TOXICOLOGICAL PROFILE FOR MALATHION

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

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UPDATE STATEMENT

A Toxicological Profile for malathion, Draft for Public Comment was released in September, 2001. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
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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:

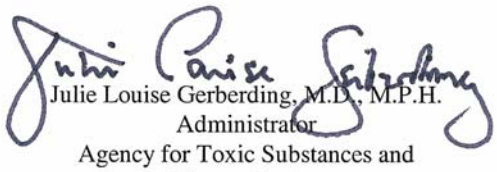
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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.



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*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 prepare 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 October 25, 2001 (66 FR 54014). For prior versions of the list of substances, see *Federal Register* notices dated 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); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); and October 21, 1999 (64 FR 56792). 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) 498-0110 ***Fax:*** (404) 498-0093
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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 Exposure*s—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.

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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 malathion. The panel consisted of the following members:

1. Dr. Lucio Costa, Department of Environmental Health, University of Washington, Seattle, Washington 98105-6099.

2. Dr. Loren D. Koller, College of Veterinary Medicine, Oregon State University, Corvallis, Oregon 97331-4801.

3. Dr. Joseph Seifert, Department of Plant and Environmental Protection Sciences, University of Hawaii, Honolulu, Hawaii 96822.

These experts collectively have knowledge of malathion'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 malathion 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. Malathion has been found in at least 21 of the 1,623 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 malathion 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 malathion, 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/them. 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 MALATHION?

Malathion is a pesticide that is used to kill insects on agricultural crops, on stored products, on golf courses, in home gardens, and in outdoor sites where trees and shrubs are grown at home; it is also used to kill mosquitoes and Mediterranean fruit flies (medflies) in large outdoor areas. Additionally, malathion is used to kill fleas on pets and to treat head lice on humans. It is usually sprayed on crops or sprayed from an airplane over wide land areas, especially in the states of California and Florida. Malathion comes in two forms: a pure form of a colorless liquid and a technical-grade solution (brownish-yellow liquid), which contains malathion (greater than

90%) and impurities in a solvent. The technical-grade malathion smells like garlic. Malathion is a manufactured chemical, so it is only found in the environment as a result of its manufacture or use. Malathion has been manufactured in the United States since 1950 and has been used to kill insects on many types of crops since this time. The Food and Drug Administration (FDA) and the EPA allow a maximum amount of 8 parts per million (ppm) of malathion to be present as a residue on specific crops used as foods. Because malathion can be dangerous to humans, the EPA requires that a certain amount of time must pass between the time of application of the insecticide and entry by a worker into a field where the chemical has been applied. Usually, at least 12 hours must pass between application and entry, but in some cases, such as when workers are entering a field to hand harvest or hand prune the crops, time periods as long as 6 days must pass between application and entry into the field. In this way, exposure to malathion can be controlled and accidental exposures can be prevented.

1.2 WHAT HAPPENS TO MALATHION WHEN IT ENTERS THE ENVIRONMENT?

Once malathion is introduced into the environment, usually from spraying on crops or in wide urban/residential areas, droplets of malathion in the air fall on soil, plants, water, or man-made surfaces. While most of the malathion 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. Malathion stays in the environment from a few days to several months, but is usually broken down within a few weeks. It is broken down to other chemical compounds by water, sunlight, and bacteria found in soil and water. Malathion does not tend to stick to the soil and is rapidly broken down by bacteria; thus, it is unlikely that malathion will reach groundwater in significant amounts. In water, malathion breaks down quickly by the action of the water and the bacteria in the water. In air, malathion is broken down by reacting with other chemicals formed naturally in the air by sunlight, to form a more toxic product called malaoxon. If malathion is present on dry soil or on man-made surfaces such as sidewalks, pavements, or playground equipment, it usually does not break down as fast as it would in moist soil. For more information, see Chapters 4, 5, and 6.

1.3 HOW MIGHT I BE EXPOSED TO MALATHION?

Most people are not exposed to malathion in the air that they breathe or on things that they touch, unless they live near areas being sprayed. The people who are at the greatest risk of being exposed to malathion are those who work with this chemical. These include farm workers, chemical sprayers, and people who work in factories that make malathion or other products that contain the chemical. They are exposed to malathion on things they touch where it can pass through their skin, or by breathing it after it has been sprayed. Other people who are at risk of being exposed to malathion are those who use it near their homes and in their gardens, and people living in areas where malathion is sprayed to control medflies or mosquitos. Overexposure to malathion 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 malathion can be protected by wearing special clothing and breathing equipment and by staying out of sprayed fields for the appropriate amount of time for the job that they are going to do in the field; this amount of time can be up to 6 days.

Individuals can also be exposed to malathion if they live near landfills where malathion has been dumped or near water containing malathion that washes off nearby land or that is accidentally spilled. The greatest amounts of malathion are expected to be present near or on the farms where malathion is used. After spraying, some malathion 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 a collection of data gathered by the EPA for the years 1971–1991, it was reported that malathion was only found in a total of 12 groundwater monitoring wells in three states. The most that was found in any of the wells was 6.17 parts of malathion per billion parts of water (ppb); this was found in a county in Virginia that is made up mainly of agricultural and forested land. More recent studies of water samples taken near where malathion was sprayed indicate that malathion is not usually found in groundwater. The risk of exposure to malathion from drinking groundwater appears to be low. For more information, see Chapter 6.

Malathion is approved for use on crops, in homes and gardens, in urban/residential areas where mosquitos or medflies pose a problem, and at agricultural sites. The maximum amount of malathion residue allowed by the FDA and EPA on crops used as food is 8 ppm of malathion.

The FDA has monitored the food supply for pesticides for a number of years. FDA purchases many kinds of foods through Total Diet Studies (also called 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. For more information, see Section 1.7 and Chapter 6.

1.4 HOW CAN MALATHION ENTER AND LEAVE MY BODY?

For the general population, the most likely way that malathion can enter the body is by eating or drinking contaminated food or water or through dermal contact with contaminated plants, soils, or surfaces such as playground equipment or pavements. It can also enter your body if you breathe air containing malathion during or after it has been sprayed for public health uses. By any means of exposure, malathion enters your body quickly and passes into the bloodstream.

Once in your bloodstream, malathion can go to many organs and tissues. Most of the malathion is broken down in your liver into other substances, called metabolites. One of these metabolites is more harmful than malathion. Malathion and its metabolites do not tend to accumulate in the body, and leave mostly in your urine within a few days.

See Chapter 3 for more information on how malathion enters and leaves the body.

1.5 HOW CAN MALATHION AFFECT MY HEALTH?

Malathion interferes with the normal function of the nervous system. Because the nervous system controls many other organs, malathion indirectly can affect many additional organs and functions. Exposure to high amounts of malathion in the air, water, or food may cause difficulty breathing, chest tightness, vomiting, cramps, diarrhea, watery eyes, blurred vision, salivation, sweating, headaches, dizziness, loss of consciousness, and death. If persons who are exposed accidentally or intentionally to high amounts of malathion are rapidly given appropriate treatment, there may be no long-term harmful effects. If people are exposed to levels of

malathion below those that affect the function of the nervous system, few or no health problems seem to occur. This has been shown in studies with volunteers who inhaled or swallowed small known amounts of malathion. There is no evidence that malathion affects the ability of humans to reproduce. There is also no conclusive proof that malathion causes cancer in humans, although some studies have found increased incidence of some cancers in people who are regularly exposed to pesticides, such as farmers and pesticide applicators. The International Agency for Research on Cancer (IARC) has determined that malathion is unclassifiable as to carcinogenicity to humans.

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.

Studies in animals have observed the same effects that occur in humans after exposure to malathion. This is because malathion also affects the nervous system of animals. Some studies in animals suggest that malathion may produce subtle changes in the immune system, but there was no evidence indicating that those animals were more susceptible to infections than animals that were not given malathion. Some studies in male rats observed temporary alterations in the testes following short-term exposure to malathion, but there is no evidence that exposure to malathion affected the reproductive ability of these animals. A longer-term study that evaluated the ability of rats to reproduce did not detect any harmful effects. Most studies of cancer in animals have not shown evidence of carcinogenicity for malathion, or have shown evidence of cancer at doses considered excessive. Still, there is some disagreement among scientists on how to interpret the results. The EPA has determined that there is suggestive evidence of

carcinogenicity for malathion in animals but it is not sufficient to assess potential carcinogenicity in humans. See Chapter 3 for more information on how malathion can affect your health.

1.6 HOW CAN MALATHION 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 can be exposed to malathion from food and drinking water, but these risks are low and not of concern. Because malathion is a widely used pesticide, greater concern exists from exposure following application to recreational areas, parks, and playgrounds and from home and garden uses of malathion. Children can also be exposed when malathion is sprayed, for example, to control mosquitos. Because children spend more time outdoors than adults, they may be at a greater risk of exposure to malathion than adults. Because of their smaller weight, children's intake of malathion per kilogram of body weight may be greater than that of adults. The EPA permits residues of pesticides to be present in crops used as food, and these amounts are considered to be safe. Children may be exposed also by dermal contact with contaminated surfaces or by placing contaminated objects in their mouths.

The main target of malathion toxicity in children is the nervous system, the same as in adults. Children who have accidentally swallowed high amounts of malathion or who had skin contact with high amounts of malathion experienced difficulty breathing, chest tightness, vomiting, cramps, diarrhea, watery eyes, salivation, sweating, headaches, dizziness, and loss of consciousness, and some died. We do not know whether or not children are more susceptible than adults to malathion toxicity. However, studies in animals have shown that very young animals are more susceptible than older ones when exposed to high amounts of malathion.

There is no evidence that exposure to malathion at levels found in the environment causes birth defects or other developmental effects in people. Malathion has caused adverse developmental effects in animals, but only when administered to the pregnant mothers in amounts high enough to affect the health of the mothers. A study of people in California found that the use of

pesticides, malathion among them, at home during pregnancy did not increase the risk of brain tumors in children.

Animal studies have shown that malathion and/or its breakdown products can be transferred from a pregnant mother to the developing fetus and that it can also be passed to newborn animals in the maternal milk. There is no information in humans regarding transfer of malathion to the fetus or to nursing infants.

More information regarding children's health and malathion can be found in Section 3.7.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO MALATHION?

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

The general population is not likely to be exposed to large amounts of malathion. The populations living in the areas where malathion is used on crops or those who use the insecticide extensively in their gardens or near their homes, however, may be exposed to greater amounts of malathion. Malathion is often detected in foods and air samples collected where malathion is used. People who live close to areas of malathion use, such as where it is sprayed over urban/residential areas to control medflies or mosquitos, may also be exposed to larger amounts of malathion, because small amounts of the pesticide will move from the place where it is used to nearby areas. These exposures may take place during activities such as touching contaminated plants, soils, or man-made surfaces such as playground equipment, sidewalks, or pavements; 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 malathion or make products that contain the insecticide, workers who spray it on crops, and farmers. Entry of malathion 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 malathion may also occur.

Families can reduce the risk of exposure to malathion in the soil, on plants, or in the air by staying away from fields that have been recently sprayed. If families wait at least a week before entering sprayed fields, then the amount of malathion present in the air or on plants is expected to be small. In areas where malathion is sprayed to control medflies or mosquitos, families may reduce the risk of exposure to the chemical by remaining inside during the spraying periods, and by washing their hands and clothes if they come into contact with sprayed surfaces within a few days of the spraying. For children who play in dry sand boxes, on sidewalks, or on playground equipment that is located in or near the treated areas, the amount of time that caution should be used (that is, the time during which they should make sure to wash thoroughly after contact with sprayed surfaces) may need to be longer. Families may also reduce the risk of exposure to malathion by wearing protective equipment, such as gloves, when applying the insecticide in their homes and gardens, and washing their hands and clothes after they have been in a backyard garden or yard that has been treated with the insecticide. Foods grown in a garden treated with malathion may contain some of the residues on their surface. To reduce the risk of exposure to malathion that may occur when contaminated vegetables or other produce grown in a backyard garden is eaten, it is important to wash the foods prior to eating them.

Families should also be aware that sometimes malathion could be illegally sprayed inside the home to kill insects. Your children may be exposed to malathion if either you or another person applies pesticides containing it in your home. In some cases, the improper use of pesticides not intended for indoor 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 intended for indoor use and are in unopened pesticide containers that are labeled and contain an EPA

registration number. Carefully follow the instructions on the label. 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 MALATHION?

There are tests available to determine whether you have been exposed to malathion. Breakdown products of malathion can be measured in the urine, but the tests need to be conducted within days of the exposure since these products are eliminated fairly rapidly. These tests, however, do not predict whether or not the exposure to malathion will produce harmful health effects. Another type of test measures the levels of a substance called cholinesterase in your blood. This test is not specific for malathion, but can be used to determine exposure to many other substances that act in a way similar to malathion. If the levels of cholinesterase in you blood are less than half of what they should be, then you may get symptoms of poisoning. Smaller decreases in cholinesterase may only indicate that you have been exposed to malathion or similar substances, but you will not necessarily experience harmful effects. Cholinesterase levels in the blood can stay low for months after you have been exposed to malathion 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 malathion include the following:

OSHA has established an exposure limit for malathion in the workplace of 15 milligrams per cubic meter (mg/m^3), for an 8-hour workday, 40 hours per week. NIOSH recommends that workers not be exposed to more than 10 mg/m^3 of malathion for a 10-hour workday, 40 hours per workweek. NIOSH also recommends that a level of 250 mg/m^3 of malathion in the air be considered as immediately dangerous to life and health.

According to EPA, the following levels of malathion in drinking water are not expected to cause effects that are harmful to health: 0.2 milligrams per liter (mg/L) for 1 day, 10 days, or longer-term exposure for children, and 0.1 mg/L for lifetime exposure of adults.

EPA also has set maximum levels of malathion residues in meat and dairy products, vegetables, fruits, tree nuts, cereal grains, and grass forage, fodder, and hay. Individual values are listed in Table 8-1.

EPA requires notification to the Agency of spills or accidental releases of 100 pounds or more of malathion to the environment. For more information on regulations and guidelines applicable to malathion, 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 contact ATSDR at the address and phone number below.

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.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles CD-ROM by calling the information and technical assistance toll-free number at 1-888-42ATSDR (1-888-422-8737), by email at atsdric@cdc.gov, or by writing at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop E-29
Atlanta, GA 30333
Fax: 1-404-498-0093

For-profit organizations may request a copy of final profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO MALATHION IN THE UNITED STATES

Malathion is an insecticide used for agricultural and non-agricultural purposes and is released to the environment primarily through spraying on agricultural crops and at agricultural sites, spraying for home and garden use, and spraying for public health use in both urban/residential and nonresidential areas; the insecticide is also released to the environment using fogging equipment. Once malathion is introduced into the environment, it may be activated by atmospheric photooxidation, or degraded by hydrolysis, or biodegradation mediated by microorganisms found in most sediment, soils, and water. Malaoxon, the oxon generated from malathion, is more toxic than malathion and is formed by the oxidation of malathion and may also be present as an impurity in the parent compound. Malathion and malaoxon can be transported from the site of application by precipitation, fog, and wind to other areas. Malathion is moderately mobile to very highly mobile in soils, creating the potential for it to move through the soil profile and into groundwater. However, because degradation of malathion occurs rapidly in the environment, the potential for malathion movement into groundwater is generally not significant, and leaching of the chemical into groundwater is usually not observed. Volatilization of malathion from ground surfaces following aerial applications has been observed. Data from limited studies suggest that bioconcentration of malathion does not occur to a significant extent in most aquatic organisms tested, and that it is rapidly metabolized when it is accumulated in such. Malathion is not widely dispersed or persistent in the environment, but is detected frequently in minute quantities in foods. Residue amounts of malathion have been detected in air, water, soil, fish, and agricultural crops consumed as food.

The general population is not likely to be exposed to large amounts of malathion. Some exposure to residues of malathion is possible, however, as many studies show that malathion has been detected in foods and atmosphere samples. Populations living within or very near areas of heavy malathion use would have an increased risk of exposure to relatively larger amounts of malathion through dermal contact with contaminated plants, soils, or nonnatural surfaces such as playground equipment and pavements; by inhalation of the mist formed from the applied insecticide; or by ingestion of water or food-borne residues. Also at increased risk of exposure are persons utilizing malathion for extensive home and garden use, particularly if they consume contaminated, unwashed backyard produce. Those likely to receive the highest levels of exposure are those who are involved in the production, formulation, handling, and application of malathion, as well as farm workers who enter treated fields prior to the

passage of the appropriate restricted entry intervals. Dermal contact appears to be the major route of exposure for workers, while ingestion is also an important route of exposure for the general population not living in areas where malathion is extensively used. Inhalation has not been shown to be a significant route of exposure to malathion.

Because malathion is one of the most frequently detected pesticides in the FDA's Total Diet Studies there is a great potential for exposure of the general population to malathion by consumption of food containing residues of the chemical. In a 10-year study of ready-to-eat foods, malathion was found in 110 foods at an average concentration of 0.0111 ppm. In a study of domestic and imported apples and rice, malathion was found at average concentrations of 0.10–0.11 ppm in apples and at 0.005–0.013 ppm in rice. Detections of malathion in apples were infrequent (<1% of the samples); however, in domestic rice, malathion was detected in 41% of the samples, at a maximum concentration of 2.3 ppm. Additional studies have reported concentrations of malathion of up to 0.40 ppm in various foods. However, based on a risk assessment of malathion conducted by the EPA using, in part, the Dietary Exposure Evaluation Model (DEEM), neither acute nor chronic dietary exposure to malathion (plus malaoxon) is a concern for the majority (95th exposure percentile) of the U.S. population. Individuals who consume unwashed, contaminated backyard produce treated with malathion may be exposed to greater levels of the chemical than others in the general population.

In areas of public health malathion usage, the potential for exposure to the compound has been reported to be greater via the dermal and ingestion routes than through inhalation. Malathion concentrations in indoor, outdoor, and personal air have been measured at two U.S. sites as part of an EPA non-occupational exposure study. The maximum concentrations detected in the indoor, outdoor, and personal air at one site were 20.8, 0.3, and 16.8 ng/m^3, respectively; at the second site, respective maximums were 5.0, 0.8, and 0.5 ng/m^3. At the first site, maximums of 32, 4, and 15% of the population was exposed to malathion in indoor, outdoor, and personal air, respectively. At the second site, however, the respective maximums were only 2, 5, and 4%. In a study of seven homes in New Jersey, from which air and dust samples were collected from two rooms per home, malathion was not detected in any of the samples. Malathion has been detected in the ambient outdoor air at up to 4.6 ng/m^3 and in the ambient air of offices and storage rooms of commercial pest control firms at up to 3.57 µg/m^3 (3,570 ng/m^3).

Dermal exposure to malathion is not likely to be a health concern for the general population, with the possible exception of individuals who live in or near areas where malathion is used extensively for public health purposes or for home and garden usage. Dermal exposure is, however, a major source of exposure

for workers who are directly involved in the production, formulation, handling, and application of malathion-containing products, as well as for field workers. Occupational exposure has been reported for workers who are not directly involved with applications of malathion, but work in facilities, such as veterinary clinics, where the products are used. Exposure levels for workers are affected by the type of work activity being conducted at the time of exposure. Dermal exposure levels may also be affected by the type and material constituents of the protective gear utilized, as well as by the carrier solvents in the formulated product.

Children are expected to be exposed to malathion by the same routes that affect adults. Small children are more likely to come into contact with malathion 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. Malathion has been detected in foods found in infant and toddler diets at concentrations of up to 0.40 ppm. Only one study was found that detected small amounts of malathion in breast milk; therefore, an adequate determination of the importance of this route of child exposure has not been made.

Populations residing near hazardous waste disposal sites may be subject to higher levels of malathion in environmental media (i.e., air, water, soil) than those experienced by the general population. Malathion has been identified in at least 21 of the 1,623 hazardous waste disposal sites that have been proposed for inclusion on the EPA National Priorities List (NPL). However, the number of sites evaluated for malathion is not known. As more sites are evaluated, the number of sites where malathion has been detected may increase.

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

2.2 SUMMARY OF HEALTH EFFECTS

Malathion is an organophosphate pesticide of relatively low acute toxicity compared to other organophosphates. Signs and symptoms of acute toxicity are typical of those induced by organophosphate insecticides as a group. Almost all of the systemic effects observed following exposure to malathion are due to the action of its active metabolite, malaoxon, on the nervous system, or are secondary to this primary action. Malaoxon inhibits the enzyme acetylcholinesterase at the various sites where the enzyme is present in the nervous system, (i.e., the central nervous system, the sympathetic and parasympathetic divisions of the autonomic nervous system, and the neuromuscular junction). Inhibition

of acetylcholinesterase results in accumulation and continuous action of the neurotransmitter acetylcholine at postsynaptic sites. Information regarding effects of malathion in humans is derived mainly from cases of accidental or intentional ingestion of malathion, studies of the general population exposed during aerial application of the pesticide for pest control, studies of pesticide users exposed to multiple pesticides including malathion, a few controlled exposure studies with volunteers, and cases of dermal exposure to malathion. Oral ingestion of high amounts of malathion resulted in typical signs and symptoms of organophosphate intoxication including reduced plasma and red blood cell (RBC) cholinesterase activity, excessive bronchial secretions, respiratory distress, salivation, pinpoint pupils, bradycardia, abdominal cramps, diarrhea, tremor, fasciculation, and occasionally death.

Epidemiological studies have found weak associations between exposure to malathion and developmental effects and certain types of cancer. Malathion has also been shown to be a contact sensitizer, and results from some studies have suggested that it may cause adverse genetic effects. No chronic effects have been documented in humans following exposure specifically to malathion. Studies in animals support the human data and confirm that the main target of malathion toxicity is the nervous system. Malathion was not a reproductive or developmental toxicant in animals at doses that did not induce maternal toxicity, but transient testicular effects were reported. Malathion induced liver carcinogenicity in female Fischer-344 rats and in male and female B6C3F_1 mice at doses that were considered excessive. Results from a series of studies in animals conducted in the last decade suggest that malathion can modulate (increase or decrease) some immunologic parameters at doses below those that induce neurotoxicity. Although the physiological significance of these effects is yet unclear, it has been suggested that enhancements of the immune response induced by malathion may be responsible for symptoms such as lacrimation, rashes, and irritation of mucous membranes seen occasionally after aerial spraying of the pesticide. The mechanism of action of malathion-induced immunologic alterations is not known. Neurotoxicity is the main effect of malathion in humans and animals, and the mechanism of neurotoxic action has been studied extensively and is well understood. Therefore, the section below will focus only on neurological effects. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for information on additional effects that may have been observed sporadically in animal studies and in human case reports, and are of unclear physiological significance.

Neurological Effects. Clinical signs and symptoms of malathion intoxication are typical of organophosphate poisoning. Malathion and its metabolite, malaoxon, inhibit the enzyme acetylcholinesterase and thus, prevent the hydrolysis of the neurotransmitter acetylcholine in the central and peripheral nervous systems. Continuous presence of acetylcholine at parasympathetic autonomic

muscarinic receptors results in ocular effects (miosis, blurred vision), gastrointestinal effects (nausea, vomiting, abdominal cramps, diarrhea), respiratory effects (excessive bronchial secretions, chest tightness, bronchoconstriction), cardiovascular effects (bradycardia, decreased blood pressure), effects on exocrine glands (increased salivation, lacrimation), and effects on the bladder (incontinence). At the level of parasympathetic and sympathetic autonomic nicotinic receptors, acetylcholine will induce tachycardia and increase blood pressure. At the neuromuscular junction, excess acetylcholine will induce muscle fasciculations, cramps, diminished tendon reflexes, muscle weakness in peripheral and respiratory muscles, ataxia, and paralysis. Finally, overstimulation of brain cholinergic receptors will lead to drowsiness, lethargy, fatigue, headache, generalized weakness, dyspnea, convulsions, and cyanosis.

The signs and symptoms described above have been documented in almost all of the cases of accidental or intentional ingestion of high amounts of malathion and in cases of dermal intoxication. Lethal doses can be estimated from case reports to have been between 350 and 2,000 mg/kg. These dose levels usually inhibited plasma and RBC cholinesterase activities to levels ranging from undetectable to 10–30% of normal. Studies of workers exposed to a combination of pesticides, including malathion, have shown decreases between 10 and 50% in both plasma and RBC cholinesterase activities. In general, plasma cholinesterase activity can be inhibited by 20–25% without significant physiological consequences. Studies also have shown that the rate of decrease of RBC cholinesterase correlates better with appearance of symptoms than the absolute value reached after exposure. It was found that plasma cholinesterase activity in workers who exhibited cholinergic symptoms and signs was 17% lower than in workers without symptoms and signs. Similar findings were reported in another study (Ernest et al. 1995). No cholinergic signs were seen in a study in which the activities of RBC and plasma cholinesterase varied less than 10% between pre- and postexposure. A study in volunteers exposed to 85 mg/m^3 of a malathion aerosol for 2 hours/day over a 42-day period observed no clinical signs and no significant inhibition of plasma or RBC cholinesterase activity over the study period. In an additional study of volunteers orally administered 0.34 mg malathion/kg/day for 56 days, there was a maximum depression of 25% in plasma cholinesterase approximately 3 weeks after cessation of treatment. A similar depression in RBC cholinesterase was observed, but occurred later. Administration of 0.11 mg malathion/kg/day for 32 days or 0.23 mg/kg/day for 47 days did not produce any significant depression of plasma or RBC cholinesterase activity. No clinical signs were seen in the volunteers. As detailed in Section 3.2, numerous studies in animals exposed to malathion by any route have shown inhibition of plasma, RBC, and brain cholinesterase activities.

There is also some evidence that exposure to malathion may result in alterations in some neurophysiological parameters. For example, electromyography testing demonstrated neuromuscular blockade in some cases of intoxication, but not in a case in which neither motor nor sensory peripheral nerve conduction velocities were significantly altered. Slightly reduced motor nerve conduction velocity was reported in a case in which the tests were conducted 10 days following the poisoning episode. Acute sensorimotor distal axonal polyneuropathy has been described. The alterations consisted of mild reductions of most compound muscle and sensory nerve action potentials amplitudes, slightly prolonged sensory distal latencies, and mildly slowed nerve conduction velocities. This was accompanied by morphological evidence of denervation and reinnervation of the gastrocnemius muscle and degenerating axons from the sural nerve. In these cases, isopropylmalathion was found in relatively large quantities in the formulation ingested. Some studies of exposure to multiple organophosphates also have reported signs of peripheral neuropathies, whereas others have reported negative findings.

Another condition that has been reported in humans as a consequence of acute exposure to high amounts of malathion is the intermediate syndrome. The intermediate syndrome is termed as such because it occurs in the time interval (24–96 hours) between the end of the acute cholinergic crisis and the usual onset of delayed neuropathy, and it is thought to be due to persistent cholinesterase inhibition leading to combined pre- and post-synaptic impairment of neuromuscular transmission. Clinically, it was characterized by weakness in the territory of several motor cranial nerves, weakness of neck flexors and proximal limb muscles, and respiratory paralysis.

A serious neurological effect of some organophosphate pesticides is delayed neurotoxicity. Organophosphorus-induced delayed polyneuropathy (OPIDP) is caused by inhibition of an enzyme known as neuropathy target esterase (NTE), which is widely distributed throughout both the central and peripheral nervous systems. The animal of choice for testing for OPIDP is the adult hen. OPIDP has been defined as a central-peripheral, distal, sensory-motor axonopathy and involves extensive morphological damage to the central and peripheral nervous system. Thus far, there is no evidence that malathion induces delayed neurotoxicity in humans or in animals. Neither malathion nor malaoxon inhibited NTE in a human neuroblastoma cell line. Furthermore, malathion did not induce OPIDP in the adult hen at oral doses of up to 300 mg/kg. These dose levels inhibited both NTE and brain acetylcholinesterase, but inhibited the latter to a greater extent, which is opposite to what is normally seen with OPIDP inducers.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

- An MRL of 0.2 mg/m^3 has been derived for acute-duration inhalation exposure (14 days or less) to malathion.

An acute-duration inhalation MRL of 0.2 mg/m^3 was derived for malathion based on a no-observed-adverse-effect-level (NOAEL) of 65 mg/m^3 for inhibition of RBC cholinesterase activity in rabbits exposed to a malathion aerosol (Weeks et al. 1977). Groups of male New Zealand rabbits (6/exposure level) were exposed for 6 hours to 0 (chamber air), 6, 34, 65, or 123 mg malathion/m^3 as an aerosol generated from a technical malathion formulation (95% pure). Blood was collected at 10 minutes, 24 hours, 72 hours, and 7 days postexposure for determination of cholinesterases activities. Tissues were also removed for histopathological examination. There were no signs of toxicity throughout the study. Exposure to the highest concentration of malathion inhibited plasma cholinesterase by 37% 24 hours postexposure and by 41% 72 hours postexposure. RBC cholinesterase was inhibited by 38, 48, and 48% by the high exposure concentration 24 hours, 72 hours, and 7 days postexposure, respectively. Exposure to malathion caused no histopathological alterations in the organs examined. One human study provided quantitative exposure information. In that study, 16 volunteers were exposed to malathion aerosols 2 hours/day for 42 days (Golz 1959). The malathion aerosol concentrations were 0 (controls), 5.3, 21, and 85 mg/m^3. There were no signs of toxicity during the study with the exception of complaints of nasal and eye irritation within 5–10 minutes of exposure to 85 mg/m^3 of malathion aerosol; no effects were reported at 21 mg/m^3. Analyses of blood samples taken weekly showed no significant effect on plasma or RBC cholinesterase activity over the study period. The MRL was derived by dividing the NOAEL of 65 mg/m^3 by an uncertainty factor of 100 (10 for extrapolation from animal to human and 10 to account for sensitive human subpopulations) (1959). A conversion factor was used to adjust from intermittent exposure to continuous exposure (6/24hours).

- An MRL of 0.02 mg/m^3 has been derived for intermediate-duration inhalation exposure (15–364 days) to malathion.

An intermediate-duration inhalation MRL of 0.02 mg/m^3 was derived for malathion based on a lowest-observed-adverse-effect-level (LOAEL) of 100 mg/m^3 for upper respiratory tract effects in rats in a 13-week study (Beattie 1994). Groups of male and female Sprague-Dawley rats (15/sex/exposure level) were exposed whole body to malathion (96.4% pure) aerosols at concentrations of 0 (air control), 100, 450, or 2,010 mg/m^3 6 hours/day, 5 days/week, for 13 weeks. Rats were monitored for clinical signs and

body weight changes. At termination, gross necropsies were conducted and tissues were processed for microscopical evaluation. Cholinesterase activity was determined in plasma, RBCs, and brain. There were no malathion-related effects on survival, body weight, or food intake. Adverse clinical signs consisting of urogenital staining, excessive salivation, and ungroomed fur were seen mostly in the high-exposure group, but also occurred sporadically in the other exposed groups. Histopathological treatment-related alterations were restricted to the respiratory epithelium. Exposure-concentration-related lesions in the nasal cavity and the larynx of both sexes were seen. The lesions in the nasal cavity consisted of slight to moderate degeneration and/or hyperplasia of the olfactory epithelium. The lesions in the larynx consisted of epithelial hyperplasia with squamous keratization seen in some rats. The effects on cholinesterase activities were concentration-related and effects on females seemed more pronounced than in males. Plasma cholinesterase activity was decreased 30 and 70% in the mid-exposure level and high-exposure level females, respectively. RBC cholinesterase activity was decreased 22 and 27% in mid-exposure level males and females, respectively, and 43 and 44% in high-exposure level males and females, respectively. Brain cholinesterase activity was decreased 41% in high-exposure level females. In the study by Golz (1959) mentioned above, the subjects were exposed to malathion 2 hours /day for 42 days, but given that malathion is rapidly eliminated from the body (see Section 3.4, Toxicokinetics), this exposure regime better reflects repeated single exposures than an intermediate-duration exposure study. The MRL was derived by dividing the LOAEL of 100 mg/m^3 by an uncertainty factor of 1,000 (10 for animal to human extrapolation, 10 for using a LOAEL, and 10 to account for sensitive subpopulations).

No chronic-duration inhalation MRL was derived for malathion because of lack of adequate data. Information on effects in humans is derived mostly from studies of workers in which both the inhalation and dermal routes of exposure play significant roles. No adequate data were available from these studies to construct dose-response relationships. No chronic inhalation studies in animals were located.

