediate syndrome, which has been reported for some organophosphate pesticides, including a mixture of parathion and methyl parathion, may cause respiratory insufficiency or arrest 1–4 days after resolution of the acute cholinergic crisis. Therefore, patients exposed to organophosphates associated with this syndrome are observed for a more prolonged period of time, and may be continued on 2-PAM therapy after resolution of the cholinergic crisis (Aaron and Howland 1998).

Following inhibition by methyl parathion, acetylcholinesterase activity recovers as a result of the synthesis of new enzyme, generally at a rate of approximately 1% per day. However, the symptoms of methyl parathion poisoning usually resolve much more rapidly. Therefore, even though they are symptom-free, persons poisoned by methyl parathion may be hypersusceptible to its effects and should avoid reexposure for several weeks (Aaron and Howland 1998; Proctor et al. 1988).

3.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of methyl parathion is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of methyl parathion.

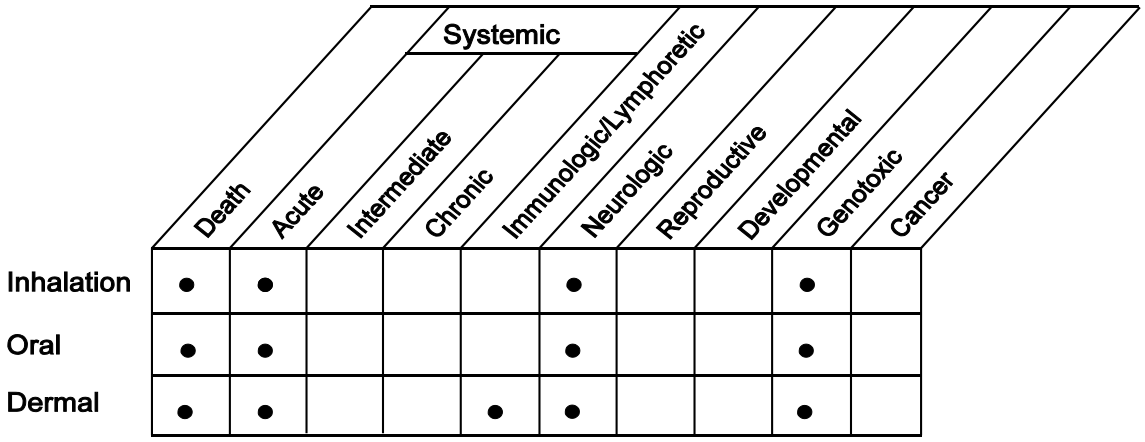
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Methyl Parathion

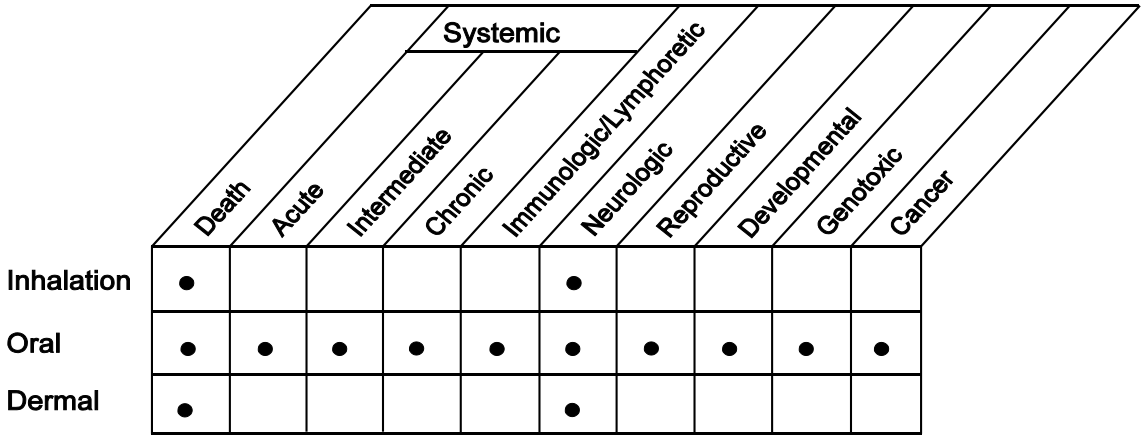
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to methyl parathion are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of methyl parathion. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 3-5 graphically depicts the information that currently exists on the health effects of methyl parathion in humans and animals by various routes of exposure. The available literature reviewed concerning the health effects of methyl parathion in humans described case reports of longer-term studies of pesticide workers and case reports of accidental or intentional ingestion of methyl parathion. The occupational exposure is believed to be via the dermal and inhalation routes. The information on human exposure is limited in that the possibility of concurrent exposure to other pesticides or other toxic substances cannot be quantified.

Figure 3-5. Existing Information on Health Effects of Methyl Parathion



Human



Animal

● Existing Studies

The database for the health effects of methyl parathion after ingestion in experimental animals is substantial. However, as can be seen in Figure 3-5, only limited information is available on the effects of inhalation and dermal exposure to methyl parathion in animals. Furthermore, the health effects such as death and neurotoxicity resulting from acute exposure in animals are more fully studied than systemic and immunotoxic effects associated with acute exposure.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Information is available regarding acute-duration exposure in humans and animals following exposure by all three routes. However, the studies in humans via the inhalation and dermal routes involved combined exposure by both routes (Dean et al. 1984; Fazekas 1971). Acute ingestion of high doses and combined exposure to methyl parathion via inhalation and dermal routes result primarily in neurological and systemic effects in humans (Dean et al. 1984; Fazekas 1971; Fazekas and Rengei 1964). However, exposure levels in these studies were not quantified. An experimental study in humans at very low oral doses resulted in no neurological effects, but involved only two subjects, and no concurrent controls (Rodnitzky et al. 1978). The target of toxicity in humans and animals following acute, high-level exposure by any route is the nervous system (Dean et al. 1984; EPA 1978e; Miyamoto et al. 1963b; Yamamoto et al. 1982; Youssef et al. 1987). The observed effects on the liver (Fazekas 1971; Fazekas and Rengei 1964; Sonnenschein et al. 1989a, 1989b) and respiratory (EPA 1978e; Fazekas 1971) systems may be primary or secondary effects of methyl parathion toxicity following acute oral exposure in experimental animals. The observed effects have also been seen in humans from oral exposure and from combined exposure by the inhalation and dermal routes (Fazekas 1971; Fazekas and Rengei 1964). For the oral route, the highest NOAEL below a LOAEL was 0.88 mg/kg/day for developmental effects in rats (Desi et al. 1998), and this dose level was too close to a serious LOAEL of 1 mg/kg/day for neurodevelopmental effects in rats (Crowder et al. 1980) to be used for MRL derivation. Additional acute oral studies that could provide dose-response information at low exposure levels are needed. Only qualitative human data (exposure level and duration not quantified) and animal LC_{50} data are available for the inhalation route of exposure (Dean et al. 1984; Fazekas 1971; Kimmerle and Lorke 1968). No dose-response data are available. Data on neurological effects in humans or animals are not sufficient to derive an acute inhalation MRL (Dean et al. 1984; EPA 1978e). Therefore additional inhalation studies are needed. The available toxicokinetic data are not adequate to predict the behavior of methyl parathion across the routes of exposure. The limited toxicity information available indicates that similar effects are observed (i.e., death, neurotoxicity) in both animals (EPA 1978e; Miyamoto et al. 1963b; Nemec et al. 1968; Yamamoto et al. 1982; Youssef et al. 1987) and humans (Dean et al. 1984;

Fazekas 1971) exposed by various routes. Because of a lack of toxicokinetic data, it cannot be assumed that the end points of methyl parathion toxicity would be quantitatively similar across all routes of exposure. The acute effects of dermal exposures to methyl parathion are not well characterized in humans or animals. Therefore, additional dermal studies are needed.

Intermediate-Duration. No information is available on the toxicity of methyl parathion to humans following intermediate-duration exposure by any route. In an oral study in humans, 30 mg of methyl parathion administered to adult males daily for 30 days depressed erythrocyte cholinesterase levels to 37% of preexposure values; this abstract did not indicate whether toxicity was produced (Rider et al. 1971). Information is available regarding intermediate-duration exposure in animals following oral exposure; toxicity in animals is manifested by neurological (Daly 1989; Desi et al. 1998; Williams et al. 1959), gastrointestinal (NCI 1979), developmental (Gupta et al. 1985), and immunological (Shtenberg and Dzhunusova 1968; Street and Sharma 1975) effects. An intermediate-duration gavage study of methyl parathion in rats identified hematological effects of anemia (decreased erythrocyte count and hematocrit) and slight leukocytosis with neutropenia and lymphocytosis (Galal et al. 1977). However, this study had severe limitations (i.e., a dosing design which did not allow establishing effect levels) that precluded its use. These limitations included increases in dose every 4 days, lack of controls, abnormal before-treatment values, irregularities in calculations, and disparities between the text and tables. A more reliable intermediate-duration gavage study in rats found no change in leukocyte counts or differential counts (Crittenden et al. 1998). Nevertheless, because erythrocyte cholinesterase has an action of controlling erythrocyte permeability (Wills 1972), experimental data on the hematological effects of intermediate-duration exposure to methyl parathion are needed. The oral exposure data in animals from the Desi et al. (1998) study are sufficient to derive an intermediate oral MRL based on adverse neurological effects. Additional studies examining the dose-response and critical periods for neurobehavioral developmental effects of intermediate-duration oral exposure to methyl parathion are needed. Since no data are available for the inhalation route of exposure, an intermediate inhalation MRL could not be derived. The available toxicity data are not adequate to predict the behavior of methyl parathion across routes of exposure. The limited toxicity information available indicates that similar effects are observed (i.e., neurotoxic) in animals following oral, inhalation, or dermal exposure. However, it cannot be assumed that the end points of methyl parathion toxicity are quantitatively similar across all routes of exposure, and, therefore, it may not be possible to predict the levels that cause these effects by all routes of exposure. The dermal and inhalation studies of intermediate duration are needed to identify more accurately the end points of toxicity and the levels at which these effects are observed.

Chronic-Duration Exposure and Cancer. No information is available on the toxicity of methyl parathion in humans following chronic-duration exposure by any route. The oral exposure data in animals from the Suba (1984) study are sufficient to derive a chronic oral MRL based on adverse hematological effects (Suba 1984). No chronic-duration exposure data are available for the inhalation or dermal routes of exposure. Therefore, no MRL for a chronic exposure duration could be derived for the inhalation route. No data regarding potential hematological effects of inhalation or dermal exposure are available for any duration. Because other effects of methyl parathion, such as neurological effects, are seen for all three routes of exposure, hematological effects also may occur following inhalation or dermal exposure; additional testing is needed. The toxicity information available for acute-duration exposures indicate that similar effects are observed in the central nervous system from oral, inhalation, and dermal exposures. Neurological effects were observed in chronic oral exposure (Suba 1984). Additional data are needed to determine whether chronic inhalation exposures by the dermal and inhalation routes also affect the nervous system. Additional studies are needed to identify end points, in addition to the hematological and nervous systems, that are affected by chronic exposures via each of these routes, and the levels at which these effects would be observed.

No reports of cancer in humans associated with exposure to methyl parathion by any route have been found. The carcinogenicity of methyl parathion has been studied in two chronic oral bioassays using rats (NCI 1979; Suba 1984) and mice (NCI 1979). The available data in experimental animals are negative. However, limitations associated with the study by NCI (i.e., a small control group, dose adjustments during the study, high mortality in high-dose female rats, and lack of cholinesterase measurements, hematology, or clinical chemistry) render this study inappropriate for use in drawing conclusions regarding the carcinogenicity of methyl parathion.

EPA (1988a) has discussed the results of another carcinogenicity bioassay on methyl parathion in rats. Results of this study have not been presented in a peer-reviewed scientific journal and are not available to the public.

Genotoxicity. No reliable data in humans exist to indicate whether methyl parathion may act by a genotoxic mechanism. One study reported a temporary but significant increase in chromatid breaks and stable chromosomal aberrations in two subjects after ingestion of methyl parathion (Van Bao et al. 1974), but another study reported no significant differences in five subjects after ingestion of methyl parathion when compared with 15 controls (Czeizel 1994). A study that involved combined inhalation and dermal exposure of workers to methyl parathion showed no increase in chromosomal aberrations in their

lymphocytes (De Cassia Stocco et al. 1982). The results of available *in vivo* studies in animals (Degraeve et al. 1985; Grover and Malhi 1985; Huang 1973; Mathew et al. 1992; Tripathy et al. 1987; Waters et al. 1982) and the results of *in vitro* studies (Chen et al. 1981; Dean 1972; Degraeve et al. 1985; Gomez-Arroyo et al. 1987; Griffin and Hill 1978; Huang 1973; Kumar et al. 1993; Mohn 1973; Rashid and Mumma 1984; Shigaeva and Savitskaya 1981; Sobti et al. 1982; Waters et al. 1982) are equivocal.

Since *in vivo* tests in exposed human populations would involve concomitant exposure to other toxicants, it would be difficult to assess the genotoxic potential of methyl parathion alone. Therefore, additional well-designed *in vitro* studies using human cell lines are needed to determine the effects of methyl parathion on various genotoxic parameters (e.g., sister chromatid exchange, chromosomal aberrations, unscheduled DNA synthesis).

Reproductive Toxicity. No information is available in humans to indicate that methyl parathion affects reproductive function. No information is available on the reproductive effects in animals of inhaled or dermally administered methyl parathion. The limited available data indicate that methyl parathion is not toxic to male germ cells of mice following oral exposure (Degraeve et al. 1985; Waters et al. 1982), except possibly at very high doses (Mathew et al. 1992; Pagulayan et al. 1994). Also, negative data exist for histopathological effects on the reproductive system of dogs following ingestion of methyl parathion in the diet (Suba 1981). Additional studies in animals are needed to fully assess the reproductive toxicity of methyl parathion.

EPA (1988a) has discussed the results of two reproductive studies in rats. Results of these studies have not been presented in peer-reviewed scientific journals and are not available to the public. If these data become available, they will provide valuable information on the reproductive hazards of methyl parathion.

Developmental Toxicity. No information is available in humans to indicate that methyl parathion affects development. Rapid (within 30 minutes to 1 hour) placental transfer of methyl parathion has been demonstrated in rats following oral (Ackermann and Engst 1970) and dermal (Abu-Qare et al. 2000) administration to the dams. Oral studies in rats indicate that methyl parathion can induce subtle behavioral alterations in offspring at doses that do not induce clinical signs of maternal toxicity and can reduce acetylcholinesterase activity in maternal and fetal brain (Crowder et al. 1980; Gupta et al. 1985). Oral administration of methyl parathion to rat dams only during gestation or gestation and lactation did not affect electrocorticograms and evoked potentials in their offspring at 12 weeks of age, but similar

administration to the dams followed by direct administration to the offspring from weaning through 12 weeks of age did affect these end points in a dose-related manner (Desi et al. 1998). Although these studies indicate that methyl parathion may be a developmental neurotoxicant, all three studies have limitations of experimental design or reporting. No NOAEL was identified for the neurobehavioral effects and the dosing regimens were inadequate to demonstrate a dose response. The reporting of experimental design and results lacked detail in the electrophysiological study. A well-designed developmental neurotoxicity study is needed to confirm and extend these observations, and to define the dose-response and critical periods for neurotoxicity. There is some evidence of neurotoxicity in adult humans and animals from inhalation and dermal toxicity. If methyl parathion is confirmed as a developmental neurotoxicant by the oral route, it would likely be a developmental neurotoxicant by these routes as well. Further testing would be needed to confirm this.

Immunotoxicity. Only a single case report of skin allergy to methyl parathion has been reported in humans (Lisi et al. 1987). No studies are available in humans exposed to methyl parathion via the inhalation or oral route. Based on limited animal studies, immunotoxicity may be a sensitive end point of methyl parathion-induced toxicity (Shtenberg and Dzhunusova 1968; Street and Sharma 1975). Thus, humans may be at risk for adverse immunological effects following exposure to methyl parathion. The limited information available on the effects of combined exposure to methyl parathion suggest the its toxicity is not route-dependent. Therefore, there is no reason to suspect that the immunotoxic effects observed following oral exposure of animals are route-specific.

Some animal studies indicate that dietary exposure to methyl parathion causes decreased humoral and cellular responses (Shtenberg and Dzhunusova 1968; Street and Sharma 1975). A more recent, well-designed animal study that included a battery of immuno/lymphoreticular end points showed few effects at the nonneurotoxic doses tested (Crittenden et al. 1998). No adequate studies are available in humans to assess the immunotoxic potential of methyl parathion. Therefore, studies measuring specific immunologic parameters in occupationally exposed populations are needed to provide useful information. Further studies are also needed to investigate the mechanism for methyl parathion-induced immunotoxicity since this information would help to identify special populations at risk for such effects.

Neurotoxicity. Information in both humans and animals indicates that the nervous system is the major target of methyl parathion-induced toxicity following acute exposure by any route (Daly 1989; Dean et al. 1984; EPA 1978e; Fazekas 1971; Gupta et al. 1985; Nemec et al. 1968; Roberts et al. 1988; Suba 1984; Yamamoto et al. 1982; Youssef et al. 1987). The most prominent signs of acute exposure to methyl

parathion in humans via the oral and concomitant inhalation and dermal exposure routes are lethargy, nausea, vomiting, increased respiratory secretion, muscle fasciculations, and miosis (Dean et al. 1984). In rodents, oral exposure to methyl parathion causes convulsions, ataxia, abnormal gait, tremors, and behavioral impairment in offspring (EPA 1978e; Gupta et al. 1985; Miyamoto et al. 1963b; Suba 1984). Since the information available on the neurotoxic effects of methyl parathion indicates that the chemical behaves similarly across routes of exposure (Dean et al. 1984; EPA 1978e; Skinner and Kilgore 1982a, 1982b), it is unlikely that the neurotoxic effects observed following oral exposure are route-specific.