Oral MRLs

No acute oral MRL was derived for malathion. Acute oral data in humans come almost exclusively from case reports of accidental or intentional ingestion of high amounts of malathion formulations and do not provide information for establishing dose-response relationships (Choi et al. 1998; Crowley and Johns 1966; Dive et al. 1994; Faragó 1967; Jušić and Milić 1978; Lee and Tai 2001; Monje Argiles et al. 1990; Morgade and Barquet 1982; Namba et al. 1970; Peedicayil et al. 1991; Stålberg et al. 1978; Tuthill 1958; Zivot et al. 1993). Almost all cases presented the typical signs and symptoms of cholinergic stimulation. Acute oral studies in animals provided information on systemic (Krause 1977; Krause et al. 1976; Lox

1983; Ojha et al. 1992; Piramanayagam et al. 1996; Simionescu et al. 1977), immunological (Casale et al. 1983; Rodgers and Xiong 1996, 1997b, 1997d; Rodgers et al. 1986), neurological (Casale et al. 1983; Ehrich et al. 1993; Mathews and Devi 1994; Vijayakumar and Selvarajan 1990; Weeks et al. 1977), reproductive (Krause et al. 1976; Lochry 1989; Ojha et al. 1992; Prabhakaran et al. 1993; Siglin 1985), and developmental effects (Khera et al. 1978; Lochry 1989; Machin and McBride 1989a, 1989b; Mathews and Devi 1994). Although there appears to be an extensive database from animal studies, the quality of many studies precludes their use for risk assessment. Some of the limitations include poor reporting of the results and/or only one dose level tested. Well-conducted studies by Rodgers and colleagues identified the lowest effects levels for immunological alterations in mice (degranulation of mast cells) administered 0.1 mg malathion/kg/day for 14 days (Rodgers and Xiong 1997d). An additional study from this series found increased serum histamine levels in rats and mice after a single dose of 10 mg/kg (Rodgers and Xiong 1997b); the NOAEL was 1 mg/kg. The physiological significance of these immunological effects is unknown and should be addressed in further studies in which the animals are challenged with pathogens. Therefore, it seems inappropriate at this time to base an acute oral MRL on subtle immunological alterations of unknown physiological significance. A relatively low LOAEL of 4.4 mg/kg (the only dose level tested) was identified for decreased hematocrit and platelet counts in rats administered malathion once by gavage in water. No other acute gavage or feeding study reported a similar effect at any dose level. Therefore, it would also be inappropriate to base an acute oral MRL on a free standing LOAEL of unknown toxicological significance.

- An MRL of 0.02 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to malathion.

An intermediate-duration oral MRL of 0.02 mg/kg/day was derived for malathion based on inhibition of plasma and RBC cholinesterase activity in humans (Moeller and Rider 1962). The study was conducted in three phases. In the first phase, five male volunteers were administered daily capsules containing malathion (purity not reported) in corn oil that provided an approximate dose of 0.11 mg malathion/kg/day for 32 days. In the second phase, which started 3 weeks after the first phase had terminated, five male volunteers received daily capsules with malathion providing about 0.23 mg malathion/kg/day for 47 days. In the third phase, five new subjects received approximately 0.34 mg malathion/kg/day for 56 days. Plasma and RBC cholinesterase was determined twice weekly before, during, and after administration of malathion. Routine blood counts and urinalyses were conducted at the end of each study period. Administration of 0.11 mg malathion/kg/day for 32 days or 0.23 mg/kg/day for 47 days did not produce any significant depression of plasma or RBC cholinesterase activity, nor did it alter blood counts or urinalyses, or induce clinical signs. In phase three, 0.34 mg malathion/kg/day for

56 days caused a maximum depression of 25% in plasma cholinesterase approximately 3 weeks after cessation of treatment. A similar depression in RBC cholinesterase was observed, but occurred later. No clinical signs were seen in the volunteers. The MRL was derived by dividing the NOAEL of 0.23 mg/kg/day by an uncertainty factor of 10 (to account for sensitive subpopulations).

- An MRL of 0.02 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to malathion.

A chronic-duration oral MRL of 0.02 mg/g/day was derived for malathion based on inhibition of plasma and RBC cholinesterase activity in rats fed malathion in the diet for 2 years (Daly 1996a). Groups of male and female Fischer-344 rats (90/sex/dose level) were administered malathion (97.1%) in the diet at levels of 0, 50, 500, 6,000, or 12,000 ppm for 2 years. This diet provided approximately 0, 2, 29, 359, or 739 mg malathion/kg/day to males and 0, 3, 35, 415, or 868 mg/kg/day to females. Ten rats/sex/group were sacrificed at 3 and 6 months primarily for ocular tissue evaluation. Additional sacrifices were conducted at 12 months for more complete assessments. Administration of malathion significantly increased mortality in males at 6,000 ppm and in both sexes at 12,000 ppm. Body weight gain was reduced both in males and females at the two highest exposure levels, but food intake was not decreased. Hemoglobin, hematocrit, mean corpuscular volume (MCV), and mean cell hemoglobin were in both sexes at the two highest dietary levels of malathion. Absolute and relative liver and kidney weights were increased in males and females from the 6,000 and 12,000 ppm groups. Relative absolute thyroid and parathyroid weights were increased in males at 6,000 ppm at 12 months and in females at 6,000 and 12,000 ppm at termination. At 24 months, at the 500 ppm malathion dietary level (29 mg/kg/day for males, 35 mg/kg/day for females), plasma cholinesterase activity was reduced 29 and 18% in males and females, respectively, RBC cholinesterase was reduced 17 and 27%, respectively, and brain cholinesterase was reduced 3 and 1%, respectively. At the 6,000 ppm level, plasma cholinesterase in males and females was reduced 64 and 61%, respectively, and brain cholinesterase was reduced 21 and 18%, respectively. No significant reduction in enzyme activities was observed at the lowest dietary level of malathion, 2 mg/kg/day for males and 3 mg/kg/day for females. The MRL was derived by dividing the NOAEL of 2 mg/kg/day by an uncertainty factor of 100 (10 for extrapolation from animal to human and 10 to account for sensitive subpopulations).

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 malathion. 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.

Many of the systemic effects observed following exposure to malathion discussed below under inhalation, oral, and dermal exposure (Sections 3.2.1, 3.2.2, and 3.2.3) are due to the inhibition by malaoxon (the active metabolite of malathion) of acetylcholinesterase at nerve terminals from the central, peripheral somatic, and autonomic divisions of the nervous system. Inhibition of acetylcholinesterase at these various levels triggers signs and symptoms that involve mainly, but not exclusively, the respiratory, cardiovascular, and gastrointestinal systems, and also induce ocular effects (see Section 3.5.2). Therefore, although listed under specific systems, the reader should keep in mind that these effects are secondary to a neurological effect, inhibition of the enzyme acetylcholinesterase. Acetylcholinesterase inhibition is a biochemical feature common to all organophosphate pesticides.

This document deals with health effects in humans and in animals that result from exposure to malathion. While studies in animals involve controlled exposures to malathion, people are rarely exposed to a single chemical in occupational settings or even in residential exposures. Many studies summarized in Section 3.2, particularly those under Inhalation Exposure and Dermal Exposure involved exposure to multiple chemicals, including malathion. These type of studies are also included in this document even though health effects cannot be ascribed to exposure to a particular chemical, but the study design may allow the study authors to at least narrow down the possibilities to a single class of chemicals.

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.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of malathion are indicated in Table 3-2 and Figure 3-2.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for malathion. 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 1990), 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

Many of the studies described below are occupational studies in which exposure to malathion occurred primarily via the inhalation and dermal routes. However, the specific contribution of each route of exposure is not possible to determine, especially in cases in which it is not known whether or not the workers were using protective clothing and/or respirators. Studies in which no specific mention is made regarding which exposure route prevailed are summarized below in Section 3.2.1, Inhalation Exposure, leaving Section 3.2.3, Dermal Exposure, for studies that explicitly indicated that exposure occurred primarily through the dermal route. This decision is somewhat arbitrary and is in part dictated by the document format, but the reader should keep in mind that both inhalation and dermal routes combined contributed to the effects described.

3.2.1.1 Death

Two reports provide information regarding inhalation exposure to malathion, or to a group of pesticides that included malathion, and death in humans, but no apparent association was found in either report. In a

single case of apparent acute inhalation exposure, a 12-year-old girl admitted to the hospital died from aplastic anemia 6 months after exposure to malathion (Reeves et al. 1981). Although aplastic anemia was diagnosed 2 weeks after a 1-hour exposure to malathion (unspecified formulation or purity), there is no evidence that anemia occurred as a consequence of exposure to malathion. This case was one of six cases of children exposed to pesticides described in this brief report and few details are presented. It is mentioned, however, that the parents of all six children recalled previously using the product in the home. The second report is a retrospective cohort study that investigated deaths among 32,600 employees of a lawn care company that used a variety of pesticides, malathion among them, as well as herbicides and fungicides (Zahm 1997). Among all employees (regardless of duration of employment or type of job activity), deaths due to bladder cancer were significantly higher than expected for the general population (standard mortality ratio [SMR]=7.10, 95% confidence interval [CI]=1.43, 20.73), but two of the three observed deaths had no direct occupational contact with pesticides. Among male applicators employed for 3 or more years, deaths due to non-Hodgkin's lymphoma (NHL) were elevated (SMR=7.11, 95% CI=1.78, 28.42), but malathion was not among the pesticides known to be in use at the branch when the subjects were employed as applicators (Zahm 1997). More details regarding the NHL cases are presented under Cancer in Section 3.2.1.7. No other cause of death was significantly elevated among lawn applicators as a group or among those employed for 3 or more years. This cohort had significantly lower than expected mortality for all causes of deaths combined, arterioesclerotic heart disease, symptoms and ill-defined conditions, and accidents.

Very limited information was located regarding death in animals following inhalation exposure to malathion. Four out of six male New Zealand rabbits died within 24 hours of exposure to 128 mg/m^3 malathion aerosol generated from a formulation containing 6% malathion and a fuel oil mixture (Weeks et al. 1977). However, no deaths or signs of toxicity were observed in a group of rabbits exposed to 123 mg/m^3 of an aerosol generated from a 95% malathion formulation (Weeks et al. 1977).

3.2.1.2 Systemic Effects

The highest NOAEL and all reliable LOAEL values from each study for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. No studies were located regarding cardiovascular, musculoskeletal, hepatic, or endocrine effects in humans or in animals following inhalation exposure to malathion. Dermal and ocular effects reported in studies in humans or animals that occurred by exposure to the chemical in the air, most likely due to direct contact with the skin or eyes, are summarized in Section 3.2.3, Dermal Exposure.

Table 3-1 Levels of Significant Exposure to Malathion - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
	ACUTE EXPOSURE						
	Systemic						
1	Human	5-10 min	Resp	21 M	85 M (nasal irritation)		Golz 1959
	Neurological						
2	Rabbit (New Zealand)	6 hr		65 M[b]	123 M (38% inhibition of RBC cholinesterase)		Weeks et al. 1977
	INTERMEDIATE EXPOSURE						
	Systemic						
3	Human	42 d 2 hr/d	Bd Wt	85 M			Golz 1959
4	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d	Resp		100[c] (hyperplasia of the olfactory epithelium and of the larynx epithelium)		Beattie 1994
			Bd Wt	2010			
	Neurological						
5	Human	42 d 2 hr/d		85 M			Golz 1959
6	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d		100	450 (22% and 27% decrease in RBC cholinesterase activity in males and females, respectively)	2010 F (70% decrease in plasma cholinesterase activity)	Beattie 1994

a The number corresponds to entries in Figure 3-1.
b Used to derive an acute-duration inhalation minimal risk level (MRL) of 0.2 mg/m3; the MRL was derived by dividing the duration-adjusted NOAEL by an uncertainty factor of 100 (10 for animal to human extrapolation; 10 for human variability).
c Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.02 mg/m3; the MRL was derived by dividing the duration-adjusted LOAEL by an uncertainty factor of 1000 (10 for animal to human extrapolation; 10 for use of a LOAEL; 10 for human variability).

Bd = body weight; d = day(s); F = Female; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; mg/m3 = milligram/cubic meter; min = minute(s); NOAEL = no-observed-adverse-effect level; RBC = red blood cell(s); Resp = respiratory; wk = week(s).

Figure 3-1 Levels of Significant Exposure to Malathion - Inhalation

Acute (≤14 days)

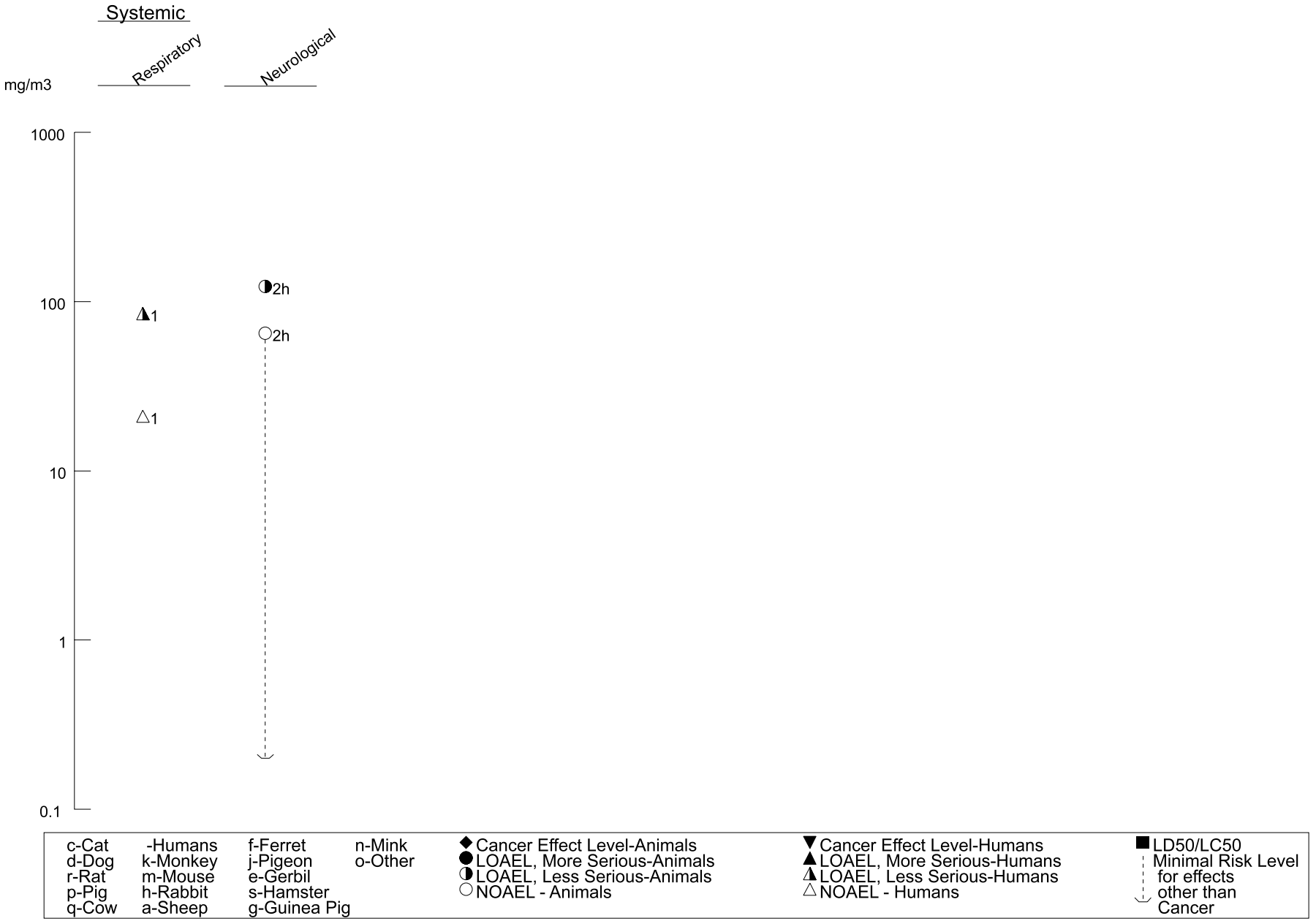
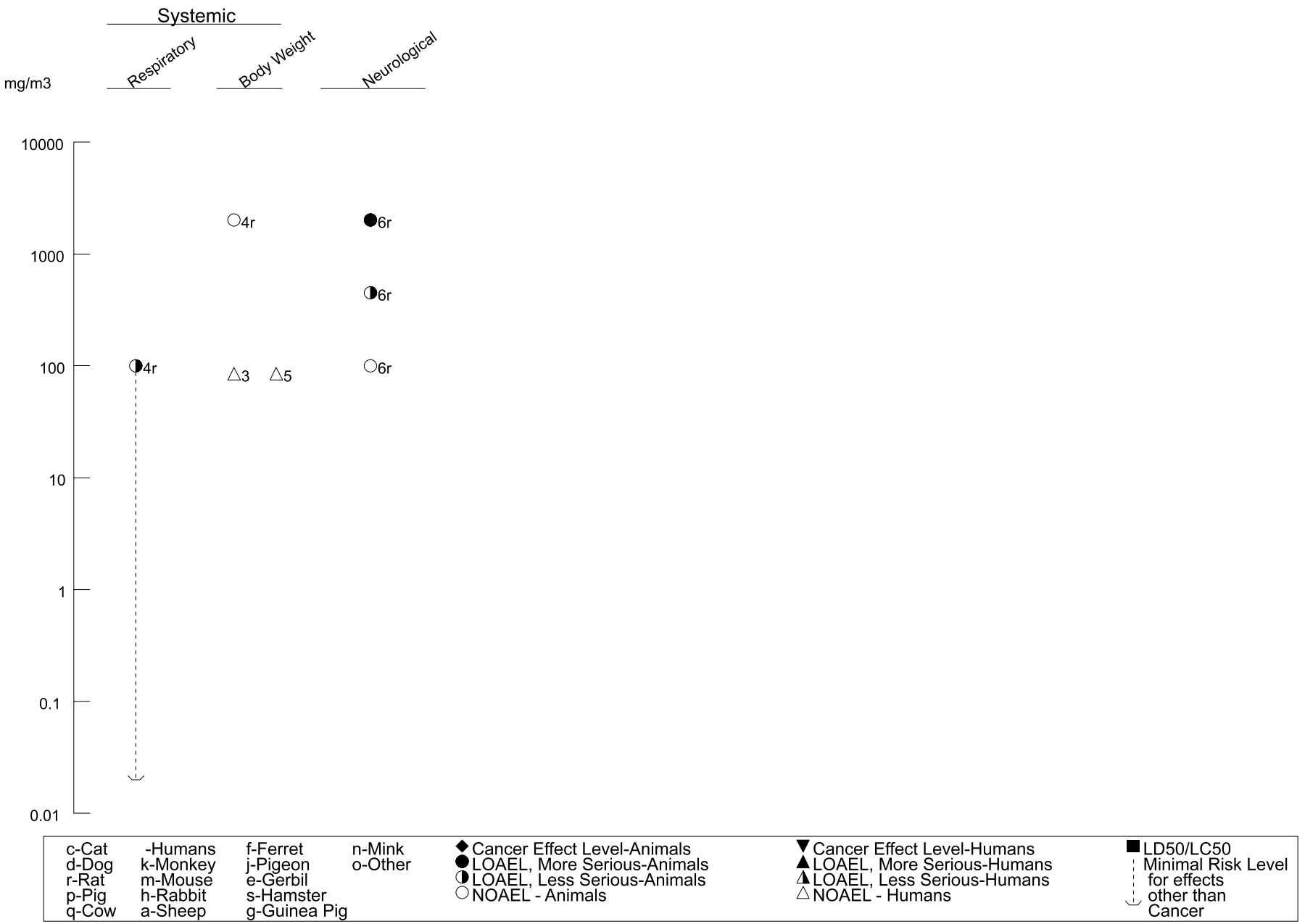


Figure 3-1 Levels of Significant Exposure to Malathion - Inhalation (*Continued*)

Intermediate (15-364 days)



Respiratory Effects. In a controlled-exposure study, 16 male volunteers (4/exposure level) were exposed to aerosol bombs that contained 0 (control), 5, or 20% malathion for 1 hour 2 times/day for 42 days (Golz 1959). The actual exposure concentrations were 0, 5.3, 21, or 85 mg/m^3. By adjusting the application rate of the 20% formation, the highest exposure groups were formed.The malathion in the formulation was 95% pure. There were no signs of toxicity during the study, with the exception of complaints of nasal irritation in men exposed to the highest concentration during the first 5–10 minutes of each exposure. One study of 85 subjects who worked in the production of six organophosphate pesticides (malathion was one of them) for periods ranging from 0.1 to 29 years found a higher frequency of upper respiratory tract infections in workers than in 67 controls (Hermanowicz and Kossman 1984) (see also information under Immunological Effects). Also, those exposed for 11–29 years had more respiratory infections than individuals exposed for 0.1–2 years. Before and during the study, total air concentrations of organophosphates remained below admissible limits. Exposure to chlorinated solvents also occurred during pesticide production and may have contributed to the effects observed. The role of malathion, if any, cannot be ascertained. Additional information was found in a study of self-reported symptoms in 22 seamen who may have been exposed to a single cloud of malathion that escaped from a nearby overheated tank (Markowitz et al. 1986). Compared with a group of controls, the seamen reported significantly more problems with sore throat, stuffy nose, and laryngitis when contacted 12 days following the incident. It should be noted, however, that there was no evidence of actual exposure to the chemical.

Following aerial application of malathion in Santa Clara County, California, in 1981, a survey was conducted to assess the acute health effects of the application (Kahn et al. 1992). The study included three indirect assessments that focused on the utilization of acute care services and two surveys to assess self-reported symptoms. The results showed no significant increase in the number of visits for the broad category, respiratory, to hospital emergency departments during the application period compared with the prespray period or the corresponding period the previous year. Furthermore, there was no significant increase in the number of asthma-related visits to a university medical school in the area, although the numbers in the study may have been too small to provide definite conclusions. The results of the surveys to assess self-reported symptoms revealed no detectable increase in acute morbidity or in organophosphate-compatible symptomatology, but again, the sample size may have been too small for marginal increases in the prevalence of various symptoms to be detected.

The only information available regarding respiratory effects in animals following inhalation exposure to malathion is provided by a study in rats in which whole body exposure to an aerosol concentration of 100 mg/m^3 of malathion (96.4% pure) 6 hours/day, 5 days/week for 13 weeks induced hyperplasia of the olfactory and larynx epithelia (Beattie 1994). The 100 mg/m^3 exposure concentration, which was the lowest exposure level tested, was used to derive an intermediate-duration inhalation MRL of 0.02 mg/m^3 for malathion.

Gastrointestinal Effects. The only information on gastrointestinal effects in humans after inhalation exposure to malathion comes from a study of self-reported symptoms in 22 seamen who may have been exposed to a single cloud of malathion that escaped from a nearby overheated tank (Markowitz et al. 1986). Compared with a group of controls, the seamen reported significantly more problems such as diarrhea, constipation, or painful bowel movements when contacted 12 days following the incident. As previously mentioned, there was no evidence of actual exposure to the chemical.

No studies were located regarding gastrointestinal effects in animals following inhalation exposure to malathion.

Hematological Effects. As previously mentioned in Section 3.2.1.1, Death, Reeves et al. (1981) reported the case of a 12-year-old girl who was admitted to the hospital and died from aplastic anemia 6 months after exposure to malathion. Aplastic anemia was diagnosed 2 weeks after a 1-hour exposure to malathion (unspecified formulation or purity), which makes the evidence that malathion was the causing agent only circumstantial. This was one of six cases of children exposed to pesticides, and few details are presented in this brief communication other than the fact that the parents of all six children recalled previously using the product in the home. A more recent study of 60 workers at a pesticide (primarily malathion) manufacturing facility who were in direct contact with malathion found an inverse relationship between hemoglobin concentration and duration of employment (Singaravelu et al. 1998). Eight individuals who had worked in the processing unit for >20 years had mean hemoglobin levels of 11.30 g/dL compared to 15.5 g/dL measured in four matched controls employed for >20 years. No information was provided regarding exposure levels or the health status of the workers. The small number of individuals studied precludes drawing meaningful conclusions from this study.

No studies were located regarding hematological effects in animals following inhalation exposure to malathion.

Renal Effects. Some limited information is available regarding renal effects in humans exposed to malathion. Albright et al. (1983) described the case of a 65-year-old man who developed transient renal insufficiency with massive proteinuria 3 weeks after spraying intensively with malathion (unknown formulation). The presence of membranous glomerulopathy and a marginally reduced C3 complement level led the authors to postulate that malathion caused an immune complex nephropathy. Another study of workers exposed to several organophosphate pesticides, including malathion, for up to 29 years, found no increase in the incidence of renal disease (inflammation of the renal parenchyma, calyces, and pelvis) compared to a group of unexposed controls (Hermanowicz and Kossman 1984).

No studies were located regarding renal effects in animals following inhalation exposure to malathion.

Body Weight Effects. Information on body weight was found in a study of 16 male volunteers (4/exposure level) who were exposed to aerosol bombs that contained 0 (control), 5, or 20% actual malathion (95% pure) (Golz 1959). The men were exposed for 1 hour twice/day for 42 days to measured concentrations of 0, 5.3, 21, or 85 mg/m^3. There were no exposure-related changes in body weight during the study. Additional information was found in a study of self-reported symptoms in 22 seamen who may have been exposed to a single cloud of malathion that escaped from a nearby overheated tank (Markowitz et al. 1986). Compared with a group of controls, the seamen reported significantly more rapid weight changes when contacted 12 days following the incident. Since there was no evidence of actual exposure to the chemical, the role of malathion, if any, is unknown.

Rats exposed to an aerosol of malathion (96.4% pure) at a concentration of up to 2,010 mg/m^3, 6 hours/day, 5 days/week for 13 weeks showed no significant alterations in body weight gain during the study (Beattie 1994). No further information was located in the available studies.

3.2.1.3 Immunological and Lymphoreticular Effects

As mentioned above, Albright et al. (1983) described the case of a 65-year-old man who developed transient renal insufficiency with massive proteinuria weeks after spraying intensively with malathion (unknown formulation). The presence of membranous glomerulopathy and a marginally reduced C3 complement level led the authors to postulate that malathion caused an immune complex nephropathy. A study of 85 workers occupationally exposed to several organophosphate pesticides, including malathion, as well as chlorinated solvents for periods ranging from 0.1 to 29 years observed marked impairments of neutrophil chemotaxis and significantly decreased neutrophil adhesion in all types of workers studied

(Hermanowicz and Kossman 1984). As noted in Section 3.2.1.2, the frequency of upper respiratory tract infections was greater in workers than in controls. The role of malathion, if any, in the observed effects cannot be determined.

The study by Kahn et al. (1992) in Santa Clara County, California, described above (Respiratory Effects), showed that there were no significant increases in the number of visits for the broad category, allergic problems, to hospital emergency departments during the application period compared with the prespray period or the corresponding period the previous year. The results of the surveys to assess self-reported symptoms revealed no detectable increase in acute morbidity or in organophosphate-compatible symptomatology, although the sample size may have been too small to detect small increases in prevalence of various symptoms.

No studies were located regarding immunological effects in animals following inhalation exposure to malathion.

3.2.1.4 Neurological Effects

Numerous studies were located that provided information on the neurological effects of exposure by humans to organophosphate pesticides in the air, but few evaluated exposure specifically to malathion, and provided quantitative exposure data. End points evaluated included measurements of red blood cell (RBC) and plasma cholinesterase activity as well as measurements of neurophysiological parameters and clinical signs. Most studies evaluated workers exposed repeatedly over periods of time ranging from weeks to years.

Effects on Cholinesterase Activity. In a controlled-exposure study, 16 male volunteers (4/exposure level) were exposed to aerosol bombs that contained 0 (control), 5, or 20% actual malathion 1 hour 2 times/day for 42 days (Golz 1959). The actual exposure concentrations were 0, 5.3, 21, or 85 mg/m^3. The malathion in the formulation was 95% pure. There were no signs of toxicity during the study and no significant effect on either plasma or RBC cholinesterase activity. Similar lack of effects on plasma and RBC cholinesterase was reported by Culver et al. (1956) among a group of men exposed outdoors for 4–5 hours to malathion concentrations between 0.5 and 4 mg/m^3, with peak concentration of up to 56 mg/m^3.

Studies in which workers were exposed to a combination of pesticides (not limited to organophosphates) that included malathion showed either a decrease of 26% in RBC cholinesterase in 85 workers exposed from 0.1 to 29 years compared with the same number of unexposed individuals (Hermanowicz and Kossman 1984) or no significant difference among 11 pesticide applicators when comparing exposure periods with periods during the year of no exposure (Stålberg et al. 1978). Among four studies that measured changes in plasma cholinesterase, levels were 8–53% lower in groups of pesticide applicators when compared with controls (Ernest et al. 1995; Hermanowicz and Kossman 1984; Peedicayil et al. 1991) or with periods of no exposure (Stålberg et al. 1978). Numbers of exposed individuals evaluated in these four studies ranged from 11 to 85 pesticide workers.

Some studies also examined the possible association between changes in cholinesterase levels and the presence or absence of clinical signs of cholinergic stimulation. For example, Peedicayil et al. (1991) found that plasma cholinesterase activity in workers who exhibited cholinergic symptoms and signs was 17% lower than in workers without symptoms and signs. Similar findings were reported by Ernest et al. (1995). No cholinergic signs were seen in the Stålberg et al. (1978) study in which the activities of RBC and plasma cholinesterase varied less than 10% between pre- and postexposure.

Neurophysiological Effects. A significantly higher percentage of peripheral neuropathies (evaluated by electromyograph [EMG] recordings) were observed among pesticide workers than in controls in a study by Ernest et al. (1995). Those who had clinical features of peripheral neuropathy had been exposed to organophosphates from 4 to 10 years. A similar finding was reported by Peedicayil et al. (1991), although the specific method to assess peripheral neuropathy was not indicated. Only a slight reduction (3%) in sensory nerve conduction velocity was seen among a group of 11 workers exposed to organophosphates for periods ranging from 1 to 24 years (Stålberg et al. 1978); however, there were no significant alterations in motor nerve conduction velocity or any indication of altered synaptic transmission. No evidence of neuromuscular insufficiency was reported by Jušić et al. (1980) among a group of 14 workers exposed to a pesticide formulation containing 57% malathion 4–5 hours/day, 4–6 months during the year.

The study by Kahn et al. (1992) described above (Respiratory Effects) on residents from an urban area where aerial spraying with malathion was conducted did not find a significant increase in visits to hospital emergency departments for the category, anxiety, following the spraying. In fact, after the spraying, there was a decrease in anxiety-related symptoms. The study also found no increase in self-reported symptoms that would indicate effects consistent with organophosphate poisoning.

Studies in animals support the findings in humans regarding cholinesterase inhibition. Exposure of rabbits to 123 mg malathion/m^3 as an aerosol generated from a technical malathion formulation (95% pure) for 6 hours inhibited plasma cholinesterase activity by 37% at 24 hours postexposure and 41% at 72 hours postexposure (Weeks et al. 1977). This exposure also resulted in inhibition of erythrocyte cholinesterase by 38, 48, and 48% at 24 hours, 72 hours, and 7 days postexposure, respectively. The NOAEL was 65 mg/m^3. Exposure to an aerosol formulation containing 6% malathion and a fuel oil mixture resulted in 38% inhibition of plasma cholinesterase with a 66 mg/m^3 concentration 72 hours after exposure and 71% inhibition with a 128 mg/m^3 concentration 10 minutes postexposure. With this formulation, erythrocyte cholinesterase was inhibited 61 and 46% with the 128 mg/m^3 concentration 10 minutes and 24 hours, respectively, postexposure. Exposure to the 6% formulation caused lethality, but no signs of toxicity or deaths were seen among rabbits exposed to the 95% malathion formulation. By comparing these results to those obtained after oral exposure in a parallel experiment, Weeks et al. (1977) estimated that it took 15–20 times more malathion by ingestion to cause an effect similar to that seen by inhalation. The NOAEL of 65 mg/m^3 was used to derive an intermediate inhalation MRL of 0.02 mg/m^3 for malathion.

In a 13-week study, Sprague-Dawley rats were exposed whole body to up to 2,010 mg/m^3 of malathion (96.4% pure) 6 hours/day, 5 days/week (Beattie 1994). At termination, the effects on cholinesterase activities were found to be exposure concentration-related and effects on females seemed more pronounced that in males. Plasma cholinesterase activity was decreased 30% at 450 mg/m^3 and 70% at 2,010 mg/m^3 in females, respectively. RBC cholinesterase activity was decreased 22 and 27% at 450 mg/m^3 in males and females, respectively, and 43 and 44% at 2,010 mg/m^3 in males and females, respectively. Brain cholinesterase activity was decreased 41% at 2,010 mg/m^3 in females. Excess salivation was seen mostly in rats from the high-exposure group, although it occurred sporadically in the other exposed groups.

NOAEL and LOAEL values from the Beattie (1994), Golz (1959), and Weeks et al. (1977) studies are presented in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

Reproductive outcomes were investigated in a group of 7,450 women who were confirmed as pregnant during periods of malathion spraying to control an infestation by the Mediterranean fruit fly in the San

Francisco Bay area (Thomas et al. 1992). Using several measures of malathion exposure and adjustment for confounders, the study found no significant association between exposure to malathion and spontaneous abortion. There was a moderate association between stillbirths and exposure accumulated up to 1 month before death. The one major weakness of the study is possible exposure misclassification, based on using residence as the surrogate for exposure, although the authors felt that this seemed much less vulnerable to recall bias than would a subject's recollection of whether or not she had been exposed (Thomas et al. 1992). Rupa et al. (1991b) investigated reproductive outcomes in 1,016 couples in which the males' main jobs were mixing and spraying pesticides (including malathion and also organochlorine pesticides) compared with 1,020 unexposed couples, and found significantly higher percent ages of stillbirths (8.73 versus 2.65%) and abortions (26.0 versus 15.0%) in exposed workers. A significantly lower percent of fertile males (80.8 versus 94.9% in controls) and decreased frequency of live births (53.0 versus 80.1%) was also observed. Rupa et al. (1991b) further stated that 80% of the males in the exposed group showed ill effects such as severe giddiness, and nervous, skin, and eye disorders. The role of malathion in these findings, if any, cannot be determined.

No studies were located regarding reproductive effects in animals following inhalation exposure to malathion.

3.2.1.6 Developmental Effects

Three studies were located that examined the association between developmental outcomes and exposure to malathion, with varying outcomes. Grether et al. (1987) examined occurrence of defects and low birth weight using newborn hospital discharge data and vital records in the San Francisco Bay area after aerial malathion spraying. The study included an exposed cohort of 24,987 births and an unexposed cohort of 15,278 births. Although the authors found some positive (and significant) associations for some anomalies, the anomalies that occurred more frequently than expected did not represent a biologically consistent pattern. No significant association was found between low birth weight and increasing exposure to malathion. Thomas et al. (1992) (described above in Section 3.2.1.5) found a statistically significant association between incidence of gastrointestinal anomalies in offspring and exposure to malathion during the second trimester of pregnancy (odds ratio [OR]=4.14; CI=1.01, 16.6). No significant associations were observed for intrauterine growth retardation or other congenital effects reportable by the California Birth Defects Monitoring Program. García et al. (1998) compared paternal pesticide exposures between offspring with congenital malformations (i.e., nervous system and cardiovascular defects, oral clefts, epispadia or hypospadias, musculoskeletal defects, unspecified defects)

and controls. In a subgroup of 14 individuals exposed to malathion, regression analysis showed no significant associations with outcomes after adjusting for confounding factors.

Two additional studies investigated a broader set of pesticides. Lin et al. (1994) studied the association between exposures to a variety of pesticides and limb reduction defects (a generally well-reported birth defect) from a register of congenital anomalies among live births in New York State. In the full sample and in a subgroup of individuals exposed to insecticides, no significant associations were observed, although odds ratios for risk of limb reduction defect plus one additional malformation were consistently higher than those for limb reduction defects only. Rupa et al. (1991b) found significantly reduced numbers of live births and significantly increased neonatal deaths and congenital defects in pregnancies/offspring of males exposed to pesticides compared with offspring of unexposed males. The possible role of malathion cannot be ascertained in these two studies.

No studies were located regarding developmental effects in animals following inhalation exposure to malathion.

3.2.1.7 Cancer

Several studies provide information on exposure to pesticides, including malathion, and cancer. The overall evidence from human studies is insufficient to draw any conclusions regarding the association between exposure to malathion and cancer. In general, the magnitude of the excesses is small, exposure assessment is unreliable, and people are seldom exposed to a single pesticide.

The possible association between pesticide exposure and non-Hodgkin's lymphoma (NHL) has been investigated in several studies. In a study of 622 white men with newly diagnosed NHL in Iowa and Minnesota and 1,245 population-based controls, the prevalence of NHL in individuals who handled malathion as a crop insecticide prior to 1965 was significantly higher than in nonfarmers (OR=2.9, CI=1.1, 7.4) (Cantor et al. 1992). The prevalence was also significantly higher in workers who used malathion as an animal insecticide than in nonfarmers (OR=1.8, CI=1.0, 3.3). Zahm et al. (1993) presented data on agricultural exposures among women from a population-based case-control study of NHL in eastern Nebraska. A total of 119 women diagnosed with NHL and 471 controls reported ever having lived or worked on a farm. No individual insecticide was associated with a significant risk of NHL among women, but there was a nonsignificant increase for malathion (OR=1.9; 9 cases, 18 controls) and for several other insecticides. Women who had personally handled organophosphates were 4.5 times

more likely (CI=1.1, 17.9) to have NHL than those who did not use organophosphates. In a retrospective cohort study that investigated deaths among 32,600 employees of a lawn care company that used a variety of pesticides, malathion among them, as well as herbicides and fungicides, a total of four deaths due to NHL were observed, three were male lawn applicators, and two of them were employed for 3 or more years (SMR=7.11, 95% CI=1.78, 28.42) (Zahm 1997). However, malathion was not among the pesticides known to be in use at the branch when the subject was employed as applicator. No significant increase in NHL was observed in a study of 1,860 men and 589 women pesticide users from Iceland (Zhong and Rafnsson 1996), but women showed elevated risks of lymphatic and haematopoietic tissue cancer (standardized incidence ratio [SIR]=5.56, CI=1.12-16.23) compared with the general population. McDuffie et al. (2001) examined the association between specific pesticide exposure and NHL in a Canadian multicenter population-based incident, case-control study (517 cases, 1,506 controls) among men in a diversity of occupations. Detailed information regarding their exposure history was obtained by telephone interview from 119 cases and 301 controls who indicated pesticide exposure of ≥10 hours/year. An additional randomly selected 60 cases and 155 controls who indicated exposure of 10 hours/year were interviewed by telephone. Exposure to the chemical classes carbamates and organophosphates, but not organochlorines, was significantly associated with NHL. In multivariate analyses, malathion was the only individual organophosphate exposure (seven organophosphate pesticides were included in the analysis) significantly associated with NHL (OR=.83, 95% CI=1.31–2.55). Among the study limitations discussed by the authors are the potential for recall bias and for misclassification of pesticide exposure and the less-than-optimal response rates.

A population-based case-control study of 578 white men with leukemia and 1,245 controls living in Iowa and Minnesota found slight, but significant elevations in risk for all leukemia (OR=1.2, 95% CI=1.0–1.5) and chronic lymphocytic leukemia (OR=1.4, 95% CI=1.1–1.9) for farmers compared to nonfarmers (Brown et al. 1990). Also, risk for all leukemia was significantly elevated for use of the organophosphate family on animals (OR=1.5, 95% CI=1.0–2.1), but not on crops. Risk of leukemia for mixing, handling, or applying malathion ever or at least 20 years prior to the interview was not significantly elevated, but the risk of leukemia for use of malathion as an animal insecticide for ≥10 days/year was significantly elevated (OR=3.2, 95% CI=1.0–10.0). A similar study of 173 white men with multiple myeloma and 650 controls from Iowa found a slight nonsignificantly increased risk for multiple myeloma among farmers, the OR for malathion was 1.9 (95% CI=0.8–4.6) (Brown et al. 1993a). However, failure to use protective equipment was not associated with increased risk.

Risks for rectal cancer were elevated in women and men combined (SIR=2.94, CI=1.07–6.40) and were even higher in a subgroup of licensed pesticide applicators who used pesticides for agricultural purposes (SIR=4.63, CI=1.49–10.80) in the study by Zhong and Rafnsson (1996). Finally, a study in Los Angeles County, California, involving mothers of 224 cases and 218 controls, who used (from pregnancy to diagnosis) household pesticides for a number of domestic purposes, found no elevated risks in pediatric brain tumors among the user group (Pogoda and Preston-Martin 1997).

No studies were located regarding cancer in animals following inhalation exposure to malathion.

3.2.2 Oral Exposure

The human data in this section are derived primarily from case reports in which the actual doses ingested are unknown. However, many cases provide enough information (i.e., volume of the formulation taken and percent malathion in the formulation) to at least make reasonable estimates. One additional factor to consider is that malathion formulations also contain many other chemicals, such as solvents and impurities, which may form during long periods of storage. Many impurities greatly increase the toxicity of malathion formulations relative to pure malathion. Therefore, caution should be exercised when comparing oral doses estimated from human cases with doses used in experiments in laboratory animals.

3.2.2.1 Death

Perhaps because of its widespread use and availability, many cases of fatal ingestion of malathion in humans (suicides and poisonings) have been documented in the literature (Faragó 1967; Jušić and Milić 1978; Morgade and Barquet 1982; Namba et al. 1970; Zivot et al. 1993). For example, Faragó (1967) described four cases of lethal intentional ingestion of a formulation containing 35% malathion, and based on the amount ingested, the lethal doses can be estimated to have been between 350 and 1,000 mg/kg. No dose can be estimated in a case described by Zivot et al. (1993), but the antemortem blood level of malathion in the patient on admission was 23.9 mg/L. A dose between 857 and 1,286 mg/kg can be estimated to have been ingested in a case described by Namba et al. (1970) and 2,000 mg/kg in one described by Jušić and Milić (1978). Talcott et al. (1979a) estimated a median lethal dose for malathion in humans of 3,655 mg/kg by using an equation relating carboxylesterase (serum and liver) and toxicity. The equation was experimentally constructed from data obtained in mice treated with various doses of malathion and carboxylesterase inhibitors. The higher estimate of Talcott et al. (1979a) probably reflects

the use of recrystallized malathion in their experiments, since, as discussed below, impurities found in commercial formulations can greatly increase the toxicity of malathion.

Numerous studies have examined the lethality of malathion in animals, particularly the acute lethality. Representative examples are summarized below, as well as relevant information on factors that play a role in the acute toxicity of this pesticide.

An early study by Frawley et al. (1957) calculated an LD_{50} of 1,400 mg/kg for technical malathion (98% pure) in young male Osborne-Mendel rats. Doses of 600 mg/kg caused no deaths, whereas all rats (10 out of 10) died when administered a dose of 2,000 mg/kg (Frawley et al. 1957). Gaines (1960) determined LD_{50} values of 1,375 and 1,000 mg/kg in adult male and female Sherman rats, respectively, administered technical malathion of unspecified purity. The apparent greater susceptibility of female rats observed by Gaines (1960) was not seen in subsequent studies by Lu et al. (1965) who reported no significant differences in LD_{50} values between male and female Hooded or Wistar rats administered malathion of 95% purity. In addition, no difference in susceptibility between strains was observed (Lu et al. 1965).

The role that impurities (i.e., trimethyl phosphorothioate and phosphorodithioate esters, isomalathion) play in the acute toxicity of malathion has been examined in detail in several studies. For example, in adult Wistar rats, the LD_{50} of 95% pure malathion was 1/4 that of 99.6% pure malathion (925 vs. 3,697 mg/kg) (Lu et al. 1965). Similar observations have been made by others in studies in rats and mice (Aldridge et al. 1979; Pellegrini and Santi 1972; Talcott et al. 1977; Toia et al. 1980; Umetsu et al. 1977). Clearly, as the purity of malathion decreases (and impurities increase), the LD_{50} values greatly decrease (toxicity of the malathion formulation increases). This is caused by the inherent toxicity of the impurities and/or potentiation of malathion toxicity. Umetsu et al. (1977) reported an LD_{50} of 9,500 mg/kg in adult Sprague-Dawley rats for malathion of 99.3% purity and 12,500 mg/kg for recrystallized malathion. In the same study, the LD_{50} for 95% pure malathion in adult mice was 1,985 mg/kg and that for 99.3% pure malathion was 3,000 mg/kg. Further studies demonstrated that these impurities, or contaminants of technical malathion, inhibit the activity of serum and liver malathion carboxylesterases, which detoxify malathion, as well as of cholinesterase, thereby increasing the toxicity of the malathion formulation (Talcott et al. 1977, 1979b).

An additional factor that plays a role in the acute toxicity of malathion is age; young animals are more susceptible than older animals. The single oral LD_{50} of 95% malathion in newborn male Wistar rats was

124.1 mg/kg, whereas in preweaning (14–16 days old) and adult (3–4 months) rats, oral LD_{50} values were 386.8 and 925.4 mg/kg, respectively (Lu et al. 1965). This difference was also observed for 4-day cumulative LD_{50}s (Lu et al. 1965). Similar findings were reported by Mendoza (1976) and Mendoza and Shields (1976) who also observed that the decrease in susceptibility more or less paralleled increases in the activities of esterases in various tissues. For example, using acetylthiocholine as substrate, a single dose of 8,000 mg/kg of malathion inhibited brain esterase by 85% in 18-day-old pups, while in 1-day-old pups, the same degree of inhibition was achieved with a dose of only 500 mg/kg.

In dogs, single doses of up to 4,000 mg/kg of 98% pure malathion in a gelatin capsule were not lethal, although the observation period was not indicated (Frawley et al. 1957). In rabbits, a single dose of 1,200 mg/kg of 95% pure malathion killed five out of six animals 6 hours after dosing; there were no deaths with 600 mg/kg (Weeks et al. 1977). In all of the species examined, death was preceded by signs of cholinergic stimulation such as salivation, respiratory distress, tremors, and convulsions.

Deaths in animals also have been reported in intermediate-duration studies. In a 6-week dietary study, five out of five male and female Osborne-Mendel rats administered approximately 2,816 mg/kg/day technical malathion (95% pure) died by week 3 (NCI 1978); no deaths were reported at 1,408 mg/kg/day. Deaths were also observed among male and female Fischer-344 rats administered approximately 1,399 mg/kg/day technical malathion, but not at ≤700 mg/kg/day in a 13-week feed study (NCI 1979a). Also, 4 out of 10 male, but no female $B6C3F_1$ mice died following dietary administration of approximately 6,432 mg/kg/day of technical malathion for 3 weeks (NCI 1978); no deaths occurred with approximately 3,216 mg/kg/day malathion or less.

Significant increased mortality was observed among male Fischer-344 rats administered approximately 166 mg/kg/day of technical malathion (95% pure) in the diet for 2 years (NCI 1979a). A more recent bioassay reported a significant increase in deaths not attributed to cancer among male Fischer-344 rats given approximately 359 mg/kg/day technical malathion (97.1% pure) or higher doses (Daly 1996a). No significant increase in mortality was seen in the females that received up to 868 mg malathion/kg/day (Daly 1996a).

The LOAEL values for death in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Table 3-2 Levels of Significant Exposure to Malathion - 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 (Wistar)	once (GO)				1500	(LD50 96.8% pure)	Lu et al. 1965
						3697	(LD50 99.6% pure)	
						925[b]	(LD50 95% pure)	
2	Rat (Wistar)	once (GO)				386.8	(LD50 in preweaning)	Lu et al. 1965
						925.4	(LD50 in adult)	
						124.1[b]	(LD50 in newborn)	
3	Rat (Wistar)	4 d 1 x/d (GO)				1599	(4-day cumulative LD50 in adult rats)	Lu et al. 1965
						331.2[b]	(4-day cumulative LD50 in preweaning rats)	
4	Rat (Wistar)	once (GO)				707	(LD50 in 6-day old)	Mendoza 1976
						1085	(LD50 in 12-day old)	
						1806	(LD50 in 17-day old)	
						209[b]	(LD50 in 1-day old)	
5	Rat (Sprague-Dawley)	once (G)				12500	(LD50 of recrystallized)	Umetsu et al. 1977
						9500[b]	(LD50 of 99.3% pure)	
6	Mouse (ICR)	2 d 1 x/d (GO)				2357	(LD50 for l-malathion)	Hassan and Dauterman 1968
						1014[b] F	(LD50 for d-malathion)	

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Death						
7	Mouse (C57BL/ 6N)	once (GO)				1430 F (LD50)	Rodgers et al. 1986
8	Mouse (Swiss)	once (GO)				3200 M (LD50 for recrystallized)	Talcott et al. 1979a
9	Mouse (C57B1)	once (GO)				2600 M (LD50)	Talcott et al. 1979a
10	Mouse (Swiss white)	once (G)				3000 (LD50 of 99.3% pure) 1850[b] (LD50 of 95% pure)	Umetsu et al. 1977
11	Rabbit (New Zealand)	once (GO)				1200 M (5 out of 6 died 6 hours after dosing)	Weeks et al. 1977
	Systemic						
12	Rat (Long- Evans)	once (GO)	Bd Wt	2000 M			Ehrich et al. 1993
13	Rat (Wistar)	14 d 1x/2d (G)	Bd Wt	10 M			Krause 1977
14	Rat (Wistar)	2 d 1x/d (G)	Bd Wt	40 M			Krause et al. 1976

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Systemic						
15	Rat (Sprague-Dawley)	once (GW)	Hemato		4.4 M (decreased hematocrit and platelet counts)		Lox 1983
16	Rat (Sprague-Dawley)	14 d ad libitum (W)	Hemato		89 F (changes in clotting factor activity)		Lox 1985
			Bd Wt	111 F			
			Other		89 F (30% decrease in water intake)		
17	Rat (Wistar)	7 d ad libitum (F)	Resp	163		411 (severe respiratory distress)	Ojha et al. 1992
			Cardio	411	593 (tachycardia)		
			Bd Wt	411	593 (17% decrease in weight)		
			Other	18.5	163 (12% decrease in food intake)		
18	Rat (Wistar)	14 d 1 x/d (GO)	Resp			130 M (interstitial pneumonia, emphysema)	Piramanayagam and Manohar 2002
			Cardio	130 M		390 M (focal hemorrhage in the heart)	
			Hepatic			130 M (diffuse hydropic degeneration)	
			Renal			130 M (atrophy of the glomeruli; degeneration of tubular epithelium)	

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Systemic						
19	Rat (Wistar)	once (G)	Resp			1950 M (hemorrhage and hyperemia in the lungs)	Piramanayagam et al. 1996
			Cardio			1950 M (congestion and hemorrhage in the heart)	
			Hepatic			1950 M (liver congestion and hemorrhage; hepatocytes vacuolation and necrosis)	
			Renal			1950 M (kidney congestion;degenerative changes in tubular epithelium)	
20	Rat (Wistar)	6 d 1x/d (GW)	Endocr		225 M (increased pituitary gland weight and serum prolactin levels; decrease pituitary prolactin)		Simionescu et al. 1977
			Bd Wt	225 M			
21	Rat (Wistar)	6 d 1x/d (GW)	Gastro		22 M (diarrhea after the first dose)		Simionescu et al. 1977
			Endocr	225 M			
			Bd Wt	225 M			
22	Mouse (C57BL/ 6N)	once (GO)	Bd Wt	715 F			Rodgers et al. 1986
	Immuno/ Lymphoret						
23	Rat (Sprague-Dawley)	once (GO)		1 F	10 F (increased serum histamine levels 4 hours after dosing)		Rodgers and Xiong 1997b

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Immuno/ Lymphoret						
24	Mouse (C57BL/ 6N)	once (GO)			720 M (suppression of primary IgM response)		Casale et al. 1983
25	Mouse (C57BL/ 6N)	4 d (GO)		240 M			Casale et al. 1983
26	Mouse (C57BL/ 6N)	once (GO)			715 F (increased proliferative response of splenocytes following exposure to polyclonal activators)		Rodgers and Ellefson 1990
27	Mouse (C57BL/ 6N)	once (GO)			450 F (stimulation of macrophage function)		Rodgers and Xiong 1996
28	Mouse (C57BL/ 6N)	once (GO)		1 F	10 F (increased serum histamine levels 4 hours after dosing)		Rodgers and Xiong 1997b
29	Mouse (C57BL/ 6N)	14 d 1 x/d (GO)			0.1 F (degranulation of mast cells associated with the small intestine)		Rodgers and Xiong 1997d
30	Mouse (C57BL/ 6N)	14 d 1 x/d (GO)			143 F (decrease in thymic lymphocyte number)		Rodgers et al. 1986
	Neurological						
31	Rat (Long- Evans)	once (GO)			600 M (increased spontaneous motor activity)		Ehrich et al. 1993

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Neurological						
32	Rat (Sprague-Dawley)	once (GO)			1000 F (34% inhibition of RBC cholinesterase)		Lamb 1994a
33	Rat (Sprague-Dawley)	8 d Gd 6-13 1 x/d (GO)		138 F	276 F (34% inhibition brain AChE)	827 F (convulsions, tremor, ataxia)	Mathews and Devi 1994
34	Rat (Wistar)	7 d 1x/d (F)		163		411 (dizziness, recurrent convulsions, and tremors observed in all rats)	Ojha et al. 1992
35	Rat (Wistar)	once (G)				1950 M (brain congestion, neuronal degeneration and gliosis)	Piramanayagam et al. 1996
36	Mouse (C57BL/ 6N)	once (GO)				720 M (tremors, fasciculations, 36% inhibition brain cholinesterase)	Casale et al. 1983
37	Mouse (C57BL/ 6N)	4 d (GO)			240 M (47 and 59% inhibition of plasma and RBC cholinesterase, respectively)		Casale et al. 1983
38	Rabbit (New Zealand)	once (G)			188 M (50-60% inhibition of brain AChE)		Vijayakumar and Selvarajan 1990
39	Rabbit (New Zealand)	once (GO)		12 M	120 M (27% inhibition of RBC cholinesterase)	600 M (61% inhibition of RBC cholinesterase)	Weeks et al. 1977

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Reproductive						
40	Rat (Wistar)	14 d 1x/2d (G)			10 M (significant increase in serum FSH levels)		Krause 1977
41	Rat (Wistar)	2 d 1x/d (G)			40 M (reversible damage to spermatogenetic tissue)		Krause et al. 1976
42	Rat (Sprague-Dawley)	10 d Gd 6-15 (GO)		800			Lochry 1989
43	Rat (Wistar)	7 d 1x/d (F)		18.5	163 (minor histopathological lesions in testes, ovaries, and uterus)		Ojha et al. 1992
44	Rat (Wistar)	once (G)				1950 M (reversible degeneration and necrosis of gonocytes in seminiferous tubules)	Piramanayagam et al. 1996
45	Rat (Sprague-Dawley)	3 d Gd 6, 10, 14 (GO)			500 F (decreased number of implants per dam)		Prabhakaran et al. 1993
46	Rabbit (New Zealand)	13 d Gd 6-18 (GO)		25		50 (increased mean number and percent resorptions)	Siglin 1985
	Developmental						
47	Rat (Wistar)	10 d Gd 6-15 1x/d (GO)		300			Khera et al. 1978

Table 3-2 Levels of Significant Exposure to Malathion - 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								
48	Rat (Sprague-Dawley)	10 d Gd 6-15 1x/d (GO)		800					Lochry 1989
49	Rat (Sprague-Dawley)	8 d Gd 6-13 1 x/d (GO)		276	827	(47% inhibition of brain AChE in pups)			Mathews and Devi 1994
50	Rat (Sprague-Dawley)	3 d Gd 6, 10, 14 (GO)					500	(reduced number of live fetuses per litter and fetal weight)	Prabhakaran et al. 1993
51	Rabbit (New Zealand)	6 d Gd 7-12 1 x/d (GO)		100					Machin and McBride 1989a
52	Rabbit (New Zealand)	3 d Gd 28-30 1 x/d (GO)					126	(79% decrease fetal plasma AChE activity; 66% decrease fetal brain AChE activity)	Machin and McBride 1989b
53	Rabbit (New Zealand)	13 d Gd 6-18 1x/d (GO)		100					Siglin 1985
	INTERMEDIATE EXPOSURE								
	Death								
54	Rat (Osborne-Mendel)	6 wk ad libitum (F)					2816	(5/5 males and 5/5 females died by week 3)	NCI 1978

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Death							
55	Rat (Fischer- 344)	13 wk ad libitum (F)				1399	(5/10 males died by week 9) (9/10 females died by week 5)	NCI 1979a
56	Mouse (B6C3F1)	6 wk ad libitum (F)				6432 M	(4/10 died by week 3)	NCI 1978
	Systemic							
57	Human	32-56 d 1 x/d (C)	Hemato	0.34 M				Moeller and Rider 1962
			Renal	0.34 M				
58	Rat (CFY)	90 d (F)	Hemato	75 F				Desi et al. 1976
			Hepatic	75 F				
			Renal	75 F				
			Bd Wt	75 F				
59	Rat (Wistar)	6 wk ad libitum (F)	Endocr	29 M				Foster 1968
			Bd Wt	29 M				
60	Rat (Wistar)	20 d 1x/d (G)	Bd Wt	20 M				Krause et al. 1976

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Systemic						
61	Rat (Sprague-Dawley)	6 mo ad libitum (W)	Hemato		0.15 F (prolonged prothrombin and partial thromboplastin times)		Lox and Davis 1983
			Hepatic		0.15 F (hepatocyte degeneration)		
			Bd Wt	0.15 F			
62	Rat (Fischer- 344)	13 wk ad libitum (F)	Bd Wt	700		1399 F (final body weight reduced 50% relative to controls)	NCI 1979a
63	Rat (albino)	15 wk 1x/d (GO)	Endocr		10 (significant decrease in serum cortizol and aldosterone levels, and congestion in zona reticularis of adrenal glands in both sexes)		Ozmen and Akay 1993
64	Mouse (Hissar)	3 -12 wk (F)	Hepatic	10.5 M	21 M (increased relative liver weight)		Banerjee et al. 1998
			Bd Wt	21 M			
65	Dog (Beagle)	28 d (C)	Gastro		125 (diarrhea)		Fischer 1988
	Immuno/ Lymphoret						
66	Rat (Wistar)	8 -22 wk ad libitum (F)		2.3 M	5.8 M (reduced humoral and cell-mediated immune responses to antigens)		Banerjee et al. 1998

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Immuno/ Lymphoret						
67	Mouse (Hissar)	3 -12 wk (F)		4.2 M	10.5 M	(decreased humoral and cell-mediated responses to antigens)	Banerjee et al. 1998
68	Mouse (C57BL/6N)	28 d 1 x/2d (GO)			0.018 F	(incrased primary humoal response to SRBC)	Johnson et al. 2002
69	Mouse (C57BL/ 6N)	90 d 1 x/d (GO)			0.1 F	(increased macrophage function and mast cell degranulation)	Rodgers and Xiong 1997c
70	Rabbit (New Zealand)	21 wk 1 x/d (G)		0.5 M	2.5 M	(significant decrease in some tests of humoral and cell-mediated immunity)	Banerjee et al. 1998
71	Rabbit (NS)	6 wk 5 d/wk (C)			5 M	(decreased humoral immune response to Salmonella vaccine)	Desi et al. 1978
	Neurological						
72	Human	32-56 d 1 x/d (C)		0.23[c] M	0.34 M	(25% depression of plasma and RBC cholinesterase)	Moeller and Rider 1962
73	Rat (CFY)	90 d ad libitum (F)		38	75 F	(increased excitability as shown by changes in the EEG and EMG)	Desi et al. 1976
74	Rat (albino)	32 d 1 x/d (GO)		55 F	137.5 F	(37% inhibition of RBC cholinesterase; 58% inhibition of plasma cholinesterase)	Husain et al. 1987

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Neurological						
75	Rat (Sprague-Dawley)	90 d ad libitum (F)		4		352 M (61% inhibition of RBC cholinesterase activity)	Lamb 1994b
76	Rat (Wistar)	14 d 1 x/d (GO)				130 M (neuronal degeneration; gliosis)	Piramanayagam and Manohar 2002
77	Dog (Beagle)	28 d (C)			125 (>20% decrease in plasma cholinesterase activity)		Fischer 1988
78	Rabbit (NS)	6 wk 5 d/wk (C)		10 M	25 M (25-30% inhibition of RBC cholinesterase following two weeks of treatment)		Desi et al. 1978
	Reproductive						
79	Rat (albino)	12 wk 1 x/d (GO)			45 M (edema, congestion, and desquamation of lining cells of seminiferous tubules)		Balasubramanian et al. 1987a
80	Rat (albino)	12 wk 1 x/d (GO)			44 M (decrease seminal vesicle pH, protein content, relative testes weight and enzyme activities)		Balasubramanian et al. 1987b
81	Rat (Wistar)	20 d 1x/d (G)			20 M (reversible damage to spermatogenic tissue)		Krause et al. 1976
82	Rat (Sprague-Dawley)	110 d 1 x/d (GO)		50 F			Lechner and Abdel-Rahman 1984

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Reproductive						
83	Rat (albino)	15 wk 1x/d (GO)			10 M (hyperemia of the veins of the testes and degenerated testicular tubuli)		Ozmen and Akay 1993
84	Rat (Sprague-Dawley)	>63 d ad libitum (F)		703 F			Schroeder 1990
	Developmental						
85	Rat (Wistar)	5 mo ad libitum (F)				240 (increased neonatal mortality 7 and 21 days after birth)	Kalow and Marton 1961
86	Rat (Sprague-Dawley)	110 d 1 x/d (GO)		50 F			Lechner and Abdel-Rahman 1984
87	Rat (Sprague-Dawley)	>63 d ad libitum (F)		153 F	394 M (reduced body weight gain during lactation)		Schroeder 1990
	CHRONIC EXPOSURE						
	Death						
88	Rat (Fischer- 344)	2 yr ad libitum (F)				359 M (significant increase in deaths not attributed to cancer)	Daly 1996a
89	Rat (Fischer- 344)	103 wk ad libitum (F)				166 M (increased mortality)	NCI 1979a

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Systemic						
90	Rat (Fischer- 344)	2 yr ad libitum (F)	Hemato	35 F	359 M	(decreased hemoglobin, hematocrit, MCV, and mean cell hemoglobin)	Daly 1996a
			Hepatic	35 F	359 M	(increased absolute and relative liver weight)	
			Renal	35 F	359 M	(increased absolute and relative kidney weight)	
			Endocr	35 F	415 F	(increased absolute and relative thyroid and parathyroid weight)	
			Ocular	868 F			
			Bd Wt	35 F	359 M	(decreased body weight gain)	
			Other	868 F			

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Systemic						
91	Rat (Osborne-Mendel)	80 wk (F)	Resp	622			NCI 1978
			Cardio	622			
			Gastro	622			
			Musc/skel	622			
			Hepatic	622			
			Renal	622			
			Endocr	622			
			Dermal	622			
			Bd Wt	622			

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Systemic						
92	Rat (Fischer- 344)	103 wk ad libitum (F)	Resp	332			NCI 1979a
			Cardio	332			
			Gastro		166 M (chronic inflammation of the stomach and stomach ulcers)		
			Musc/skel	332			
			Hepatic		166 F (fatty metamorphosis of the liver)		
			Renal	332			
			Endocr	332			
			Dermal	332			
			Bd Wt	166	332 M (>10% reduction in final body weight)		

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Systemic								
93	Mouse (B6C3F1)	80 wk ad libitum (F)	Resp		2980	(coughing and sneezing from week 72 until end of study)			NCI 1978
			Cardio	2980					
			Gastro	2980					
			Musc/skel	2980					
			Hepatic	2980					
			Renal	2980					
			Endocr	2980					
			Dermal	2980					
			Bd Wt		1490	(>10% lower body weight than controls)			
94	Mouse (B6C3F1)	18 mo ad libitum (F)	Resp	17.4 M	167 F	(increased incidence of non-neoplastic nasal lesions)			Slauter 1994
			Hepatic	167 F	1476 M	(hepatocellular hypertrophy)			
			Bd Wt	167 F	1476 M	(14-20% decreased body weight)			
			Other	167 F	1476 M	(decreased food consumption)			
	Neurological								
95	Rat (Fischer- 344)	2 yr ad libitum (F)		2 M[d]	29 M[e]	(29% inhibition of plasma cholinesterase)	359 M	(64% inhibition of plasma cholinesterase)	Daly 1996a
					35 F	(27% inhibition of RBC cholinesterase)			

Table 3-2 Levels of Significant Exposure to Malathion - 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
	Neurological						
96	Mouse (B6C3F1)	80 wk ad libitum (F)				2980 F (generalized body tremors from week 71 to 79)	NCI 1978
97	Mouse (B6C3F1)	18 mo ad libitum (F)		20.8 F	143 M (24% and 44% inhibition of plasma and RBC cholinesterase activity, respectively)	1476 M (90% inhibition of plasma and RBC cholinesterase activity)	Slauter 1994
	Reproductive						
98	Mouse (B6C3F1)	80 wk ad libitum (F)			1490 F (cystic endometrial hyperplasia)		NCI 1978
	Cancer						
99	Rat (Fischer- 344)	2 yr ad libitum (F)				868 F (CEL: increased incidence of combined hepatocellular adenoma and carcinoma)	Daly 1996a
100	Mouse (B6C3F1)	18 mo ad libitum (F)				1476 M (CEL: increased incidence of combined hepatocellular carcinomas and adenomas)	Slauter 1994

a The number corresponds to entries in Figure 3-2
b Only this dose level, the lowest effect level, is plotted in Figure 3-2.
c Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.02 mg/kg/day; The MRL was derived by dividing the NOAEL by an uncertainty factor of 10 to account for human variability.
d Used to derive a chronic-duration oral minimal risk level (MRL) of 0.02 mg/kg/day; The MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 for animal to human extrapolation; 10 for human variability).
e Differences in levels of health effects and cancer 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.