Neuropsychiatric disturbances have been seen in humans who had long-term exposure to high levels of organophosphates (Gershon and Shaw 1961); one case was associated with methyl parathion (Dille and Smith 1964). Moreover, the injection of methyl parathion into animals resulted in changes in brain components, such as increases in lipid content of the brain (Hasan and Khan 1985). Reliable information is lacking in humans on potential neurological effects of long-term, low-level exposure to methyl parathion as well as on potential long-term effects of acute high exposure to methyl parathion. This information can only be obtained from evaluation of cohorts exposed exclusively to methyl parathion, but data from subjects exposed to more than one organophosphate would still be helpful.

Epidemiological and Human Dosimetry Studies. The vast majority of reviewed literature concerning the health effects of methyl parathion in humans described case reports of occupational exposure or accidental or intentional ingestion of methyl parathion (Dean et al. 1984; Fazekas 1971; Fazekas and Rengei 1964; Rider et al. 1969; Rodnitzky et al. 1978). No epidemiological studies are available. The information on human exposure is limited because of the possible concurrent exposure to other chemicals, and the duration and the level of exposure to methyl parathion cannot be quantified from the information presented in these reports. Differences in formulation can also be a confounding factor. The most likely identifiable subpopulations exposed to methyl parathion are pesticide applicators, farm workers, individuals involved in the production of methyl parathion, or individuals exposed in recently and illegally sprayed homes or offices. Well-designed epidemiological studies of these exposed workers are needed. Specific assessments of cancer risks and examination of the effects of methyl parathion on the nervous, hematological, and immune systems would be important since these appear to be the major end points of toxicity in experimental animals. If methyl parathion causes adverse effects in any of these target organs or systems, then these human end points can be used to monitor methyl parathion exposure in individuals living near hazardous waste sites or in recently and illegally sprayed homes or offices.

Biomarkers of Exposure and Effect.

Exposure. Data are available on biomarkers of exposure of methyl parathion in humans and experimental animals. The data on the persistence of methyl parathion and its metabolites indicate that they are not reliable indicators for assessing long-term, low-level exposure (Abu-Qare et al. 2000; Dean et al. 1984; EPA 1978e; Fazekas 1971; Morgan et al. 1977; Ware et al. 1975) largely because methyl parathion is extensively metabolized and the metabolites are rapidly eliminated. Short-term (<1 day) biomarkers are total urinary 4-nitrophenol and alkyl phosphates (Morgan et al. 1977); these biomarkers are nonspecific. Blood methyl parathion is also a short-term biomarker (Abu-Qare et al. 2000; Ware et al. 1975) and is specific. Additional studies of the general population correlating methyl parathion metabolite levels with health status as well as with dietary habits would provide useful information for risk characterization and risk assessment.

Effect. There are no biomarkers of effects specific for methyl parathion. As an organophosphate pesticide, methyl parathion, in sufficient amounts, produces typical signs and symptoms of cholinergic stimulation. Plasma and RBC cholinesterase activities are widely used as biomarkers of exposure and effect for organophosphates, but alone, their levels do not predict whether adverse health effects will occur except in cases of significant inhibition. Data are available on cholinesterase levels in humans and animals following exposure to methyl parathion (Midtling et al. 1985; NIOSH 1976; Tafuri and Roberts 1987). Because baseline data for plasma and erythrocyte cholinesterase are not usually available for nonoccupationally exposed individuals, additional studies of normal values by age and sex are needed for assessing potential adverse effects. As mentioned under biomarkers of exposure, additional studies of the general population correlating methyl parathion metabolite levels with health status and dietary habits would be useful.

Absorption, Distribution, Metabolism, and Excretion. Evidence of absorption comes from the occurrence of toxic effects following exposure to methyl parathion by all three routes (Fazekas 1971; Miyamoto et al. 1963b; Nemec et al. 1968; Skinner and Kilgore 1982b). These data indicate that the compound is absorbed by both humans and animals. No information is available to assess the relative rates and extent of absorption following inhalation and dermal exposure in humans or inhalation in animals. A dermal study in rats indicates that methyl parathion is rapidly absorbed through the skin (Abu-Qare et al. 2000). Additional data further indicate that methyl parathion is absorbed extensively and rapidly in humans and animals via oral and dermal routes of exposure (Braeckman et al. 1983; Hollingworth et al. 1967; Ware et al. 1973). However, additional toxicokinetic studies are needed to elucidate or further examine the efficiency and kinetics of absorption by all three exposure routes.

Limited information from case reports is available regarding the distribution of methyl parathion in humans following dermal exposure with possible concomitant inhalation exposure (Ware et al. 1973, 1974, 1975). Following accidental oral or inhalation exposure to methyl parathion, clinical signs and symptoms or histopathological findings indicated that the compound was distributed to various tissues (Dean et al. 1984; Fazekas 1971; Fazekas and Rengei 1964). Although no quantitative information is available on the rate and extent of methyl parathion distribution in animals, the qualitative information for oral exposure does provide evidence as to the most likely target organs following both short- and long-term exposure (Galal et al. 1975; Gupta et al. 1985; Miyamoto et al. 1963b; Shtenberg and Dzhunusova 1968; Sonnenschein et al. 1989a, 1989b; Street and Sharma 1975; Williams et al. 1959). Only limited data exist for the distribution of methyl parathion in humans following dermal exposure. Information regarding distribution in animals following dermal exposure is available, but quantitative data may have been compromised since some degree of oral exposure may have also occurred (Abu-Qare et al. 2000). Therefore, additional data in animal studies are needed to determine the distribution and half-life in various tissues following inhalation, oral, dermal, and intravenous exposure.

The available information in humans regarding the metabolism of methyl parathion is limited to *in vitro* studies (Hollingworth et al. 1973). However, the *in vitro* (Benke and Murphy 1975; Benke et al. 1974; Hollingworth et al. 1973; Nakatsugawa et al. 1968; Neal and DuBois 1965) metabolic pathway of this chemical has been characterized in animals.

No studies were located regarding excretion of methyl parathion in humans following inhalation exposure. The limited information available from human case studies indicates that the chemical's metabolites are rapidly excreted primarily in the urine in humans following oral (Morgan et al. 1977) or dermal (Ware et al. 1974, 1975) exposure and in animals following oral (Hollingworth et al. 1973) or dermal (Abu-Qare et al. 2000) exposure.

Practically all toxicokinetic properties reported are based on the results from acute exposure studies. Generally, no information was available regarding intermediate or chronic exposure to methyl parathion. Because methyl parathion is an enzyme inhibitor, the kinetics of metabolism during chronic exposure could differ from those seen during acute exposure. Similarly, excretion kinetics may differ with time. Thus, additional studies on the distribution, metabolism, and excretion of methyl parathion and its toxic metabolite, methyl paraoxon, during intermediate and chronic exposure are needed to assess the potential for toxicity following longer-duration exposures.

Comparative Toxicokinetics. The data available on the toxicity of methyl parathion in humans are from acute exposure where neurotoxicity is the end point of concern (Dean et al. 1984; Fazekas 1971). This effect is also seen in animals after acute exposure (EPA 1978e; Miyamoto et al. 1963b; Yamamoto et al. 1982; Youssef et al. 1987). In addition, hepatic and gastrointestinal effects have also been observed in humans (Fazekas 1971; Fazekas and Rengei 1964) and animals (NCI 1979; Sonnenschein 1989a, 1989b). It is unclear whether these effects are primary or secondary. No toxicokinetic studies have been performed in humans, and information on the rate and extent of absorption, distribution, half-life in various animal tissues, and excretion is primarily limited to a single dermal study in a single animal species (Abu-Qare et al. 2000). Additional studies on the comparative toxicokinetics of both methyl parathion and methyl paraoxon by various routes of exposure are needed to resolve uncertainty associated in assessing the health risks.

Methods of Reducing Toxic Effects. There is good information on the procedures used to limit absorption and to interfere with the mechanism of action of methyl parathion after acute exposures (Aaron and Howland 1998; Bronstein and Currance 1988; EPA 1989b; Proctor et al. 1988; Stutz and Janusz 1988). However, no information is available on dealing with long-term, low-level exposures. This may be due, in part, to the limited information on toxic effects associated with such exposures. If additional information becomes available indicating adverse health effects of long-term exposures, then studies examining methods for mitigating the effects of such exposures would become a data need.

Children's Susceptibility. Present information indicates a potential for age-related differences in susceptibility to methyl parathion. However, data are limited in both human and animal studies. In future incidents involving methyl parathion poisoning of both children and adults, better estimates should be made on exposure levels, exposure routes, and urinary metabolite levels relative to the observed symptoms of toxicity. Additional animal studies are needed to further investigate the effects of methyl parathion on developing nervous systems. Other studies could compare neurological effects in immature animals of various ages with those seen in adults, particularly via the oral or inhalation exposure routes. Specific data needs relating to both pre- and postnatal exposures and development are discussed above under Developmental Toxicity. Furthermore, metabolic pathways and enzymatic activity for methyl parathion should be more clearly elucidated since potential age-related differences in the ability to metabolize methyl parathion could result in age-related differences in toxicity; suggestive evidence of age-related differences in metabolism was reported in rats (Benke and Murphy 1975). Biomarkers of exposure need to be further studied in order to better estimate human exposure at all age levels following acute or chronic exposure to methyl parathion. No information was located regarding pediatric-specific

methods for reducing peak absorption following exposure to methyl parathion or reducing body burden. The information available indicates that methods to reduce peak absorption of methyl parathion and to interfere with the mechanism of action used for intoxication in adults are applicable to children. Developmental studies in animals are needed to quantitatively measure placental transfer of methyl parathion, to determine whether methyl parathion can be metabolized by placental tissue, and to further evaluate the transfer of methyl parathion and its metabolites to breast milk.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

A study of the dermal toxicokinetics of methyl parathion in female rats, sponsored by ATSDR, is being conducted at the University of Mississippi Medical Center. The principal investigator is Dr. Ing K. Ho, Department of Pharmacology and Toxicology, 500 North State Street, Jackson, Mississippi 39216-4505.

ATSDR is conducting a health study to investigate the lasting health effects of methyl parathion exposure on children. In this study, ATSDR will be testing children in two states, Ohio and Mississippi. The principal Investigator is Dr. Rubina Imtiaz, ATSDR Division of Health Studies, 1600 Clifton Road, Atlanta, Georgia 30333.

4. CHEMICAL AND PHYSICAL INFORMATION

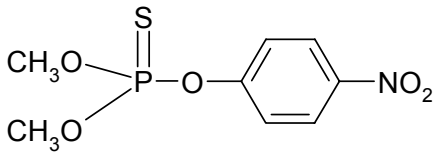
4.1 CHEMICAL IDENTITY

The chemical identity of methyl parathion is shown in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of methyl parathion are summarized in Table 4-2.

Table 4-1. Chemical Identity of Methyl Parathion

Characteristic	Value	Reference
Chemical name	Methyl parathion	Budavari 1989
Synonyms	Dimethyl 4-nitrophenyl phosphorothioate; dimethyl *p*-nitrophenyl phosphorothioate; dimethyl *p*-nitrophenyl thiophosphate; dimethyl parathion; O,O-dimethyl O-(*p*-nitrophenyl) phosphorothioate	HSDB 1999
Trade names	A-Gro; Metaphos; Bay 11405; Bladan-M; Cekumethion; Dalf; Devithion; Drexel Methyl Parathion 4E; ENT 17,292; Floidal M; Gearphos; M40 & 80; ME-Parathion	IARC 1983; NPIRS 1986; RTECS 1989
Manufacture trade names	Paratox; Bladan; Metacide; Morphos; Frog; Parataf; Romethyl-P; Prompt; Sweeper; Fortune-P1; Silmepar; Metpar; Paramet; Foxy	Meister et al. 1999
Formulators' trade names	Amithion; Agrodol; Paration Metilico 500 or 720; Agro-Parathion; Vitamethion; Cekmethion; Devithion; Dhanudol; Penncap-M; Bration; Methion; Kikdot; Parathol; Woprophos-M; Parasul; Gearphos; Kilex Parathion; Metaphos; Patron M; Tekwaisa	Meister et al. 1999
Discontinued names	Paraton; Wofatox; Veto; Fosferna M50; Nitrox 80; Parapest M050; Sytemp	Meister et al. 1999
Chemical formula	$C_8H_{10}NO_5PS$	Budavari 1989
Chemical structure		Budavari 1989
Identification numbers:		
CAS registry	298-00-0	HSDB 1999
NIOSH RTECS	TG0175000	HSDB 1999
EPA hazardous waste	P071	HSDB 1999
OHM/TADS	7216537	HSDB 1999
DOT/UN/NA/IMCO shipping	Methyl parathion, liquid (DOT); Methyl parathion mixture, dry (DOT); methyl parathion, solid (DOT); UN 3017; organophosphorus pesticides, liquid, toxic, flammable, not otherwise specified	HSDB 1999; RTECS 1989
HSDB	NA 2783 (DOT)	HSDB 1999
NCI	1168 NCI-C02971	RTECS 1989 HSDB 1999

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data Systems; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Methyl Parathion

Property	Information	Reference
Molecular weight	263.23	Budavari 1989
Color	White solid (pure) or brownish liquid (technical)	Weiss 1986
Physical state	Solid (crystals from cold methanol)	Budavari 1989
	Solid	Weiss 1986
Melting point	37–38 EC	Budavari 1989
Boiling point	154 EC at 136 Pa Decomposes above ambient temperature	HSDB 1999
	Decomposes violently at 120 EC	Keith and Walters 1985
Density at 20 EC	1.358 g/mL	Budavari 1989
Odor	Characteristic, like rotten eggs or garlic	Keith and Walters 1985; Weiss 1986
Odor threshold:		
Water	No data	
Air	0.012 ppm	Ruth 1986
Solubility:		
Water at 25 EC	50 ppm	Budavari 1989
Organic solvents	Soluble in ethanol, chloroform, and aromatic and aliphatic solvents	Sunshine 1969
	$10 mg/mL (at 23 EC) in DMSO and ethanol; very soluble in acetone	Keith and Walters 1985
	Sparingly soluble in petroleum ether and some types of mineral oil	Tomlin 1994
Partition coefficients:		
Log octanol/water (K_{ow})	2.86	Hansch et al. 1995
Log K_{oc}	2.7	EPA 1980c
Vapor pressure at 20 EC	$9.7x10^{-6}$ mm Hg	Keith and Walters 1985
Henry's law constant	$6.2x10^{-6}$ atm m^3/mol	Sanders and Seiber 1983
	$4.4x10^{-7}$ atm m^3/mol	Mackay and Shiu 1981
Autoignition temperature	No data	
Flashpoint	31.9 EC (open cup)	NFPA 1986
Flammability limits	No data	
Conversion factors	1 ppm = 10.8 mg/m^3	
Explosive limits	May develop sufficient internal pressure at ambient temperature to cause a container to rupture violently	NFPA 1986
	Explosion risk when heated	Hawley 1987

DMSO = dimethylsulfoxide

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Methyl parathion is an organophosphorus insecticide that is commercially produced in the United States and abroad. Methyl parathion, O,O-dimethyl O-(4-nitrophenyl) phosphorothioate, is not known to occur as a natural substance (IARC 1983). It is commercially produced by the reaction of O,O-dimethyl phosphorochloridothionate and the sodium salt of 4-nitrophenol in acetone solvent (EPA 1974b; HSDB 1999; NIOSH 1976; NRC 1977; Worthing 1979).

Methyl parathion was first commercially produced in the United States in 1952 (U.S. Tariff Commission 1953) and was registered as an organophosphate insecticide in 1954 (NPIRS 1986). Production volume data are not available for the 1950s and 1960s and are sporadically available for the 1970s. In 1973, domestic production of methyl parathion was approximately 23.2 million kg (NRC 1977), while in 1975, it had increased to 24.4 million kg (USITC 1977a). A significant decline in production of methyl parathion occurred in 1977; the production levels dropped by 5.6 million kg from 1975 levels to 18 million kg (USITC 1979). Production volume statistics for methyl parathion are not listed separately after 1977. In 1983, the combined domestic production capacity of methyl parathion and parathion was estimated at 29 million kg (IARC 1983). In the same year, production in western Europe was estimated in the range of 10–15 million kg annually (IARC 1983). No recent production data are available.

Methyl parathion is produced or formulated in the United States by Cheminova Agro A/S, Griffin Corporation, and Elf Atochem North America (EPA 1999c). A summary of all of the manufacturers of methyl parathion in the United States was not located. Monsanto Co. and Kerr-McGee Chemical Corp. were the major producers for the period 1972 through 1988 (USITC 1973, 1975, 1977b, 1979, 1981, 1982, 1983, 1984, 1985, 1986a, 1986b, 1987, 1989). Table 5-1 provides the production year, number of facilities, and the state of their location for each known domestic producer or formulator required to report Toxics Release Inventory (TRI) data to satisfy EPA requirements. TRI data are available for this chemical because it is on the list of chemicals for which annual releases are required to be reported to the EPA.