AchE = acetylcholinesterase; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); (EEG) = electroencephalogram; (EMG) = electromyogram; Endocr = endocrine; (F) = feed; F = female; FSH = follicle stimulating hormone; (G) = gavage; gastro = gastrointestinal; gd = gestation day; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-effect level; M = male; MCV = mean corpuscular volume; mg/kg/day = milligram/kilogram/day; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; RBC = red blood cell(s); Resp = respiratory; (W) = water; wk = week(s); x = times; yr = year(s)

Figure 3-2 Levels of Significant Exposure to Malathion - Oral

Acute (≤14 days)

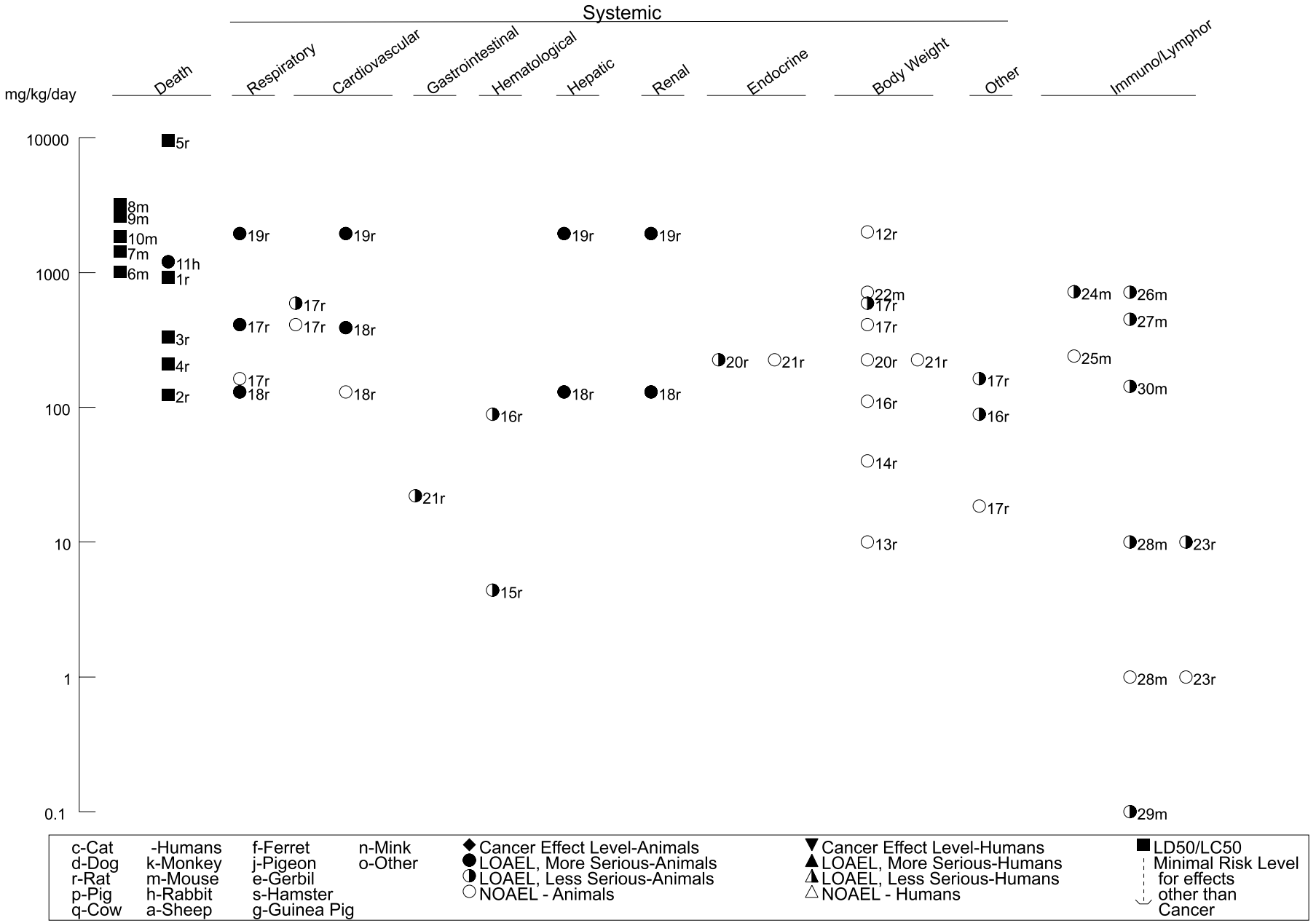


Figure 3-2 Levels of Significant Exposure to Malathion - Oral (*Continued*)

Acute (≤14 days)

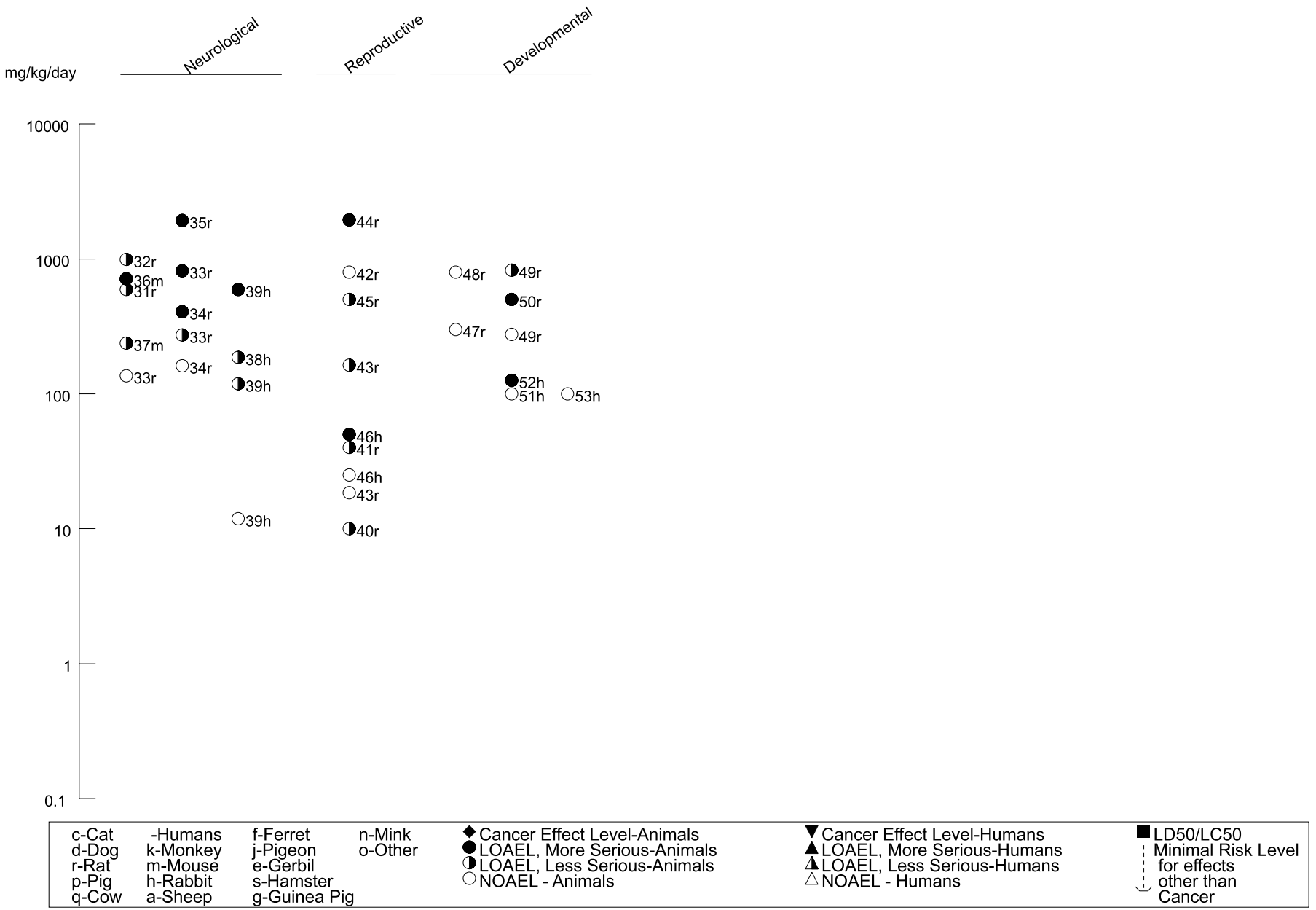


Figure 3-2 Levels of Significant Exposure to Malathion - Oral (*Continued*)

Intermediate (15-364 days)

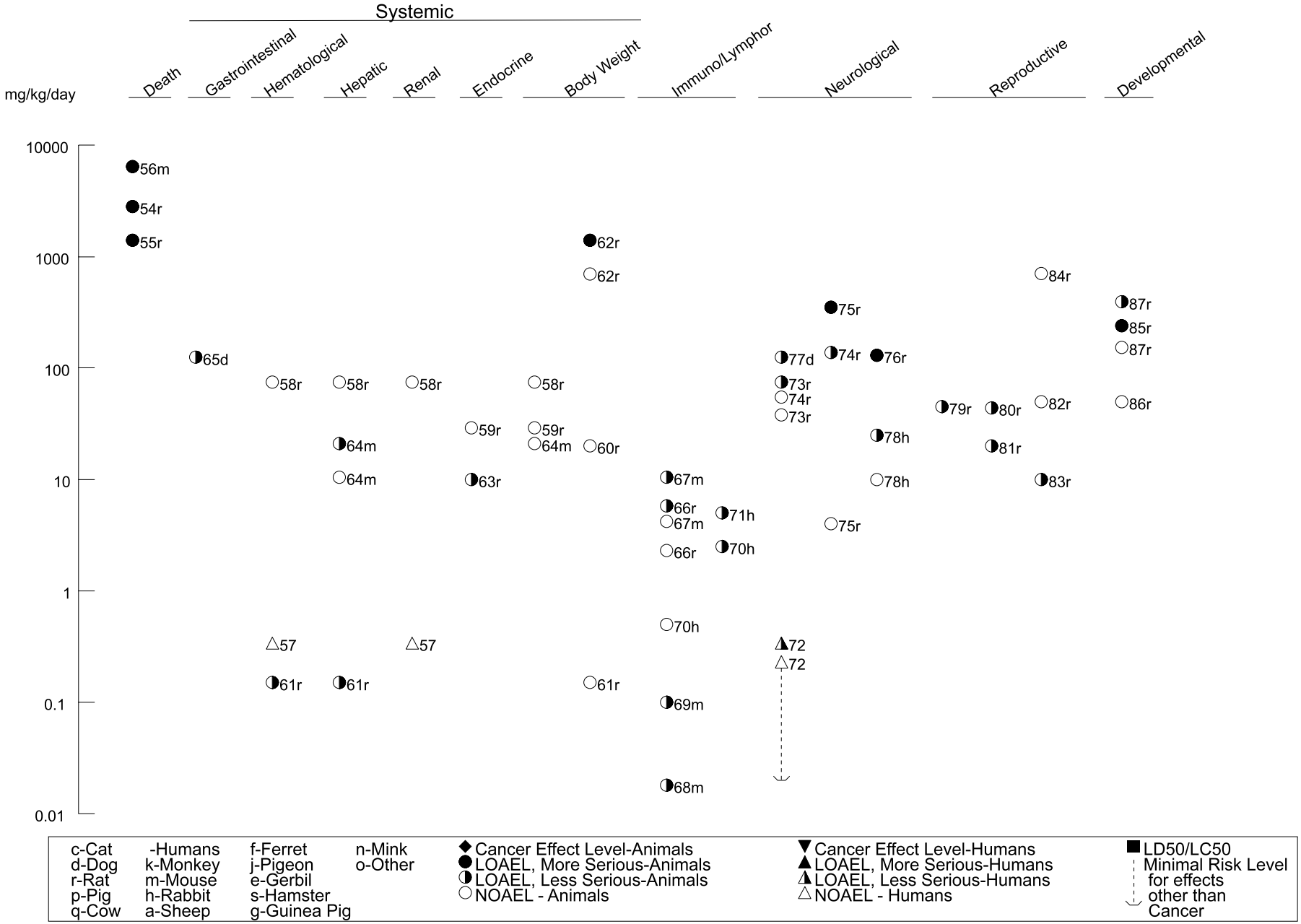
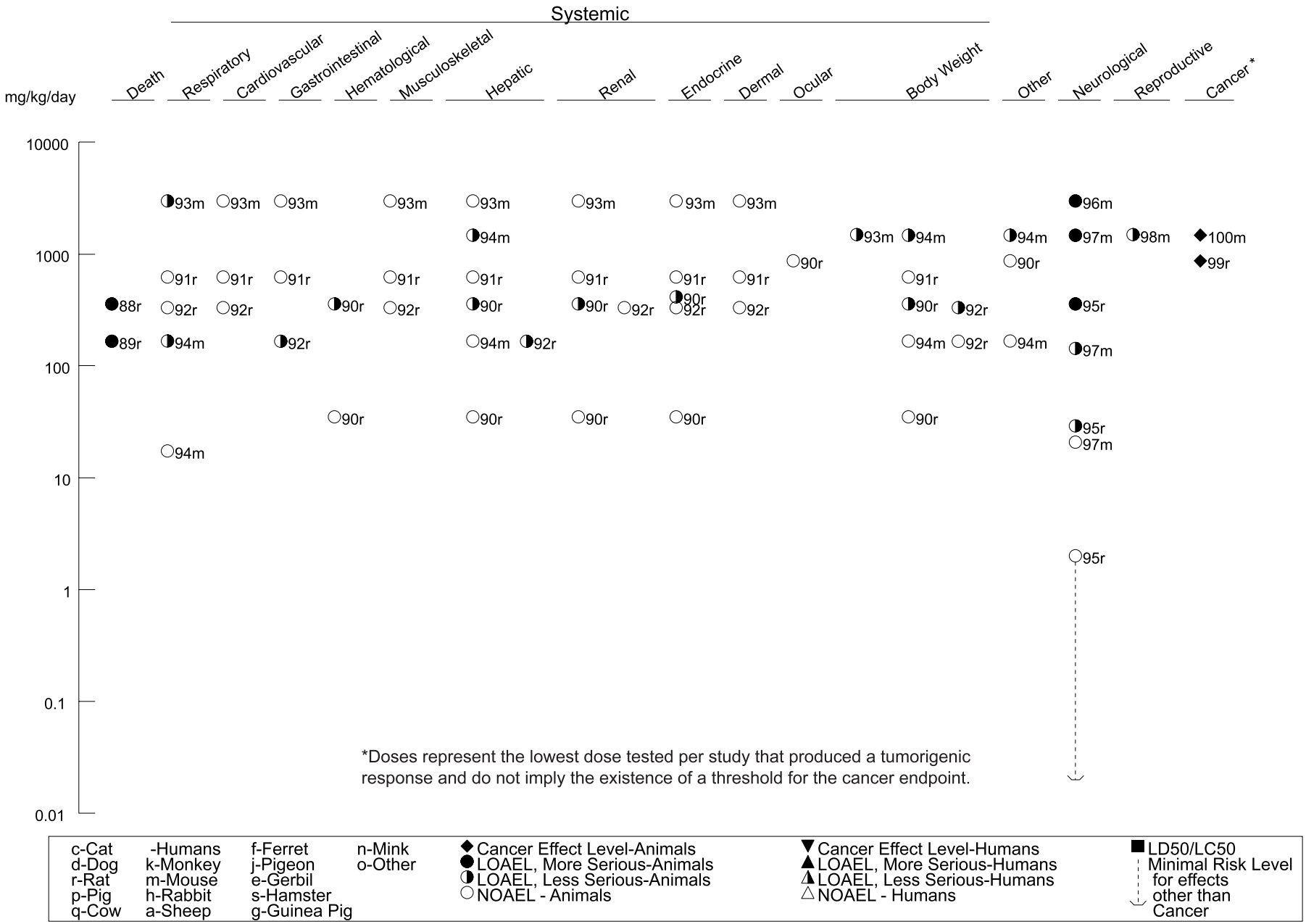


Figure 3-2 Levels of Significant Exposure to Malathion - Oral (*Continued*)

Chronic (≥365 days)



3.2.2.2 Systemic Effects

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

Respiratory Effects. Several reports of malathion poisoning document respiratory difficulties typical of parasympathetic autonomic stimulation shortly after poisoning (Amos and Hall 1965; Choi et al. 1998; Crowley and Johns 1966; Dive et al. 1994; Jušić and Milić 1978; Monje Argiles et al. 1990; Namba et al. 1970; Tuthill 1958; Zivot et al. 1993). Doses could be estimated from information in some studies, and ranged from 214 to 1,071 mg/kg. Even at the lower dose estimates, respiratory distress and bronchorrhea were common, and most patients required ventilatory support, some for more than 30 days (Monje Argiles et al. 1990). Pulmonary fibrosis that developed in the second week following the poisoning episode was also observed in two reports (Dive et al. 1994; Monje Argiles et al. 1990).

Adverse respiratory effects have been described in animals after acute oral exposure to malathion. Severe respiratory distress was observed in Wistar rats administered approximately 411 mg/kg/day malathion of unspecified purity in a 7-day dietary study (Ojha et al. 1992). Hemorrhage and hyperemia in the lungs was reported in male Wistar rats 2 days following administration of a single gavage dose of 1,950 mg/kg of technical malathion (95% pure), the only dose level tested (Piramanayagam et al. 1996). Without providing details, the authors (Piramanayagam et al. 1996) stated that by day 12, almost all organs examined appeared normal. Rats treated for 1–2 weeks with 130 mg malathion/kg/day (purity unspecified) by gavage developed interstitial pneumonia and emphysema (Piramanayagam and Manohar 2002). Also, pregnant Sprague-Dawley rats administered 500 mg/kg/day technical malathion (purity unspecified) by gavage 3 times during gestation exhibited dyspnea 2 hours after each dosing (Prabhakaran et al. 1993). Dyspnea and respiratory distress may be due to stimulation of parasympathetic postganglionic nerves (muscarinic effects) or to diaphragmatic failure (nicotinic effects).

No respiratory effects (clinical signs or histopathology) were reported in Osborne-Mendel rats administered up to 622 mg/kg/day technical malathion (95% pure) in the diet for 80 weeks (NCI 1978) or in Fischer-344 rats administered up to 332 mg/kg/day technical malathion (95% pure) also in the diet for 103 weeks (NCI 1979a). In studies in mice, NCI (1978) reported that male and female $B6C3F_1$ mice given approximately 2,980 mg/kg/day malathion (95% pure) in the diet began coughing and sneezing after 72 weeks of treatment; this condition persisted until the end of the study (80 weeks). No such

effects were observed in mice from the low-dose group administered approximately 1,490 mg malathion/kg/day. Another long-term study (18 months) in mice reported an increased incidence of nonneoplastic nasal lesions in female $B6C3F_1$ mice treated with 96.4% pure malathion in the diet at 167 mg/kg/day and in males and females at approximately 1,500 mg/kg/day (Slauter 1994). These lesions were characterized as exudate, suppurative, increased glandular secretion, olfactory atrophy, and olfactory respiratory metaplasia. No such lesions were seen in animals treated with about 20 mg/kg/day of malathion or less.

Cardiovascular Effects. Cardiovascular effects were observed in almost all reported cases of malathion poisoning (Crowley and Johns 1966; Dive et al. 1994; Healy 1959; Jušić and Milić 1978; Monje Argiles et al. 1990; Namba et al. 1970; Rivett and Potgieter 1987; Zivot et al. 1993). In general, signs and symptoms on admission included bradycardia and low blood pressure as expected from vagal stimulation. Several cases also observed atrio-ventricular conduction disturbances within a few days after ingestion of the pesticide (Crawley and Johns 1966; Dive et al. 1994; Monje Argiles et al. 1990). Doses estimated in these cases ranged from 214 to 2,117 mg/kg. In contrast, Choi et al. (1998) reported a normal electrocardiogram and chest x-ray performed in the emergency room in a woman who ingested approximately 1,071 mg/kg malathion.

Tachycardia was reported in many Wistar rats treated with about 593 mg/kg/day of malathion (unspecified purity) in the diet for 7 days, but not in those treated with ≤411 mg/kg/day malathion (Ojha et al. 1992). Tachycardia may be the result of cholinergic stimulation of parasympathetic and sympathetic autonomic ganglia. Administration of gavage doses of 390 mg malathion/kg/day (unspecified purity) for 1–2 weeks to rats caused focal hemorrhage in the heart (Piramanayagam and Manohar 2002). A single gavage dose of 1,950 mg/kg of malathion (95% pure), the only dose level tested, caused congestion and hemorrhage in the hearts of male Wistar rats 2 days after dosing, females were not tested (Piramanayagam et al. 1996). Although the authors did not specifically mention the heart, they stated that by day 12 after dosing, almost all organs examined appeared normal.

No adverse cardiovascular effects were reported in long-term dietary studies in rats (up to 622 mg malathion/kg/day) (NCI 1978, 1979a) and mice (up to 2,980 mg malathion/kg/day) (NCI 1978; Slauter 1994).

Gastrointestinal Effects. Abdominal cramping, diarrhea, nausea, and vomiting were common signs and symptoms observed following ingestion malathion in some of the reports available (Amos and Hall

1965; Crowley and Johns 1966; Healy 1959; Rivett and Potgieter 1987). These effects result from the stimulation of parasympathetic autonomic postganglionic nerves by organophosphates and the lack of reporting of these effects in the additional studies reviewed most likely reflects incomplete reporting rather than the absence of gastrointestinal effects.

Diarrhea was observed in beagle dogs treated with 125 mg/kg/day (the lowest dose tested) malathion (92.4% pure) in gelatin capsules for 28 days (Fischer 1988). Rats administered malathion (22 mg/kg/day) by gavage in a mixture of alcohol and water for 6 days suffered diarrhea (Simionescu et al. 1977). Diarrhea is a common muscarinic sign of organophosphate pesticide intoxication. Rats treated with gavage doses of 130 mg/kg/day of malathion (unspecified purity) for 1–2 weeks showed gastrointestinal alterations described by the authors as catarrhal changes (Piramanayagam and Manohar 2002). Information from a single dose study in rats suggested that malathion may alter gastrointestinal absorption. Absorption was examined in an isolated portion of the intestines from male Wistar rats 48 hours after administration of a single gavage dose of 1,000 mg/kg/day of technical malathion (purity unspecified) (Chowdhury et al. 1980). Absorption of glucose and glycine were reduced and the activities of some brush border enzymes were depressed in the malathion-treated rats. In a subsequent study from the same group in which rats were treated for 45 days with 50 mg/kg/day malathion, the authors found that treatment with malathion significantly increased the absorption of glucose, phenylalanine, and lysine, but not glycine, and increased brush border enzyme activities (Wali et al. 1984).

No gastrointestinal effects were reported in Osborne-Mendel rats administered up to approximately 622 mg/kg/day malathion (95% pure) in the diet for 80 weeks or in B6C3F_1 mice treated with up to 2,980 mg/kg/day in the diet for 80 weeks (NCI 1978). However, male Fischer-344 rats administered 166 mg/kg/day malathion (95% pure) or more in the diet for 103 weeks developed chronic inflammation of the stomach and stomach ulcers.

Hematological Effects. Almost all of the case reports of oral ingestion of malathion described the results of laboratory tests conducted on the patients on or following admission to treatment centers. In most cases, these included complete and differential blood counts, which may or may have not deviated from the normal ranges. However, observed deviations are probably not unique to malathion intoxication, or to organophosphates in general, but represent stress reactions (Aaron and Howland 1998). For example, it is not uncommon to find high hematocrit secondary to hemoconcentration due to large fluid losses (Aaron and Howland 1998). Therefore, a detailed discussion of specific alterations from the individual cases is of little utility.

Moeller and Rider (1962) conducted a controlled study in which male volunteers were administered daily capsules containing malathion (purity not reported) in corn oil that provided an approximate dose of 0.11 mg malathion/kg/day for 32 days, 0.23 mg malathion/kg/day for 47 days, or 0.34 mg malathion/kg/day for 56 days. Routine blood counts conducted at the end of each study period did not detect any significant changes.

Few reports were available that provided some information on hematological effects in animals following oral exposure to malathion. A study reported no hematological effects in pregnant Sprague-Dawley rats administered the relatively low dose of 0.73 mg/kg/day of malathion (analytical grade) bound to wheat during gestation days (Gd) 5–11 (Bitsi et al. 1994). Lox (1983) observed a decrease in hematocrit and in platelet counts in rats 2 hours after being gavaged once with a suspension of malathion (99% pure) in water; no other dose level was tested. Treatment of Sprague-Dawley rats with approximately 89 mg/kg/day malathion in the drinking water for 14 days resulted in a significant increase in fibrinogen and decrease in clotting factor XII, whereas a high dose of about 111 mg/kg/day decreased clotting factor II and XII and increased factor X (Lox 1985). A much smaller dose of approximately 0.15 mg/kg/day of malathion (99% pure), also in drinking water, for 6 months significantly prolonged prothrombin and partial thromboplastin times in female Sprague-Dawley rats, but had no significant effect on fibrinogen or coagulation factors II, VII, or X (Lox and Davis 1983); this treatment caused no significant alterations on hematocrit or platelet counts. A 90-day-duration study found no significant effect of malathion (95% pure) on blood counts (differential or quantitative) following administration in the diet at a level of 75 mg/kg/day (Desi et al. 1976). A 2-year-duration study in Fischer-344 rats observed a decrease in hemoglobin, hematocrit, mean corpuscular volume, and mean cell hemoglobin in males and females following dosing of 6,000 ppm malathion (97.1% pure) in the diet (359 mg/kg/day for males, 415 mg/kg/day for females) (Daly 1996a).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following oral exposure to malathion. The only information available regarding musculoskeletal effects of malathion in animals is that from chronic studies. These studies reported no gross or microscopic alterations in bone (unspecified) from Osborne-Mendel rats treated with up to 622 mg/kg/day of malathion (95% pure) for 80 weeks (NCI 1978), in Fischer-344 rats given up to 332 mg/kg/day for 103 weeks (NCI 1979a), or in B6C3F_1 mice administered up to 2,980 mg/kg/day malathion for 80 weeks (NCI 1978).

Hepatic Effects. No specific reports were located of hepatotoxicity in humans following oral exposure to malathion. Several studies provide information on hepatic effects in animals following oral exposure to malathion. A single high-dose of 1,950 mg/kg malathion (95% pure) administered by gavage to male Wistar rats caused liver congestion and hemorrhage 2 days after dosing (Piramanayagam et al. 1996). Microscopic examination revealed vacuolation of the hepatocytes, necrosis, portal mononuclear cell infiltration, and microgranuloma formation up to the second day after treatment; these changes appeared to reverse in subsequent days. Rats treated by gavage with 130 mg malathion/kg/day (unspecified purity) for 1–2 weeks showed diffuse hydropic degeneration of the liver and those treated with 390 mg/kg/day had focal necrosis, vacuolar degeneration in the portal hepatocytes, Kupffer cell hyperplasia and microgranuloma (Piramanayagam and Manohar 2002); without providing details, the authors indicated that these changes persisted after a recovery period of 7 weeks. A considerable lower dose of approximately 0.15 mg/kg/day (only dose level tested) of malathion (99% pure) administered in the drinking water to female Sprague-Dawley rats for 6 months caused hepatocyte degeneration (Lox and Davis 1983). This finding is puzzling since no significant nonneoplastic alterations have been reported in the livers of rats and mice administered much higher doses for prolonged periods of time. For example, NCI (1978) reported no liver alterations in Osborne-Mendel rats administered approximately 622 mg/kg/day malathion (95% pure) in the diet for 80 weeks, but female Fischer-344 rats given approximately 166 mg/kg/day for 103 showed fatty metamorphosis of the liver, but no degeneration. B6C3F_1 mice treated with up to 2,980 mg/kg/day malathion for 80 weeks had no significant liver effects (NCI 1978), but a similar study in the same mice strain found hepatocellular hyperplasia at 1,476 mg/kg/day malathion and no significant effect at 167 mg/kg/day (Slauter 1994).

Other studies have monitored liver or serum enzymes commonly used as biomarkers of liver damage. A dose of 500 mg/kg/day malathion (98% pure) for 3 days induced a decrease in glutathione content and increased lipid peroxide in the liver of Sprague-Dawley rats (Prabhakaran and Devi 1993; Prabhakaran et al. 1993). A single gavage dose of 500 mg/kg malathion (96% pure) or intermittent gavage doses of 500 mg/kg/day for 4 weeks increased serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities, also in rats (Enan 1983). A NOAEL of 50 mg/kg (following either single dose or 21-day dosing) for serum transaminase activities in rats was reported by Abdel-Rahman et al. (1985). A dose of 137.5 mg/kg/day for 32 days significantly increased AST, ALT, and alkaline phosphatase (AP) activities in the liver (Husain et al. 1987). A dose of 25 mg/kg/day malathion (unspecified purity) administered by gavage for 7 days to female Sprague-Dawley rats had no significant effect on the activities of liver microsomal enzymes (Lechner and Abdel-Rahman 1985). Data on hepatic effects in mice following acute exposure of malathion are limited to a report of increased glutathione

peroxidase activity in the liver of female Swiss albino mice treated with 30 mg/kg/day malathion (98% pure) for 14 days (Chhabra et al. 1993). The same result was obtained following 21 days of treatment, with the added finding of a significant decrease in liver glutathione reductase activity (Chhabra et al. 1993).

No significant effects on liver weight were reported in rats following a single gavage dose of 500 mg/kg of malathion (unspecified purity) (Bulusu and Chakravarty 1984) or following administration of approximately 11.5 mg/kg/day malathion (>99% pure) in the food to Wistar rats for 8–22 weeks (Banerjee et al. 1998) or 75 mg/kg/day malathion (95% pure) to CFY rats in the food for 90 days (Desi et al. 1976). However, mice given approximately 21 mg/kg/day malathion (>99% pure) in the diet for 3–12-weeks had increased relative liver weight (Banerjee et al. 1998). Increased absolute and relative liver weight was reported in male and female Fischer-344 rats administered 359 or 415 mg/kg/day of malathion (97.1% pure), respectively, in the diet for 2 years (Daly 1996a), no significant effects were seen at 29 mg/kg/day in males or 35 mg/kg/day in females.

The data in animals suggest that the nonneoplastic liver changes may represent adaptive responses unless very high bolus doses are administered, which may cause more serious histopathologic damage.

Renal Effects. Renal abnormalities in humans have been observed in several case reports. Five poisoning cases (Crowley and Johns 1966; Dive et al. 1994; Healy 1959; Namba et al. 1970; Zivot et al. 1993) reported a variety of urinary/renal changes following malathion ingestion. It should be kept in mind, however, that many of these cases resulted in death or near death, such that the true toxicological significance of the findings is unclear. In a subject who ingested approximately 514 mg/kg of malathion, protein was found in the urine, and mild renal insufficiency (measured by creatinine clearance) was observed (Dive et al. 1994). In another case, after ingestion of approximately 600 mg/kg of malathion, protein, sugar, and white blood cells were found in the urine (Crowley and Johns 1966). At a dose of approximately 1,045 mg/kg, protein and glucose again were also seen (Namba et al. 1970). Decreased urine production and a urinary tract infection (with *Escherichia coli*) were observed prior to death in an 80-year-old woman who ingested an undetermined amount of malathion (Zivot et al. 1993). Healy (1959) found increased secretion of ketone bodies and glucose in the urine in an 18-month-old boy who ingested malathion.

No remarkable alterations in urynalises were observed in a study in which male volunteers were administered daily capsules containing malathion (purity not reported) in corn oil that provided an

approximate dose of 0.11 mg malathion/kg/day for 32 days, 0.23 mg malathion/kg/day for 47 days, or 0.34 mg malathion/kg/day for 56 days (Moeller and Rider 1962).

Limited information exists regarding renal effects in animals following oral exposure to malathion. A single gavage dose of 1,950 mg/kg malathion (95% pure) (only level tested) induced kidney congestion in male Wistar rats during 2 days after dosing and kidney enlargement on the second and third day (Piramanayagam et al. 1996). Microscopically, the kidneys showed hyperemia, degeneratives changes in the tubular epithelium, and microgranuloma. Without specifically mentioning the kidneys, Piramanayagam et al. (1996) indicated that by day 12 after dosing, almost all organs appeared normal. Treatment of rats by gavage with ≥130 mg malathion/kg/day (purity unspecified) for 1–2 weeks induced atrophy of the glomeruli, degeneration of the tubular epithelium, and epithelial casts (Piramanayagam and Manohar 2002). A lower dose of 75 mg/kg/day of malathion (95%) in the food for 90 days had no significant histopathologic effects on the kidneys from female CFY rats (Desi et al. 1976).

Other studies have provided information of biochemical parameters in the kidney of unclear toxicological significance. Increased lipid accumulation and decreased glutathione content were reported in female Sprague-Dawley rats following three gavage doses of 500 mg/kg/day malathion (98% pure) (Prabharakan and Devi 1993; Prabhakaran et al. 1993). A 32-day gavage study in rats reported increased AST, ALT, and AP enzyme activities in the kidneys (Husain et al. 1987). An additional study in Sprague-Dawley rats reported increased blood urea nitrogen (BUN) after 5 weeks of treatment with approximately 0.067 mg/kg/day malathion (98%) pure bound to milled rice (Syed et al. 1992). Increased BUN may indicate glomerular disease, but may also have many other causes unrelated to kidney function.

None of the long-term studies reported any significant kidney lesions in rats administered malathion in doses of up to 622 mg/kg/day (NCI 1978) or in mice administered up to 2,980 mg/kg/day (NCI 1978). However, increased absolute and relative kidney weight was reported in male and female Fischer-344 rats administered 359 or 415 mg/kg/day of malathion (97.1% pure), respectively, in the diet for 2 years (Daly 1996a); the corresponding NOAELs were 29 and 35 mg/kg/day. The available information in animals suggests that the kidney is not a sensitive target for malathion toxicity.

Endocrine Effects. The only relevant information available of endocrine effects in humans is that from a study of 22 patients with organophosphate poisoning that resulted from intentional ingestion of undetermined amounts of malathion (Güven et al. 1999). Upon admission to the hospital, all patients showed signs of organophosphate intoxication. Blood levels of several hormones, particularly pituitary

hormones, were measured in 22 patients. Of eight hormones, adrenocorticotropic hormone (ACTH), cortisol, and prolactin (PRL) levels were significantly higher shortly after poisoning than 3 days after appropriate treatment had been provided; blood levels of all three hormones had decreased by about 50% 3 days after treatment. Follicle-stimulating hormone (FSH) levels were slightly, but not significantly lower before treatment (by 20.5%) than after treatment. In addition, seven patients showed transient lowering in thyroid hormone levels (low fT_3, fT_4) and thyroid-stimulating hormone (TSH) before treatment. The toxicological significance of these findings is unknown.

Relatively little information is available on the endocrine effects of malathion after oral exposure in animals. Increased pituitary gland weight and serum prolactin levels and decrease pituitary levels of prolactin were reported in male Wistar rats administered approximately 225 mg/kg/day of malathion for 6 days (Simionescu et al. 1977). An intermediate-duration study found congestion in the *zona reticularis* of the adrenal glands from rats treated by gavage with 10 mg/kg/day of malathion (94% pure) for 15 weeks (Ozmen and Akay 1993). Serum cortisol and aldosterone levels were increased at 10 mg/kg/day, but not at 100 mg/kg/day. Serum T_4, T_3, testosterone, and 17β-estradiol levels were not significantly affected by treatment with malathion and there were no histopathologic changes in the thyroid in the treated animals (Ozmen and Akay 1993).

A chronic-duration study in Osborne-Mendel rats did not reveal gross or microscopical lesions in the adrenal glands, thyroid, or parathyroid from rats administered 0, 359, or 622 mg/kg/day malathion (95% pure) in the diet for 80 weeks (NCI 1978). However, cysts of the pituitary were seen more often in treated males (0% in controls, 28% incidence in low-dose, and 22% in the high-dose) than in controls. Since only one high-dose female showed this lesion, the authors (NCI 1978) did not consider the lesion treatment-related. In the bioassay with Fischer-344 rats, there were no significant treatment-related lesions in endocrine organs during treatment with up to 332 mg/kg/day malathion (95% pure) in the diet for 103 weeks (NCI 1979a). Similar results were obtained in $B6C3F_1$ mice administered up to 2,980 mg/kg/day malathion in the diet for 80 weeks (NCI 1978). Increased relative and absolute thyroid and parathyroid weights were seen in female Fischer-344 rats administered 415 mg/kg/day of malathion (97.1% pure) in the diet for 2 years (Daly 1996a); the NOAEL was 35 mg/kg/day.

The limited information available does not suggest that endocrine organs are direct targets for malathion toxicity. The adrenal congestion reported by Ozmen and Akay (1993) in rats treated with 10 mg/kg/day malathion may be a nonspecific effect since hyperemia and petechial hemorrhages in some organs is not

an uncommon finding following organophosphate intoxication. Interestingly, no such congestion was seen in the chronic studies with much larger doses.

Dermal Effects. No studies were located regarding dermal effects in humans following oral exposure to malathion. The only information regarding dermal effects in animals following exposure to malathion is that provided in the long-term bioassays, which reported no gross or microscopic alterations in the skin from rats or mice treated with malathion in the diet for periods between 80 and 103 weeks. Rats were dosed with up to 622 mg/kg/day malathion (NCI 1978, 1979a) and mice with up to 2,980 mg/kg/day (NCI 1978).

Ocular Effects. Pupillary constriction and blurred vision were observed in many cases of malathion intoxication (Amos and Hall 1965; Crowley and Johns 1966; Ekin 1971; Jušić and Milić 1978; Matsukawa et al. 1997; Monje Argiles et al. 1990; Rivett and Potgieter 1987; Sudakin et al. 2000). These effects are typical signs of organophosphate poisoning resulting from stimulation of parasympathetic autonomic postganglionic nerves.

The only information regarding ocular effects in animals following oral exposure to malathion is that no significant ocular effects were observed in Fischer-344 rats administered up to 868 mg/kg/day of malathion (97.1% pure) in the diet for 2 years (Daly 1996a) (retinal degeneration has been observed in rats treated long-term with other organophosphates such as fenthion, see Dementi [1993]).

Body Weight Effects. No information was located regarding body weight effects in humans following oral exposure to malathion. Of several studies providing information on body weight in animals after acute oral administration of malathion, only two studies in rats reported significant effects. Ojha et al. (1992) reported a 17% decrease in final weight relative to controls in rats administered approximately 593 mg/kg/day malathion (unspecified purity) in the food for 7 days. This decrease was accompanied by a significant decrease in food consumption; the NOAEL was 451 mg/kg/day. The other study reported a decrease of 22% in body weight gain during pregnancy in rats administered 500 mg/kg/day malathion (98% pure) by gavage on gestation days 6, 10, and 14 (Prabhakaran et al. 1993). In this case, food intake was not affected by treatment with malathion. Other representative acute-duration studies in rats reported NOAELs of 225 mg/kg/day after 6 days gavage administration of malathion, and 286 mg/kg/day after 14 days of administration of malathion in drinking water (Lox 1985). A NOAEL of 715 mg/kg/day (only dose tested) was reported in a study in mice given a single gavage dose of malathion and monitored for 5 days (Rodgers et al. 1986). Administration of 100 mg/kg/day

malathion (98% pure) to mice on lactation days 1–14 had no significant effect on body weight gain (Chhabra et al. 1993).

In intermediate-duration oral studies in rats, the only one that reported a significant effect of malathion on body weight was NCI (1979a) in which female Fischer-344 rats showed a 50% reduction in final body weight after administration of approximately 1,399 mg/kg/day malathion (95% pure) in the diet for 13 weeks; no significant effects were seen in males at this dose level or in females dosed approximately 700 mg/kg/day. No information on food intake was provided in the NCI (1979a) study. Other NOAELs in rats include 75 and 29 mg/kg/day in 90-day (Desi et al. 1976) and 6-week (Foster 1968) dietary studies, respectively, and 20 mg/kg/day in a 20-day gavage study (Krause et al. 1976). A 3–12-week feeding study in mice reported a NOAEL for body weight of approximately 21 mg/kg/day (Banerjee et al. 1998), whereas a NOAEL of 100 mg/kg/day was reported for female mice in a 21-day gavage study (Chhabra et al. 1993). The only significant finding in mice is that dose of approximately 4 mg/kg/day (only level tested) of malathion (95% pure) given in the drinking water to Swiss mice for 15 weeks induced a 23% decrease in body weight gain (Barlas et al. 1996). Without providing quantitative data, the investigators indicated that the mice may have reduced their food and water intake during the study.

Administration of approximately 622 mg/kg/day of malathion (95% pure) to Osborne-Mendel rats in the diet for 80 weeks had no significant effect on body weight (NCI 1978), but dietary doses of approximately 332 mg/kg/day for 103 weeks reduced final body weight of male Fischer-344 rats by more than 10% (NCI 1979a); no significant effects were seen in females. Food intake data were not provided in the latter study. Decreased body weight gain was also reported in male and female Fischer-344 rats administered 359 or 415 mg/kg/day, respectively, of malathion (97.1% pure) in the diet for 2 years (Daly 1996a); no significant effects were observed at 35 mg/kg/day. In the latter study, food intake was not reduced by administration of malathion. Male and female B6C3F_1 mice also showed a reduction in body weight gain after administration of approximately 1,490 mg/kg/day of malathion (95% pure) for 80 weeks (NCI 1978). A similar finding was reported by a Slauter (1994) in male B6C3F_1 mice after dietary administration of 1,476 mg/kg/day malathion (96.4% pure) for 18 months; in this case, the reduced weight gain was associated with a decrease in food intake.

The significance of the reduction in body weight reported in some studies is unknown, but may reflect decreased palatability of the food with added malathion. However, in the chronic study by Daly (1996a), there was reduction of body weight gain in rats without a decrease in food intake. There is no evidence from any other study suggesting that malathion decreases food utilization.

Metabolic Effects. The only study that specifically reported metabolic effects was that of Zivot et al. (1993) in which severe metabolic acidosis was observed in an 80-year-old woman who ingested an unspecified, but fatal, amount of malathion. Anion gap acidosis is common in organophosphate poisoning from poor tissue perfusion (Aaron and Howland 1998). No relevant information was found in animal studies.

Other Systemic Effects. The incidence of pancreatic involvement in malathion intoxication was investigated in 75 patients who ingested unspecified amounts of liquid formulations of the pesticide (Dagli and Shaikh 1983). Serum amylase levels over 500 units (normal range 80–200 units) in 10 patients suggested that these patients had acute pancreatitis, whereas milder elevations in 37 patients suggested mild pancreatic dysfunction; all amylase levels returned to within normal values within 3 days following treatment for organophosphate poisoning. Dagli and Shaikh (1983) stated that the occurrence of pancreatitis was the result of functional ductal obstruction caused by an increase in exocrine flow rate, which is consistent with activation of muscarinic receptors in the pancreas by malathion. The occurrence of pancreatic involvement could not be confirmed by surgery or autopsy because all patients recovered.

Hyperglycemia and/or glucosuria were reported in several cases of acute malathion poisoning (Crowley and Johns 1966; Dive et al. 1994; Healy 1959; Zivot et al. 1993). The exact cause of these findings is unknown.

As previously mentioned, there are some oral studies in animals that provided information on food and/or water consumption during administration of malathion. For example, decreased food intake was reported in rats given 163 mg/kg/day malathion in the diet for 7 days (Ojha et al. (1992) and in water intake when malathion was administered in the drinking water at a target dose of 95 mg/kg/day for 14 days (Lox 1985). A chronic-duration study reported a significant decrease in food consumption in rats fed approximately 1,476 mg/kg/day malathion in the diet for 18 months (Slauter 1994). These effects may reflect aversion to the taste or smell of the diet and have no toxicological significance. There is no evidence that malathion may affect food utilization.

3.2.2.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological effects in humans following oral exposure to malathion. In animals, the effects of malathion on the immune system have been examined in numerous

studies, particularly in rats and mice. When assessing effects on the immune system, it became apparent that a distinction had to be made between a direct action of the pesticide on any component of the immune system and responses that may be mediated indirectly by the pesticide-induced cholinergic stimulation and resulting stress. An early study by Casale et al. (1983) sought to investigate this specific issue. Administration of a single gavage dose of 720 mg/kg of malathion (95% pure) to C57BL/6N mice significantly suppressed the primary IgM response following immunization with sheep red blood cells (SRBC). This dose of malathion, which caused moderate to severe cholinergic signs, also decreased relative spleen weight and the number of viable cells per spleen. When malathion was given in four daily doses of 240 mg/kg/day, a regimen that did not produce cholinergic signs, it did not suppress the primary IgG response to SRBC. Furthermore, results of experiments with a cholinomimetic agent suggested that cholinergic stimulation played a major role in malathion-induced suppression of the primary immune response (Casale et al. 1983).

It is interesting that other studies that used almost the same dose level (715 mg/kg) of malathion (>99% pure) in the same strain of mice did not observe any clinical signs of cholinergic poisoning or reduction of total acetylcholinesterase activity in plasma, but still observed alterations in some immune parameters (Rodgers et al. 1986). In this study, the single 715 mg/kg dose of malathion had no effect on the generation of a cytotoxic T lymphocyte (CTL) response to alloantigen by splenocytes, increased the ability of splenocytes to generate a response to SRBC 5 days after malathion treatment, significantly increased the proliferative response to concanavalin A (Con A) and lipopolysacchraride (LPS), and did not alter thymic lymphocyte number. In contrast, 14 days of daily treatments with 143 mg/kg of malathion had no effect on the response to SRBC or the mitogenic responses to Con A or LPS, but significantly decreased thymic lymphocyte number. This set of experiments pointed out the differences between results from single and repeated dosing. Further studies by Rodgers and coworkers showed that *in vitro* exposure of splenocytes to malathion resulted in a suppression of the proliferative response to Con A and LPS (Rodgers and Ellefson 1990). However, treatment with malathion activated with a crude liver system capable of regenerating reduced nicotinamide adenine dinucleotide phosphate (NADPH) resulted in an unchanged proliferative response. Rodgers and Ellefson (1990) also showed that administration of single doses of 715 or 900 mg/kg malathion to mice significantly elevated respiratory burst activity, a measure of macrophage activation of peritoneal leukocytes following stimulation with 12-phorbol 13-myristate acetate (PMA). However, no such elevation was evident after treatment of the cells *in vitro*, unless malathion had been metabolically activated with the NADPH-regenerating system. Rodgers and Ellefson (1990) concluded that in order for the effects of a compound on the immune response to be examined following *in vitro* exposure, the applicability of this type of exposure to that

class of compound and the necessity for a metabolism system should be determined for each parameter assessed.

The mechanism of malathion-induced macrophage activation has been examined in more detail in recent studies. Using a wide range of doses, Rodgers and Ellefson (1992) observed that peritoneal cells from mice treated with a single dose of 0.25 mg/kg of malathion exhibited an increased respiratory burst activity, as measured by hydrogen peroxide production following stimulation with PMA; there was also an increase in the percentage of degranulated mast cells. The authors suggested that malathion-induced degranulation of mast cells and subsequent release of mast cell inflammatory mediators such as histamine (Rodgers and Xiong 1997b) or arachidonic acid metabolites and tumor necrosis factor (Rodgers and Xiong 1997a) may increase macrophage function. Increased serum levels of histamine occurred in both rats and mice after administration of malathion, and the increase was maximum 4 hours after a dose of 10 mg/kg (Rodgers and Xiong 1997b). In rats, lower and higher doses produced smaller increases, whereas in mice, a significant but smaller increase occurred 8 hours after dosing with 700 mg/kg malathion. Degranulation of mast cells associated with the small intestine was seen in mice after administration of as low as 0.1 mg/kg/day of malathion for 14 days (Rodgers and Xiong 1997d) or 90 days (Rodgers and Xiong 1997c), but differences in tissue sensitivities were apparent. Rodgers and Ellefson (1992) speculated that degranulation of mast cells by malathion may be accomplished by inhibition of an esterase on the surface of the mast cell. Administration of malathion (300 mg/kg) to mast cell-deficient mice reduced macrophage function; however, exposure of mast cell-deficient mice reconstituted with bone marrow-derived mast cells from wild-type mice resulted in enhanced macrophage function and the production of circulating IgM, but not IgG antibodies to SRBC on days 3 and 5 after immunization (Rodgers et al. 1996). This suggested that the presence of mast cells is necessary for the increase in macrophage function and humoral immunity observed after the administration of malathion.

Intermediate-duration studies by Banerjee et al. (1998) provide comparative information on the effects of non-cholinergic doses of malathion on the humoral and cell-mediated immune responses in rats, mice, and rabbits. Humoral immune responses were assessed by measuring IgM and IgG concentrations, antibody titer against antigens (SRBC, tetanus toxoid, ovalbumin), and splenic plaque forming cells (PFC). The cell-mediated immune (CMI) response was studied by using the leucocyte migration inhibition (LMI) and macrophage migration inhibition (MMI) tests. Male Wistar rats were treated with malathion (>99% pure) in the diet (approximately 2.3, 5.8, or 11.5 mg/kg/day) for 8–22 weeks. There was no effect on thymus weight, but relative spleen weight was significantly decreased at 22 weeks in the mid- and high-dose rats that were immunized with ovalbumin or tetanus toxoid. There was no effect on

serum IgG or IgM levels; however, malathion (11.5 mg/kg/day) significantly attenuated the normal increase in IgG level that occurs after administration of the antigens tetanus toxoid and ovalbumin. The IgM fraction after antigen stimulation was not affected. Antibody titers against tetanus toxoid and ovalbumin were significantly decreased in high-dose rats throughout the study and in the mid-dose rats after 22 weeks. The MMI response in ovalbumin immunized rats was significantly decreased in mid- and high-dose rats in a time-related manner. Rats exposed to malathion and immunized with ovalbumin or tetanus toxoid showed a significant decrease in LMI response especially with the high dose and at longer times with the mid-level dose. Mild lymphoid depletion of the spleen was described in another intermediate-duration study in rats treated with 130 mg malathion/kg/day for 6 weeks, whereas marked depletion occurred at 390 mg/kg/day (Piramanayagam and Manohar 2002).

Male Hissar mice received malathion (approximately 4.2, 10.5, or 21 mg/kg/day) in the diet for 3–12-weeks (Banerjee et al. 1998). Mice exposed to 10.5 mg/kg/day malathion for 12 weeks and immunized with SRBC showed a significant decrease in relative spleen weight. There was no significant change in thymus weight. Malathion did not significantly alter levels of IgG or IgM. Exposure to 21 mg/kg/day for 3 weeks did not alter primary antibody titer against SRBC, but significantly decreased the secondary antibody titer against SRBC throughout the experiment. Serum antibody titer to ovalbumin was also decreased in high-dose mice after 8 weeks of exposure to malathion. Exposure to the high-dose for 3 weeks caused a reduction in the PFC response only after secondary immunization, but exposure to 10.5 or 21 mg/kg/day for more than 6 weeks caused a dose-related decrease in PFC response after both primary and secondary immunization. Exposure to malathion (mid- and high-dose) produced a marked decrease in the MMI response to ovalbumin and tetanus toxoid immunization. In male New Zealand rabbits treated by gavage with 0.5 or 2.5 mg/kg/day malathion for 21 days, there was no significant effect on serum IgG or IgM levels. High-dose rabbits showed a significant decrease in antibody titer to ovalbumin after 7 and 11 weeks of primary immunization (5 and 9 weeks after secondary immunization, or 3 and 7 weeks after tertiary immunization) with the antigen. No effect was seen with the low-dose. Rabbits exposed to malathion for 15 weeks and immunized with ovalbumin or tetanus toxoid showed a significant decrease in LMI response after 7 weeks of antigen.

The effects of a commercial malathion formulation (50% malathion) on the immune system of female SJL/J mice was investigated by Johnson et al. (2002). The mice were gavaged with 0, 0.018, 7.2, or 180 mg of malathion/kg on alternate days for 28 days. Malathion did not stimulate cholinergic activity as monitored by the lack of significant change in brain acetylcholinesterase activity. The only significant effect observed was a significant enhancement of the primary IgM response to SRBCs when the response

was expressed per viable spleen cells or per spleen; the increases appeared similar with the three doses tested and no dose-response was apparent. Malathion did not affect splenic cellularity or the viability of the splenocytes. Furthermore, lymphocyte blastogenesis was not affected and there was no significant effect on Con A- or phytohemagglutinin-induced T-lymphocyte proliferation or LPS-induced B-lymphocyte proliferation.

Chronic-duration studies in rats administered up to approximately 622 mg/kg/day of malathion for 80 weeks (NCI 1978) or 332 mg/kg/day for 103 weeks (NCI 1979a) or in mice given up to approximately 2,980 mg/kg/day for 80 weeks (NCI 1978) reported no significant treatment-related alterations in the gross or microscopical appearance of lymph nodes or the spleen; no functional immunological end points were evaluated in these studies.

Overall, the findings in animal studies suggest that malathion has at least a modulatory effect on some immune parameters and that this can occur at relatively low doses. However, as Rodgers and Ellefson (1992) stated, the physiological significance of alterations in respiratory burst and mast cell degranulation of the magnitude observed are unknown. Nevertheless, these findings could explain the symptoms of rashes and irritation of mucous membranes reported by individuals following exposure to malathion and suggest that these responses may be systemic in nature rather than localized. Results from animal studies also warned about extrapolating data obtained from *in vitro* studies to *in vivo* situations (Rodgers and Ellefson 1990) and from one animal species to another (Banerjee et al. 1998).

3.2.2.4 Neurological Effects

Several reports of accidental or intentional ingestion of malathion formulations, some with fatal consequences, were located. In all cases, the patients showed many of the characteristic signs of organophosphate poisoning (i.e., excessive salivation, lacrimation, abdominal cramps and diarrhea, pupillary constriction, nausea, respiratory distress, fasciculations). Cholinesterase levels were measured in many of these cases. Both RBC cholinesterase and plasma cholinesterase activity levels ranged from undetectable to 70–90% inhibition shortly after poisoning (Choi et al. 1998; Dive et al. 1994; Jušić and Milić 1978; Lee and Tai 2001; Matsukawa et al. 1997; Namba et al. 1970; Sudakin et al. 2000). Doses of malathion could be estimated to have been between 214 and 2,000 mg/kg, but dose-response relationships could not be established with this set of studies. Treatment with cholinesterase-reactivating agents reversed the enzyme inhibition to various degrees in some but not all cases.

Neurophysiological assessments were performed in some case reports. For example, electromyography testing demonstrated neuromuscular blockage in case reports described by Crowley and Johns (1966), but not in a case described by Jušić and Milić (1978); in the latter case, neither motor nor sensory peripheral nerve conduction velocities were significantly altered. Slightly reduced motor nerve conduction velocity was reported by Dive et al. (1994) in a case when measured 10 days following the poisoning episode.

Acute sensorimotor distal axonal polyneuropathy was described in a case by Monje Argiles et al. (1990). The alterations consisted of mild reductions of most compound muscle and sensory nerve action potential amplitudes, slightly prolonged sensory distal latencies, and mildly slowed nerve conduction velocities. This was accompanied by morphological evidence of denervation and reinnervation of the gastrocnemius muscle and degenerating axons from the sural nerve. In both the Monje Argiles et al. (1990) and Dive et al. (1994) cases, isopropylmalathion was found in relatively large quantities in the formulation ingested.

Several cases on intermediate syndrome were described following malathion intoxication (Benslama et al. 1998; Choi et al. 1998; Lee and Tai 2001; Sudakin et al. 2000). The intermediate syndrome is termed as such because it occurs in the time interval (24–96 hours) between the end of the acute cholinergic crisis and the usual onset of delayed neuropathy and it is thought to be due to persistent cholinesterase inhibition leading to combined pre- and postsynaptic impairment of neuromuscular transmission (De Bleecker 1995; De Bleecker et al. 1992). Clinically, it was characterized by weakness in the territory of several motor cranial nerves, weakness of neck flexors, proximal limb muscles, and respiratory paralysis. Healy (1959) described the case of an 18-month-old boy who developed flaccid paralysis involving the lower and upper limbs 3 days after malathion intoxication that lasted for several weeks.

Worth noting separately is a controlled dosing study conducted by Moeller and Rider (1962) in volunteers. The study was conducted in three phases. In the first phase, five male volunteers were administered daily capsules containing malathion (purity not reported) in corn oil that provided an approximate dose of 0.11 mg malathion/kg/day for 32 days. In the second phase, which started 3 weeks after the first phase had terminated, five male volunteers received daily capsules with malathion providing about 0.23 mg malathion/kg/day for 47 days. In the third phase, five new subjects received approximately 0.34 mg malathion/kg/day for 56 days. Plasma and RBC cholinesterase was determined twice weekly before, during, and after administration of malathion. Administration of 0.11 mg malathion/kg/day for 32 days or 0.23 mg/kg/day for 47 days did not produce any significant depression of plasma or RBC cholinesterase activity nor did it induce clinical signs. In phase three, 0.34 mg malathion/kg/day for 56 days caused a maximum depression of 25% in plasma cholinesterase

approximately 3 weeks after cessation of treatment. A similar depression in RBC cholinesterase was observed, but occurred later. No clinical signs were seen in the volunteers in phase three. The NOAEL of 0.23 mg/kg/day was used to derive an intermediate-duration oral MRL of 0.02 mg/kg/day.

Many studies have evaluated the effects of oral administration of malathion on neurological end points in animals. End points examined include activity of plasma, RBC and/or brain cholinesterase as an indicator of potential neurological effects, neurophysiological effects, occurrence of clinical signs, and morphological effects. Some representative examples are summarized below.

Effects on Cholinesterase Activity. In rats, single dose studies have reported 37% inhibition for plasma cholinesterase after a dose of 500 mg/kg malathion (96% pure) (Enan 1983) and 11–48% inhibition in female rats administered a range of 500–2,000 mg/kg malathion (96.4% pure) (Lamb 1994a), although the magnitude of the inhibition was not dose-related. Also, no significant inhibition was detected in male rats with that same dose range (Lamb 1994a). A 34% inhibition was reported for RBC cholinesterase in female rats given 1,000 mg/kg malathion and 39% with 2,000 mg/kg (Lamb 1994a). Brain cholinesterase appears much less susceptible, as a 2,000 mg/kg dose of malathion had no significant effect on the enzyme activity in either male or female rats (Lamb et al. 1994a). However, a 2,000 mg/kg dose of 88% pure malathion decreased brain cholinesterase activity 44%, suggesting a possible role for malathion impurities. A similar pattern can be seen in intermediate-duration studies in rats. For example, Lamb (1994b) found that in female rats (effects were similar in males), a dose of 395 mg/kg/day malathion (96.4% pure) for 90 days caused a 15–30% decrease in plasma cholinesterase activity, a 49–53% decrease in RBC cholinesterase, and a 12–20% decrease in brain cholinesterase; no significant effects were seen at 4 mg/kg/day. Similar observations were made by Husain et al. (1987) in a 32-day study. In a chronic-duration study, after 24 months of treatment, plasma and RBC were inhibited 12–29% with doses between 29 and 35 mg/kg/day malathion, whereas brain cholinesterase was only inhibited 1–3% (Daly 1996a); the NOAEL was 2 mg/kg/day for males and 3 mg/kg/day for females. The NOAEL for males was used to derive a chronic-duration oral MRL of 0.02 mg/kg/day.

Acute studies in mice also suggest that brain cholinesterase is less susceptible than plasma or RBC cholinesterase to inhibition by malathion, but the differential susceptibility seems to be less marked than in rats. For example, a single dose of 720 mg/kg of malathion (only dose level tested) diminished the activities of plasma, RBC, and brain cholinesterase by 41, 47, and 36%, respectively, 6 hours after treatment (Casale et al. 1983). The corresponding percent inhibition after four doses of 240 mg/kg/day was 47, 59, and 15% (Casale et al. 1983). The same trend was seen in an 18-month study in mice in

which doses of 143 mg/kg/day of malathion inhibited plasma, RBC, and brain cholinesterase activities by 24, 44, and <10%, respectively (Slauter 1994).

In rabbits, maximum decreases in cholinesterase activity of 50–60% occurred in the cerebral right and left frontal lobes, cerebellum lateralis, and cerebellum flocculus 5 days after a single gavage dose of 188 mg/kg (only dose tested) of technical-grade malathion (Vijayakumar and Selvarajan 1990). Another study in rats reported dos- related inhibition of RBC and plasma cholinesterase after single doses of between 12 and 1,200 mg/kg of malathion (95% pure) (Weeks et al. 1977). Six hours after dosing, RBC cholinesterase inhibition ranged from 10% with the lowest dose to 79% with the highest dose. In dogs, doses of 125 mg/kg/day (the lowest dose tested) of malathion (92.4% pure) inhibited plasma cholinesterase by more than 20% and RBC cholinesterase by 17% after 28 days of treatment (Fischer 1988). A longer-duration study in dogs reported no significant inhibition of plasma cholinesterase and a 20% inhibition of RBC cholinesterase with 5.3 mg/kg/day (the highest dose tested) of malathion (98% pure) for 6 weeks (Frawley et al. 1957); there was no significant inhibition of RBC cholinesterase activity with 2.1 mg/kg/day malathion.

Neurophysiological and Neurobehavioral Effects. Ehrich et al. (1993) evaluated rats with a functional observation battery (FOB) that tested behavioral and central nervous system excitability, autonomic effects, muscle tone and equilibrium, and general physiology 7, 14, and 21 days after administering a single gavage dose of 600, 1,000, or 2,000 mg/kg malathion (88% pure). Significant changes occurred mostly in the examination 21 days after dosing and were mostly indicative of increased excitability, as for example, spontaneous motor activity was increased. There seemed to be no significant effects on autonomic functions. A similar study was conducted by Lamb (1994a) who found somewhat different results. Rats treated once with 500–2,000 mg/kg malathion (96.4% pure) and tested on a FOB 15 minutes and 7 and 14 days postdosing showed no significant alterations with the possible exception of decreased motor activity in the high-dose group. Results from a 90-day feeding study showed no significant effects of treatment with malathion (96.4% pure) doses between 4 and 1,575 mg/kg/day on parameters of a FOB or on motor activity (Lamb 1994b), tests were conducted on weeks 3, 7, and 13. In contrast, another 90-day feeding study reported changes indicative of increased excitability in the electroencephalogram (EEG) and EMG in rats after dosing with 75 mg/kg/day malathion (95% pure); doses of 38 mg/kg/day had no significant effects (Desi et al. 1976). In the latter study, rats from both dose groups made more errors than controls in a maze learning experiment.

Clinical Signs. Frank signs of cholinergic stimulation have been reported in many studies following short- and long-term exposure to malathion. For example, rats from all dosed groups (500–2,000 mg/kg/day) in the Lamb (1994a) acute study showed clinical signs of organophosphate intoxication. This was also seen in the 90-day feeding study in rats administered approximately 1,500 mg/kg/day malathion (Lamb 1994b). Convulsions, tremor, and ataxia were reported among pregnant rats after each of five gavage treatments with 827 mg/kg/day malathion (98% pure); the NOAEL was 138 mg/kg/day (Mathews and Devi 1994). Feeding a diet that provided 411 mg/kg/day of malathion (unspecified purity) to rats for 7 days resulted in dizziness, recurrent convulsions, and tremors; no significant effects were seen at 163 mg/kg/day (Ojha et al. 1992). Tremors, fasciculations, and excessive salivation were seen in mice following administration of a single 720 mg/kg dose of malathion (95% pure) (Casale et al. 1983), but no such signs were seen after a single dose of 715 mg/kg or 14 doses of 143 mg/kg/day of recrystallized malathion (>99% pure) (Rodgers et al. 1986). Also, generalized body tremors were seen in mice treated with approximately 2,980 mg/kg/day malathion from week 71 to 79 in an 80-week feeding study (NCI 1978); no tremors were seen in rats dosed with approximately 1,490 mg/kg/day.

Morphological Effects. Limited information was found regarding morphological changes in the nervous system after exposure to malathion. A single dose of up to 2,000 mg/kg of malathion (88% pure) caused no neuropathologic lesions in segments of the medulla, cervical and lumbar spinal cord, branches of the tibial nerve, and cerebellum from rats sacrificed 21 days after dosing (Ehrich et al. 1993). However, brain congestion, neuronal degeneration, and gliosis was seen in the brain of rats during the first few days after administration of a single dose of 1,950 mg/kg of malathion (Piramanayagam et al. 1996). Without providing much detail, the latter authors stated that both gross and microscopical changes appeared reversible, which could explain the apparent lack of lesions in the Ehrich et al. (1993) study. Histological sections of the brain from male Wistar rats treated with ≥130 mg malathion/kg/day (purity unspecified) for 6 weeks showed neuronal degeneration, gliosis, perivascular cuffing, necrosis, and hemorrhages (Piramanayagam and Manohar 2002). These lesions appeared to be reversible after a 6-week post-treatment recovery period. No gross or microscopic lesions were seen in the brains from rats administered up to 622 mg/kg/day malathion for 80 weeks (NCI 1978) or 332 mg/kg/day for 103 weeks (NCI 1979a), or from mice given up to 2,980 mg/kg/day for 80 weeks (NCI 1978).

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to malathion. Several studies are available that provide information on the reproductive effects of malathion in animals after oral exposure; most of them have been conducted in rats.

Effects in Males. The effect of malathion on spermatogenesis was examined in juvenile Wistar rats by Krause et al. (1976). Rats were sacrificed at various times up to the 50th day of life following two single gavage doses of 40 mg/kg/day of malathion (unspecified purity) on the 4th and 5th day of life, and the testes were examined. According to the authors, significant findings included a slight reduction in the number of Sertoli and Leydig cells on the 6th day, reduction of spermatogonia on days 6 and 12, and reduction of pachytene spermatocytes on day 18. All abnormalities disappeared by day 50. Seven daily gavage doses of 20 mg/kg/day of malathion over a 14-day period given to adult male Wistar rats did not induce any histological alterations in the spermatogenic epithelium and had no significant effect on serum levels of luteinizing hormone (LH) or testosterone, but increased serum FSH (Krause 1977). A higher dose of 163 mg/kg/day of malathion (unspecified purity) given mixed in the food for 7 days to Wistar rats damaged the seminiferous tubules and produced an abnormal pattern of Sertoli cells; no significant alterations were seen with 18.5 mg/kg/day (Ojha et al. 1992). A considerably higher gavage dose of 1,950 mg/kg of malathion (95% pure) given once to 8-week-old male Wistar rats reduced the number of germinal layers and produced degeneration and necrosis of gonocytes in the seminiferous tubules during the first 3 days after dosing (Piramanayagam et al. 1996). These alterations appeared mild by the 6th day and almost all tubules showed spermatogenic activity by day 12.