Methyl parathion is marketed as a technical grade solution (80% methyl parathion) or in emulsifiable concentrate, wettable powder, ultra-low volume (ULV) liquid, dustable powder, and encapsulated suspension forms (HSDB 1999). The technical grade solution contains 80% active ingredient, 16.7%

Table 5-1. Facilities that Produce, Process, or Use Methyl Parathion

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
GA	1	1,000,000	9,999,999	8
MS	1	10,000	99,999	8
TX	1	10,000	99,999	13

Source: TRI99 2001

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses

xylene, and 3.3% inert ingredients. Stabilized methyl parathion solution is also available and contains 80.0% active ingredient, 14.8% xylene, and 5.3% inert ingredients (IARC 1983). Methyl parathion is formulated and sold in mixtures with parathion (ethyl), malathion, and endosulfan (Berg 1981; EPA 1999c). There are over 50 trade names for formulations and preparations of methyl parathion, including Methaphos, Gearphos, Cekumethion, and Devithion (IARC 1983; Meister et al. 1999; NPIRS 1986).

5.2 IMPORT/EXPORT

In 1971, 3 million kg of methyl parathion were imported into the United States (U.S. Tariff Commission 1972). There was a decline in imports in the mid-1970s with levels of 499,000 kg in 1972 and only 40,000 kg in 1975 (HSDB 1999). By 1980, this downward trend had reversed, and imports of methyl parathion were up to 413,000 kg (USITC 1981).

In 1972, 5.68 million kg of methyl parathion were exported from the United States (HSDB 1999). Exports dropped to 3.01 million kg in 1984 (Bureau of the Census 1984). However, in 1985, exports increased to 4.14 million kg (Bureau of the Census 1986). No recent import/export data addressing methyl parathion are available.

5.3 USE

Methyl parathion is a broad-spectrum, nonsystemic, contact and stomach insecticide with some respiratory action used to control insects on a wide variety of crops (HSDB 1999; Tomlin 1994). Methyl parathion controls a wide variety of insects including plant lice, thrips, aphids, and boll weevils (International Labour Office 1983; Meister 1988; NPIRS 1986; Weir and Hazleton 1981). Methyl parathion has also been used to control mites and tadpole shrimp (NPIRS 1986). Methyl parathion has been applied to cotton, field vegetables, rice, fruit trees, soybeans, alfalfa, nut crops, tobacco, ornamentals, forest trees, aquatic food crops, and mosquito breeding sites (IARC 1983; NPIRS 1986; Spencer 1982). Methyl parathion is generally applied to the leaves or the aerial portion of the crop using either aircraft or ground spray equipment (NPIRS 1986).

Because of its very high acute toxicity, methyl parathion is a restricted-use pesticide (EPA 1985b). In the United States, methyl parathion formulations must be used under the direct supervision of a certified pesticide applicator (EPA 1980b). The certified pesticide applicator must be physically present during mixing, loading, application, equipment repair, and equipment cleaning (NPIRS 1986). Originally, no

worker was allowed to enter a field treated with methyl parathion <48 hours after the treatment (EPA 1980b); that interval has been increased to 4–5 days (EPA 1999d). EPA has canceled many of the food crop uses of methyl parathion, including fruits and vegetables commonly eaten by children, some other vegetable uses, some feed uses, and all nonfood uses such ornamental plants and nursery stock uses. This action was taken because of a concern for risks to children and to workers. Some food and feed uses are to be maintained (EPA 1999d, 1999e).

Data related to the domestic use of methyl parathion by volume for the years 1973–1984 show that use of methyl parathion was estimated to be 18.1 million kg in 1973 (NRC 1977) and 21.8 million kg in 1974 (USDA 1978). In 1976, only 10.4 million kg of methyl parathion were used by U.S. farmers on major crops; however, this represents 17.5% of the total quantity of all active insecticide ingredients used on those crops in 1976 (USDA 1978). In 1978, total usage of methyl parathion is estimated to have been 11.3 million kg; of this amount, an estimated 9.7 million kg of methyl parathion were used on cotton (USDA 1978). The reduction in use from 1974 to 1978 is generally attributed to the development of resistant insect strains and the use of integrated pest management practices (USDA 1978). The use of methyl parathion as a substitute for DDT in the late 1970s and early 1980s served to increase usage and reverse this downward trend (Butler et al. 1981b). The amount of methyl parathion used in the United States in 1989 was estimated to be 7.65 million pounds active ingredient/year (HSDB 1999). For the period 1987–1997, the annual amount used was 4.2 million pounds of methyl parathion per 5 million acres treated (EPA 1999c).

Data collected from federal and state pesticide surveys of insecticide use (Giannessi and Anderson 1995) show the following crops were treated with methyl parathion in the United States during the 1992 crop year: alfalfa, apples, artichokes, barley, broccoli, brussel sprouts, cabbage, cantaloupes, carrots, cauliflower, celery, cherries, collards, corn, cotton, dry bean, dry peas, grapes, green beans, green peas, lettuce, nectarines, oats, onions, other hay, peaches, pears, pecans, potatoes, rice, soybeans, spinach, strawberries, sugarbeets, sunflowers, sweet corn, sweet peppers, tomatoes, watermelons, and wheat. Table 5-2 shows the total number of pounds per acre of methyl parathion that were applied to crops in each state in 1992.

Table 5-2. Methyl Parathion Use in Crop Production in 1992

State	Pounds active ingredient/acre/year
Alabama	365,640
Arizona	87,203
Arkansas	237,731
California	85,432
Colorado	12,682
Connecticut	1,449
Delaware	21,125
Florida	19,939
Georgia	75,576
Idaho	14,893
Illinois	101,443
Indiana	17,390
Iowa	5,927
Kansas	201,749
Kentucky	8,700
Louisiana	889,789
Maryland	6,654
Massachusetts	1,264
Michigan	61,118
Minnesota	21,080
Mississippi	1,818,501
Missouri	50,311
Montana	31,341
Nebraska	507,880
New Jersey	7,101
New Mexico	6,146
New York	28,018
North Carolina	5,227
North Dakota	163,620
Ohio	1,984
Oklahoma	484,960
Oregon	12,266
Pennsylvania	14,758

Table 5-2. Methyl Parathion Use in Crop Production in 1992 *(continued)*

State	Pounds active ingredient/acre/year
Rhode Island	178
South Carolina	83,670
South Dakota	12,540
Tennessee	3,850
Texas	274,446
Utah	5,328
Virginia	19,972
Washington	115,689
West Virginia	11,337
Wisconsin	59,485
Wyoming	169

5.4 DISPOSAL

In 1974, EPA recommended the incineration of methyl parathion at organic pesticide incinerators. If appropriate incineration facilities were not available, then open field burial at designated landfills was permitted (EPA 1974a). EPA also recommended that combustible containers used for methyl parathion be disposed of in pesticide incinerators or in designated landfills. Noncombustible containers should first be triple rinsed and, if in good condition, returned to the manufacturer or a drum reconditioner for reuse with methyl parathion. Noncombustible containers that are not to be reused should be punctured and transported to a scrap metal facility for recycling or buried in a designated landfill site (EPA 1974a).

In 1980, methyl parathion waste became subject to the Resource Conservation and Recovery Act (RCRA). According to RCRA, when methyl parathion becomes a waste (e.g., as an off-specification batch produced by a manufacturer) it must be managed as a hazardous waste according to federal and/or state regulations. Any containers used to hold this waste must also be managed as a hazardous waste (EPA 1980a). The RCRA hazardous waste code for methyl parathion is P071. When there is an accidental release of methyl parathion, the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) reportable quantity is 45.4 kg or 100 pounds (EPA 1985f). Methyl parathion is on the list of chemicals for which annual releases to the environment must be reported to the TRI as established by the EPA (EPA 1999c).

Improved methods for the disposal of methyl parathion are being considered. In 1981, methyl parathion was considered as a potential candidate for rotary kiln incineration and fluidized bed incineration (EPA 1981b). An accelerated degradation process for methyl parathion, which involved reducing the compound in soil with acid and zinc to its less toxic degradates, was found to be effective (Butler et al. 1981b). No recent information on disposal is available.

Effluent containing methyl parathion may not be discharged into lakes, streams, ponds, estuaries, oceans, or public waters unless the compound is specifically identified in a National Pollutant Discharge Elimination System (NPDES) permit. Moreover, discharge of effluent that contains methyl parathion is forbidden without prior notice to the sewage treatment plant authority (NPIRS 1986).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Methyl parathion is a broad-spectrum agricultural insecticide that is released to the environment primarily through spraying of the insecticide on a variety of agricultural products. Once methyl parathion is introduced to the environment, it is degraded by hydrolysis, photolysis, or by biodegradation from microorganisms found in most sediment, soils, and water. Methyl parathion is primarily confined to the application area, but some can be transported by rain, fog, and wind to other areas. Methyl parathion adsorbs to the soil and is relatively immobile. As a result, leaching into groundwater is not usually observed. Volatilization has been observed to occur from plants and soil postapplication, with volatilization from plants being the faster of the two. Limited studies show that bioconcentration of methyl parathion does not occur to a significant extent and that what is accumulated in plants and animals is rapidly metabolized. Methyl parathion is not widely dispersed or persistent in the environment. Residue amounts of methyl parathion have been detected in air, water, fish, soil, and agricultural crops consumed as foods.

Methyl parathion is approved by the EPA only for use on agricultural crops. As a result, the general population is not likely to be exposed to large amounts of methyl parathion. Some exposure to residues of methyl parathion is possible, however, as many studies show that methyl parathion has been detected in foods and atmosphere samples. Populations living within or very near areas of heavy methyl parathion use would have an increased risk of exposure to large amounts of methyl parathion through dermal contact with contaminated plants, by inhalation of the mist formed from the applied insecticide, or by ingestion of water or food-borne residues. Those likely to receive the highest levels of exposure are those who are involved in the production, formulation, handling, and application of methyl parathion. Dermal contact appears to be the major route of exposure, while inhalation may also be an important route of exposure for those working in these operations.

Methyl parathion has been identified in at least 16 of the 1,585 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2001). However, the number of sites evaluated for methyl parathion is not known. The frequency of these sites can be seen in Figure 6-1.

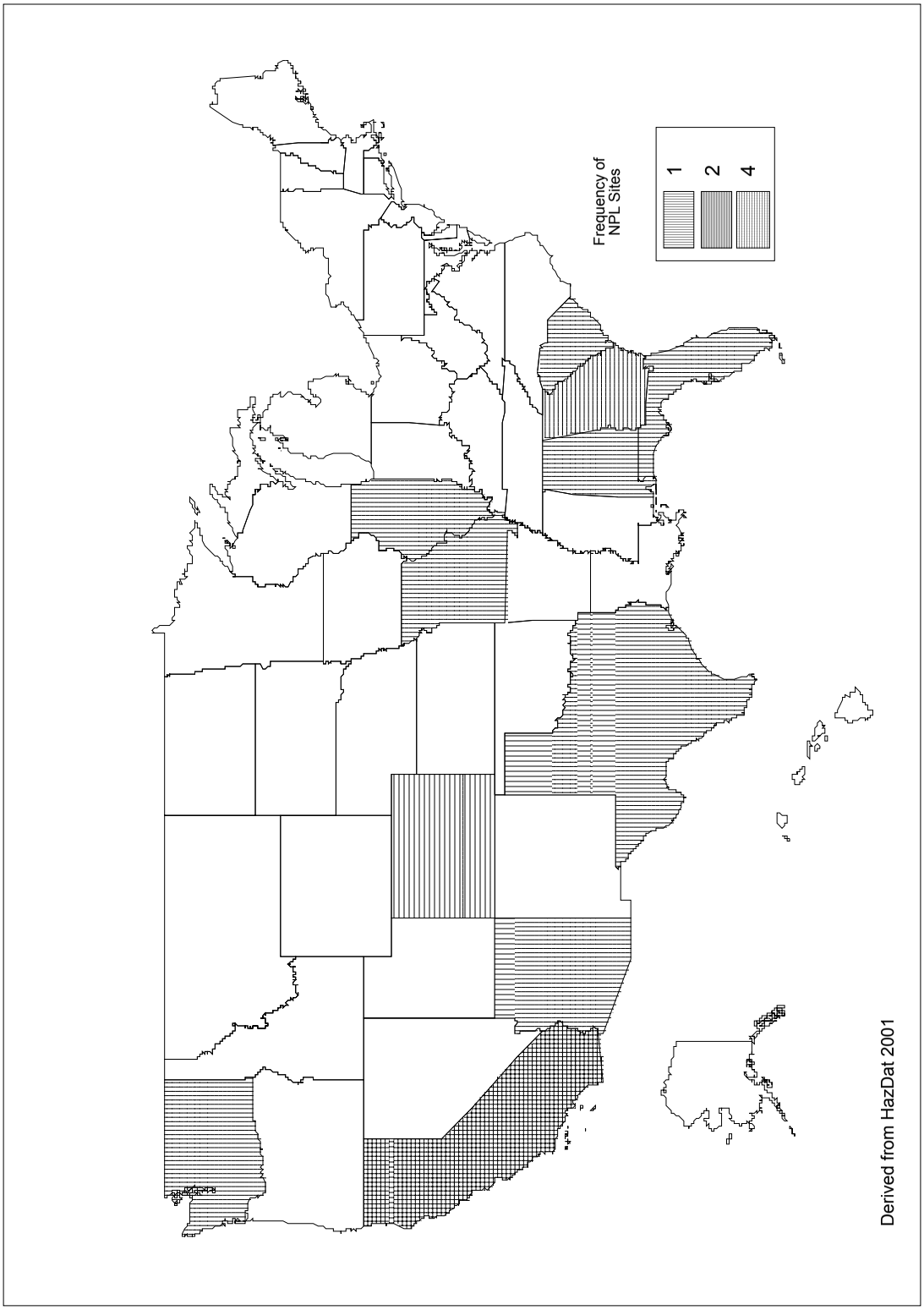


Figure 6-1. Frequency of NPL Sites with Methyl Parathion Contamination

6.2 RELEASES TO THE ENVIRONMENT

Methyl parathion has been released to the environment mainly as a result of its use as an insecticide on crops. It is applied to agricultural crops by aerial or ground spraying equipment. Methyl parathion has been detected in surface waters and sediments, rainwater, aquatic organisms, and food. There are no known natural sources of the compound. Methyl parathion has been identified in at least 16 of the 1,585 hazardous waste sites on the NPL (HazDat 2001).

According to recent Toxics Release Inventory (TRI) data, methyl parathion was discharged to air from two processing sites in the United States in 1999 (TRI99 2001). No releases to soil or water were reported. The TRI data should be used with caution because only certain facilities are require to report. This is not an exhaustive list.

6.2.1 Air

As a result of its use as an insecticide on cotton, fruit trees, vegetables, and other crops, methyl parathion is released directly to the atmosphere during application. It is applied primarily by spraying from aircraft or ground equipment (NPIRS 1986). Aerial application of methyl parathion to agricultural fields releases the insecticide to the air.

Methyl parathion may also be introduced into the air as a result of its volatilization from plant surfaces, and somewhat from soil, especially in the period just after application. Under simulated field conditions (20 EC; air velocity 1 meter/second; relative air humidity 40–60%), an emulsifiable concentrate formulation of methyl parathion was applied to bare soil and bean plants. After 24 hours, the amounts of methyl parathion that had volatilized from bare soil and bean plants were 5 and 64% of the applied amount, respectively (Rudel 1997).

Releases to the atmosphere from production facilities and disposal sites have also been reported. Studies have shown that releases of methyl parathion to the atmosphere occur in the vicinity of pesticide-producing factories. At two predominately downwind sites located 1 mile from a plant producing methyl parathion, average monthly concentrations were <0.57 and <0.64 ng/m^3 (Foster 1974). Air emissions from methyl parathion production facilities have been reported to contain 1.0 kg/1,000 kg pesticide produced. In addition, evaporation from holding ponds for pesticide waste potentially contributes 7.4 mg/1,000 kg pesticide produced to the atmosphere (EPA 1978d).

The most recent TRI data indicate that six sites in the United States processed methyl parathion in 1999 (TRI99 2001). The total of reported releases to air was 15 pounds, representing 100% of all environmental releases (Table 6-1). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

No information was found on the occurrence of methyl parathion in air samples collected at NPL sites.

6.2.2 Water

Methyl parathion can be released to surface waters by storm runoff from sprayed fields; atmospheric deposition following aerial application (wet deposition from rain and fog water); waste water releases from formulation, manufacturing, or processing facilities; and spills.

Methyl parathion has been detected in runoff water from a cotton field at a concentration of 15 ppb. A semi-empirical prediction formula used to predict maximum concentrations of pesticides in agricultural runoff water estimated methyl parathion concentrations could be as high as 40 ppb (Wauchope and Leonard 1980). Methyl parathion has been detected in fog water near sites of application (Schomburg et al. 1991) and in rainwater (Nations and Hallberg 1992), suggesting that methyl parathion can be released to surface waters by wet deposition, the process that occurs after airborne residues dissolve in water. Methyl parathion could be released to water through atmospheric deposition following aerial application, but no data are available for evaluating the importance of this route of surface water contamination. Methyl parathion can be released to surface water by the release of waste water containing pesticide residues. In one report, methyl parathion was detected in pre-, mid-, and posttreatment waste water from a methyl parathion production plant (EPA 1978e).

Spills may represent the greatest point source release of methyl parathion to groundwater and surface water. An accidental spill caused by a warehouse fire in Nebraska released methyl parathion to a drainage ditch that emptied into the Missouri River (Kawahara et al. 1967). In another incident, 10 tons of methyl parathion spilled in the Mediterranean Sea near Egypt as a result of a collision between two ships (Badawy et al. 1984).