Edema, congestion, and desquamation of lining cells of the seminiferous epithelium were observed in rats gavaged daily for 12 weeks with 45 mg/kg/day of malathion (unspecified purity) (Balasubramanian et al. 1987a). The same treatment also resulted in lower pH of the seminal fluid, decreased testicular protein, decrease relative testis weight, decreased activities of testicular LDH, AP, and acid phosphatase, and no change in AST or ALT activities (Balasubramanian et al. 1987b). Without providing details, the investigators indicated that all the changes seemed to be at least partially reversible over a 2-week post-dosing period. Wistar rats treated with 390 mg malathion/kg/day (purity unspecified) for 6 weeks had a reduction in the number of germinal layers in the testes, accumulation of eosinophilic cellular debris in the lumen of the seminiferous tubules, and intertubular edema (Piramanayagam and Manohar 2002); these changes appeared reversible after a 6-week post-treatment recovery period. No treatment-related gross or microscopical alterations were seen in the prostate or testis from rats administered up to 622 mg/kg/day of

malathion (95% pure) in the diet for 80 weeks (NCI 1978) or 332 mg/kg/day for 103 weeks (NCI 1979a), or in mice administered up to 2,980 mg/kg/day for 80 weeks (NCI 1978).

Effects in Females. Administration of 827 mg/kg/day malathion (98% pure) to pregnant Sprague-Dawley rats on Gd 6–13 induced abortions after the 5th dose, but this dose level also induced lethality among the dams (Mathews and Devi 1994). A slight but significant decrease in the number of implants was observed on Gd 20 in Sprague-Dawley rats administered doses of 500 mg/kg/day of malathion (98% pure) on Gd 6, 10, and 14; this level of malathion exposure also reduced maternal body weight gain by 22% (Prabhakaran et al. 1993). However, a similar study in which Sprague-Dawley rats were administered 800 mg/kg/day malathion (94% pure) on Gd 6–15 found no effects on the number of implantations or resorptions upon examination on Gd 20 (Lochry 1989). A study in rabbits treated with 25, 50, or 100 mg/kg/day malathion (92.4% pure) on Gd 6–18 reported an increase in the number and percent on resorptions sites/doe at ≥50 mg/kg/day; there were no effects on fertility, number of corpora lutea, or implantation sites (Siglin 1985). It should be noted that body weight gain was also decreased at ≥50 mg/kg/day. Treatment of female Sprague-Dawley rats with 50 mg/kg/day of malathion (unspecified purity) for 3 months prior to mating and during Gd 1–20 did not affect the ability to mate or conceive or the number of total implants or number of implants per dam (Lechner and Abdel-Rahman 1984). No reproductive toxicity was reported in a 2-generation study in Sprague-Dawley rats (Schroeder 1990). In this study, male and female rats (F0) were administered 612 and 703 mg/kg/day malathion (94% pure), respectively, for 63 days before mating, after which time, the rats were mated to produce the F1A litters. After weaning, F0 rats were mated again to produce the F1B litters. F1B males and females were treated for 79 days before mating twice to produce F2A and F2B litters. Parameters examined included reproductive performance, fertility indices, and gestation length.

Limited information exists on the effects of malathion on the histology of female reproductive organs. An acute study observed disquamation of cells lining the ovary, absence of grafian follicle, distortion of the uterine epithelium, and enlargement of the tubular uterine glands in Wistar rats that received approximately 163 mg/kg/day of malathion (unspecified purity) in the diet for 7 days (Ojha et al. 1992); no significant effects were seen at 18.5 mg/kg/day. An intermediate-duration study reported no significant histopathological alterations in the ovaries from rats given 10 mg/kg/day of malathion (94% pure) by gavage for 15 weeks (Ozmen and Akay 1993). In chronic-duration studies, no significant histopathological alterations were seen in the mammary gland, uterus, or ovaries from rats following dietary administration of up to 622 mg/kg/day malathion (95%) for 80 weeks (NCI 1978) or 332 mg/kg/day for 103 weeks (NCI 1979a). However, increased incidence of cystic endometrial

hyperplasia was seen in B6C3F_1 mice administered 1,490 mg/kg/day malathion (95% pure) for 80 weeks (NCI 1978).

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to malathion. The developmental toxicity of malathion has been investigated primarily in rats, although some information is also available in mice and rabbits.

Embryotoxicity. In acute studies in rats, embryotoxicity was evident only in a study by Prabhakaran et al. (1993) who reported a reduction in the number of live fetuses per litter and reduced fetal weight in Sprague-Dawley rats treated with 500 mg/kg/day (only level tested) malathion (98% pure) on Gd 6, 10, and 14. It should be noted, however, that treated dams gained significantly less weight during pregnancy than controls. No embryotoxicity was observed in Wistar rats treated with 100 mg/kg/day malathion (unspecified purity) on Gd 6–15 (Khera et al. 1978) or in Sprague Dawley rats treated with 800 mg/kg/day malathion (94% pure) also on Gd 6–15 (Lochry 1989). Reduced fetal weight and crown-rump length were seen in mice gavaged once on Gd 6 with 125 mg/kg malathion (unspecified purity) and examined on Gd 15; however, no information was provided on maternal effects (Asmatullah et al. 1993). Two studies in rabbits provided no evidence of embryotoxicity following gavage administration of 100 mg/kg/day malathion on Gd 7–12 (Machin and McBride 1989a) or Gd 6–18 (Siglin 1985).

Increased neonatal mortality (days 7 and 21 after birth) was reported in Wistar rats following maternal exposure to 240 mg/kg/day malathion (95% pure) in the diet for at least 5 months starting before mating (Kalow and Marton 1961). It is unclear, however, whether the rats were exposed during gestation. Furthermore, no information was provided regarding maternal effects. Schroeder (1990) conducted a 2-generation study in Sprague-Dawley rats in which the animals were administered malathion (94% pure) in the diet at various levels between 43 and 703 mg malathion/kg/day. The only developmental effect noticed was a decrease in body weight gain in pups from the F1A and F2B litter during the lactation period at parental doses of 394 mg/kg/day for males and 451 mg/kg/day for females. The corresponding NOAELs were 131 and 153 mg/kg/day. In this study, there were no significant effects on clinical signs, growth before mating, food consumption, or maternal weight gain during gestation.

Teratogenicity. Acute studies in rats found no teratogenic effects of malathion after gavage administration of doses of 300 mg/kg/day on Gd 6–15 (Khera et al. 1978), 500 mg/kg/day on Gd 6, 10, and 14 (Prabhakaran et al. 1993), or 800 mg/kg/day on Gd 6–15 (Lochry 1989). No teratogenic effects were seen in rabbits given up to 100 mg/kg/day malathion on Gd 6–18 (Siglin 1985). No teratogenic effects were observed in rats administered 50 mg/kg/day malathion for 3 months prior to mating and during gestation (Lechner and Abdel-Rahman 1984) or in the 2-generation study by Schroeder (1990) summarized above.

Other Effects. Administration of technical malathion (98% pure) by gavage (0, 138, 276, or 827 mg/kg) from Gd 6 through 13 to Sprague-Dawley rats resulted in inhibition of brain cholinesterase in a dose-dependent manner both in dams and pups on postnatal day 21 (Mathews and Devi 1994). The extent of inhibition was similar in dams and pups and was approximately 14, 37, and 47% in the low-, mid-, and high-dose groups, respectively. Also, treatment with malathion significantly increased the activities of carboxylesterase, glutathione-S-transferase, and cytochrome P-450 content in the liver from both dams and pups. Malathion also reduced the glutathione content and the activities of glutathione reductase and glutathione peroxidase and increased lipid peroxide content in the liver from both dams and pups. A study in rabbits administered 126 mg/kg/day malathion on Gd 28–30 and killed after the last dose reported a decrease between 54 and 79% in fetal plasma cholinesterase activity and between 60 and 66% in fetal brain cholinesterase (Machin and McBride 1989b). An additional study in mice administered 30 or 100 mg/kg malathion (98% pure) by gavage in corn oil from day 1 to day 14 of lactation (Ld) found that glutathione-S-transferase activity was increased in the liver from male pups from both treated groups and in high-dose female pups (Chhabra et al. 1993). Glutathione reductase activity was increased only in high-dose male pups. Glutathione peroxidase activity was significantly increased (dose-related) in both dose groups of pups. These changes in pups' liver followed the same trend as in maternal liver (see Hepatic Effects) except for glutathione reductase activity.

Based on the available information, malathion is not a developmental toxicant when administered at doses that do not cause maternal toxicity.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located regarding cancer in humans following oral exposure to malathion, but several bioassays have been conducted to examine the carcinogenicity of malathion in animals.

NCI (1978) did an 80-week study in Osborne-Mendel rats administered malathion (95% pure) in the diet at approximate doses of 0, 359, and 622 mg/kg/day. In addition to a matched controls group, the study used pooled controls, which included controls used in assays for other pesticides. Most tissues and organs were examined microscopically from animals that died early, and at the end of the study. Higher incidences of proliferative lesions in the thyroids were observed in treated rats compared with matched controls. No statistically dose-related trends of differences from controls (either matched or pooled) were found for C-cell (parafollicular cells) or follicular cell adenomas or carcinomas in male rats. In females, the combined incidence of follicular cell adenoma and carcinoma in the high-dose group was 4/49 (8%) versus none in either set of controls. The Cochran-Armitage test indicated a significant positive linear trend (p=0.026) in incidence using pooled controls, but the Fisher Exact test was not significant. No other tumor appeared in the rats at any site in statistically significant incidences. It was concluded that under the conditions of the assay, there was no evidence of carcinogenicity attributable to malathion in Osborne-Mendel rats. A study was also conducted in Fischer-344 rats administered malathion (95% pure) in the diet at approximate dose levels of 0, 166, or 332 mg/kg/day for 103 weeks (NCI 1979a). Administration of malathion resulted in a variety of neoplasms in both control and dosed animals, with the exception of adrenal pheochromocytomas in male rats, which not believed to be compound-related. The incidences of adrenal pheochromocytomas were 2/49 (2%), 11/48 (23%), and 6/49 (12%) in controls, low-dose, and high-dose rats, respectively. The result of the Fisher Exact test for the low-dose group relative to the controls was significant (p=0.006), but the high-dose group was not. The result of the Cochran-Armitage test also was not significant. A lower incidence of leukemia and of carcinomas of the pituitary was observed in male rats, which according to the authors, may have accounted for the shorter survival of the dosed animals compared to controls. The conclusion was that under the conditions of the study, malathion was not carcinogenic for Fischer-344 rats of either sex, but females may have not received the maximum tolerated dose.

More recent information is provided by a study by Daly (1996a), also in Fischer-344 rats, that used a wider dose range. In this 2-year study, four dose levels of 2–868 mg/kg/day were used in addition to controls. Administration of malathion (97.1% pure) significantly increased mortality in males at 359 mg/kg/day and in both sexes at the highest dose levels, 739 mg/kg/day for males and 868 mg/kg/day

for females. The combined incidences of liver adenomas and carcinomas in females were 0, 3.6, 3.6, 5.5, and 10.9%. The incidence of hepatocellular carcinoma was not significantly increased at any dose level in females. Because the incidence at 868 mg/kg/day was statistically significant by pair wise comparison, there was a statistical trend, and was outside the range of both the testing facility and NTP (National Toxicology Program) historical control databases, it was concluded that at 868 mg/kg/day, there was evidence of carcinogenicity in female rats. A very small number of nasal tumors in males and females and of oral cavity tumors in females was observed, but it could not be determined whether these tumors were treatment-related or due to random occurrence. Other tumors that were considered not attributable to treatment with malathion included thyroid follicular cell tumors and C-cell tumors observed in male rats, pituitary tumors in females, uterine tumors, testicular tumors, and incidence of mononuclear cell leukemia.

NCI (1978) also tested $B6C3F_1$ mice in the 80-week dietary study. Mice were administered a diet that provided approximately 0, 1,490, or 2,980 mg/kg/day of 95% pure malathion. There were no statistically significant incidences of any tumors in female dosed groups when compared with those of either set of matched or pooled controls. In males, the combined incidence of hepatocellular carcinoma and neoplastic nodules showed a significant linear trend when either the matched controls ($p=0.041$) or pooled controls ($p=0.019$) were used. Separately, these incidences were not statistically significantly greater in either treated group compared with either control. The Fisher Exact test for the comparison between high-dose (17/49) and pooled control groups had a p value of 0.031. However, the authors indicated that when time-adjusted analysis was performed, eliminating the male mice that died before 52 weeks on study, the following incidences resulted: matched controls, 2/9 (22%), pooled controls, 8/48 (17%), low-dose, 7/47 (15%), and high-dose, 17/49 (35%). Neither the Fisher Exact test nor the Cochran-Armitage test of the time-adjusted incidences are significant ($p>0.05$) when the matched controls are used. NCI (1978) concluded that under the conditions of the assay, there was no clear evidence of the association of the tumor incidence with the administration of malathion in $B6C3F_1$ mice. The NCI (1978) bioassay in $B6C3F_1$ mice was repeated by Slauter (1994) in a study that included four treatment levels of malathion (96.4% pure) from 17.4 to 3,448 mg/kg/day in addition to controls. Administration of malathion had no significant effect on mortality. Both male and female mice showed a treatment-related increase in the incidence of hepatocellular tumors at the two highest dietary levels of malathion. In males, the percent incidences of hepatocellular adenomas were 1.9, 7.3, 3.6, 21.8, and 94.1%; the incidences of liver carcinomas were 0, 10.9, 5.5, 10.9, and 2.0%; the combined incidences were 1.9, 18.2, 9.1, 32.7, and 96.1%. Analysis of these data for males showed that there was a positive dose trend. The corresponding incidences of hepatocellular adenomas for females were 0, 1.8, 0, 17, and 80.8; the incidences for liver

carcinomas were 1.8, 0, 3.7, 1.9, and 3.8%; and the combined incidences were 1.8, 1.8, 3.7, 18.9, and 84.6%. As with males, there was a positive dose trend. Examination of the nasal tissues showed no evidence of carcinogenic response. It was concluded that there was evidence of carcinogenicity in both sexes at the two highest doses tested, 1,476 and 2,978 mg/kg/day for males and 1,707 and 3,448 mg/kg/day for females.

The active metabolite of malathion, malaoxon, also has been tested for carcinogenicity in rats and mice. In the NCI (1979b) study, male and female Fischer-344 rats were administered malaoxon in the diet (approximately 0, 41, and 82 mg/kg/day) and to male and female B6C3F_1 mice (approximately 0, 91, and 182 mg/kg/day) for 103 weeks. The only possibly carcinogenic response seen was the incidence of C-cell adenomas and carcinomas of the thyroid among treated female rats. However, comparison of the incidences in treated rats with historical controls precluded relating the incidence of the tumors seen in the study to administration of malaoxon. NCI (1979b) concluded that under the conditions of the study, malaoxon was not carcinogenic to Fischer-344 rats or B6C3F_1 mice. A more recent study in male and female Fischer-344 rats administered one of three dietary levels of malaoxon in the range of 1–141 mg/kg/day for 103 weeks found no treatment-related neoplasia (Daly 1996b).

In response to increased concern about the widespread use of malathion in agriculture, the NTP, in consultation and agreement with NCI, reevaluated the histopathology of the NCI studies on malathion in Osborne-Mendel rats (NCI 1978) and Fischer-344 rats (NCI 1979a), and of malaoxon on Fischer-344 rats (NCI 1979b). The results of the reevaluation confirmed the original conclusions of NCI regarding the lack of carcinogenicity of malathion in rats (Huff et al. 1985), and slightly modified the original interpretation for the C-cell neoplasms of the thyroid in the malaoxon study by concluding that there was equivocal evidence of carcinogenicity for male and female Fischer-344 rats (Huff et al. 1985).

CEL values from each reliable study in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.3 Dermal Exposure

As stated in the introduction to Section 3.2.1, Inhalation Exposure, occupational exposure to malathion involves mostly exposure by the inhalation and dermal routes, but the contribution of each specific route is impossible to ascertain, especially if it is not known whether or not workers were using protective clothing or masks. This section includes summaries of studies in which direct skin contact was explicitly

suggested by the study authors as being the primary route of exposure. However, the reader should keep in mind that considerable dermal absorption may have also occurred in many studies summarized in Section 3.2.1.

3.2.3.1 Death

A large study of 7,500 workers in 1976 in Pakistan who sprayed various malathion formulations reported that at least five workers (two mixers and three sprayers) died, probably as a result of exposure to the pesticide (Baker et al. 1978). Poor work practices (e.g., wearing clothing soaked with pesticide for several days without washing, mixing chemicals with bare hands) resulted in excessive skin contact and absorption of the pesticide through the skin. Baker et al. (1978) estimated that the daily dermal exposure for the spraymen was 330 mg of malathion. Isomalathion, an inhibitor of carboxylesterase and therefore a synergist for malathion, was suspected to be a major contributor in the toxicity of at least two of three formulations used. Ramu et al. (1973) reported the death of a 9-year-old child 5 days after exposure to malathion through a hair wash containing 50% malathion in xylene. No other studies describing death specifically linked to dermal exposure were found.

A dermal LD_{50} of >4,444 mg/kg was reported in Sherman rats for malathion (Gaines 1960). Application of a single dose of 4,444 mg/kg of a 57% emulsifiable concentrate of malathion in xylene to a clipped area of the back resulted in the death of 4 out of 10 males within 1 hour of dosing (Gaines 1960, 1969). The only additional information available regarding dermal lethality is from a 30-day intermediate-duration study in male guinea pigs in which application of 200 mg/kg/day of malathion (98% pure) in acetone to a 36 cm^2 clipped area of the skin killed 4 out of 10 animals during days 20–30 (Dikshith et al. 1987). Signs of toxicity before dying included tremors, dyspnea, salivation, convulsions, and paralysis of the hind limbs. The lethality values from these two studies are presented in Table 3-3.

3.2.3.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-3. No studies were located regarding cardiovascular, gastrointestinal, or musculoskeletal effects in humans or animals following dermal exposure to malathion.

Table 3-3 Levels of Significant Exposure to Malathion - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form
ACUTE EXPOSURE								
Death								
Rat (Sherman)	once					4444 M mg/kg/day	(4/10 males died)	Gaines 1960
Systemic								
Human	5-10 min	Ocular	21 M mg/m³	85 M mg/m³	(slight conjunctival irritation)			Golz 1959
Immuno/ Lymphoret								
Rat (Sprague- Dawley)	once			2 F mg/kg/day	(increased serum histamine levels 4 hours after dosing)			Rodgers and Xiong 1997b
Mouse (BALB/c)	2 d 1 x/d		148 F mg/kg/day					Cushman and Street 1983
Mouse (C57BL/ 6N)	once		2 F mg/kg/day	20 F mg/kg/day	(increased serum histamine levels 4 hours after dosing)			Rodgers and Xiong 1997b
INTERMEDIATE EXPOSURE								
Death								
Gn Pig (NS)	30 d 1 x/d					200 M mg/kg/day	(4/10 died during days 20-30)	Dikshith et al. 1987
Systemic								
Rat (Long- Evans)	4 wk 5 d/wk (topical)	Ocular		500 M mg/kg/day	(mild eye irritation)			Boyes et al. 1999
		Bd Wt	500 M mg/kg/day					

Table 3-3 Levels of Significant Exposure to Malathion - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL				Reference Chemical Form
				Less Serious		Serious		
Systemic								
Rabbit (New Zealand)	3 wk 5 d/wk 6 hr/d	Hemato	1000 mg/kg/day					Moreno 1989
		Hepatic	1000 mg/kg/day					
		Renal	1000 mg/kg/day					
		Endocr	1000 mg/kg/day					
		Dermal	1000 mg/kg/day					
		Bd Wt	1000 mg/kg/day					
Neurological								
Rat (Long- Evans)	4 wk 5 d/wk (topical)		500 M mg/kg/day					Boyes et al. 1999
Gn Pig (NS)	30 d 1 x/d			200 M mg/kg/day	(45-52% inhibition of brain and RBC cholinesterase)			Dikshith et al. 1987
Rabbit (New Zealand)	3 wk 5 d/wk 6 hr/d		50 M mg/kg/day	300 F mg/kg/day	(26% inhibition of RBC cholinesterase)	1000 M mg/kg/day	(65% inhibition of cerebrum cholinesterase)	Moreno 1989

Bd Wt = body weight; d = day(s); Endocr = endocrine; F = female; Gn Pig = Guinea Pig; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-effect level; M = male; mg/kg/day = milligram/kilogram/day; min = minute(s); NOAEL = no-observed-adverse-effect level; RBC = red blood cell(s); wk = week(s); x = times

Respiratory Effects. Dyspnea and excessive secretions in the respiratory tract were observed in cases of malathion intoxication in children by dermal application to the hair of a solution containing 50% malathion in xylene reported by Ramu et al. (1973). No studies were located regarding respiratory effects in humans or in animals following dermal exposure to malathion.

Hematological Effects. No studies were located regarding hematological effects in humans following dermal exposure to malathion. No hematological alterations were reported in guinea pigs applied 400 mg/kg/day malathion (98% pure) in acetone on a 36 cm^2 area of the skin for 30 days (Dikshith et al. 1987). Application of up to 1,000 mg/kg/day of malathion (94% pure) 6 hours/day, 5 days/week for 3 weeks to skin of rabbits resulted in no significant alterations in hematological variables and clinical chemistry parameters (Moreno 1989).

Hepatic Effects. Limited information on hepatic effects in humans is provided by a study of 12 agricultural workers who sprayed malathion over a period of 6 months (Grech 1965). The study was prompted by reports of ill-defined complaints and the finding that because the workers were not wearing the recommended protective clothing, significant dermal absorption was occurring. Serum levels of ALT, AST, aldolase, and albumin were determined at intervals during several periods of exposure and compared with preexposure levels and control subjects. No significant differences were observedbetween exposed and controls subjects, but in general, mean preexposure levels of the workers were higher than during exposure and than the control subjects. The toxicological significance of these findings is unknown.

Unspecified mild hepatic changes were reported in guinea pigs applied 400 mg/kg/day of malathion (98% pure) in acetone for 30 days, no alterations were seen at 200 mg/kg/day (Dikshith et al. 1987). No gross or microscopical lesions were observed in the livers from rabbits treated dermally with up to 1,000 mg/kg/day malathion (94% pure) for 3 weeks (Moreno 1989). No further information was located in the available literature.

Renal Effects. No studies were located regarding renal effects in humans following dermal exposure to malathion. No gross renal alterations were reported in guinea pigs applied 400 mg/kg/day malathion (98% pure) in acetone on a 36 cm^2 area of the skin for 30 days (Dikshith et al. 1987). No gross or microscopical lesions were observed in the kidneys from rabbits treated dermally with up to 1,000 mg/kg/day malathion (94% pure) for 3 weeks (Moreno 1989).

Endocrine Effects. No studies were located regarding endocrine effects in humans following dermal exposure to malathion. No significant alteration in the weight of the adrenals was reported in guinea pigs applied 400 mg/kg/day malathion (98% pure) in acetone on a 36 cm^2 area of the skin for 30 days (Dikshith et al. 1987). No gross or microscopical lesions were observed in endocrine glands from rabbits treated dermally with up to 1,000 mg/kg/day malathion (94% pure) for 3 weeks (Moreno 1989).

Dermal Effects. A few cases of dermal injury from assumed skin contact with malathion have been found in the literature. Baker et al. (1978) observed burns and skin rashes in an unspecified number of workers spraying malathion in Pakistan. As noted above, the daily dermal exposure was estimated to have been 330 mg of malathion. However, a survey of residents from an urban area in California who underwent aerial spraying with malathion found no significant increase in dermatologic problems (skin rash) that would require the utilization of health care services or in the prevalence of self-reported dermal symptoms (Kahn et al. 1992). In an absorption study in 31 healthy volunteers, it was found that application of an aqueous dose of malathion of 2.5 mg/cm^2 to the volar surface of the arm caused a marked and long-lasting erythema which, according to the investigators, could have been due to malathion-induced accumulation of acetylcholine within the tissue space in quantities enough to cause visible erythema (Boutsiouki et al. 2001).

Mild dermatitis was reported in mice following a brief whole-body submersion in a dip preparation containing 8% malathion (Relford et al. 1989); submersion in a 2% solution induced no significant effects. Hyperkeratosis of the epidermal layer of the skin was reported in guinea pigs following repeated applications of 200 mg/kg/day of malathion (98% pure) in acetone in a 30-day study (Dikshith et al. 1987). Also in an intermediate-duration study, repeated application of up to 1,000 mg/kg/day of malathion (94% pure) to the skin of rabbits resulted in no gross or microscopical alterations of the skin (Moreno 1989).

Ocular Effects. In a controlled-exposure study, 16 male volunteers (4/exposure level) were exposed to aerosol bombs that contained 0 (control), 5, or 20% actual malathion (95% pure) for 1 hour, 2 times/day for 42 days (Golz 1959). The actual exposure concentrations were 0, 5.3, 21, or 85 mg/m^3. There were no signs of toxicity during the study with the exception of occasional conjunctival irritation. A study of residents from an urban area in California found no significant increase in the number of visits to health care services for ocular problems or in the prevalence of self-reported ocular symptoms after aerial spraying of the area with malathion (Kahn et al. 1992). Kamel et al. (2000) used cross-sectional data from self-administered questionnaires completed by licensed pesticide applicators from Iowa and

North Carolina to evaluate the relationship between retinal degeneration and pesticide application. They compared pesticide use in 154 applicators with the disease and 17,804 applicators with no retinal degeneration. Organophosphate use was significantly associated with retinal degeneration only in North Carolina, but not in Iowa or both states together, nor in various subgroups, and no dose-response was observed. Kamel et al. (2000) suggested that because nearly all applicators (both cases and controls) evaluated in their study used organophosphate insecticides, exposures could not be effectively evaluated. At the same time, they pointed out that it would be premature to conclude that no risk existed. Anecdotal information was found in a study of self-reported symptoms in 22 seamen who may have been exposed to a single cloud of malathion that escaped from a nearby overheated tank (Markowitz et al. 1986). Compared with a group of controls, the seamen reported significantly more problems associated with swelling or irritation, blurring, double vision, or poor vision when contacted 12 days following the incident. It should be noted that there was no evidence of actual exposure to the chemical; therefore, the role of malathion, if any, cannot be determined.

Transient conjunctivitis was observed in mice following a brief whole-body submersion in a dip preparation containing 2 or 8% malathion (Relford et al. 1989). A recent study by Boyes et al. (1999) examined the ocular toxicity of malathion in Long-Evans rats. Malathion alone or with insect bait was applied directly to the eyes at a level of 100 mg per eye, 5 days/week for 4 weeks. Assuming a body weight of about 0.4 kg for a 60-day-old Long-Evans rat, the daily dose can be estimated at 500 mg/kg/day. Approximately 38 days after completion of the study, the eyes were examined by an ophthalmologist. Application of malathion caused only slight signs of ocular irritation described as mild redness of the periocular tissue. The ophthalmologic examination did not reveal any significant changes in the anterior or posterior segment of the eye. Boyes et al. (1999) pointed out that while there was no apparent damage, the possibility cannot be ruled out that acute alterations detectable shortly after dosing could have resolved during the 38–42-day posttreatment period. They also estimated that the amount of malathion applied would yield a dose of 2,000 μg of malathion per mm^2, which is about 84,000 times greater than what would be expected from an aerial application of the pesticide.

Body Weight Effects. No information was located regarding body weight effects in humans following dermal exposure to malathion. No significant effects on body weight were reported in rats treated topically in the eye with approximately 500 mg/kg/day of malathion for 4 weeks (Boyes et al. 1999). No significant effect on body weight was observed in rabbits treated dermally with up to 1,000 mg/kg/day malathion (94% pure) for 3 weeks (Moreno 1989).

Other Effects. Hyperglycemia and glucosuria were found in four children with severe malathion intoxication following application to the hair of a solution containing 50% malathion in xylene (Ramu et al. 1973). Since the hyperglycemia was accompanied with hyperinsulinemia, Ramu et al. (1973) suggested that it may have not been mediated by release of catecholamines, which are known to inhibit insulin secretion.

3.2.3.3 Immunological and Lymphoreticular Effects

Laboratory studies conducted by Milby and Epstein (1964) in 87 volunteers showed that a single exposure to 10% malathion (95% pure) induced contact sensitization in almost half of the subjects, and that 0.1 and 0.01% concentrations of 99.3% malathion were able to evoke positive responses in previously sensitized individuals. Field experiments conducted with occupationally exposed subjects showed that only about 3% reacted to a 1% malathion patch test (Milby and Epstein 1964). The field study results, however, showed that three of the four positive reactions in mosquito workers were in a district that used malathion dissolved in diesel oil, which was subsequently found to cause irritation. Cases of possible immediate and delayed type hypersensitivity reactions to malathion or to a corn syrup bait were investigated among 10 subjects who had developed dermatitis within a week of exposure to aerial application of malathion in Southern California (Schanker et al. 1992). The authors found one case of possible immediate IgE reaction to malathion bait and another case of irritant reaction to malathion and to the bait, but there were no cases of delayed type hypersensitivity. Schanker et al. (1992) noted that due to the low participation rate in the study, no specific conclusions regarding the rate of sensitivity in the population could be drawn.

Three studies were located that provided information on immunological effects of malathion in animals following dermal exposure. One of them examined the effect of acute administration of malathion on serum levels of histamine in Sprague-Dawley rats and C57BL/6N mice (Rodgers and Xiong 1997b). Doses from 2 to 2,000 mg/kg of malathion (>99% pure) in dimethyl sulfoxide (DMSO) were applied once to the shaved skin under an occlusive bandage. Both in rats and mice, treatment with malathion produced a dose-related increase in serum histamine levels, which was maximum 4 hours after dosing. Eight hours after dosing, histamine levels had returned to near control levels. The investigators (Rodgers and Xiong 1997b) suggested that signs such as lacrimation, rashes, and irritation of mucous membranes that may have reported by individual exposed to malathion may be of systemic origin rather than the result of localized action. A study in BALB/c mice sensitized with two daily applications of malathion (25 µL at 17.8 or 177.6 mg/mL) to the shaved abdomen showed no delayed-type hypersensitivity when challenged

with malathion 6 days after the second sensitization (Cushman and Street 1983). The findings of Rodgers and Xiong (1997b) and Cushman and Street (1983) are listed in Table 3-3. An additional study examined the effects of a malathion dip preparation on selected immunologic parameters in BALB/c mice (Relford et al. 1989). Mice were briefly submersed in a solution of 2 or 8% malathion twice with a 10-day interval in between doses. The cellular immune response was assessed by *in vitro* exposure of lymphocytes to mitogens, whereas the humoral response was measured by quantifying antibody production against SRBC. Sampling started 3 days after the second treatment and continued at 6-day intervals for a total of 5 samplings. Treatment with malathion did not significantly alter the cellular immune response to mitogens (*Concanavalin A*, phytohemagglutinin, pokeweed mitogen, lipopolysaccharide), with the exception of a suppressed B cell response to LPS on day 3 in both treated groups. This suppression was not seen at other sampling times. Responses to the SRBC were no different among control and treated groups. No exposure level could be estimated in this study.

3.2.3.4 Neurological Effects

A case of dermal poisoning with malathion was described by Parker and Chattin (1955). The victim was a 10-year-old girl who had extensive dermal contact with a commercial malathion formulation in the form of flakes and became semi-comatose 48 hours after exposure. On admission, there was stiffness of the neck and back and there were signs of meningeal irritation; deep reflexes of the lower extremities were absent. Following treatment with atropine, there was gradual recovery towards normality. Cholinesterase levels were measured in two studies that had significant dermal exposure to malathion. Ramu et al. (1973) described several cases of intoxication in children following a hair wash with a solution containing 50% malathion in xylene. In four severely intoxicated children, serum cholinesterase levels increased from undetected on admission to almost within the normal range 72 hours later, after appropriate treatment for organophosphate poisoning. Baker et al. (1978) measured RBC cholinesterase activity in occupationally exposed subjects at the beginning and end of the day during the period of pesticide use. The percent decreases varied by pesticide formulation; in mixers and spraymen, the average decrease from morning to evening (after a day of exposure) was about 40–45% with a formulation that contained the lowest concentration of malathion and the highest concentration of four breakdown products, including isomalathion.

Few studies were available providing information on neurological effects of malathion following dermal exposure of animals. Lethargy and anorexia were described in mice following a brief submersion in a dip preparation of 2 or 8% malathion (Relford et al. 1989). Vestweber and Kruckenberg (1972) studied the

dermal toxicity of a malathion formulation commonly used to treat house pets. A dog was sprayed over the entire body with a solution containing 0.5% malathion 3 times in a week and was observed for up to 41 days following the treatment; plasma and RBC cholinesterase were also determined. No clinical signs of toxicity were observed during the study, but both plasma and RBC cholinesterase activities were inhibited by application of malathion. A maximum inhibition of 36% of the plasma cholinesterase activity and 34% of the RBC activity occurred the day of the second treatment, but by day 19, enzyme activities had recovered to pretreatment values. No doses could be estimated from these two studies.

Repeated dermal doses of 200 mg/kg/day of malathion (98% pure) in acetone, which were lethal to guinea pigs, inhibited brain and RBC cholinesterase activity by 45–52% after 30 days of treatment, but did not induce gross or microscopical alterations in the brain (Dikshith et al. 1987). The animals that died showed frank signs of cholinergic stimulation before dying. A 65%, inhibition of cerebrum cholinesterase activity was reported in male New Zealand rabbits applied malathion (94% pure) on the skin for 6 hours/day, 5 days/week for 3 weeks (Moreno 1989). Doses of 300 mg/kg/day decreased RBC cholinesterase activity by 26% in females, whereas the lowest dose level tested, 50 mg/kg/day, caused no significant inhibition of plasma, RBC, cerebrum, or cerebellum cholinesterase activities (Moreno 1989). No signs of toxicity were observed in this study.

In the Boyes et al. (1999) study that was briefly described under Ocular Effects, the authors also examined the effects of malathion on visual evoked potentials (VEP) in Long-Evans rats by implanting the animals with cranial electrodes for recording of VEP. The amount of malathion applied to the eye resulted in approximate doses of 500 mg/kg/day for 4 weeks. Treatment with malathion had no significant effect on the amplitude or phase, or the first harmonic of the VEPs. During the study, there were no signs of cholinergic activation. Examination of the retina and optic nerve 42 days after termination of the study revealed no treatment-related alterations.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 3-3.

3.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following dermal exposure to malathion. A study in male guinea pigs reported a decrease in absolute testes weight following application of 400 mg/kg/day of malathion (98% pure) in acetone to the skin for 30 days; however, doses

of 200 mg/kg/day induced an increase in relative weight (Dikshith et al. 1987). Since body weight data were not provided, the significance of the changes in testes weight is unknown. There were no gross or microscopical alterations in the testes. Another intermediate-duration study did not observe significant changes in weight or gross or microscopical alterations in the ovaries, testes, or epididymis from rabbits applied up to 1,000 mg/kg/day on the skin for 6 hours/day, 5 days/weeks for 3 weeks (Moreno 1989). Only the latter study is listed in Table 3-3 since few details were provided in the former.

3.2.3.6 Developmental Effects

No relevant information was located regarding developmental effects of malathion in humans after dermal exposure with the exception of a report discussing a possible link between a mother's use of a hair lotion containing 0.5% malathion during the 11^{th} and 12^{th} weeks of pregnancy and the birth of a severely malformed child who died shortly after birth (Lindhout and Hageman 1987). The child's condition resembled amyoplasia congenita in which skeletal muscle is almost completely replaced by fatty tissue. Although no causal link can be established, the mother and father were healthy and had two other children who were healthy.

No studies were located regarding developmental effects in animals following dermal exposure to malathion.

3.2.3.7 Cancer

No studies were located regarding cancer in humans or animals following dermal exposure to malathion.

3.3 GENOTOXICITY

Many *in vivo* and *in vitro* studies in humans and animals have investigated the genotoxic effects of malathion, and evidence suggests that technical-grade malathion has the potential to be a genotoxic agent. Most studies (many with positive results) have used technical or commercial grades of malathion rather than the purified form. This, plus positive genotoxicity results of studies on malaoxon, suggests the possibility that impurities in commercial formulations might be the active genotoxicity agents (Flessel et

al. 1993). There is also some evidence that malathion is a weak DNA alkylating agent *in vitro* (Flessel et al. 1993). Results of *in vivo* and *in vitro* studies are discussed below.

Four *in vivo* studies of genotoxicity associated with malathion exposure in humans show varying results (Table 3-4). Actual exposure levels were not available in any of the studies. In a study of 60 workers in direct contact with malathion who were exposed from 5 to 25 years, significant differences in chromatid aberrations were observed both in groups of individuals exposed for 11–15 years and those exposed for more than 20 years when compared with control groups employed at the plant for similar exposure periods (Singaravelu et al. 1998). A study of individuals acutely exposed to malathion showed significant chromatid breaks, total chromatid aberrations, numbers of cells with non-modal chromosomes, and unstable and stable chromosome aberrations in lymphocytes cultured immediately after exposure (van Bao et al. 1974). One month after exposure, lymphocytes showed only significant levels of stable and unstable chromosome aberrations, and at 6 months postexposure, significant differences were observed only in numbers of cells with nonmodal chromosomes. In a study of workers who applied malathion as ground treatment during the Southern California med-fly eradication program, both a pilot program and a full scale investigation found no significant differences in the level of micronuclei in lymphocytes between the exposed and unexposed groups (Windham et al. 1998). The frequency of variant cells was not associated with malathion exposure in either the pilot or full-scale study. Similarly, Titenko-Holland et al. (1997) studied 38 workers involved in the med-fly eradication program, and found no change on proliferation or micronucleus level when compared with an unexposed control group.

Several additional *in vivo* studies have investigated the genotoxicity of malathion in mammals after intraperitoneal or oral administration (Table 3-4). In the bone marrow of treated mice, significantly higher numbers of chromosomal aberrations and abnormal metaphases were observed after single intraperitoneal doses of 230 and 460 mg/kg body weight when compared with controls (Dulout et al. 1983). Chromosome abnormalities were observed at a dose of 1.5 mg/kg body weight administered by gavage to mice for 7 days (Kumar et al. 1995). A dose-response relationship was observed in this study up to the highest dose of 6.0 mg/kg. Feeding male mice with grains treated with a commercial malathion formulation induced chromosomal aberrations in bone marrow cells and chromosomal abnormalities in spermatocytes (Amer et al. 2002); maximal responses were seen with the highest dose tested (approximately 7.5 mg/kg/day) in mice that ate grains pre-stored for 24 weeks and were given to the mice for 12 weeks. Amer et al. (2002) also found an increase in chromosome aberrations and sister chromatid exchanges in cultures of spleen cells from the mice that ate the contaminated grains. Numbers of cells with chromosome aberrations were significantly higher in hamsters given single intraperitoneal injections

Table 3-4. Genotoxicity of Malathion *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Mouse bone marrow	Chromosomal abnormalities	+	Kumar et al. 1995
Mouse bone marrow	Chromosomal aberrations	–	Degraeve and Moutschen 1984
Mouse spermatogonia	Chromosomal aberrations	–	Degraeve and Moutschen 1984
Mouse spermatogonia	Dominant lethal mutation	–	Degraeve and Moutschen 1984
Mouse spermatogonia	Chromosomal aberrations	+	Salvadori et al. 1988
Mouse bone marrow	Micronuclei	+	Dulout et al. 1982
Mouse bone marrow	Chromosomal aberrations	+	Dulout et al. 1983
Hamster bone marrow	Chromosomal aberrations	±	Dzwonkowska and Hubner 1986
Mouse bone marrow	Chromosomal aberrations	+	Abraham et al. 1997
Mouse bone marrow	Micronuclei	+	Abraham et al. 1997
Mouse spermatocytes	Meiotic index	+	Hoda et al. 1993
Mouse bone marrow	Chromosomal aberrations	+	Amer et al. 2002
Mouse spermatocytes	Chromosomal aberrations	+	Amer et al. 2002
Mouse spleen cells	Chromosomal aberrations	+	Amer et al. 2002
Mouse spleen cells	Sister chromatid exchange	+	Amer et al. 2002
Mouse bone marrow	Chromosomal aberrations	+	Giri et al. 2002
Human lymphocytes	Micronuclei	–	Titenko-Holland et al. 1997
Human lymphocytes	Chromosomal aberrations	+	Singaravelu et al. 1998
Human lymphocytes	Chromosomal aberrations	+	van Bao et al. 1974
Human lymphocytes	Micronuclei	–	Windham et al. 1998
Human erythrocytes	Mutation frequencies	–	Windham et al. 1998
Eukaryotic organisms:			
Drosophila (food)	Dominant lethal	+	Kumar et al. 1995
Drosophila (food)	Sex linked recessive lethal	+	Kumar et al. 1995
Drosophila (food)	Wing spot test	–	Osaba et al. 1999
Drosophila (food)	Sex linked recessive lethal	–	Velázquez et al. 1987
Drosophila (food)	Sex chromosome losses	–	Velázquez et al. 1987

– = negative result; + = positive result; ± = weak positive result

of 240 mg/kg (all aberrations except gaps) and 2,400 mg/kg (all aberrations) (Dzwonkowska and Hubner 1986). Results were not significant at intervening doses. Dulout et al. (1982) observed a significantly higher number of micronucleated cells in mice at single intraperitoneal doses of 120 and 240 mg/kg, but not at the highest dose of 480 mg/kg. No differences were observed after dermal administration. After 10 days of gavage dosing with 0.2 μg/kg/day, mice spermatocytes had slower rates of meiotic cell division than controls (Hoda et al. 1993). Another study showed no significant numbers of chromosome aberrations in bone marrow or spermatogonia and no dominant lethal mutations after a single intraperitoneal dose of 300 mg/kg was administered to mice (Degraeve and Moutschen 1984). Administration of single intraperitoneal doses of malathion in the range of 2.5–10 mg/kg to mice resulted in significant dose-dependent increases in the frequency of chromosome aberrations in bone marrow cells and sperm abnormalities, but did not affect the total sperm count (Giri et al. 2002). A study in male mice treated dermally with multiple doses of 500 mg/kg/day of commercial malathion (unspecified purity) found a significant increase in chromosome aberrations in primary spermatocytes (Salvadori et al. 1988). Malathion (250 mg/kg/day) also produced an increase in univalent chromosomes (lacking centromeres). However, the significance of results of Salvadori et al. (1988) has been questioned by some investigators who noted that "while higher frequencies of spermatocytes containing univalents were observed in both sex chromosomes and autosomes in malathion-exposed mice, the statistical strength of the effect was stronger in the sex chromosomes, diminishing the significance of the effect" (Flessel et al. 1993). It was also pointed out that "the reported increase in univalents among the sex chromosomes exhibited a positive dose-response relationship, whereas the increase among the autosomes did not."

In vivo studies in *Drosophila* are more equivocal (Table 3-4). Kumar et al. (1995) did observe increased failure of eggs to hatch after untreated females were mated with treated males, assumed to be due to dominant lethal mutations. The study also found increased sex-linked recessive lethal mutations. Another study, however, showed no differences in sex-linked recessive lethal mutations, although this test used a *Drosophila* strain selected for increased malathion resistance (Velázquez et al. 1987). Results of the wing spot test, which can test genotoxic activity without exogenous metabolic activation, were negative (Osaba et al. 1999).

Results from *in vitro* studies are summarized in Table 3-5. Assays in bacteria show conflicting results. Shiau et al. (1980) observed some mutagenicity of malathion without metabolic activation in one strain of *Bacillus subtilis* (and greater mutagenicity with activation) and weak DNA damaging potential in several *B. subtilis* strains. In another study, purified colicinogenic plasmid E1 DNA from malathion-treated *Escherichia coli* was found to have significantly more breaks than DNA from control bacteria in a test

Table 3-5. Genotoxicity of Malathion *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium (TA97a)	Gene mutation	–	–	Pednekar et al. 1987
S. typhimurium (TA98)	Gene mutation	–	–	Pednekar et al. 1987
S. typhimurium (TA100)	Gene mutation	–	–	Pednekar et al. 1987
S. typhimurium (TA102)	Gene mutation	–	–	Wong et al. 1989
S. typhimurium (TA1535)	Gene mutation	–	–	Wong et al. 1989
S. typhimurium (TA1537)	Gene mutation	–	–	Wong et al. 1989
Bacillus subtillis (TKJ5211)	Gene mutation	–	–	Shiau et al. 1980
B. subtillis (TKJ6321)	Gene mutation	+	±	Shiau et al. 1980
B. subtillis (rec assay)	DNA damage	±	±	Shiau et al. 1980
Isolated DNA from *Escheria coli* K-12	DNA damage	NT	+	Griffin and Hill 1978
Mammalian cells:				
CHO cells	Sister chromatid exchange	NT	+	Nishio and Uyeki 1981
Human fetal fibroblasts	Sister chromatid exchange	NT	+	Nicholas et al. 1979
Human lymphoid cells	Sister chromatid exchange	+	+	Sobti et al. 1982
Human lymphocytes	Sister chromatid exchange	+	+	Garry et al. 1990
Human lymphocytes	Sister chromatid exchange	NT	+	Balaji and Sasikala 1993
Human lymphocytes	Micronuclei	NT	±	Titenko-Holland et al. 1997
Human lymphocytes	Chromosomal aberrations	+	+	Garry et al. 1990
Human lymphocytes	Chromosomal aberrations	NT	+	Balaji and Sasikala 1993
Human lymphocytes	Chromosomal aberrations	NT	+	Walter et al. 1980
Human lymphocytes	DNA repair	NT	–	Blasiak et al. 1999
Human lymphocytes	Mutation frequency	NT	+	Pluth et al. 1996, 1998

– = negative result; + = positive result; ± = weak positive result; CHO = Chinese hamster ovary; DNA = deoxyribose nucleic acid; NT = not tested

performed without activation, although the breakage rate was fairly slow (Griffin and Hill 1978). Studies in various *Salmonella typhimurium* strains dosed with malathion reported no significant differences in gene mutations both with and without activation (Pednekar et al. 1987; Wong et al. 1989).

Mammalian cells tested *in vitro* exhibited genotoxicity after malathion dosing both with and without activation (Table 3-5). Sister chromatid exchanges were observed in human lymphoid cells and lymphocytes, when assays were conducted with activation (Garry et al. 1990; Sobti et al. 1982). More studies report results of tests using no activation; even without activation, malathion-associated sister chromatid exchange occurred in human fetal fibroblasts, lymphoid cells, and lymphocytes, and Chinese hamster ovary cells (Balaji and Sasikala 1993; Garry et al. 1990; Nicholas et al. 1979; Nishio and Uyeki 1981). Several studies in human lymphocytes report significant levels of chromosome aberrations both with activation (Garry et al. 1990) and without activation (Balaji and Sasikala 1993; Garry et al. 1990; Walter et al. 1980). Titenko-Holland et al. (1997) found a significant increase in micronucleated cells in isolated human lymphocytes, whereas the genotoxic effects in whole blood cultures (although still significant) were smaller. Pluth et al. (1996, 1998) studied the frequency of mutations in human lymphocytes and found significantly greater mutations in cells dosed with malathion (without activation). DNA damage and repair in human lymphocytes was investigated in one study, which showed no significant effects of malathion (Blasiak et al. 1999). The study did find, however, that two analogues present in commercial malathion formulations (malaoxon and isomalathion) damaged DNA in a dose-dependent manner. In a more recent study, Blasiak and Stańkowska (2001) suggested that hydrogen peroxide and reactive oxygen species may be involved in the formation of DNA lesions induced by malaoxon. Weak evidence of *in vitro* methylation of DNA bases by malathion was presented by Wiaderkiewicz et al. (1986). Also, malathion and several impurities were able to alkylate nitrobenzyl-pyridine, a synthetic substrate, but none of the impurities was mutagenic in tests in *Salmonella* (Imamura and Talcott 1985).

3.4 TOXICOKINETICS

Absorption of ingested malathion is rapid, followed by efficient biotransformation and elimination, mostly in urine. Dermally applied malathion is readily absorbed, although the fraction absorbed varies with the site and dose. Little direct information exists for the fate of inhaled malathion. Malathion requires for its acute toxicity the bioactivation to the ultimate neurotoxic metabolite, malaoxon. It is the level of this metabolite at the target that determines acute toxicity. Although the liver is the richest source of the bioactivation enzyme among various mammalian organs, the source organ of malaoxon responsible

for acute toxicity has not been determined. The overriding factor that makes the mammalian toxicokinetics of malathion unique is the rapid hydrolytic cleavage of carboxylic ester linkages that counters the buildup of the neurotoxic metabolite malaoxon. The impact of carboxylesterase on acute toxicity is evident in the rat in which the oral LD_{50} of malathion may be as low as 7.5 mg/kg when carboxylesterase is artificially suppressed (Dauterman and Main 1966; Main and Braid 1962) and as high as 10,000 mg/kg when carboxylesterase is fully active in the absence of interfering impurities. A similar, though less dramatic, effect of carboxylesterase inhibition has also been observed for malaoxon toxicity (Dauterman and Main 1966).

Malathion also undergoes various other forms of biotransformation. Both malathion and malaoxon are subject to phosphate linkage hydrolysis as well as glutathione-linked cleavage, both of which are detoxicative. Carboxylesterase is quite active in rat blood, but not in human blood (Main and Braid 1962). In contrast, in both species, the enzyme is highly active in the liver. Since the blood enzyme in the rat apparently plays a major role in keeping the toxicity of this insecticide low, whether rats serve as a correct toxicokinetic model for humans is uncertain, particularly in view of the observed inter-specific variations. The efficient carboxylesterase hydrolysis masks various other pathways of biotransformation, and makes studies of toxicokinetics difficult. Further confounding the toxicokinetics is the varying amounts of impurities in commercial formulations, which inhibit carboxylesterase to varying degrees depending on the formulation. As a result, toxicokinetics depends not only on variations in the recipient sensitivity, but also on the purity of the malathion preparation at hand.

3.4.1 Absorption

Absorption of malathion has been studied either indirectly by following the urinary output of metabolites or directly by studies of disappearance of malathion from the site of application, typically by using malathion radiolabeled with ^{14}C at various parts of the molecule, including the methoxy, succinyl, and ethyl groups. Though many of these studies also provide information regarding elimination, studies concerning elimination as evidence of absorption are presented in this section, while other studies more directly addressing elimination are reviewed in Section 3.4.4, Elimination and Excretion.

3.4.1.1 Inhalation Exposure

While inhalation of malathion vapor or spray mist is well anticipated to be an efficient route of absorption of malathion, especially in occupational applications, no specific studies were located in the literature on absorption of malathion through inhalational exposure.

3.4.1.2 Oral Exposure

The many case reports of malathion intoxication following accidental or intentional ingestion (see Section 3.2.2, Oral Exposure) of the pesticide provide ample evidence that malathion is well absorbed through the gastrointestinal tract in humans. Also, a controlled study with volunteers who received malathion in capsules provides direct evidence of absorption, as ingestion of malathion induced a decrease in both plasma and RBC cholinesterase activity levels (Moeller and Rider 1962).

In mice, rapid absorption of oral doses of malathion was shown by its decrease from the gastrointestinal tract. ^{14}C-Succinyl malathion gavaged at 1 mg/kg to fasted female ICR mice was rapidly absorbed (20% in 1 minute, 28% in 5 minutes, 40% in 15 minutes, 45% in 30 minutes, and 89% in 60 minutes) (Ahdaya et al. 1981). The half-time of absorption was 34 minutes. Ligation of the pylorus to measure stomach absorption resulted in absorption of 20% in 1 hour, indicating that most absorption occurred in the intestine (Ahdaya and Guthrie 1982).

As described in the section on elimination, ingested malathion is rapidly eliminated, mainly into urine, further indicating rapid absorption of ingested doses.

3.4.1.3 Dermal Exposure

There is extensive information on dermal absorption of malathion in humans and animals. The dermal route constitutes a major route of exposure during and following malathion application to fields and following aerial spraying for pest control and residential use. Dermal absorption occurs as a result of high capacity of the skin and the affinity of the plasma proteins for malathion (Menczel et al. 1983).

Interplay of such factors was analyzed in a direct study of dermal absorption employing the isolated perfused porcine skin flap (IPPSF) and revealed modest rates of absorption. Percutaneous absorption kinetics for the ^{14}C-labeled insecticides including malathion were examined in viable epidermis and dermis with a functional microcirculation (Chang et al. 1994). Measured venous flux values during the 8-hour perfusion were fitted to the 4-compartment pharmacokinetic model, and rate constants were estimated. The model yielded estimates of rate constants for surface-to-skin (transitional), skin (transitional)-to/from-skin (reservoir), skin (transitional)-to/from-vascular, and vascular-to-effluent compartments. Absorption, defined as cumulative flux of radioactivity appearing in the venous perfusate for malathion, was 1.29% of the applied dose in 8 hours.

In contrast, very rapid dermal absorption was observed in a study involving succinyl ^{14}C-malathion applied to 7–8-week-old female Duplin ICR mice. The dermal dose of 1 mg/kg was rapidly absorbed (5.5% in 1 minute, 13% in 5 minutes, 23% in 15 minutes, 25% in 60 minutes, 67% in 8 hours, and 98% in 48 hours) (Shah et al. 1981). Of 14 pesticides examined, malathion showed the slowest absorption rate, with an absorption half-life of 130 minutes.

Dary et al. (2001) used a factorial design of three factors, vehicle, the source of the chemical (technical grade 95% pure vs. 50% emulsifiable concentrate), and exposure duration (0.5 vs. 1 hour) to examine dermal penetration of ^{14}C-malathion through the skin of rats. Penetration of malathion was detected by instant electronic autoradiography. The result showed no significant interactions between the factors, penetration was influenced solely by the vehicle; malathion was found to penetrate the stratum corneum and the underlying layers of the skin more efficiently from an aqueous vehicle than from an organic solvent. The portion of the applied dermal dose that was absorbed into the system amounted to a mean total of 6.0±1.0% for the various groups studied.

The rate of percutaneous absorption of malathion in human skin *in vivo* was measured using microdialyisis probes in 31 healthy volunteers (Boutsiouki et al. 2001). The authors also examined the relationship between tissue levels of malathion and changes in local skin blood flow. An aqueous solution of malathion was applied to the volar surface of the forearm at a concentration of 2.5 mg/cm^2. Malathion was detected in the dialysate collected from the perfused probes within 30 minutes of application to the skin and the concentration increased to reach a steady state of 50 ng/mL at 3 hours. There was no significant further increase up to 5 hours of continuous exposure. The total amount of malathion recovered was relatively low, approximately 71 ng. No malaoxon could be detected in the dialysate at any time. When a commercial aqueous solution of 0.5% malathion was applied, no malathion

was detected in the dialysate for up to 5 hours after application. Malathion caused a marked and long-lasting erythema which, according to the investigators, could have been due to malathion-induced accumulation of acetylcholine within the tissue space in quantities enough to cause visible erythema. Reducing the skin blood flow by the addition of the vasoconstrictor noradrenaline produced an 8-fold increase in the recovery of malathion in the dialysate, indicating significantly reduced absorption.

Other studies of dermal absorption relied on the urinary excretion of dermally-applied malathion as evidence of dermal absorption. Although widely ranging doses employed by researchers may underlie some of the variations, interspecies difference in absorption rates (based on urinary elimination) have been cited by Wester and Noonan (1980) (64.6% for rabbits, 15.5% for pigs, 19.3% for monkeys, and 8.2% for humans), precluding quantitative generalization (Rabovsky and Brown 1993). Furthermore, even in a single species, the rate of dermal absorption may vary in different skin areas. For example, in humans, the extent of malathion absorption from the forearm was similar to that from the palm and foot, but was less than from the abdomen and hand dorsum; absorption from the forehead and the axilla was 3–4 times more extensive than from the forearm (Maibach et al. 1971).

Urinary excretion was studied to assess percutaneous penetration of 12 pesticides, including malathion, in humans (Feldmann and Maibach 1974). Six volunteers received 4 μg/cm^2 of ^{14}C-malathion (label position unspecified) in acetone on the ventral forearms, and urinary excretion was followed over a 5-day period. The total urinary excretion of an intravenous dose was 90.2%, and this was used to correct for the urinary excretion of the dermal dose. Presumably reflecting the blood concentrations, urinary ^{14}C level from the dermal dose reached a peak in the 4–8-hour sample and declined after 12 hours. The total urinary excretion of the dermal dose was 8.2%.

In an effort to establish reliable methods to estimate dermal absorption from urinary excretion data, the data of Feldmann and Maibach (1974) were reanalyzed by Thongsinthusak et al. (1999) by fitting a model with a lag time. The model-derived maximum excretion of dermal dose predicted that 6.3%, instead of 8.2%, of the dermal dose will be eliminated via urine. The figure of 7.0% was obtained when the model was also applied to the intravenous data of Feldmann and Maibach (1974).

In another study in humans, the effect of repeated dermal exposure on absorption was examined in male volunteers. Tests began with a single application of ^{14}C-malathion (label position unspecified; mixed with nonlabeled malathion) onto the ventral forearm skin, followed by repeated daily application of nonlabeled malathion to the same site (Wester et al. 1983). The daily dose was 23 mg (5 mg/cm^2 over a

4.6-cm^2 area). On day 8, the same cycle began for the second week. The absorption estimated on the basis of urinary excretion from the first radiolabeled malathion dose was 4.48% and that from the second dose was 3.53%, a value not significantly different.

A similar study was carried out with guinea pigs of both sexes by using ^{14}C-malathion (label position unspecified) (Bucks et al. 1985). Daily doses of 22.7 mg were administered to the bald area behind the ear at 24-hour intervals for 15 days, with labeled doses on days 1, 8, and 15. In the group in which the application site was washed with soap and water 1 hour before daily application, absorption rates of the three radiolabeled doses were 1.63, 3.52, and 5.34% of the applied doses for 1, 8, and 15 days, respectively. This suggested a decrease of barrier function of the skin by washing. Without the washing, absorption rates were fairly steady at 2.28, 2.13, and 3.67% of the applied doses, respectively. In all cases, more than half of the excretion occurred within 24 hours. Absorption from a single dermal dose of 15 μg of labeled malathion was 6.8% of the applied dose for nonwashed animals and 7.5% for washed animals, comparable to human data obtained by Feldmann and Maibach (1974).

Absorption of malathion was examined in 32 healthy volunteers (17 male and 15 female, 18–61 years of age; mean age, 34.1 years) treated with one of four head lice preparations containing malathion (Dennis and Lee 1999). Typical doses of 0.1–0.2 g malathion were applied to the scalp, and urinary excretion was determined after alkaline hydrolysis. A total of 0.2–3.2% of the dose was excreted over 96 hours, indicating low rates of dermal absorption.

^{14}C-Malathion (label position unspecified) was used to estimate dermal absorption in humans and rats by using a curve-fitting model (Dary et al. 1994). In humans, absorption rate constants estimated from urinary excretion ranged from 0.007 to 0.028/hour (absorption half-time of 95–25 hours) for pure malathion and from 0.003 to 0.020/hour (absorption half-time of 232–35 hours) for 10% aqueous solution. In rats, the average absorption rate constant and absorption half-time were 0.029/hour and 23.9 hours, respectively; however, comparison with human data is difficult due to a large variation among the latter.

^{14}C-Methoxy malathion was used to trace technical malathion and a 50% emulsifiable concentrate following a dermal application onto the shaved backs of male Sprague-Dawley rats at one-tenth the LD_{50} (410 mg/kg) (Abou Zeid et al. 1993). The ^{14}C in blood was higher for the unformulated malathion than for the formulation; in the latter case, ^{14}C in blood increased steadily over 7 days. Most of the excretion occurred via urine (>90%) in the first day, while some ^{14}C appeared in the feces. Excretion during the

first 3 days was greater for the emulsifiable concentrate formulation than for unformulated malathion, suggesting the effect of adjuvants.

3.4.2 Distribution

Most work on distribution relied on radio-labeled malathion. In general, such data represent the composite data for the parent chemical and metabolites, but in the case of malathion, metabolites are likely to dominate the chemical profile. This is true both in studies involving extraction and in autoradiographic work. When analytical techniques such as chromatography were employed, more specific information can be revealed for individual chemicals. Extremely rapid metabolism of malathion in certain tissues, but not in others, however, makes it difficult to gain a definitive picture of distribution of malathion and its metabolites.

3.4.2.1 Inhalation Exposure

No information was located in the literature on distribution of malathion or metabolites following inhalation exposure.

3.4.2.2 Oral Exposure

A few cases of intentional ingestion of malathion with fatal consequences provide some information on distribution of malathion and metabolites in humans. In four cases studied by Faragó (1967), aside from the stomach, intestine, and blood, malathion was found by thin layer chromatography in significant amounts in the liver and kidneys. In a case of a 53-year-old white female described by Morgade and Barquet (1982), malathion was found by column and gas chromatographic procedures in the spleen, adipose tissue, kidney, and brain, but not in the liver shortly after death (specific times of death and autopsy were not available). Adipose tissue had the most, 76.4 μg/g, whereas the kidney had 17.5 μg/g. Malaoxon was detected a very low levels in some tissues, although adipose tissue had 8.2 mg/kg. The metabolites malathion monocarboxylic acid and malaoxon dicarboxylic acid were identified in all tissues; the monocarboxylic acid was the more abundant, 221 μg/g in bile, 106 μg/g in kidney, and 103 μg/g in gastric content. Jadhav et al. (1992) used high performance liquid chromatography (HPLC) to examine six cases in which autopsies were conducted within 24 hours after death; tissues examined included the

liver, kidney, lungs, heart, brain, spleen, and muscles. The highest concentration of malathion was found in the kidneys (294–614 μg/g), whereas the muscles had the least (8–40 μg/g).

Plasma ^{14}C level was measured in rats over 48 hours following gavage of a dose of 10 mg/kg of ethyl ^{14}C-malathion or in combination with 10 mg/kg carbaryl (Lechner and Abdel-Rahman 1986). The ^{14}C levels of malathion alone and in combination with carbaryl reached a peak in plasma of 12.5 and 19.9 μg/mL 1 hour after dosing, and the absorption half-times were 1.82 and 1.91 hours, respectively. The α-phase half-lives of elimination were 18.5 and 14.5 hours and those for the β-phase were 7.16 and 10.6 hours, for malathion alone and in combination with carbaryl, respectively.

In an autoradiographic study, a single gavage dose of 3 mg/kg of methoxy ^{14}C-malathion in corn oil was administered to male Sprague-Dawley rats (Saleh et al. 1997). Rats were frozen in dry ice/hexane after 4 hours and sectioned for whole-body autoradiography. About 75% of the radioactivity electronically recorded in sagittal sections was in the stomach and 18% was in the small intestine; 7% was excreted in saliva. The authors concluded that a very small percentage of the dose was absorbed. This unusual finding could be partly related to the relatively large amount of the vehicle used (1 mL of corn oil to small nonfasted rats, weighing 80–120 g), and needs confirmatory work.

Garcia-Repetto et al. (1995) analyzed the distribution of a single dose of malathion administered by gavage to male albino rats at the rate of 467 mg/kg by using olive oil as a vehicle (20 mg/mL). Rats were sacrificed under ether anesthesia and tissues were obtained. Malathion was extracted from tissues and quantified by gas chromatography. Data were reported for days 4, 8, 12, 16, 20, and 30. Malathion was detected in blood only on day 4 (3.58 μg/g). Malathion in adipose tissue was highest on day 4 (2.63 μg/g) and declined through day 12. Muscle showed 4.24 μg/g on day 4 and decreasing levels through day 16. In the liver, malathion increased to day 16 (1.13 μg/g) and declined to day 20. The brain level reached the peak on day 16 (0.88 μg/g). No malathion was detected on day 30.

Transfer of malathion and/or metabolites to the fetus across the placenta was demonstrated in a study in rabbits (Machin and McBride 1989b). Gavage doses of 126 mg malathion/kg/day administered to the pregnant animals on gestation days 28 through 30 resulted in decreases between 54 and 79% in fetal plasma cholinesterase activity and between 60 and 66% in fetal brain cholinesterase 1 hour after the last dose.

3.4.2.3 Dermal Exposure

Methoxy ^{14}C-malathion (5 mg) was applied in 320 µL on a 10-cm^2 area of dorsal skin of male Sprague-Dawley rats from which hair had been clipped 24 hours before, and 8 hours after the treatment animals were frozen in dry ice/hexane for autoradiography (Saleh et al. 1997). Electronic autoradiography showed that 28% of the total recorded radioactivity was at the application site and 29% was distributed over the remaining skin. Other areas with significant distribution were the small intestine (23%), large intestine (10%), and liver (5.4%).

3.4.2.4 Other Routes of Exposure

A single dose of 2.5 mg/kg of methoxy ^{14}C-malathion in 0.3 mL of saline was intravenously administered to male Sprague-Dawley rats and the whole animal was frozen in a dry ice/hexane for autoradiography after 30 minutes (Saleh et al. 1997). As a percent of the radioactivity in sagittal sections, the highest radioactivity was found in the liver (38%), small intestine (21%), kidney (19%), lung (11%), and urinary tract (7%).