The most recent TRI data indicate that no releases of methyl parathion to water for the six sites in the United States that processed methyl parathion in 1999 (TRI99 2001). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Methyl Parathion

State[b]	Number of facilities	Reported amounts released in pounds per year[a]						
		Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
AR	1	No data	No data	No data	No data	No data	No data	No data
GA	1	5	No data	No data	No data	5	No data	5
MS	1	10	0	No data	No data	10	No data	10
NE	1	No data	No data	No data	No data	No data	No data	No data
TX	2	0	No data	No data	No data	0	No data	0
Total	6	15	0	0	0	15	0	15

Source: TRI99 2001

[a]Data in TRI are maximum amounts released by each facility.
[b]Post office state abbreviations are used.
[c]The sum of fugitive and stack releases are included in releases to air by a given facility.
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[e]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

Methyl parathion is listed in the HazDat database of chemicals detected in surface water or groundwater at NPL sites.

6.2.3 Soil

Most of the methyl parathion deposited onto soils is through deposition of spray droplets that fall to the ground following spraying. An estimated 5.95 million pounds of methyl parathion were used on a variety of crops in the United States in 1992 (Gianessi and Anderson 1995).

Methyl parathion may also be released to soils by improper handling of pesticide formulations during processing or handling. In a sampling of soils collected from processing facilities in Illinois, methyl parathion was detected in soil at 2 of the 49 sites tested (Krapac et al. 1995).

The most recent TRI data indicate that no releases to soil were reported for the six sites in the United States that processed methyl parathion in 1999 (TRI99 2001). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.
Methyl parathion is listed in the HazDat database of chemicals detected in soils at NPL sites.

6.3 ENVIRONMENTAL FATE

The methyl parathion released to the atmosphere can be transported back to surface water and soil by wet deposition. Methyl parathion that is released to the atmosphere can also be transformed by indirect photolysis to its oxygen analog, methyl paraoxon, by oxidation with photochemically produced oxygen radicals. However, methyl parathion is not expected to undergo significant transformation to methyl paraoxon.

In surface waters, methyl parathion degrades by biotransformation, hydrolysis, volatilization, and photolysis (EPA 1978c, 1981a). Biodegradation is expected to be the predominant degradation process. Adsorption to sediment and suspended matter may significantly affect the degradation processes (Lartiges and Garrigues 1995).

In soil and sediments, methyl parathion adsorbs to soil and is expected to display moderate mobility (EPA 1980c). The major degradation process of methyl parathion in soil is biodegradation by microbes (Badway and El-Dib 1984). Degradation by hydrolysis has been observed to occur at higher temperatures

(Sharmila et al. 1988). Little methyl parathion appears to volatilize from soil (EPA 1984a) or leach into groundwater (Albanis et al. 1988a, 1988b; Jury et al. 1983, 1987a, 1987b; McLean et al. 1988).

6.3.1 Transport and Partitioning

Data indicate that methyl parathion generally does not remain in the air for long periods or migrate far from the application site following aerial application when wind conditions are satisfactory. Studies following application of methyl parathion indicate that it is rapidly removed from the atmosphere (Jackson and Lewis 1978), probably by wet and dry deposition. Methyl parathion has been detected in the water phase of fog (Glotfelty et al. 1987; Sharmila et al. 1988), suggesting wet deposition processes. Its deposition has been found to be confined primarily to the intended application site with negligible exposure estimated to occur 100 yards from the center of the target field (Draper and Street 1981). Wind conditions, which would be expected to be a factor in methyl parathion transport in air, were negligible in this study.

The vapor pressure of methyl parathion is relatively low ($9.7x10^{-6}$ mmHg), as is the Henry's law constant ($6.2x10^{-6}$ atm-m^3/mol) (EPA 1984a; HSDB 1999; Rice et al. 1997; Sanders and Seiber 1983). The volatilization of methyl parathion from soil and water has generally been found to be correspondingly low.

Mathematical models have also predicted a low volatility for methyl parathion (Jury et al. 1983; McLean et al. 1988). One study using a laboratory model designed to mimic conditions at soil pit and evaporation pond disposal sites (Sanders and Seiber 1983) did find a high volatility from the soil pit model (75% of the deposited material), but a low volatility for the evaporation pond model (3.7% of the deposited material). A study of methyl parathion and the structurally similar compound ethyl parathion, which have similar vapor pressures, found that methyl parathion underwent less volatilization than ethyl parathion; in a review of the data, the reduced level of volatilization for methyl parathion was determined to be due to its adsorption to the soil phase (Álvarez-Benedi et al. 1999).

Methyl parathion is only slightly soluble in pH 7 water (55–60 ppm). This affects its mobility in water and its ability to be leached or solubilized into the water phase of a soil-water system. Factors most likely to affect the adsorption of methyl parathion in soil are organic matter content and cation exchange capacity. In soils of low organic matter (e.g., subsurface soils), calcium concentration, which affects the hardness of the water, may also be important (Reddy and Gambrell 1987). Several studies have shown

that, in most cases, methyl parathion does not move very far from the soil surface following application (Albanis et al. 1988a, 1988b; Jury et al. 1983, 1987a; McLean et al. 1988). One reason for this limited mobility is that most of the methyl parathion may degrade before significant migration can occur.

The solubility of methyl parathion is not sufficient to pose a problem in runoff water as determined by an empirical model of Wauchope and Leonard (1980). Some recent monitoring data, however, indicate that methyl parathion has been detected in surface waters (Senseman et al. 1997). In a study to determine the residue levels of pesticides in shallow groundwater of the United States, water samples from 1,012 wells and 22 springs were analyzed for methyl parathion. No methyl parathion was detected in any of the water samples (Kolpin et al. 1998). In a study of water from near-surface aquifers in the Midwest, no methyl parathion was detected in any of the water samples from 94 wells that were analyzed for pesticide levels (Kolpin et al. 1995). Leaching to groundwater does not appear to be a significant fate process.

When the concentrations of methyl parathion in soil are high, such as those found at hazardous waste or spill sites, leaching may be a significant source of contamination (Albanis et al. 1988b; Jury et al. 1987a). Several authors have found soil adsorption isotherms to be linear at lower concentrations, but nonlinear at higher concentrations (EPA 1980c; Rao and Davidson 1979). This suggests that while methyl parathion may be relatively immobile in soil at the lower concentrations used in agriculture, it may be more mobile at the higher concentrations found at hazardous waste sites and spills.

One of the most important factors affecting the mobility of methyl parathion in the environment is its strong adsorption to soils. One study showed that after a 49-day incubation, 54% of the initial applied methyl parathion remained in the soil (Gerstl and Helling 1985). Factors affecting the adsorption of methyl parathion are organic matter content of the soil and sediment, and the cation exchange capacity of the soil. Values for organic-carbon normalized soil adsorption coefficients, K_{oc}, in five soil types were determined by EPA (1980c) and were found to average 496, equal to a log K_{oc} of 2.7. Estimates of log K_{oc}, calculated from the octanol-water coefficient (K_{ow}), solubility, and melting point data ranged from 2.93 to 3.47, and compared favorably with literature values (Karickhoff 1981). McLean et al. (1988) estimated a lower K_{oc} of 39, equal to a log K_{oc} of 1.59. More recently, a K_{oc} of 5,100, equal to log K_{oc} 3.7, has been reported (HSDB 1999). These K_{oc} values indicate that methyl parathion is moderately mobile to immobile in soil (Swann et al. 1983).

Estimates of bioconcentration factors, BCF, in aquatic organisms, based on calculations from water solubility and K_{oc}, gave a log BCF of 1.80–2.89 (Kenaga 1980). Studies in outdoor ponds yielded log

BCF factors in fish ranging from 1.08 to 1.85, indicating that bioconcentration of methyl parathion is not an important fate process (Crossland and Bennett 1984). In another study, methyl parathion was added to the water of a carp-rearing pond and the concentration of methyl parathion was measured in water, soil, macrophytes, and carp over a 35-day period. Results showed that methyl parathion accumulated in macrophytes for 1 day and in carp for 3 days following exposure, and then dissipated. The concentrations of methyl parathion decreased in macrophytes by 94% by day 35 and by 98% in carp tissue by day 28 (Sabharwal and Belsare 1986). These data indicate the potential for biomagnification in the food chain is likely to be low because methyl parathion appears to be metabolized in aquatic organisms.

6.3.2 Transformation and Degradation

6.3.2.1 Air

Very little information exists in the literature on the transformation and degradation of methyl parathion in air. An early study indicated that direct photolysis of methyl parathion may occur; however, the products of this photolysis were not determined (Baker and Applegate 1974). A later study found a transformation product of methyl parathion, methyl paraoxon, in air samples taken from areas where methyl parathion had been applied. Formation of methyl paraoxon was attributed to the vapor phase oxidation of methyl parathion (Seiber et al. 1989). Recent monitoring studies in California have also found both methyl parathion and methyl paraoxon (Baker et al. 1996).

6.3.2.2 Water

Methyl parathion is rapidly degraded in natural water systems. The degradation of methyl parathion occurs much more rapidly in alkaline (pH 8.5) than in neutral (pH 7) or acidic (pH 5) conditions (Badawy and El-Dib 1984). A hydrolysis half-life of 72–89 days was calculated for fresh water at 25 EC and pH<8 (EPA 1978c; Mabey and Mill 1978) compared with about 4 days at 40 EC and pH$8 (EPA 1978c). Under conditions typically encountered in the environment, with pHs between 5 and 9, methyl parathion is not expected to be a significant fate process.

The degradation of methyl parathion by hydrolysis and biodegradation was studied in four types of water (ultrapure water, pH 6.1; river water, pH 7.3; filtered river water, pH 7.3; and seawater, pH 8.1) maintained at 6 and 22 EC, in the dark. The half-lives of methyl parathion at 6 EC in the four water types were determined to be 237, 95, 173, and 233 days, respectively, and the half-lives at 22 EC were

determined to be 46, 23, 18, and 30 days, respectively. The study shows that degradation rates increase with pH and temperature, and are fastest in river water (Lartiges and Garrigues 1995).

Transformation and degradation of methyl parathion in water appear to be primarily biological (i.e., microbial), but chemical degradation (i.e., hydrolysis) may be important in some systems (EPA 1978c, 1981a). In oligotrophic waters (i.e., low in microbial populations), hydrolysis is the major degradation mechanism (Baughman and Lassiter 1978; EPA 1978c, 1981a). The rate of chemical hydrolysis depends on pH and temperature.

Studies in which methyl parathion is added to the water phase of sediment samples have detected no methyl parathion in the sediment, probably because the degradation rate exceeds the rate of deposition to the sediment (Crossland and Bennett 1984; EPA 1982b). This degradation appears to be primarily microbial. Experiments comparing the degradation of methyl parathion in tap water and natural pond water show similar rates of disappearance of methyl parathion. Loss rates increased in both water types when plants, sediment, or plants and sediment were added (Crossland and Bennett 1984). In experiments with seawater systems, seawater plus sediment contained only 3% of the applied methyl parathion after 7 days, compared with 75% in seawater alone and 104% in sterile seawater (EPA 1981a). Degradation in water alone was also found to be significantly less than in water plus sediment in an estuarine system (Pritchard et al. 1987). Several studies in water systems have demonstrated that methyl parathion is rapidly degraded by the bacteria within aufwuchs communities (i.e., the microorganisms attached to plants, sediments, and mats) found in aquatic ecosystems (Crossland and Bennett 1984; Holm et al. 1983; Lewis and Holm 1981). Chemical/toxicity testing using natural river die-off water with sediment and a toxicity sensitive organism (mysid shrimp) demonstrated that methyl parathion degraded rapidly (half-life of 2.3 days) to nontoxic products (Cripe et al. 1987).

In freshwater systems, the only biodegradation product detected was 4-nitrophenol, which was rapidly utilized and transformed to undetectable metabolites by the microorganisms present. In seawater, the main initial product was methyl aminoparathion, formed by reduction of the nitro group (Badawy and El-Dib 1984). Studies in raw river water showed that 4-nitrophenol and dimethyl thiophosphoric acid are the main degradation products (Eichelberger and Lichtenberg 1971).

Photolysis studies of methyl parathion have been reported. A study examining the photodegradation of methyl parathion in river and seawater at variable temperatures showed the half-lives to be 11 and 34 days, respectively (Lartiges and Garrigues 1995). During photolysis in natural water 50% of the

original methyl parathion concentration was degraded in 8 days in the summer and 38 days in the winter (EPA 1978c). In a photolysis study of methyl parathion in fresh waters of Portugal, a half-life of 3 days in groundwater and a half-life of 4 days in river water were observed. The authors noted that the transformation products, which included methyl paraoxon, were more stable than the parent compounds studied (Castillo et al. 1997).

6.3.2.3 Sediment and Soil

In soils and sediments, microbial degradation and hydrolysis are important degradation processes. Studies have found that methyl parathion degrades more rapidly in anaerobic soil than in aerobic soils (Adhya et al. 1981, 1987; Brahmaprakash et al. 1987). An average half-life of 64 days was determined for nonflooded (aerobic) soils compared to an average half-life of 7 days in flooded (anaerobic) soils (Adhya et al. 1987). In experiments with ^{14}C-labeled methyl parathion, 35% of the labeled compound was recovered from nonflooded soil after 28 days, compared with 9% recovered from flooded soil (Brahmaprakash et al. 1987).

Results from other studies support the rapid degradation of methyl parathion in soils with a high water (i.e., low oxygen) content (Adhya et al. 1981, 1987; Brahmaprakash et al. 1987). Experiments in flooded and nonflooded soils showed that the redox potential affected both the rate of degradation and the transformation products of methyl parathion (Adhya et al. 1981, 1987). Transformation to volatile products was suggested by Brahmaprakash et al. (1987) as the reason that significant amounts of ^{14}C from labeled methyl parathion could not be accounted for, especially in flooded soils.

In a study of the degradation of methyl parathion in flooded (anaerobic), alluvial (pH 6.2) soil, samples were maintained at 6, 25, and 35 EC for 12 days. Methyl parathion did not degrade at 6 EC, while at 25 EC, methyl aminoparathion, formed from the reduction of the nitro group, was the sole metabolite. At 35 EC, methyl aminoparathion was formed from the reduction of the nitro group, and 4-nitrophenol was formed by hydrolysis. For the 25 EC samples, 50 and 28% of the applied amount remained in the soil by day 4 and day 6, respectively. No methyl parathion remained in the soil by day 6 in the 35 EC samples (Sharmila et al. 1988). Studies show that methyl parathion forms bound residues in moist soils, and is degraded by reduction of the nitro group. The primary metabolites detected were 4-nitrophenol and 4-aminophenol, which were further transformed to carbon dioxide by the soil microbiota (Ou et al. 1983). Biodegradation is affected by temperature, pH, and moisture content of the soil (Adhya et al. 1987; EPA 1980c; Ou et al. 1983).

Low concentrations of methyl parathion, such as those associated with normal use, degrade fairly rapidly in the environment (EPA 1980c). For example, 75–85% of an applied concentration of 24.5 ppm was found to decompose in 52 days (EPA 1980c). Degradation rate is affected by temperature. Studies by Baker and Applegate (1970) showed that the methyl parathion loss over a 50-day period increased by a factor of 1.3–1.4 when the temperature was increased from 30 to 50 EC. The pH of the soil also affects degradation rate, with methyl parathion degrading faster at more alkaline pH values (Adhya et al. 1987). When the concentration of methyl parathion is high, as in bulk disposal and spills, degradation appears to be significantly retarded (Butler et al. 1981a; EPA 1980c). In a study simulating spill conditions (EPA 1980c) for an applied concentration of 10,015 ppm methyl parathion, losses of only 0.1% were observed after 52 days. In another simulated spill study, 42.7% of a concentration of 48,900 ppm of methyl parathion still remained in the soil after 1 year, and 35.8% remained after almost 4 years (Butler et al. 1981a).

Direct photolysis does not appear to be a significant transformation process in soils. Only 5–17% of the methyl parathion concentration was lost over 50–60 days (half-life equal to 330 days) during a photolysis study (Baker and Applegate 1970).

6.3.2.4 Environmental Media

Decomposition of methyl parathion was studied in central Greece in apples remaining on trees after spraying (emulsifiable concentrate; 40% active ingredient) and in apples harvested and stored under ambient-temperature, refrigerated-room temperature, and controlled-atmosphere conditions (Pappas et al. 1999). Methyl parathion degraded fastest on the apples remaining on the trees. Half-lives were found to be 8 days for apples on trees, 45 days for apples stored at ambient conditions, 68 days for apples stored in a controlled-atmosphere room, and 62 days for apples stored in a refrigerated room.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

In a study to determine the concentrations of pesticides in air collected during times of peak pesticide use in California, air samples were collected at applications sites and at locations adjacent to the application sites (Baker et al. 1996). Of the samples collected adjacent to the application sites, 50% had levels of methyl parathion greater than the detectable limit of 0.2 ng/m^3, while 21% had levels of methyl paraoxon

greater than the detectable limit of 0.2 ng/m^3. The maximum amount of methyl parathion detected was 26 ng/m^3; the maximum amount of methyl paraoxon detected was 4.8 ng/m^3. At the application sites, the maximum amount of methyl parathion detected was 520 ng/m^3. Air samples collected at the application sites were not analyzed for methyl paraoxon.

Air samples collected in the Sacramento Valley area of California near sites where methyl parathion was heavily used on rice were analyzed by Seiber et al. (1989). Methyl parathion concentrations ranged from 0.2 (minimum detectable level) to 25.67 ng/m^3 depending on the location and time of sampling. Methyl paraoxon, the oxygen analog of methyl parathion, was also detected at a maximum of 3.07 ng/m^3. The highest concentrations of both compounds were found at sites near locations of heaviest use.

Airborne pesticide residues were determined from air samples collected along the Mississippi River from Louisiana to Minnesota during a 10-day period in June of 1994. Methyl parathion, used throughout Mississippi and in parts of Louisiana and Arkansas primarily on cotton, was detected in 8 of the 10 samples collected over this 10-day study. The maximum concentration (0.30 ng/m^3 detection limit) of methyl parathion was 0.85 ng/m^3 (range of 0.05–3.4 ng/m^3), and the median concentration was 0.07 ng/m^3 (Majewski et al. 1998). In a similar study conducted in April–September 1995 at urban and agricultural sites along the Mississippi River in Mississippi, Iowa, and Minnesota, airborne methyl parathion (35 pg/m^3 detection limit) was detected in 70% of the samples collected at the Mississippi agricultural site, and was present at the highest level of any of the 19 insecticides monitored in the study, at a maximum concentration of 62 ng/m^3 (Foreman et al. 2000). In the same study, the median concentration of methyl parathion in all agricultural site air samples collected in the study was 2.5 ng/m^3, and methyl parathion was detected in the air samples of urban areas at a maximum concentration of 0.99 ng/m^3 (Coupe et al. 2000).

Atmospheric concentrations of methyl parathion following application of the pesticide to tobacco fields were studied by Jackson and Lewis (1978). They found that levels of methyl parathion decreased rapidly following application of either the emulsifiable concentrate or the microencapsulated form. Air concentrations for the emulsifiable concentrate ranged from 7,408 ng/m^3 immediately following application to 13 ng/m^3 9 days later. The corresponding measurements for the microencapsulated form were 3,783 and 16 ng/m^3.

6.4.2 Water

Several studies have been conducted to measure methyl parathion in streams, rivers, and lakes. A U.S. Geological Survey (USGS) of western streams detected methyl parathion in five river samples taken from four states during a 14-month period in 1970 and 1971. The amount of methyl parathion detected ranged from 0.04 to 0.23 µg/L (Schultz et al. 1973). A later and more extensive USGS study analyzed water samples from major rivers of the United States four times yearly in the period of 1975–1985. Of the 2,861 water samples, 0.1% had detectable levels of methyl parathion (Gilliom et al. 1985). In a study of Arkansas surface waters, samples of lake and river/stream water were collected and analyzed over a three-year period (Senseman et al. 1997). Of the 485 samples collected, methyl parathion was found in one river/stream sample at a maximum concentration of 3.5 µg/L. Results from an EPA study in California detected methyl parathion in 3 of 18 surface drain effluent samples at concentrations of 10–190 ng/kg. Subsurface drain effluent water had concentrations of 10–170 ng/kg in 8 of 60 samples (IARC 1983).

Groundwater has also been surveyed for methyl parathion. In a study of well water in selected California communities, methyl parathion was not detected (detection limit of 5 ppb) in the 54 wells sampled (Maddy et al. 1982), even though the insecticide had been used in the areas studied for over 15 years. An analysis of 358 wells in Wisconsin produced the same negative results (Krill and Sonzogni 1986). In a sampling of California well water for pesticide residues, no methyl parathion was detected in any of the well water samples (California EPA 1995). In a study to determine the residue levels of pesticides in shallow groundwater of the United States, water samples from 1,012 wells and 22 springs were analyzed. Methyl parathion was not detected in any of the water samples (Kolpin et al. 1998). In a study of water from near-surface aquifers in the Midwest, methyl parathion was not detected in any of the water samples from 94 wells that were analyzed for pesticide levels (Kolpin et al. 1995).

Methyl parathion has been reported in groundwater in Idaho at a median level of 0.01 ppb with contamination due to a point source (EPA 1988c). A study of tap water in Ontario showed no detectable methyl parathion at a detection limit of 1 ng/L (Le Bel et al. 1979).

Samples of rainfall in Iowa have been analyzed for levels of pesticides (Nations and Hallberg 1992). Samples collected in April, May, and June of the three years in the study period of 1987–1990 had the highest levels of methyl parathion, corresponding to the application to crops. Methyl parathion was found in 4 of the 318 rain samples analyzed at a maximum concentration of 2.77 µg/L. In a study of

pesticides in rain and air, conducted in April–September 1995 at urban and agricultural sites along the Mississippi River in Mississippi, Iowa, and Minnesota, methyl parathion was present at the highest level of any of the 47 pesticides monitored in the rain samples collected in the study (Coupe et al. 2000). Methyl parathion was detected in the agricultural and urban site rain samples at maximum concentrations of 22.9 µg/L (median of 0.12 µg/L) and 0.3 µg/L (median of 0.024 µg/L), respectively (Coupe et al. 2000). In the same study, at the agricultural site in Mississippi, the total wet deposition of methyl parathion during the 6-month study was 1,740 $\mu g/m^2$ (89% of the total wet depositional loading at that site), greater than the totals for each of the other 46 compounds monitored in the study (Majewski et al. 2000). Methyl parathion was not detected in the wet deposition at the Iowa site and was detected only once at each of the two Minnesota sites (Majewski et al. 2000).

Methyl parathion and methyl paraoxon concentrations were measured in the condensate from coastal fog in California. Levels ranged from 0.046 to 0.43 µg/L methyl parathion and from 0.039 to 0.49 µg/L methyl paraoxon. The authors noted that the transformation of the methyl parathion to the methyl paraoxon appeared to take place during atmospheric transport of methyl parathion away from the agricultural areas (Schomburg et al. 1991).

6.4.3 Sediment and Soil

In random samples of soil taken from five Alabama counties, only 3 of 46 soil samples contained methyl parathion. The concentration in these samples was <0.1 ppm (Albright et al. 1974). As part of the National Soils Monitoring Program, soil and crop samples from 37 states were analyzed for methyl parathion during 1972. Methyl parathion was detected in only 1 soil sample, at a concentration of <0.1 ppm and taken from South Dakota, out of 1,246 total samples taken from the 37 states (Carey et al. 1979). In soil and sediment samples collected from a watershed area in Mississippi, methyl parathion was not detected in the soil samples. In three wetland sediment cores, however, measurable concentrations of methyl parathion were detected during application season (Cooper 1991).

A USGS study analyzed bed sediment samples from major rivers of the United States twice yearly in the period of 1975–1985. Methyl parathion was not detected in any sediment sample (Gilliom et al. 1985).

In a study of a highly contaminated soil evaporation pit in California, methyl parathion was found to a depth of 90 cm in the soil bed. The concentration at this depth was 18 ppm. Highest concentrations were found in the top 7.5 cm of the soil surface and ranged from 32 to 392 ppm (Winterlin et al. 1989). In a

study to determine if spills caused by poor handling, storage, or containment practices of agricultural products released pesticides to soil, samples were collected from agrichemical sites in Illinois (Krapac et al. 1995). Of the 822 soil samples collected at 49 sites, methyl parathion was found at 2 of the sites, at a median concentration of 112 ppb and a mean concentration of 584 ppb.

Marine sediments, adjacent to a pesticide manufacturing plant in Denmark, contained methyl parathion levels of 40.6 and 44.1 µg/kg dry weight at depths of 0–3 and 4–8 cm, respectively (Kjolholt 1985).

6.4.4 Other Environmental Media

Methyl parathion was monitored in crops from 37 states in 1972 as part of the National Soils Monitoring Program (Carey et al. 1979). The pesticide was detected in 40% of cotton stalk, 6.3% of cotton seed, 2.3% of mixed hay, and 9.1% of sorghum samples. Mean concentrations ranged from 0.15 ppm in cotton stalks to <0.1 ppm in cotton seeds, mixed hay, and sorghum. The compound has also been reported in the outer shuck of sweet corn at a concentration of 0.13–0.14 µg/cm^2, 1–2 days after application, but was not detectable in the inner shuck (Wicker et al. 1979). Imported flowers were reported to contain a mean concentration of 0.3 mg/kg in 10.5% of samples tested (Morse et al. 1979).

In a Food and Drug Administration (FDA) summary of the levels of pesticides in ready-to-eat foods in the 10-year period from 1982 to 1991, methyl parathion was found 12 times in 8 kinds of food, at an average concentration of 0.0035 ppm (Kan-Do Office and Pesticides Team 1995). A 5-year analysis of domestic and imported foods and animal feeds for the years 1982–1986 detected 94 samples out of 19,851 total samples that contained methyl parathion (Hundley et al. 1988). Eighty-nine of the samples had concentrations in the range of 0.05–0.5 ppm, and five had levels ranging from 1.0 to 2.0 ppm. Methyl parathion was found in celery, citrus, coriander, cantaloupe, Chinese peas, hay, alfalfa feed, Italian squash, lettuce, mustard greens, okra, parsley, peppers, spinach, strawberries, tomatillos, and tomatoes. An FDA study of pesticide residues in infant and adult foods eaten by infants/children for the period 1985–1991 reported results for methyl parathion as total parathion (Yess et al. 1993). Of the 2,464 apples analyzed, total parathion was detected in 158 samples at a maximum of 1.3 ppm. Of the 862 oranges analyzed, total parathion was detected in 25 samples at a maximum of 1.4 ppm. Of the 571 pears analyzed, total parathion was detected in 8 samples at a maximum of 0.12 ppm.

A large study of fruits and vegetables available in Canada examined 5,784 Canadian samples and 16,198 imported (including from the United States) samples (Neidert and Saschenbrecker 1996). Of the

Canadian samples analyzed, 1 sample (carrots) contained a methyl parathion residue at a level of <0.05 ppm. Of the imported samples, 14 contained methyl parathion residues. Levels of methyl parathion ranged from <0.05 ppm (in pears and snowpeas), to 0.10 ppm (in apples, oranges, pears, and tomatoes), to a maximum of 0.50 ppm (in grapes, apples, oranges, and pears, plus another unspecified sample).

Citrus fruits from markets in Spain were analyzed for residues of methyl parathion along with other organophosphorus insecticides (Torres et al. 1997). Of the 171 orange samples analyzed, 14 had levels of methyl parathion <0.2 ppm, while 5 had levels >0.2 ppm. Levels ranged from the 0.1 ppm limit of detection to 3.8 ppm depending on the type of orange. Of the 15 grapefruit samples analyzed, 1 was found to contain methyl parathion at a level of 0.3 ppm.

A study of estuarine fish in 21 coastal states conducted from 1972 to 1976 as part of the National Pesticide Monitoring Program detected a mean concentration of 47 ppb in 3.9% of the fish tissue samples collected (Butler and Schutzmann 1978). In another study (Cooper 1991), fish collected in a watershed area of Mississippi were analyzed for residues of methyl parathion. Methyl parathion was detected in seven species of fish, with white bass having the greatest mean concentration, at 15.96 ppm. Methyl parathion was found in 3 of the 32 fish samples collected before spraying of methyl parathion and in 12 of the 25 samples of fish collected after methyl parathion spraying.

Methyl parathion was not detected (detection limit of 1.0 ppb) in a study of 21 market samples and 4 producer samples of milk obtained in Portugal. However, the oxygen analog and metabolite of methyl parathion, methyl paraoxon, was found (detection limit of 1.0 ppb) in 22 of the 25 samples, at concentrations ranging from 1.5 to 8.7 ppb, with an average level of 3.6 ppb (Lino and da Silveira 1992). All of the market samples contained methyl paraoxon, while only one of the producer samples contained the compound. In a study of milk and cheese products obtained in Greece, of the 38 bovine milk samples analyzed, two contained methyl parathion at levels that ranged from 43 to 280 ppb of milk fat, with a mean concentration of 161 ppb of milk fat (Mallatou et al. 1997). In a study of milk and yogurt samples from Egypt, methyl parathion and its metabolites methyl paraoxon and 4-nitrophenol were not detected in any of the samples (Ahmed 2000).

One FDA study (Roy et al. 1997) determined the levels of pesticide residues in rice and apples. Of the 769 domestic apples analyzed, methyl parathion was found in 72 samples at a maximum concentration of 0.15 ppm. Of the 1,062 imported apples analyzed, methyl parathion was found in 4 samples at a

maximum concentration of 0.05 ppm. Of the 598 samples of domestic rice, methyl parathion was found in 4 samples at a maximum concentration of 0.13 ppm. Of the 612 imported rice samples analyzed, 1 sample contained methyl parathion, at a concentration of 0.04 ppm.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

There are insufficient data to determine potential daily inhalation and dermal exposure levels. However, based on the information presented in Sections 6.3 and 6.4, exposure levels for the general population are probably very low by these routes. Inhalation exposure is not important for the general population, with the possible exception of those individuals living near areas where methyl parathion is frequently sprayed. Since methyl parathion is readily adsorbed through the skin, dermal contact may be the most relevant exposure pathway. Dermal contact is most likely to occur in people who are occupationally exposed.

In a study to determine if the general population living near an area of heavy pesticide use is exposed to high levels of pesticides from foods, the diets of occupants residing in nine homes in the Lower Rio Grande Valley were analyzed for residue levels of pesticides (Berry et al. 1997). Food samples obtained from markets in Texas or Mexico were analyzed in the summer and spring of the study year. In the 30 types of food analyzed in the spring and the 24 types analyzed in the summer, methyl parathion was detected in 1 food sample at a concentration of 0.018 ppm in the spring and 0.004 ppm in the summer. In another study in the Lower Rio Grande Valley region to determine pesticide exposure in certain homes, samples of air from both inside and outside the homes and household dust were analyzed (Mukerjee et al. 1997). Indoor air samples collected in the spring contained methyl parathion at <0.4 ng/m^3, while the outdoor air samples contained 0.4 ng/m^3. In the summer, the indoor air samples contained 13.8 ng/m^3 methyl parathion while the outdoor air samples contained 12.4 ng/m^3. The household dust was found to contain 21 ppb of methyl parathion in both the spring and summer. It is not known at this time if these levels are significant. Studies are currently underway to address this issue (EPA 1999b).

The FDA Total Diet Studies/Market Basket Surveys examine foods for levels of pesticides. Estimates are then made of the mean intake of a pesticide (in µg/kg/day) using the amounts of pesticides found in foods and food consumption patterns. For the period of 1984–1986, the estimates were <0.0001 µg/kg/day for all eight age groups: 6–11 months, 2 years, 14–16 years female, 14–16 years male, 25–30 years female, 25–30 years male, 60–65 years female, and 60–65 years male (Gunderson 1995a). For the period of 1986–1991, the estimates were 0.0002 µg/kg/day for the 6–11 months group, 0.0001 µg/kg/day for the 2 years group, <0.0001 µg/kg/day for the 14–16 years and 25–30 years groups, and 0.0001 µg/kg/day for

the 60–65 years group (Gunderson 1995b). FDA Market Basket Surveys from 1979 to 1980 and from 1980 to 1982 estimated mean adult average daily exposure to pesticide residues to be 0.0126–0.0596 µg/day (Gartrell et al. 1985, 1986). No data indicate that inhalation or dermal exposure are concerns for the general population, except for people living near the areas where methyl parathion is used.

Exposure of the general population to higher concentrations of methyl parathion may result from contact with, or ingestion of, contaminated hazardous waste site media, principally soils and water. No information was found in the available literature regarding the size of the human population potentially exposed to methyl parathion through contact with contaminated waste site media.

NIOSH estimated that approximately 150,000 U.S. workers are potentially exposed to methyl parathion in occupational settings (NIOSH 1976). The OSHA workplace air environmental limit of 1.2 mg/m^3 is only exceeded for a short while after spraying and only within a short radius of the application area (Draper and Street 1981). Exposure is mainly through the dermal route, although inhalation can also be a route of exposure. Workers most likely to be exposed are those directly involved with the manufacture, application, and cleanup of the chemical, and field workers (NIOSH 1976). Studies on exposure to methyl parathion following reentry of workers into a sprayed field showed exposures to be above safe levels for up to 48 hours after application (Ware et al. 1973, 1974). Analyses of methyl parathion residues on protective garments before and after washing indicate that laundry workers cleaning these garments may also be exposed (Hild et al. 1989; Laughlin and Gold 1987, 1989a, 1989b; Leonas et al. 1989).

Samples of the indoor and outdoor air at the homes of workers occupationally exposed to pesticides, farmers and pesticide formulators, were taken monthly and analyzed for methyl parathion. Methyl parathion was found in 13 of 52 indoor air samples of formulators' homes at a mean concentration of 0.26 $µg/m^3$ (range of 0.04–9.4 $µg/m^3$). Outdoor air samples of formulators' homes showed that 3 of 53 samples contained methyl parathion at concentrations ranging from 0.15 to 0.71 $µg/m^3$. Methyl parathion was not detected in the indoor and outdoor air samples from farmers' homes (Tessari and Spencer 1971).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 3.7 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children and the general population living in areas far from where methyl parathion is sprayed are not likely to be exposed to high levels of methyl parathion. For those living near the areas where methyl parathion is used, the children within the general population are likely to be exposed to methyl parathion in the same way as the adults, by contact with sprayed plants, breathing contaminated air, eating contaminated foods, or drinking contaminated water. Children living in agricultural areas may be exposed to higher pesticide levels than other children because of pesticides that may get tracked into the homes by household members, by pesticide spray drift, or from playing in the fields near where methyl parathion has been sprayed. Dermal exposure is expected to be the most common route of exposure.

Methyl parathion has been illegally used inside the home to kill insects (ATSDR 1999; EPA 1999b). This practice can result in high exposure levels to the occupants, including children. In an analysis of samples taken from a home nearly two weeks after the home had been illegally sprayed with a 4% solution of methyl parathion, air samples contained 0.041 mg/m^3, and water samples, collected from water kept in an open jar, contained 138–275 ppb (0.138–0.275 mg/kg) (Dean et al. 1984). National Alerts published by the EPA and ATSDR (ATSDR 1999; EPA 1999b) on the illegal use of methyl parathion in the home state that children are particularly vulnerable to methyl parathion, and deaths have been reported. (See also Section 2.2.1.1.) A recent study of U.S. inner-city children's exposure to pesticides states that such children are still being exposed to illegally used pesticides, as when methyl parathion was illegally used in cities in 1996, with illegal spraying occurring in 1,100 homes in Chicago, Cleveland, and on the Gulf Coast (Landrigan et al. 1999).

Additionally, children of workers who are exposed to methyl parathion through their employment could be exposed to high levels of methyl parathion. The workers in the manufacture, formulation, and use of methyl parathion may come into contact with methyl parathion on their skin or clothing. Children who reside in the homes of these workers could be exposed to methyl parathion by contact with any methyl parathion that might be on the workers' clothing, hair, or skin, or from contact with tools or other contaminated items brought home from work. Also, if children of farm workers enter fields shortly after methyl parathion has been applied to crops, they may be exposed to high levels of methyl parathion from coming into contact with sprayed plants or by breathing the mist containing methyl parathion.

Small children are more likely than adults to come into contact with pesticide residues that may be present in soil outside the home and in dust inside the home. The tendency for young children to ingest soil, either intentionally through pica-related behavior or unintentionally through hand to mouth activity, may expose children to residues in the soil. Hand to mouth activity indoors may expose the children to residues that may be present in carpets or in dust on uncovered floors. Methyl parathion strongly adsorbs to soil, but after being adsorbed, it rapidly degrades. If the children are playing in soil in regions where methyl parathion is used on crops, then they may be exposed to elevated levels depending on the amount of time that has passed since the spraying has occurred. Since methyl parathion degrades rapidly in soil, it is anticipated that soil-borne exposure concentrations will decrease with increasing time from any spray event. Children who are playing in soil in regions far from where methyl parathion is used would not be expected to be exposed to soil-borne methyl parathion.

Some quantitative estimates of exposure in the infant and child populations have been reported in a number of FDA Total Diet Monitoring Studies conducted in the 1980s using the amounts of pesticide residues in foods thought to be in the diets of infants or children. Estimates of the mean intake of methyl parathion were made for the 6–11 months age group, 2 years age group, and the 14–16 years female and 14–16 years male age groups. For the period of 1984–1986, the estimates were <0.0001 μg/kg/day for all of the age groups (Gunderson 1995a). For the period of 1986–1991, the estimates were 0.0002 μg/kg/day for the 6–11 months group, 0.0001 μg/kg/day for the 2 years group, and <0.0001 μg/kg/day for both the female and male 14–16 years groups (Gunderson 1995b).

An extensive study was undertaken to determine if pesticide residues are present in any infant formula products (Gelardi and Mountford 1993). Milk- and soy-based formulas were analyzed, as was the water used to make the formula. No pesticide residues, including methyl parathion, were detected in any infant formula manufactured in the United States. Thus, it does not appear that infants will be exposed to

methyl parathion residues through consuming formula. As reported previously, methyl parathion was not detected in a study of 21 market samples of milk obtained in Portugal (1 ppm detection limit). However, the oxygen analog of methyl parathion, methyl paraoxon, was found in all samples, ranging from 1.5 to 8.7 ppm, with an average level of 3 ppm (Lino and da Silveira 1992). In the analysis of bovine milk in Greece for pesticide residues, 2 of the 38 bovine milk samples had concentrations of methyl parathion that ranged from 43 to 280 ppb of milk fat (Mallatou et al. 1997). Samples (9 of 19) of cow's milk obtained from the Central Asian Republic of Kazakhstan were found to contain methyl parathion at concentrations that ranged from 3 to 20 ppb (Lederman 1996). These data suggest that milk from animals in the United States may also contain low levels of methyl parathion or methyl paraoxon and, thus, that children, who typically consume large volumes of milk relative to the general population, may be exposed to methyl parathion through milk consumption.

A potential source of exposure in infants is the presence of methyl parathion in breast milk. No data were found in the available literature on the presence of malathion or its residues in breast milk in the United States. However, data from foreign countries indicate that methyl parathion residues may be excreted in breast milk. In a study of breast milk samples obtained in 1988–1990 from 10 regions within the Central Asian Republics of Turkmenistan, Tajikistan, and Kazakhstan, samples from 5 of the regions contained methyl parathion residues (Lederman 1996). Of the 90 samples for which data were reported, 8 contained methyl parathion, at a range of 1–100 ppb. Methyl parathion was also detected in 11 of 50 breast milk samples obtained from two regions in Kazakhstan in 1987 and 1992, at a range of 1.6–80 ppb (Lederman 1996). In a study of the breast milk of 11 Italian women from which samples were obtained at both the 5th and 30th day of lactation, methyl parathion was not detected in any of the samples (Roggi et al. 1991).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Those populations most at risk for exposure to high levels of methyl parathion are workers who mix and apply the chemical and field workers who go into sprayed areas. Individuals living near the NPL sites currently known to be contaminated with methyl parathion and those living near production facilities or other point sources might also be at risk for higher exposure. People living in areas very close to application sites may be exposed to amounts higher than the general population. In addition, laundry workers who wash the garments worn by field workers or by workers involved with mixing and applying methyl parathion may be exposed to higher concentrations (Hild et al. 1989; Laughlin and Gold 1987, 1989a, 1989b; Leonas et al. 1989).

In a study of 135 workers in the chemical industry who handle methyl parathion, the methyl parathion concentration in plasma, the 4-nitrophenol concentration in urine, and the cholinesterase and acetylcholinesterase activities were determined to assess the pesticide burden in such workers (Leng and Lewalter 1999). The mean concentration of methyl parathion in the plasma of the workers was 233 µg/L; no clinical symptoms were reported by the workers. In an additional group of 19 workers handling methyl parathion, who were also exposed to the pyrethroid cyfluthrin, the mean concentrations of methyl parathion in plasma were 269 and 241 µg/L (for groups without and with clinical symptoms, respectively), and 7 of the workers exhibited skin paraesthesia, while none of the 427 workers exposed only to the pyrethroid experienced the symptom (Leng and Lewalter 1999).

Methyl parathion is only for use on agricultural crops. The reports that methyl parathion has been illegally/improperly used inside homes to kill insects (ATSDR 1999; EPA 1999b) show that people in homes that are sprayed with methyl parathion may be exposed to dangerously high levels of methyl parathion.

The sizes of these populations and the concentrations of methyl parathion in all of the contaminated media to which these people would potentially be exposed have not been adequately characterized.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of methyl parathion is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of methyl parathion.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of methyl parathion are sufficiently well characterized to allow assessment of the environmental fate of the compound to be made (Budavari 1989; EPA 1980c; Hawley 1987; Keith and Walters 1985; NFPA 1986; Ruth 1986; Sanders and Seiber 1983; Schimmel et al. 1983; Sunshine 1969; Tomlin 1994; Weiss 1986).

Production, Import/Export, Use, Release, and Disposal. Methyl parathion is commercially produced in the United States and abroad. Since 1977, production volume statistics for methyl parathion have been combined with those of ethyl parathion, also known as parathion. In 1983, the combined production capacity was estimated at 29 million kg for the United States and 10–15 million kg for western Europe (IARC 1983). Data on recent production in the United States were not located. In 1980, 413,000 kg of methyl parathion were imported (USITC 1981). Exports in 1984 amounted to 5.68 million kg (Bureau of the Census 1984). More current information on the manufacture, import, and export of the insecticide are needed so that an assessment can be made of potential human exposure to methyl parathion.

The use of methyl parathion as a broad-spectrum insecticide for a variety of food and nonfood crops, ornamentals, trees, and mosquito breeding areas is well documented (IARC 1983; International Labour Office 1983; Meister 1988; NPIRS 1986; Spencer 1982; Tomlin 1994; Weir and Hazleton 1981). While the annual use of methyl parathion, a restricted-use compound, in the United States has also been well documented in general (EPA 1999c; Giannessi and Anderson 1995), there are few studies that document the illegal use of the compound in the home (Landrigan et al. 1999). It would be helpful to have an estimate of the amounts of methyl parathion used illegally in the home and the frequency of these usages so that the potential for exposure to children in such homes can be assessed. It would also be helpful to have updated use information that was collected after EPA cancelled many of the food crop uses of the compound, including on several crops commonly eaten by children (EPA 1999d; 1999e).

Releases to air, land, and water occur primarily through its use as a restricted-use insecticide. The media of most importance for human exposure are contaminated air and soil. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxic Release Inventory (TRI), which contains this information for 1987, became available in May of 1988. This database is updated yearly and provides a list of industrial production facilities and emissions.

Methods suggested for the disposal of methyl parathion are incineration and open field burial at designated landfills (EPA 1974a). In the past, improved methods for the disposal of methyl parathion were being considered (EPA 1981b). Regulations pertaining to the disposal of methyl parathion include the requirement that containers contaminated with methyl parathion residues be emptied, decontaminated, and either recycled, incinerated, or disposed of in a landfill depending on their condition (EPA 1974a). No recent data are available. Thus, further information on the optimal method for disposal of methyl parathion is needed to evaluate the potential for the release of and exposure to methyl parathion.

Environmental Fate. While methyl parathion degrades fairly rapidly and is relatively immobile in the environment at lower concentrations, there is still some uncertainty regarding the degradation and mobility of very high concentrations of methyl parathion, such as might be found at spill sites, and at pesticide disposal and other hazardous waste sites (Albanis et al. 1988b; Butler et al. 1981a; EPA 1980c; Jury et al. 1987a; Rao and Davidson 1979). Further studies with high concentrations of methyl parathion are needed to assess the environmental fate of the compound in these particular situations. Additional studies of methyl parathion degradation in air, particularly to methyl paraoxon, and the subsequent degradation of methyl paraoxon, are needed to better assess releases to air. Additionally, the methyl aminoparathion metabolite, which forms under anaerobic soil conditions, binds strongly to organic matter (Sharmila et al. 1988). Studies on the fate of methyl aminoparathion and the potential for it to become oxidized to methyl parathion are needed to characterize the fate of methyl parathion in the environment.

Bioavailability from Environmental Media. Methyl parathion can be absorbed following inhalation or dermal contact with contaminated air and by ingestion of contaminated water or food (Dean et al. 1984; Fazekas 1971; Morgan et al. 1977; Nemec et al. 1968; Ware et al. 1973, 1974, 1975). Dermal contact with or ingestion of methyl parathion that is tightly bound to soil particles is an exposure route of concern at hazardous waste sites and areas where spills have occurred. No information is available on the absorption of methyl parathion from soil following ingestion or dermal contact with contaminated soils. Therefore, additional information is needed on the uptake of methyl parathion from contaminated soil following ingestion or dermal contact.

Food Chain Bioaccumulation. There are a few studies to determine residues of methyl parathion in organisms in the environment. These have consistently shown low methyl parathion residues, indicating that methyl parathion does not bioconcentrate to a significant extent in aquatic organisms, plants, or animals (Crossland and Bennett 1984; Sabharwal and Belsare 1986). The methyl parathion that does get into organisms is rapidly degraded (Sabharwal and Belsare 1986). Some recent analyses of fish in a

watershed region in the United States indicates ppm (16 μg/g) levels of methyl parathion suggesting that methyl parathion sometimes persists long enough for uptake by fish to occur, and thus, could possibly play a role in bioaccumulation (Cooper 1991). Additional studies to verify that bioaccumulation is not occurring are needed.

Exposure Levels in Environmental Media. Methyl parathion has been detected in ambient air (Baker et al. 1996; Jackson and Lewis 1978; Majewski et al. 1998; Seiber et al. 1989), surface water (Gilliom et al. 1985; Senseman et al. 1997), groundwater (EPA 1988c), rainfall (Nations and Halbert 1992), coastal fog (Schomburg et al. 1991), soil (Albright et al. 1974; Carey et al. 1979; Krapac et al. 1995; Winterlin et al. 1989), sediments (Cooper 1991), fish (Butler and Schutzmann 1978; Cooper 1991), and foodstuffs (Neidert and Saschenbrecker 1996; Torres et al. 1997). Estimates of human intake of methyl parathion have been made for ingestion of foodstuffs (Gartrell et al. 1985, 1986), but improved estimates of exposure from air, water, and soil are needed to assess human exposure to methyl parathion. Information concerning concentrations in the air, water, and soil at the NPL hazardous waste sites known to be contaminated with these compounds are needed to estimate the exposure of populations living in the vicinity of these sites.

Exposure Levels in Humans. Methyl parathion has been detected in serum and tissue shortly after acute exposure (EPA 1978e; Ware et al. 1975). It is rapidly metabolized and does not persist in serum and tissues for long (Braeckman et al. 1983). Two metabolites of methyl parathion, 4-nitrophenol and dimethyl phosphate, can be detected in urine and tissues for up to 2 days following exposure (Morgan et al. 1977). These compounds are specific for methyl parathion when there is a history of exposure. Methyl parathion has been detected in blood within 1 day of exposure and is a specific biomarker (Fazekas 1971).

A recent method to screen the urine for alkyl phosphates as an indicator of exposure to organophosphate insecticides shows that the method can be used to determine environmental exposure to a specific organophosphate pesticide. The method was found to be sensitive, identifying low levels of exposure to insecticides in the environment by quantitation of urinary phosphates (Davies and Peterson 1997). The test is limited in that it is only useful for assessing recent exposure, due to the short half-life of the organophosphate pesticides.

A recent method, still in development, for determining total 4-nitrophenol in the urine of persons exposed to methyl parathion is based on solid phase microextraction (SPME) and GC/MS; previously, the method

has been used in the analysis of food and environmental samples (Guidotti et al. 1999). The method shows promise for use in determining exposures at low doses, as it is very sensitive. There is a need for additional development of this method, as the measurement of acetylcholinesterase (the enzyme inhibited by exposure to organophosphates such as methyl parathion) is not an effective indicator of low-dose exposures.

Exposures of Children. More studies are needed to assess the exposures of children living in agricultural areas to methyl parathion residues in air, soil, or water. More studies are also needed to assess the exposures of children in the general population to residues of methyl parathion that might be present in food, milk, or water, or on contaminated clothing and skin from occupationally exposed household members.

Additional studies to determine breast milk contamination by methyl parathion are needed to be able to assess exposures to nursing infants.

Child health data needs relating to susceptibility are discussed in 3.12.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for methyl parathion were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to methyl parathion.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP) database provides additional information from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-2.

No ongoing studies regarding release, disposal, environmental fate, bioavailability, bioaccumulation, exposure levels, or exposure registries were located.

Table 6-2. Ongoing Studies of Methyl Parathion Found in Federal Research in Progress

Investigator	Affiliation	Research description
Brindley, WA	USDA	Planning insecticide resistance management for methyl parathion.
Chambers, HW	USDA	Investigation of the nature of esterases involved in organophosphate detoxification including methyl parathion.
Johnson, SJ	USDA	To determine the resistance by soybean looper insects to methyl parathion and permethrin.
Meinke, LJ	USDA	To study the influence of methyl parathion on western corn rootworm behavior and population dynamics.
Meinke, LJ	USDA	Western corn rootworm resistance to methyl parathion–development of resistance management strategies
Nesheim, ON	USDA	To collect, develop, and maintain information related to pesticides and the crops on which they are used for the state of Florida.
Obendorf, SK	USDA	Methods to limit worker exposure to various pesticides, including methyl parathion.
Webster, E	USDA	To collect, develop, and maintain information related to pesticides and the crops on which they are used for the state of Arkansas.
Wild, JR	USDA	To develop an effective and complete biological remediation system capable of hydrolyzing organophosphorous neurotoxins from agricultural and chemical warfare munitions, contaminations, and wastes.
Wright, RJ	USDA	To document the extent of adult corn rootworm beetles resistence to methyl parathion throughout Nebraska.

USDA = United States Department of Agriculture

Ongoing remedial investigations and feasibility studies conducted at the NPL sites known to be contaminated with methyl parathion will add to the available database on exposure levels in environmental media, exposure levels in humans, and exposure registries.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring methyl parathion, its metabolites, and other biomarkers of exposure and effect to methyl parathion. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL SAMPLES

The primary method for detecting methyl parathion and metabolites in biological tissues is gas chromatography (GC) coupled with electron capture (ECD), flame photometric (FPD), or flame ionization detection (FID). Sample preparation for methyl parathion analysis routinely involves extraction with an organic solvent (e.g., acetone or benzene), centrifugation, concentration, and resuspension in a suitable solvent prior to GC analysis. For low concentrations of methyl parathion, further cleanup procedures, such as column chromatography on silica gel or Florisil are required. Table 7-1 summarizes the analytical methods used to detect methyl parathion and its metabolites in biological tissues and fluids.

Methyl parathion was determined in dog and human serum using a benzene extraction procedure followed by GC/FID detection (Braeckman et al. 1980, 1983; DePotter et al. 1978). An alkali flame FID (nitrogen-phosphorus) detector increased the specificity of FID for the organophosphorus pesticides. The detection limit was in the low ppb (μg/L). In a comparison of rat blood and brain tissue samples analyzed by both GC/FPD and GC/FID, Gabica et al. (1971) found that GC/FPD provided better specificity. The minimum detectable level for both techniques was 3.0 ppb, but GC/FPD was more selective. The EPA-recommended method for analysis of low levels (<0.1 ppm) of methyl parathion in tissue, blood, and urine is GC/FPD for phosphorus (EPA 1980d). Methyl parathion is not thermally stable above 120 °C (Keith and Walters 1985).

Table 7-1. Analytical Methods for Determining Methyl Parathion and Metabolites in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Acidify and heat to hydroloyze; add NaOH to pH=11; extract with benzene-diethyl ether; reacidify and dry with sodium sulfate; derivatize with hexamethyl disilizane on GC column (PNP)	GC/ECD	50 µg/L (50 ppb)	95.4	Cranmer 1970; EPA 1980d
Urine	Acidify and heat to hydrolyze; add NaOH extract with anhydrous ethyl ether; derivatize with diazoethane; concentrate; add hexane; concentrate and cleanup on silica gel; elute with benzene-hexane (PNP)	GC/ECD	20 µg/L (20 ppb)	85–98	Shafik et al. 1973b
Urine, blood, tissues	Add acetone; centrifuge; extract on ion exchange column; derivatize with diazopentane; cleanup on silica gel if needed (metabolites)	GC/FPD	40–150 µg/L (40–150 ppb)	36–97	EPA 1980d; Lores and Bradway 1977
Blood, tissues	Homogenize, if tissue; mix sample with acetone; centrifuge; concentrate; saturate with sodium chloride; evaporate organic layer; cleanup on silica gel eluting with hexane-benzene; concentrate	GC/FPD	<100 ppb	No data	EPA 1980d
Serum	Extract with benzene; dry; resuspend in ethyl acetate	GC/FID	2 µg/L (2 ppb)	57–109	Braeckman et al. 1980; DePotter et al. 1978

EDC = electron capture detector; FID = flame ionization detector; FPD = flame photometric detector; GC = gas chromatography; NaOH = sodium hydroxide; PNP = paranitrophenol

Methyl parathion rapidly forms hydrolysis products after absorption by the body. 4-Nitrophenol and the alkyl phosphate, dimethyl phosphate, are major metabolites that are frequently found in biological fluids and tissues following exposure. Sample preparation steps are generally more extensive for the metabolites than for the parent compound. Usually, several extractions and a derivation are required prior to GC analysis. Total 4-nitrophenol has been measured in human and rat urine using GC/ECD of the diazoethane or hexamethyl disilizane derivatives of 4-nitrophenol (Cranmer 1970; Morgan et al. 1977; Shafik et al. 1973b). The minimum detectable level was 0.02 ppm. For the analysis of 4-nitrophenol in biological tissues and fluids, EPA recommends extraction with benzene-ether and derivatization with hexamethyl disilizane prior to analysis by GC/ECD (EPA 1980d). The diazoethane derivative of dimethyl phosphate was quantitatively measured in human urine by GC/FPD in the phosphorus mode (Morgan et al. 1977). EPA recommends GC/FPD for the detection of the diazopentane derivatives of dimethyl phosphate and other alkyl phosphates. Diazopentane derivatives are more easily resolved and separated from interfering compounds than diazoethane derivatives. The detection limit of dimethyl phosphate by the EPA method was 0.04–0.15 ppm (EPA 1980d; Lores and Bradway 1977; Shafik et al. 1973a). The problem with the use of the above metabolites for the analysis of methyl parathion exposure is that they are not specific. Other organophosphate insecticides may also form these degradates.

A recent method, still in development, for determining total 4-nitrophenol in the urine of persons exposed to methyl parathion is based on solid phase microextraction (SPME) and GC/MS; previously, the method has been used in the analysis of food and environmental samples (Guidotti et al. 1999). The method uses a solid phase microextraction fiber, is inserted into the urine sample that has been hydrolyzed with HCl at 50 EC prior to mixing with distilled water and NaCl and then stirred (1,000 rpm). The fiber is left in the liquid for 30 minutes until a partitioning equilibrium is achieved, and then placed into the GC injector port to desorb. The method shows promise for use in determining exposures at low doses, as it is very sensitive. There is a need for additional development of this method, as the measurement of acetyl-cholinesterase, the enzyme inhibited by exposure to organophosphates such as methyl parathion, is not an effective indicator of low-dose exposures.

Organophosphates, such as methyl parathion, are known to inhibit cholinesterase activity. A method has been developed to measure the extent of this inhibition and relate it to organophosphate exposure (EPA 1980d; Nabb and Whitfield 1967). In this EPA-recommended method, blood is separated into plasma and red blood cell fractions. The fractions are treated with saline solution, brought to pH 8 with sodium hydroxide, and dosed with acetylcholine perchlorate. The ensuing acetic acid releasing enzyme reaction

is automatically titrated using an automatic titrator. This method is sensitive, simple, and fast, but is not specific for methyl parathion.

In a study of the metabolism of methyl parathion in intact and subcellular fractions of isolated rat hepatocytes, a high performance liquid chromatography (HPLC) method has been developed that separates and quantitates methyl parathion and six of its hepatic biotransformation products (Anderson et al. 1992). The six biotransformation products identified are methyl paraoxon, desmethyl parathion, desmethyl paraoxon, 4-nitrophenol, *p*-nitrophenyl glucuronide, and *p*-nitrophenyl sulfate. This method is not an EPA or other standardized method, and thus it has not been included in Table 7-1.

7.2 ENVIRONMENTAL SAMPLES

The predominant method of analyzing environmental samples for methyl parathion is by GC. The detection methods most used are FID, FPD, ECD, and mass spectroscopy (MS). HPLC coupled with ultraviolet spectroscopy (UV) or MS has also been used successfully. Sample extraction and cleanup varies widely depending on the sample matrix and method of detection. Several analytical methods used to analyze environmental samples for methyl parathion are summarized in Table 7-2.

In air, methyl parathion has been determined to the sub-ppt (ng/m^3) level by GC equipped with FPD or a nitrogen-phosphorus detector (NPD). Sample preparation methods varied from simple extraction and concentration (EPA 1980d, 1987d; Jackson and Lewis 1978; Seiber et al. 1989) to inclusion of column cleanup and fractionation steps (Stanley et al. 1971; Tessari and Spencer 1971). The widest variation in methods centered around sample collection. Multilevel collectors (EPA 1980d; Jackson and Lewis 1978; Stanley et al. 1971), resins (Seiber et al. 1989), and nylon cloth (Tessari and Spencer 1971) have all been used successfully. Recoveries ranged from 53 to over 100%. The best recovery and sensitivity data was reported by Seiber et al. (1989) during studies of atmospheric methyl parathion concentrations in the Sacramento Valley area of California. Using a macroreticular resin sampler, extraction with ethyl acetate, and GC/NPD analysis, over 85% of injected methyl parathion was recovered with a sensitivity of 0.2 ng/m^3 (sub-ppt). However, the precision of the method was low. The EPA-recommended method is similar, employing a glass fiber filter/solid sorbent sampler, extraction with diethyl ether in hexane, and analysis by GC/FPD (EPA 1980d). Both of these methods detect methyl paraoxon, the oxidized metabolite of methyl parathion, as well. Methyl parathion has also been detected in hazardous waste incinerator effluents. Using GC/FID and GC/MS, detection limits of 4.8 and 2.0 ng and precisions of 6 and 10%, respectively, were achieved (James et al. 1985).

Table 7-2. Analytical Methods for Determining Methyl Parathion in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect on hexylene glycol-alumina adsorbent sampler; extract; cleanup with Florisil	GC/FPD	0.1 ng/m^3	53.4	Stanley et al. 1971
Air	Collect on XAD-4 macroreticular resin; extract with ethyl acetate	GC/NPD	0.2 ng/m^3	85–111	Seiber et al. 1989
Air	Collect on solid sorbent; extract with diethyl ether in hexane	GC/FPD	No data	72–105	EPA 1980d
Water (run-off)	Collect on XAD-2 macroreticular resin; extract with diethyl ether	HPLC/UV	2–3 µg/L	99.75	Paschal et al. 1977
Water	Extract with benzene plus anhydrous potassium carbonate; concentrate; cleanup on silica gel	GC/ECD	0.1 µg/L	79	Lee et al. 1984
Water	Extract with methylene chloride; concentrate; cleanup on silica gel	GC/FPD	No data	93	EPA 1980d
Water, plant tissue	Extract with acetonitrile; filter if necessary	HPLC/UV/EC	No data (water); 50 µg/kg (plants)	95–99	Clark et al. 1985
Sediments	Dry with sodium sulfate; extract with acetone/methylene chloride; concentrate	GC/FPD	No data	73–95	Belisle and Swineford 1988
Water, plant tissue, animal tissue	Extract with hexane; cleanup with hexane/acetonitrile	GC/ECD	0.1 µg/L (water); 0.01 mg/kg (tissue)	100	Kadoum 1968

Table 7-2. Analytical Methods for Determining Methyl Parathion in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Plant tissue	Extract with ethyl acetate and sodium sulfate; filter through silanized glass wool	GC/TID	No data	No data	AOAC 1984
Food (butter fat)	Extract and cleanup on semipreparative HPLC column; elute with methylene chloride-hexane	GC/ECD	No data	No data	Gillespie and Walters 1986

EC = electrical conductivity detector; ECD = electron capture detector; FPD = flame photometric detector; GC = gas chromatography; HPLC = high performance liquid chromatography; NPD = nitrogen phosphorus detector; TID = thermionic detector; UV = ultraviolet spectroscopy

Analysis of water for methyl parathion in the ppb (ng/L) range has been done using GC/ECD, GC/FPD, and HPLC/UV. With water samples, the primary problems are concentration of the sample and selectivity of the method. Water samples generally contain only trace amounts of methyl parathion. Usually, other pesticides and interfering compounds are present. Several concentration, cleanup, and separation techniques have been tested in an attempt to improve the sensitivity and selectivity of analysis by GC/ECD (Agostiano et al. 1983; Kadoum 1968; Kawahara et al. 1967; Le Bel et al. 1979; Lee et al. 1984). EPA recommends fractionation on silica gel prior to detection by GC/FPD. The FPD detector is selective for organophosphates. Recoveries for these methods ranged from 74 to 94% with detection limits in the sub- and low-ppb range. HPLC/UV and HPLC/UV/electrochemical detectors have been used to simplify sample preparation and increase selectivity (Clark et al. 1985; Paschal et al. 1977). High recoveries (>99%) and precision, as well as detection limits in the low-ppb range, were reported.

Analysis of methyl parathion in sediments, soils, foods, and plant and animal tissues poses problems with extraction from the sample matrix, cleanup of samples, and selective detection. Sediments and soils have been analyzed primarily by GC/ECD or GC/FPD. Food, plant, and animal tissues have been analyzed primarily by GC/thermionic detector or GC/FPD, the recommended methods of the Association of Official Analytical Chemists (AOAC). Various extraction and cleanup methods (AOAC 1984; Belisle and Swineford 1988; Capriel et al. 1986; Kadoum 1968) and separation and detection techniques (Alak and Vo-Dinh 1987; Betowski and Jones 1988; Clark et al. 1985; Gillespie and Walters 1986; Koen and Huber 1970; Stan 1989; Stan and Mrowetz 1983; Udaya and Nanda 1981) have been used in an attempt to simplify sample preparation and improve sensitivity, reliability, and selectivity. A detection limit in the low-ppb range and recoveries of 100% were achieved in soil and plant and animal tissue by Kadoum (1968). GC/ECD analysis following extraction, cleanup, and partitioning with a hexane-acetonitrile system was used.

Using a simple, modified GC method with nitrogen-phosphorus detection (GC/NPD), Pappas et al. (1999) determined methyl parathion residues in apples with a recovery of 88–108% and a limit of detection of 2 ppb. Recent work by Sheridan and Meola (1999) suggests that analysis using GC coupled with tandem or ion trap MS (MS/MS) is a highly selective method capable of achieving clear compound identification and identity confirmation, with identification of compounds present in agricultural samples at the ppb level. The method is not as susceptible to interfering co-extractives as methods involving selective detectors; GC/MS/MS was able to detect methyl parathion in pears down to 2 ppb, while a selective detection method was limited to the level “<3 ppb” (Sheridan and Meola 1999).

Using established extraction and cleanup methods, followed by GC/FPD and GC/thermionic detection, Carey et al. (1979) obtained detection limits in the ppb range and recoveries of 80–110% in soil and 70–100% in plant tissue. Good sensitivity and recovery were maintained in a simplified extraction procedure of sediments followed by GC/FPD analysis (Belisle and Swineford 1988). Bound methyl parathion residues that were not extracted with the usual methods were extracted using supercritical methanol by Capriel et al. (1986). They were able to remove 38% of the methyl parathion residues bound to soil, but 34% remained unextractable, and 28% could not be accounted for.

HPLC has been recommended as a cleanup and fractionation procedure for food samples prior to analysis by GC/ECD (Gillespie and Walters 1986). The advantages over the AOAC-recommended Florisil column are that it is faster, requires less solvent, and gives better resolution. HPLC coupled with various detectors MS, MS/MS, UV/electrochemical detector, or UV/polarographic detection has been tested as a rapid, simplified separation and detection system to replace GC (Betowski and Jones 1988; Clark et al. 1985; Koen and Huber 1970). Recoveries, detection limits, and precisions were generally good, but further work is needed before the techniques are adopted for general use.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of methyl parathion is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of methyl parathion.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Sensitive, accurate methods exist for the measurement of erythrocyte and plasma cholinesterase levels (EPA 1980d; Nabb and Whitfield 1967). Organophosphates, including methyl parathion, inhibit cholinesterases. There are some problems with the reliability of this method because normal erythrocyte cholinesterase values vary widely (Midtling et al. 1985; Tafuri and Roberts 1987) and plasma cholinesterase can be suppressed by a variety of diseases (Henry 1984; Tafuri and Roberts 1987). Further studies to improve the reliability of cholinesterase levels might be useful in establishing this as a reliable measure of organophosphate exposure. Studies are needed regarding the measurement of methyl paraoxon in biological tissues, as this is the most toxic metabolite of methyl parathion.

Sensitive analytical methods exist to measure methyl parathion (Braeckman et al. 1980; DePotter et al. 1978; EPA 1980d) and some of its metabolic products (Anderson et al. 1992; Cranmer 1970; EPA 1980d; Lores and Bradway 1977; Morgan et al. 1977; Shafik et al. 1973b) at background levels and levels at which biological effects occur. The most sensitive and selective method for methyl parathion is currently GC/FPD (EPA 1980d; Gabica et al. 1971). The most sensitive and selective method for metabolites is derivitization followed by GC/FPD analysis (EPA 1980d; Lores and Bradway 1977); however, the metabolites found following methyl parathion exposure are not specific for methyl parathion.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods exist to measure low levels of methyl parathion in air (EPA 1980d, 1987d; Jackson and Lewis 1978; Seiber et al. 1989; Stanley et al. 1971; Tessari and Spencer 1971), water (Agostiano et al. 1983; Clark et al. 1985; Kadoum 1968; Kawahara et al. 1967; Le Bel et al. 1979; Lee et al. 1984), soil, and other media (Alak and Vo-Dinh 1987; AOAC 1984; Belisle and Swineford 1988; Betowski and Jones 1988; Capriel et al. 1986; Carey et al. 1979; Clark et al. 1985; Gillespie and Walters 1986; Kadoum 1968; Koen and Huber 1970; Stan 1989; Stan and Mrowetz 1983; Vdaya and Nanda 1981). These methods can be used to identify potentially contaminated areas to determine if there is a risk to human health. The media of most concern for human exposure are air, water, and soil. Sensitive methods exist to measure both background levels and levels at which health effects occur. Gas chromatography continues to be the most frequently used technique for the separation and identification of methyl parathion. Paired with an ECD or FPD, the detection limit is generally in the low- to sub-ppb range for air (EPA 1980d), water (Agostiano et al. 1983; Clark et al. 1985; Kadoum 1968; Kawahara et al. 1967; Le Bel et al. 1979; Lee et al. 1984), soil, and plant and animal tissue (Belisle and Swineford

1988; Carey et al. 1979; Kadoum 1968). Some problems still exist with sample preparation and separation, which affect the precision, accuracy, and specificity of analyses. Further studies to improve sample preparation and selectivity of detection might be beneficial in improving the reliability of existing methods.

7.3.2 Ongoing Studies

No ongoing studies concerning the methods of analysis of methyl parathion in biological samples and environmental media were located.

8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding methyl parathion in air, water, and other media are summarized in Table 8-1.

Methyl parathion is a restricted-use pesticide (EPA 1985b, 1999a). Methyl parathion formulations must be used under the direct supervision of a certified pesticide applicator (EPA 1980b). The certified pesticide applicator must be physically present during mixing, loading, application, equipment repair, and equipment cleaning (NPIRS 1986). Originally, no worker was allowed to enter a field treated with methyl parathion less than 48 hours after the treatment (EPA 1980b); that interval has been increased to 4–5 days (EPA 1999d). Methyl parathion is not registered for use by homeowners or for use indoors.

EPA (1999d, 1999e) has canceled many food crop uses of methyl parathion, including uses on fruits and vegetables commonly eaten by children (apples, peaches, pears, grapes, nectarines, cherries, plums, carrots, succulent peas and beans, and tomatoes) and some other vegetables, and some nonfood uses such as ornamental plants and nursery stock uses. Pesticide tolerances on these food crops also have been canceled for methyl parathion (EPA 2001). The cancellations occurred because of a concern for risks to children and workers. Existing stocks of methyl parathion products with canceled crop uses were allowed to be applied through December 31, 1999 (EPA 1999d). As listed in Table 8-1, tolerances have been retained for a large number of raw agricultural commodities (EPA 2001).

ATSDR has derived an intermediate-duration oral MRL of .0007 mg/kg/day for methyl parathion based on a minimal LOAEL of 0.22 mg/kg/day for electrophysiological effects in the central and peripheral nervous systems in rats (Desi et al. 1998).

ATSDR has derived a chronic-duration oral MRL of .0003 mg/kg/day for methyl parathion based on a NOAEL of 0.025 mg/kg/day for reduced hematocrit and erythrocyte counts in rats (Suba 1984).

EPA has derived an RfD of .00025 mg/kg/day, based on a NOAEL of 0.025 for reduced hematocrit, erythrocyte counts, and hemoglobin (cholinesterase inhibition was also listed as a critical effect but the reason for this was not explained). This NOAEL appears to be from the same study as for the ATSDR chronic-duration oral MRL, although the study is referenced differently (IRIS 2001).

Table 8-1. Regulations and Guidelines Applicable to Methyl Parathion

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenic classification	Group 3[a]	IARC 2001
WHO	No evidence of carcinogenicity		WHO 2001
NATIONAL			
Regulations and guidelines:			
a. Air			
ACGIH	TLV–TWA[b]	0.2 mg/m^3	ACGIH 2000
NIOSH	REL[b]	0.2 mg/m^3	NIOSH 2001
OSHA	PEL (8-hour TWA)[b]	0.2 mg/m^3	OSHA 2001
b. Water			
EPA	1-Day health advisory (10-kg child) 10-Day health advisory (10-kg child)	0.3 mg/L 0.3 mg/L	EPA 2000a
	Lifetime health advisory	2x10^{-3} mg/L	
	DWEL	9x10^{-3} mg/L	
c. Food			
EPA	Revocation of tolerances for fruits and vegetables commonly eaten by children, and other vegetables		EPA 1999e
	Establishment/retention of tolerances for residues in or on raw agricultural commodities in food crops (ppm)		EPA 2001
	Almonds	0.1	
	Apricots	1.0	
	Avocados	1.0	
	Barley	1.0	
	Beans (dried)	1.0	
	Beets (sugar), including tops	0.1	
	Blackberries	1.0	
	Blueberries	1.0	
	Boysenberries	1.0	
	Cabbage	1.0	
	Clover	1.0	
	Corn	1.0	

Table 8-1. Regulations and Guidelines Applicable to Methyl Parathion *(continued)*

Agency	Description	Information	References
NATIONAL *(cont.)*			
EPA *(cont.)*	Establishment/retention of tolerances for residues in or on raw agricultural commodities in food crops (ppm)		EPA 2001
	Cottonseed	0.75	
	Cranberries	1.0	
	Cucumbers	1.0	
	Currants	1.0	
	Dates	1.0	
	Dewberries	1.0	
	Eggplants	1.0	
	Endive (escarole)	1.0	
	Figs	1.0	
	Filberts	0.1	
	Garlic	1.0	
	Gooseberries	1.0	
	Guavas	1.0	
	Hops	1.0	
	Mangoes	1.0	
	Melons	1.0	
	Mustard seed	0.2	
	Oats	1.0	
	Okra	1.0	
	Olives	1.0	
	Onions	1.0	
	Parsley	1.0	
	Parsnips	1.0	
	Parsnip greens	1.0	
	Peanuts	1.0	
	Peas (dried)	1.0	
	Pecans	0.1	
	Peppers	1.0	
	Pineapple	1.0	
	Potatoes	0.1	
	Pumpkins	1.0	
	Quinces	1.0	
	Radishes (with or without tops)	1.0	
	Rape (canola) seed	0.2	
	Raspberries	1.0	
	Rice	1.0	
	Safflower seed	0.1	
	Sorghum	0.1	
	Soybeans	0.1	
	Squash	1.0	
	Strawberries	1.0	

Table 8-1. Regulations and Guidelines Applicable to Methyl Parathion *(continued)*

Agency	Description	Information	References
NATIONAL *(cont.)*			
EPA *(cont.)*	Establishment/retention of tolerances for residues in or on raw agricultural commodities in food crops (ppm)		EPA 2001
	Summer squash	1.0	
	Sunflower seeds	0.2	
	Sweet potatoes	0.1	
	Swiss chard	1.0	
	Walnuts	0.1	
	Wheat	1.0	
	Youngberries	1.0	
d. Other			
ACGIH	Carcinogenic classification	A4[c]	ACGIH 2000
EPA	RfD	2.5×10^{-4} mg/kg/day	IRIS 2001
	Carcinogenic classification	Group D[d]	EPA 2000a
	Designated hazardous substance in accordance with Section 311(b)(2)(a)		EPA 2000b 40CFR116.4
	Pesticide chemicals manufacturing discharges		EPA 2000c 40CFR455.20
	RCRA—identification and listing as a hazardous waste	P071	EPA 2000d 40CFR261.33
	CERCLA—reportable quantity	100 pounds	EPA 1999f 40CFR302.4
	Toxic chemical release reporting; Community Right-to-Know —effective date	01/01/95	EPA 1999g 40CFR372.65
STATE			
Regulations and guidelines:			
a. Air:			
Arkansas	Hazardous Air Pollutant		ADEQ 2001
	RAC	0.3 µg/m^3	BNA 2001
California	RAC	0.3 µg/m^3	BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Methyl Parathion *(continued)*

Agency	Description	Information	References
STATE *(cont.)*			
California	Toxic Air Contaminant		California EPA 2001
Colorado	Hazardous air pollutant		BNA 2001
	8 hour	4 µg/m^3	
	30 minutes	20 µg/m^3	
Delaware	RAC	0.3 µg/m^3	BNA 2001
Idaho	Toxic air pollutants		BNA 2001
	OEL	0.2 mg/m^3	
	EL	0.013 pounds/hour	
	AAC	0.01 mg/m^3	
Illinois	RAC	0.3 µg/m^3	BNA 2001
Kentucky	RAC	0.3 µg/m^3	BNA 2001
New Hampshire	Regulated toxic air contaminant		BNA 2001
	OEL	0.2 mg/m^3	
South Carolina	RAC	0.3 µg/m^3	BNA 2001
Tennessee	RAC	0.3 µg/m^3	BNA 2001
Wisconsin	Proposed threshold		Wisconsin DNR 2001
	24 hour<25 feet (pounds/hour)	0.0107	
	24 hour$25 feet<75 feet (pounds/hour)	0.0417	
	24 hour$75 feet (pounds/hour)	0.324	
	AAC	4.8 µg/L	
Wyoming	RAC	0.3 µg/m^3	BNA 2001
b. Water:			
Arizona	Drinking water guideline	1.8 µg/L	HSDB 2001
California	Drinking water guideline	30 µg/L	HSDB 2001
Florida	Drinking water guideline	10 µg/L	HSDB 2001
Kentucky	Hazardous constituent for groundwater monitoring		BNA 2001
Maine	Drinking water guideline	2 µg/L	HSDB 2001

Table 8-1. Regulations and Guidelines Applicable to Methyl Parathion *(continued)*

Agency	Description	Information	References
STATE *(cont.)*			
Vermont	Enforcement standard Preventive action level	2.0 µg/L 1.0 µg/L	BNA 2001
c. Food:		No data	
d. Other:			
Arizona	Soil remediation level Residential Non-residential	 16.0 mg/kg 170 mg/kg	BNA 2001
Massachusetts	RfD	$2.5x10^{-4}$ mg/kg/day	BNA 2001
Missouri	Hazardous constituent		BNA 2001
New Jersey	Requires field posting		CDC 2001
Ohio	Extremely hazardous substance		Ohio EPA 2001

[a]Group 3: not classifiable as to its carcinogenicity to humans
[b]Skin notation: danger of cutaneous absorption
[c]A4: not classifiable as a human carcinogen
[d]Group D: inadequate or no human or animal evidence of carcinogenicity

AAC = acceptable ambient concentration; ACGIH = American Conference of Governmental Industrial Hygienists; ADEQ = Arizona Department of Environmental Quality; BNA = Bureau of National Affairs; CDC = Center for Disease Control; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DNR = Department of Natural Resources; DWEL = drinking water equivalent level; EL = emissions level; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute of Occupational Safety and Health; OEL = occupational exposure limit; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; RAC = reference air concentration; REL = recommended exposure limit; RCRA = Resource Conservation and Recovery Act; RfD = reference dose; TLV = threshold limit value; TWA = time-weighted average; WHO = World Health Organization

9. REFERENCES

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL-from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A
ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

APPENDIX A

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Methyl parathion
CAS Number: 298-00-0
Date: June 22, 2001
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to Figure: 32
Species: Rats

Minimal Risk Level: 0.0007 [X] mg/kg/day [ ] mg/m^3

Reference: Desi I, Nagymajtenyi L, Papp A, et al. 1998. Experimental model studies of pesticide exposure. Neurotoxicology 19:611-616.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Male rats were treated with methyl parathion in an aqueous vehicle through gavage administration to their dams during days 5–15 of gestation and days 2–28 of lactation at doses of 0.22, 0.44, or 0.88 mg/kg/day, followed by direct treatment of the male offspring in the same manner for 8 weeks, from weaning through 11–12 weeks of age. Electrophysiological testing was performed on the male offspring at the end of the treatment period.

Effects noted in study and corresponding concentrations: Dose-related changes on electrocorticograms of the somatosensory, visual, and auditory centers, on evoked potentials, and on tail nerve conduction velocity and refractory period were observed in the male offspring (Desi et al. 1998). The results were stated to be significantly different from controls at all three dose levels, but results specifically for methyl parathion were shown only for the electrocorticograms of the somatosensory area. No overt signs of toxicity or effects on body weight were seen in the male offspring.

In the same study (Desi et al. 1998), no significant effects on these end points were seen in male rats exposed to methyl parathion only through the treatment of their dams during gestation or during gestation and lactation, and then maintained without treatment until testing at 11–12 weeks of age.

Concentration and end point used for MRL derivation: 0.22 mg/kg/day; electrophysiological effects in the central and peripheral nervous systems

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? NA

Other additional studies or pertinent information that lend support to this MRL: Methyl parathion affects the nervous system by inhibiting acetylcholinesterase activity. Cholinesterase inhibition and neurological effects have been observed in humans and animals, for all exposure routes and durations (for example, Dean et al. 1984; Desi et al. 1998; EPA 1978e; Gupta et al. 1985; Nemec et al. 1968; Suba 1984).

Agency Contact (Chemical Manager): Jewell D. Wilson, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Methyl parathion
CAS Number: 298-00-0
Date: June 22, 2001
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to Figure: 38
Species: Rats

Minimal Risk Level: 0.0003 [X] mg/kg/day [ ] mg/m^3

Reference: Suba, LA. 1984. Additional information to support the registration of methyl parathion: Two year chronic feeding study of methyl parathion in rats. St. Louis, MO: Monsanto Agricultural Products Company.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Sprague-Dawley CD rats (60/sex/dose) were fed methyl parathion at dietary concentrations of 0, 0.5, 5, or 50 ppm (0, 0.025, 0.25, or 2.5 mg/kg/day) for 26 months (males) or 28 months (females). Animals were observed twice daily for clinical signs and weighed weekly. Hematological and clinical chemistry, and urinalysis determinations were performed at 6, 12, 18, and 24 months and at study termination. Five rats/sex/group were killed at approximately 24 months for examination of the brain, spinal cord and sciatic nerves. Complete necropsies and histopathological examinations of a wide range of organs and tissues were performed.

Effects noted in study and corresponding concentrations: No adverse effects were observed in the low-dose male and female rats. Mean hemoglobin, hematocrit, and erythrocyte counts were significantly reduced in the high-dose females at 6–24 months of treatment; mean hematocrit and erythrocyte counts were significantly reduced in the mid- and high-dose males at 24 months of treatment.

Abnormal gait involving the hind legs was observed in 1 mid-dose female from week 77 until termination, in 4–14 of the high-dose female rats from week 19 to termination, and in 1 high-dose male around the beginning of the second year. Slight tremor was noted during the first 3 weeks to 4 months of treatment in both sexes of the high-dose group. Peripheral neuropathy of the proximal and distal sciatic nerve was considered to be related to exposure to methyl parathion at the high dose. Methyl parathion did not induce histopathological effects in the brain or spinal cord. Statistical significance was not reported for these clinical signs and histopathological effects. Mean plasma, erythrocyte, and brain cholinesterase activities were significantly reduced by 67–88, 9–20, and 76–79%, respectively, in rats of both sexes following 2-year exposures only at the high dose of methyl parathion.

Additional effects, which occurred only at the high dose, were retinal degeneration or atrophy and posterior subcapsular cataracts in the females. Slightly reduced body weights occurred in both sexes at the high dose at 2 years, but not consistently throughout the study, and food consumption was slightly elevated in the high-dose females.

Concentration and end point used for MRL derivation: 0.025 mg/kg/day; decreased mean hematocrit and erythrocyte counts

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes. A chronic food factor of 0.05 kg feed/kg body weight/day for rats was used to convert from ppm in food to mg/kg as follows: 0.5 ppm x 0.05 = 0.025 mg/kg/day. (Data regarding body weight and food consumption were not available.) This is the food factor used in the original MRL derivation.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? NA

Other additional studies or pertinent information that lend support to this MRL: An intermediate-duration gavage study in rats found decreased hematocrit and erythrocyte counts relative to before-treatment values (Galal et al. 1977), but this study had some limitations, including lack of a control group and disparities between text and tables. Another intermediate duration gavage study in male rats demonstrated dose-related significant decreases in mean corpuscular volume (Undeger et al. 2000). An effect on the erythrocyte is plausible because erythrocyte cholinesterase has a function in the control of erythrocyte permeability (Wills 1972).

Agency Contact (Chemical Manager): Jewell D. Wilson, Ph.D.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 9 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 6

Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

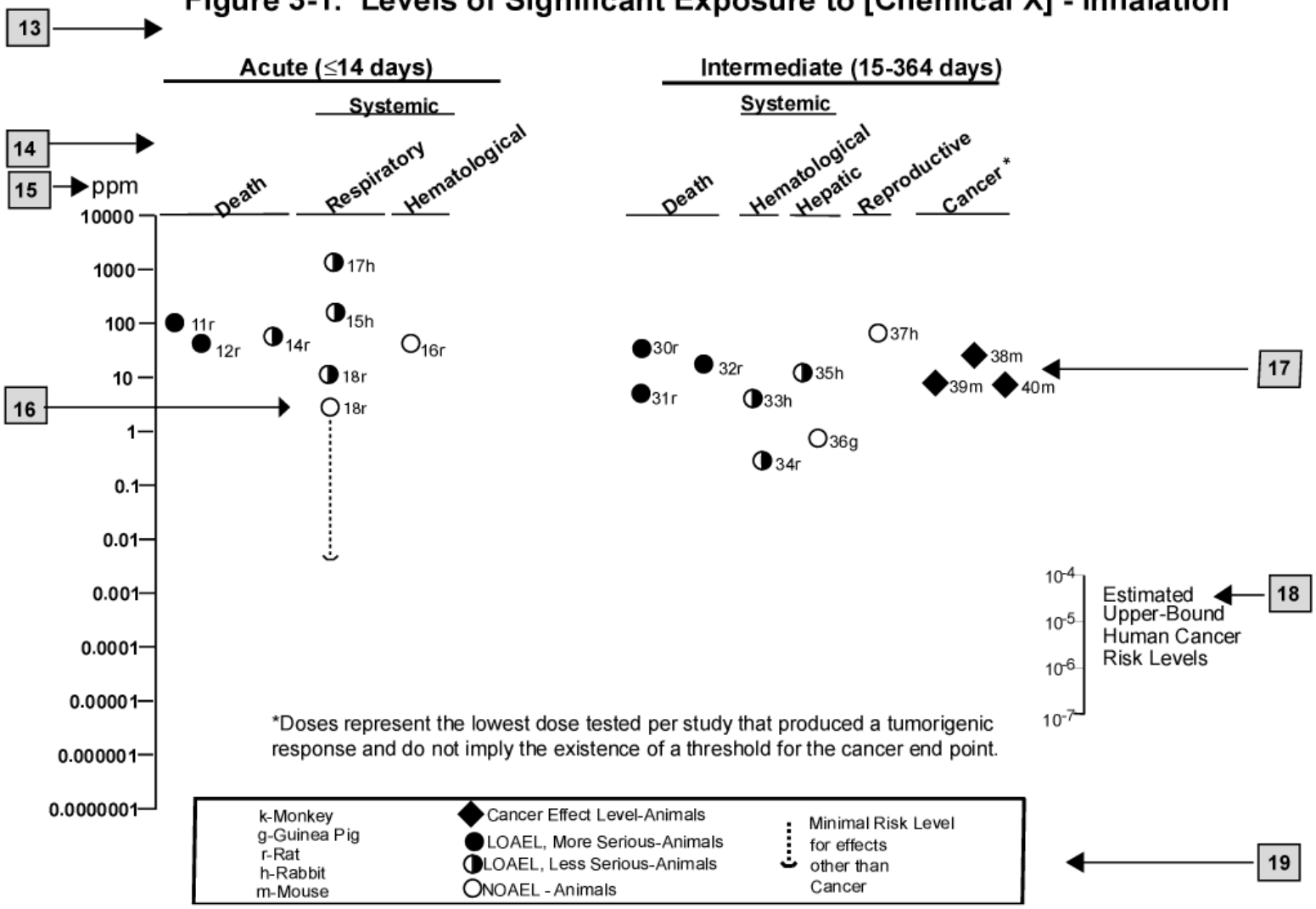
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 6 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 6 Systemic	9	9	9	9	9		9
4 6 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					9		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 3-1.

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram

EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter

mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector

pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer

µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D

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