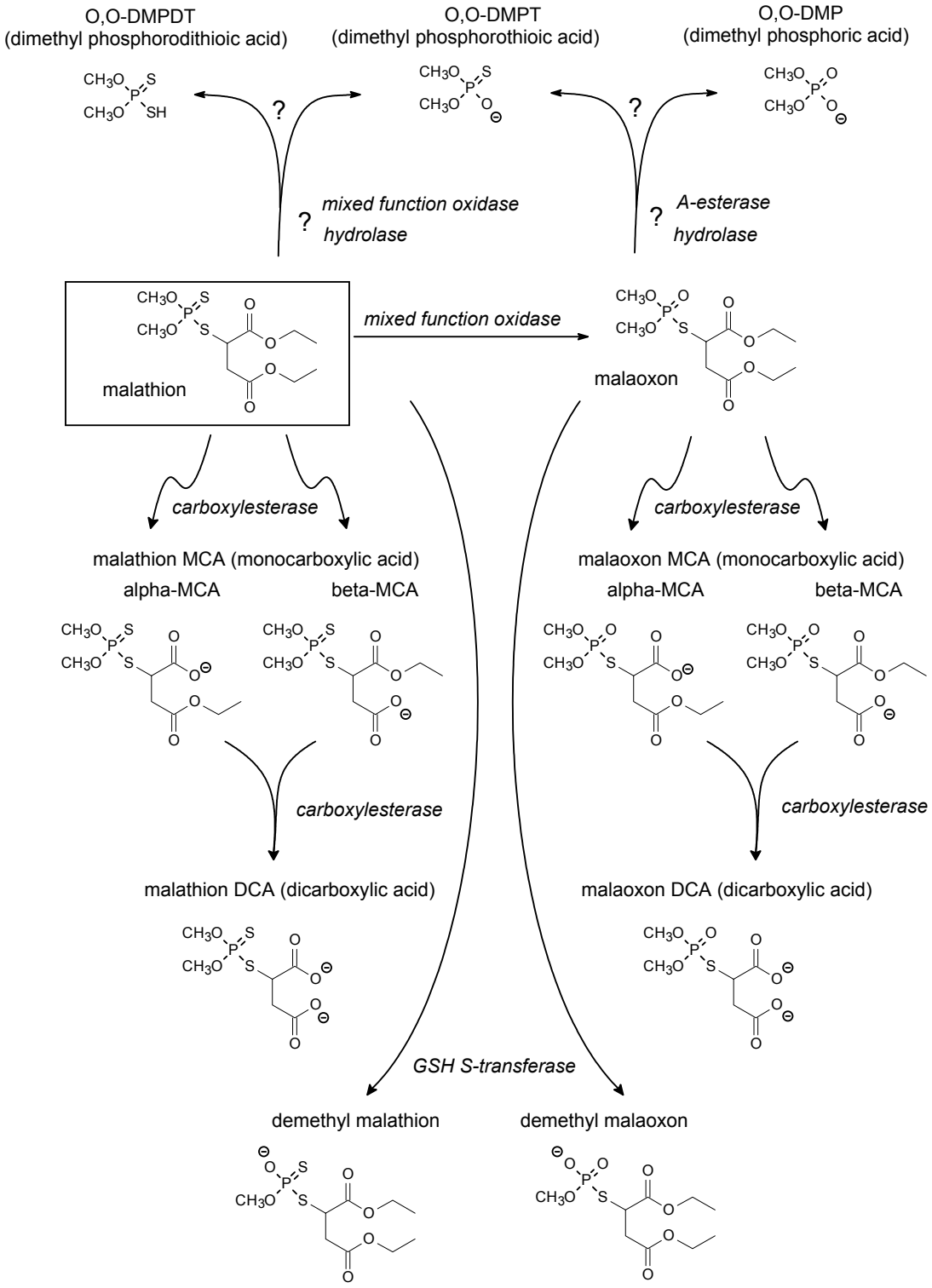
Another whole-body autoradiographic study with ethyl-^{14}C malathion injected in the tail vein of male Wistar rats (0.9 mg/kg) showed a rapid disposition of malathion (Muan and Nafstad 1989). Within 1–3 minutes of dosing, label was found throughout, but was high in the kidney, liver, lung, heart, skin, muscles, and blood. Ten minutes after the intravenous dose, the radioactivity in the liver had decreased and the highest radioactivity was in the renal cortex, the medulla of the kidney, and the intestine. At 12 and 24 hours after dosing, radioactivity was barely detectable.

3.4.3 Metabolism

Knowledge of malathion metabolism comes from analyses of metabolites in the urine of animals and humans exposed to malathion, *in vitro* biotransformation studies, and understanding of the acute mode of action of malathion.

Malathion concurrently encounters three types of metabolic modifications in animals, one oxidative and another hydrolytic, and the elimination of a methyl group catalyzed by glutathione (GSH) S-transferase (Figure 3-3). The most important metabolite of the former biotransformation is malaoxon, the ultimate

Figure 3-3. Metabolic Pathways for Malathion



neurotoxic molecule responsible for the acute toxicity. Among the latter reactions, hydrolysis of one of the two carboxylic ester linkages abolishes the potential of acute toxicity and is mainly responsible for the well-known low acute toxicity of malathion to mammals.

Oxidative Metabolism. While lacking in detailed analysis with malathion, the oxidative reaction catalyzed by mixed function oxidase is considered a general one for phosphorothioate esters and involves cytochrome P-450. In the case of the well-studied phosphorothioate parathion, the reaction involves CYP2B (Wolf et al. 1990). Although malaoxon is toxicologically the most important product of this enzyme reaction, it is most likely only one of the products arising from the putative sulfur oxide intermediate. In a few dialkyl aryl phosphorothioates studied in detail, such as parathion and diazinon, the sulfur oxide intermediate undergoes a rearrangement to yield "oxon" on the one hand, and hydrolysis to yield dialkyl phosphorothioic and dialkyl phosphoric acid on the other (Nakatsugawa 1992). This scheme is likely to apply to malathion as well, and it would be expected that dimethyl phosphorothioic acid and dimethyl phosphoric acid arise as products from the rearrangement of the sulfur oxide intermediate.

Probably reflecting the technical difficulty in the presence of carboxylesterase activity, the process of oxidative malathion metabolism has not been studied specifically. Oxidative metabolism of parathion demonstrated in the pig skin (Chang et al. 1994) suggests similar reactions for malathion.

Carboxylester Hydrolysis. A group of urinary metabolites in malathion-exposed animals is produced by the hydrolysis of the succinate ester moiety. Included in this group are α- and β-malathion monocarboxylic acid (*O,O*-dimethyl-S-(1-carboxy-2-carbethoxy)ethyl phosphorodithioate and *O,O*-dimethyl-S-(1-carbethoxy-2-carboxy)ethyl phosphorodithioate, respectively), α- and β-malaoxon monocarboxylic acid (corresponding α- and β-anologs of malathion monocarboxylic acids), and malathion dicarboxylic acid.

Enzymes involved in producing these metabolites are called carboxylesterases after the type of ester linkages they target. Multiple forms of carboxylesterases are widely distributed in mammalian tissues. Even the brain tissue has a detectable level of carboxylesterase activity as observed in female mice (Sakai and Matsumura 1968). In the rat, the liver contains the highest level of carboxylesterase among various organs. Total enzyme activities (in terms of nmol/minute) among the various organs were 370 for lung, 4,720 for kidney, 24,000 for liver, and 7,490 for serum. Intestinal villi and brain homogenates revealed little activity. Three-fourths of the hepatic carboxylesterase were found in the microsomal fraction. In

rats, however, carboxylesterase in the serum may play at least as important a role as the hepatic carboxylesterase (Talcott 1979). In humans, carboxylesterase is essentially absent in the blood, though it is quite active in the liver (see Section 3.5.3).

Malathion monocarboxylic acid produced by partially purified rat liver carboxylesterase *in vitro* and that in the urine of male Duplin rats fed 1,500 mg/kg malathion were identified as α-monoacid, indicating that the initial hydrolysis to monocarboxylic acid occurs strictly at the α-position in this rat strain (Chen et al. 1969).

In other strains of rats, however, both α- and β-monocarboxylic acids are found in the urine of treated animals. In female Sprague-Dawley rats, a gavage dose of 1 mg/kg malathion yielded approximately similar amounts of α- and β-monocarboxylic acids over 24 hours, measured both in the blood and in the urine (Ryan and Fukuto 1985). Production of β-monocarboxylic acid and dicarboxylic acid were severely suppressed by pretreatment with 1 mg/kg of isomalathion or O,S,S-trimethyl phosphorodithioate.

Mallipudi et al. (1980) prepared two chromatography fractions of malathion carboxylesterase from solubilized microsomes of Sprague-Dawley rat livers. When tested with malathion as the substrate, these enzymes yielded different ratios of α- and β-acid. With carboxylesterase in the fraction A (50,000-60,000 dalton), fraction B (110,000–130,000 dalton), and crude homogenate, the respective ratios were 1.5, 0.2, and 0.56. In comparison, the ratio for rat serum carboxylesterase was 1.17. In rabbit liver, both metabolites were produced by monomeric and oligomeric forms of carboxylesterases, with ratios of 2.33 and 4.55, respectively (Lin et al. 1984a).

Matsumura's textbook (Matsumura 1985) lists the ratio of α- and β-malathion monocarboxylic acids for pure horse liver aliesterase, rat liver microsomes, beef liver acetone powder, pig pancreas acetone powder, pig kidney acetone powder, partially purified pig liver esterase, housefly homogenate, and Tribolium beetle homogenate. The α/β ratio ranges from 0.07 to 5.0.

Malaoxon is hydrolyzed by a carboxylesterase, and its acute toxicity increases when this enzyme is inhibited (Dauterman and Main 1966). The kinetics of carboxylesterase are complicated since the substrate malaoxon inhibits carboxylesterase (Main and Dauterman 1967).

Malathion dicarboxylic acid is a major urinary metabolite of malathion, but the enzyme that yields this metabolite by hydrolyzing the second carboxylester linkage has not been studied. In rats, the dicarboxylic

acid was produced more than monocarboxylic acid, with the ratio of mono/dicarboxylic acids decreasing with the decreasing dosage. In male Sprague-Dawley rats receiving 69–0.069 mg/day by gavage for 3 days, the ratios of monocarboxylic acids to dicarboxylic acid were 0.66, 0.21, 0.14, and 0.08 for 69, 6.9, 0.69, and 0.069 mg/day doses, respectively (Bradway and Shafik 1977). In this study, the carboxylic acid metabolites comprised the majority (60–90% range), with the remainder consisting of phosphate metabolites. Referring to historic data, the authors suggest that monocarboxylic acid may be the predominant of the carboxylic acid metabolites at higher doses and at the earlier period following exposure.

In a urinary analysis of volunteers ingesting gelatin capsules containing 7.7 or 15.6 mg malathion (Krieger and Dinoff 2000), malathion monocarboxylic acids were more abundant than the dicarboxylic acid, and dimethyl phosphorothioic acid was the main alkylphosphate metabolite.

Phosphorus Ester Hydrolysis. Urine of malathion-treated animals often contains significant amounts of dimethyl phosphorus esters such as dimethyl phosphoric acid, dimethyl phosphorothioic acid, and dimethyl phosphorodithioic acid. Pathways leading to these metabolites, however, have not been clarified.

Dimethyl phosphoric acid is the anticipated metabolite in the hydrolysis of malaoxon. Such an enzyme resistant to the inhibitory action of organophosphates, or A-esterase, was detected in the serum of 100 human subjects. The assay determined the free thiol-containing leaving group of malaoxon. Contribution of A-esterase to the detoxication of malaoxon appears less than for other neurotoxic organophosphates assayed (Sams and Mason 1999). Dimethyl phosphoric acid is also a potential product of the oxidative metabolism as previously mentioned.

Dimethyl phosphorothioic acid would be assigned to the oxidative metabolism as the sole source in the case of related dimethyl phosphorothioate like methyl parathion since no hydrolytic enzymes have been found to yield this metabolite. Hydrolytic characteristics of malathion, however, makes it difficult to interpret the data. According to Mattson and Sedlak (1960), who cite an early German report by Mühlmann and Schrader (1957), "malathion is readily hydrolyzed by acid chiefly to *O,O*-dimethyl-phosphorothionic acid and by alkali chiefly to *O,O*-dimethylphosphorodithioate". The same authors also note that "phosphorodithioate is rather unstable and is converted at least partially to the phosphorothionate". In the absence of further information, the possibility may exist that dimethyl phosphorothioic acid is partially derived from malaoxon hydrolysis.

Dimethyl phosphorodithioic acid can only arise from malathion, and not from malaoxon. The enzymes responsible for this metabolism have not been studied. In a gavage study using doses of 0.069–69 mg/day in 10-fold increments for 3 days to 400–450 g male Sprague-Dawley rats, dimethyl phosphorothioic acid was the dominant phosphate metabolite, followed by dimethyl phosphorodithioic acid and dimethyl phosphoric acid (Bradway and Shafik 1977). The proportion of the latter two metabolites seems to shift with the dose, with dimethyl phosphoric acid dominating at lower doses and dimethyl phosphorodithioic acid being the dominant metabolite at the highest dose.

Glutathione-linked Metabolism. Mouse liver homogenate contains a glutathione (GSH) S-transferase which demethylated malathion to yield demethyl malathion (Nomeir and Dauterman 1978). This may account for an earlier observation of a 10-fold enhancement of malathion metabolism by GSH with mouse liver homogenate in which esterases were suppressed by DFP (di-isopropyl fluorophosphate) (Bhagwat and Ramachandran 1975). A substantial yield of demethyl malathion in rat liver homogenate has also been reported though involvement of GSH is unknown (Matsumura and Ward 1966).

Hepatocytes isolated from male Wistar rats were used to study the depletion of GSH by malathion, isomalathion, and trimethyl phosphorus esters (Malik and Summer 1982). Isomalathion was the most effective. GSH depletion by malathion was greatly increased when carboxylesterase was pre-inhibited by isomalathion, indicating the greater involvement of GSH-linked metabolism of malathion under those conditions.

3.4.4 Elimination and Excretion

Studies on elimination provide the rate of excretion of metabolites and identification of metabolites, mostly in urine (Rabovsky and Brown 1993). As is the case in studies of distribution, the use of radiolabeled malathion often yields a composite profile of malathion metabolites. No metabolic half-life information is available either for malathion or malaoxon. Many studies of malathion absorption provide information on urinary excretion, as discussed in Section 3.4.1.

3.4.4.1 Inhalation Exposure

No information was located regarding elimination of malathion following inhalation exposure. However, in the studies of occupational exposures discussed in Section 3.4.4.3 below, workers were most likely exposed by both the inhalation and dermal routes, but the contribution of each route is difficult to establish.

3.4.4.2 Oral Exposure

In a study by Krieger and Dinoff (2000), malathion metabolites were analyzed in the urine of a volunteer who ingested single doses of 7.7 or 15.6 mg of malathion in gelatin capsules. Monocarboxylic acids were more abundant than dicarboxylic acid, and dimethyl phosphorothioic acid was the main alkylphosphate metabolite; more than 95% was recovered in urine. In an earlier study of a subject who ingested a high amount of malathion (200 mL of 50% malathion), analysis of the second 24-hour urine sample also showed monocarboxylic acids as the major metabolites followed by dimethyl phosphorothioic acid (Bradway and Shafik 1977). An estimated half-life of 6.2 hours for the fast phase of elimination was reported for a 43-year-old woman who ingested malathion (Vasilic et al. 1999).

In animals, elimination of ingested malathion occurs rapidly mainly via the kidney. For instance, male Holtzman rats eliminated 91.7% of radioactivity of a dose of 25 mg of ^{14}C-ethyl malathion within 24 hours (83.4% in urine, 5.51% in feces, and 2.77% as CO_2); 7.75% remained in the gastrointestinal contents (Bourke et al. 1968). Urinary excretion at 8 hours was 44.1% of the administered dose.

Similarly, in a study of pesticide combination on toxicokinetics, 10 mg/kg ^{14}C-ethyl malathion given to fasted female Sprague-Dawley rats by gavage in 0.25 mL corn oil was excreted rapidly in the urine, 68% in 8 hours and 93% in 24 hours (Lechner and Abdel-Rahman 1986). A thin layer chromatography (TLC) analysis of chloroform extracts from acidified 24-hour urine provided a urinary metabolite profile: malathion 0.01%, malaoxon 1.44%, malathion monoacid 0.42%, and malathion diacid 0.06% of the dose. Carbaryl coadministered at 10 mg/kg altered the profile and raised malaoxon to 7.5% and malathion dicarboxylic acid to 1.48%. No additional confirmation of identity of malaoxon was reported.

In a study in male Sprague-Dawley rats, about 90% of ^{14}C-methoxy malathion (280 mg/kg by gavage) was excreted into urine within 24 hours of ingestion (Abou Zeid et al. 1993). In another study in male

Sprague-Dawley rats in which the animals were gavaged with malathion at 0.00001–0.1 (69 mg) the LD_{50} dose, metabolites in urine comprised predominantly (up to 90%) dicarboxylic acid, followed by monocarboxylic acid; alkyl phosphates were minor components (Bradway and Shafik 1977).

3.4.4.3 Dermal Exposure

A study of dermal absorption of ^{14}C-malathion (label position unspecified) in humans provides estimates of kinetic parameters of malathion elimination via the urine. Fitting urinary data to a model yielded elimination rate constants for humans, ranging from 0.094 to 0.129/hour (elimination half-time of 0.74-5.4 hours) for pure malathion and 0.079–0.130/hour (elimination half-time of 8.7–5-3 hours) for 10% aqueous malathion (Dary et al. 1994).

Studies of occupationally exposed subjects have identified and quantified several malathion metabolites in the urine. In these cases, exposure is assumed to have been by both the inhalation and dermal routes, but the contribution of each specific route is unknown.

In a study of date farm workers continually exposed to malathion in dusting and harvesting operations, mid-season Monday morning prework urine samples contained low or unmeasurable levels of malathion acids, indicating rapid metabolism and elimination (Krieger and Dinoff 2000). Estimated daily clearance of malathion metabolites provided a measure of daily dose. Depending on the task of the crew, the clearance ranged from 1 to 92 mg malathion equivalent/day. For loaders/applicators, the dose estimates were 0.4–1 mg malathion equivalent/kg/day. The profile for major urinary metabolites was: *O,O*-dimethylphosphorotioate (48–53%), malathion monocarboxylic acids (23–27%), and malathion dicarboxylic acid (13–16%). These levels of "subchronic" exposure did not result in depression of either plasma or RBC cholinesterases. Dermal doses (281 or 51 mg) of malathion self-administered on forearms produced metabolite profiles similar to that obtained from oral dosing (Krieger and Dinoff 2000).

A study of workers and residents exposed to malathion during a spraying operation in Haiti showed urinary malathion monocarboxylic acid at various times after the operation ranging from 0.9 to 6.8 mg/L after the spraying week and from 0.047 to 0.13 mg/L after the weekend (Warren et al. 1985). Residents having negligible levels of monocarboxylic acids when they returned home showed an increase to 0.084–1.4 mg/L over the weekend. In a group of residents who were tested 1 week after the operation, malathion monocarboxylic acids ranged from negligible to 0.31 mg/L, suggesting that malathion and/or metabolites may be more persistent in the environment than it had been previously thought. A study of

agricultural workers (mixers and applicators) evaluated dermal exposure to malathion by monitoring urinary dimethyl phosphorothioic acid and *O,O*-dimethyl phosphorodithioate (Fenske 1988). Urinary metabolites monitored for 3 days following exposure showed that applicators excreted 17% of the applied dose estimated by fluorescent tracer technique, and mixers 23%.

3.4.4.4 Other Routes of Exposure

In a poisoning case involving suicidal intravenous injection of about 1.8 g of malathion, serum concentration of malathion in the range of 0.029–0.349 μg/ml between 6 and 24 hours postinjection indicated a half-life of ≤ 2.89 hours for serum malathion (Lyon et al. 1987).

A single dose of 2.5 mg/kg of methoxy ^{14}C-malathion in 0.3 mL of saline was intravenously administered to male Sprague-Dawley rats and the whole animal was frozen in a dry ice/hexane for autoradiography after 30 minutes (Saleh et al. 1997). As a percent of the recorded radioactivity of sagittal sections, the small intestine contained 21% of the radioactivity and the urinary tract contained 7%, leading the authors to conclude that the bile is a major route of excretion.

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.

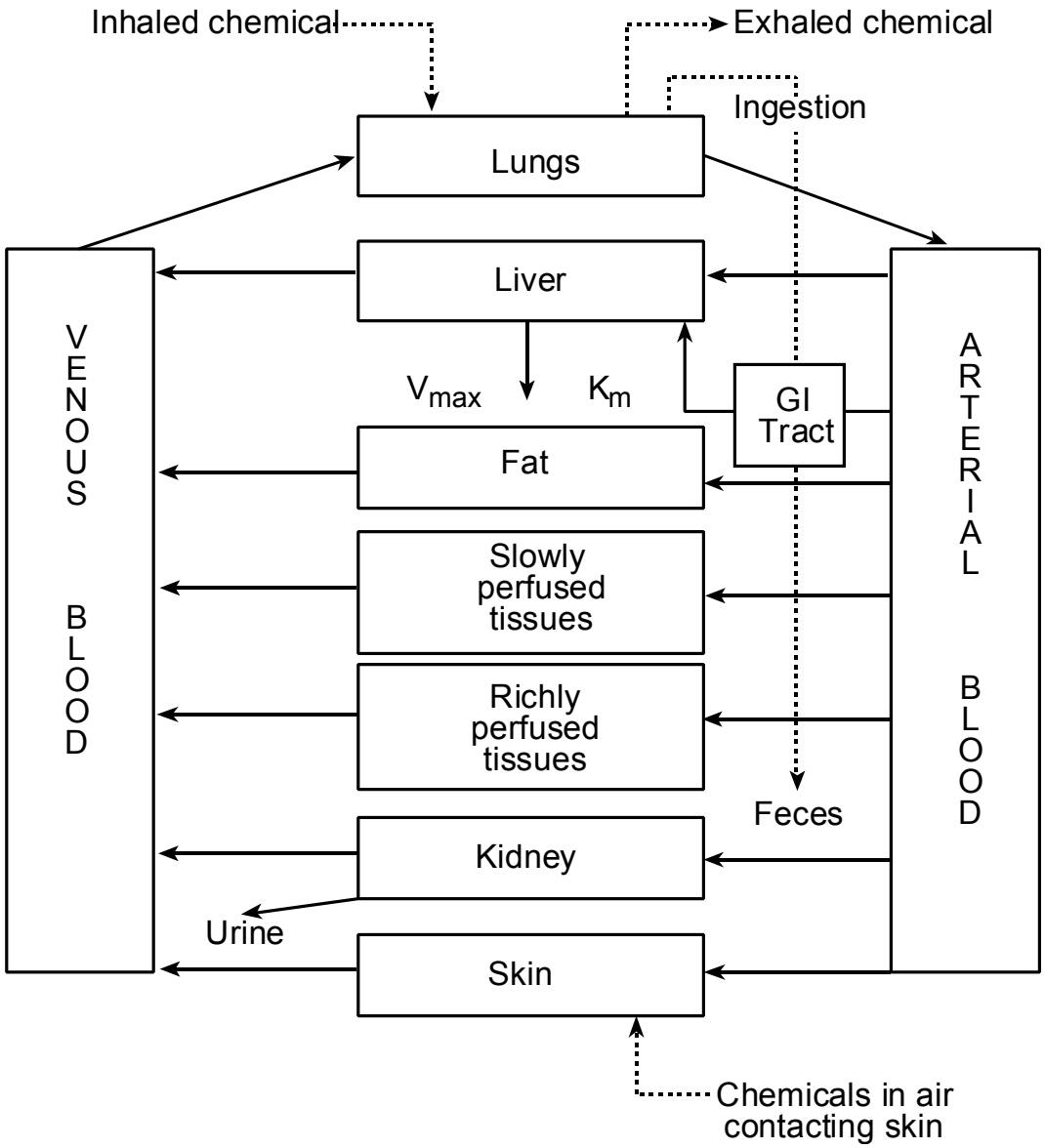
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically 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.

A PBPK model for dermal exposure was developed by the California Office of Environmental Health Hazard Assessment (Rabovsky and Brown 1993). Unlike most PBPK models developed and validated by using laboratory animals, this model was unique as it directly dealt with human exposure cases. The model was used to estimate the exposure doses of southern California residents who may have been exposed to aerial sprays of malathion mixed with a corn-syrup protein bait. Urine samples were collected

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.

within 48 hours of spraying during the Mediterranean fruit fly eradication campaign in the fall of 1989 (Dong et al. 1994).

Description of the Model. Cumulative values for malathion carboxylic acid metabolites were simulated by the model. When simulation approximated biomonitoring estimates, the sum of the amounts for all compartments will yield the total absorbed dose. The model assumed that a portion of the dermal dose diffuses into the skin whereas the rest is either lost to the atmosphere or remains on the skin. The model has seven body compartments (skin surface, skin perfused, fat, muscle, kidney-vessel rich group, intestine, and liver) and four external compartments (air, urine, feces, and acid metabolites).

Typical kinetic and physiological parameters and constants used are listed in Table 3-6 (Rabovsky and Brown 1993). Similar values are also given for children of different ages (Dong et al. 1994). Hydrolytic constants were based on animal data (Mallipudi et al. 1980) and apparent V_{max} was scaled by the body weight ratio to the 0.75 power. Oxidation constants were estimated from rodent data that showed 1–2% oxidation (Lechner and Abdel-Rahman 1986). Tissue/blood partition coefficients were estimates from the malathion octanol/water partition coefficient (776.25). Of the total of 67 individuals who participated in the Los Angeles biomonitoring study (30 women, 20 men, and 17 children), 11 subjects with detectable malathion acid metabolites in their urine were included in the PBPK simulation. Urinalysis provided only the data for malathion dicarboxylic acid. Since the model required the data on total malathion carboxylic acid metabolites (mono- and di-carboxylic acids), this was estimated to be 3 times the amount of dicarboxylic acid based on available measurements.

Validation of the Model. The model was later modified and applied to cases reported in Dary et al. (1994) and cases in Wester et al. (1983). The model is designed to estimate the absorbed doses of malathion in an exposed individual based on a single urine sample at a given time period after exposure. The validation study revealed that most of the predictions were within 2-fold of the measured values, with none exceeding 3-fold. The model would be more accurate with multiple samples collected within the first 24 or 36 hours of exposure (Dong et al. 1996).

Risk Assessment. The model estimates dermal doses by using urinary metabolites collected from exposed human populations. The doses then can be used to assess health risks of the exposure, although elaborate risk assessment has not been published in these California epidemiological studies to which this PBPK model has been applied.

Table 3-6. Kinetic and Physiological Parameters and Constants Used in PBPK Human Malathion Deposition Model

Values	Adult (70 kg)	Child (10 kg)
Hydrolytic liver metabolism		
Apparent V_{max} (moles x min-1)	$4.89x10^{-4}$	$1.12x10^{-4}$
Apparent K_m (M)	$1.35x10^{-4}$	$1.35x10^{-4}$
Oxidative liver metabolism		
Apparent V_{max} (moles x min^{-1})	$2.0x10^{-5}$	$4.65x10^{-6}$
Apparent K_m (M)	$2.10x10^{-4}$	$2.10x10^{-4}$
Other kinetic parameters[b]		
Permeability constant (skin surface to viable epidermis)(min^{-1})	$1.0x10^{-5}$–$5x10^{-4}$	
Evaporation constant (skin surface to air)(min^{-1})	$1x10^{-4}$–$5x10^{-4}$	
Fecal constant (intestine to feces)(min^{-1})	0.1–0.25	
Tissue volumes (liter)		
Fat	10.0	1.420
Intestine	2.4	0.343
Kidney VRG	2.7	0.386
Liver	1.5	0.404
Muscle	30.0	6.185
Skin	2.6	0.371
Tissue perfusion rates (liter x min^{-1})		
Fat	0.2	0.073
Intestine	1.2	0.276
Kidney VRG	2.25	0.517
Liver	1.5	0.380
Muscle	1.2	0.276
Skin	0.065–0.15	0.015
Cardiac output	6.4–6.5	1.540
Tissue/blood partition coefficients[a]		
Fat		775
Intestine		15
Kidney VRG		17
Liver		34
Muscle		23
Skin		25

[a]These values pertain to adults and children.

Source: Rabovsky and Brown 1993

Target Tissues. This model does not attempt to estimate the level of active toxic molecular species at the target tissues or at any other tissue. Instead, the goal of the model, for which validation and optimization have been conducted, is to predict the dose based on the end product of metabolism. While the model incorporates kinetic constants for metabolic processes, the main elements that controlled the fit of output with actual data appear to be skin permeability constants (Dong et al. 1996), and for the purpose of this model, other internal elements appear less important and hence less suited for predictions of target tissue levels of the toxicant.

Species Extrapolation. Although some parameters and constants have been adapted from rodent data, the model has been formulated for human simulation from the outset and reverse extrapolation to animals, while useful, has not been tested.

Interroute Extrapolation. This model has been optimized solely for the purpose of estimating dermal doses. As stated above under "Target Tissues", internal elements have not been optimized. Further validation and adjustments will be needed for the model to be useful in oral or inhalation routes of exposure.

3.5 MECHANISMS OF ACTION

The typical acute neurotoxic action of malathion is cholinergic. It involves the inhibition of the neural acetylcholinesterase by its active metabolite, malaoxon (Ecobichon 1994). The inhibition occurs due to the similarity of malaoxon to the neurotransmitter acetylcholine. Mimicking acetylcholine, malaoxon first binds to the active serine residue of acetylcholinesterase, undergoes a double displacement reaction involving the serine hydroxyl group, and yields dimethyl-phosphorylated acetylcholinesterase. Since the phosphorylated acetylcholineterase is stable within the time frame of poisoning, the inhibition prevents the normally extremely rapid hydrolysis of neurotransmitter acetylcholine, prolonging the impulse transmission.

The expression of toxic signs depends on which of the divisions of nervous systems is affected. Thus, commonly observed cholinergic signs of poisoning including salivation, lacrimation, perspiration, and constriction of the pupils are due to the stimulation of muscarinic acetylcholine receptors in the parasympathetic autonomic synapse at exocrine glands and eyes. Other consequences of stimulating

muscarinic cholinergic receptors include nausea, vomiting, abdominal cramps, diarrhea, tightness of the chest, incontinence, miosis, and breathing difficulty. The action on nicotinic receptors in the somatic motor endplates at the skeletal muscles leads to muscle fasciculations, generalized muscle weakness, cramping, flaccid or rigid paralysis, and ataxia. Bradycardia or tachycardia with accompanying decrease or increase in blood pressure may occur depending on the relative impact of cholinergic stimulation on the muscarinic parasympathetic neurons or on the nicotinic neurons that innervate the heart. Effects on cholinergic neurons in the central nervous system also yield a variety of effects including mental confusion, insomnia, headache, convulsions, coma, and depression of respiratory centers.

Which effects may dominate depends on the sensitivity of the target enzyme at various synapses and the level of the ultimate toxic molecule, malaoxon, which may be produced at or near the nerve from malathion or transported from the site of malathion activation such as the liver, lung, or kidney. Generation and distribution of malaoxon is poorly understood, but undoubtedly depends on the route of exposure to malathion.

3.5.1 Pharmacokinetic Mechanisms

No special feature has been found in the absorption of malathion, which most likely undergoes passive diffusion. Barrier function of the epidermis may be reduced when the skin is washed, as shown by the increased absorption of ^{14}C-labeled malathion (Bucks et al. 1985). Adjuvants in malathion formulation may also affect the rate of dermal absorption since different patterns of ^{14}C distribution were observed between unformulated and formulated malathion (Abou Zeid et al. 1993). No information was located in the literature regarding pharmacokinetic factors in inhalation and ingestion of malathion.

Distribution of absorbed malathion among components in the skin has been modeled and analyzed experimentally (Chang et al. 1994). Although this analysis revealed a high affinity compartment that serves as a reservoir for malathion in circulation, it has not clarified a variation in the percent absorption of widely ranging dermal doses. In the only autoradiographic study of distribution of malathion (Saleh et al. 1997), a suggestion has been made that the entire skin, rather than merely the site of dermal application, may serve as a reservoir of dermally applied malathion, but the conclusion has not been validated by others. The role of blood proteins in the distribution of absorbed malathion or its active metabolite malaoxon has not been examined.

Pharmacokinetics of malathion is uniquely influenced by the high degree of carboxylester hydrolysis in mammalian tissues, though other pathways of metabolism also operate, contributing to the ready excretion of absorbed doses. Aldridge et al. (1979) observed that about 10,000 mg/kg of purified malathion (an LD_{50} dose) caused little evidence of poisoning in female Lac:P rats for the first 6 hours of malathion ingestion, and most fatalities occurred 20–40 hours following the dose. Clearly, in the absence of impurities to inhibit carboxylesterase activity, rapid detoxification in rats precludes the buildup of an effective level of malaoxon at the target site for hours.

In technical malathion, pharmacokinetics of malaoxon is a complex function of malathion level, carboxylesterase titer, concentration of carboxylesterase inhibitors including isomalathion and malaoxon, malathion dose level, and exposure frequency. A glimpse of this complexity may be seen in the multiple role that just one of the malathion impurities (isomalathion) plays, competing with malathion for glutathione (Malik and Summer 1982), and reducing the hydrolytic metabolism of both malathion and malaoxon by inhibiting carboxylesterase (Talcott et al. 1979b). The level of malaoxon will also affect the activity of carboxylesterase (Main and Dauterman 1967), which in turn affects the levels of malathion and malaoxon. Such interaction of malathion would be dose-dependent, but this relationship has not been examined.

The source organ of malaoxon molecules that interact with the target has not been elucidated. While overall kinetic constants for the process of oxidative metabolism of malathion have been derived (Lechner and Abdel-Rahman 1986; Rabovsky and Brown 1993), rates of malaoxon production for individual organs and tissues remains unknown. The fact that the liver has the highest capacity to activate malathion to malaoxon cannot be taken as evidence that malaoxon that reaches specific targets originates in the liver in view of the complexity found in parathion (Nakatsugawa 1992). Thus, other organs of lesser activative capacity may be significant sources of malaoxon reaching the target, especially in view of the high hepatic level of carboxylesterase that can counter the activation in this organ (Talcott 1979). Pharmacokinetics of malaoxon in humans must reflect the absence of serum carboxylesterase (Main and Braid 1962; Talcott et al. 1982), which may be as important as the hepatic carboxylesterase in the rat. This is not the only difference between the species; the rat liver, but not the human liver, has a substantial capacity to demethylate malathion in addition to hydrolyzing at carboxylester linkages (Matsumura 1966).

3.5.2 Mechanisms of Toxicity

The acute toxicity of malathion is basically similar to that of other phosphorothioate insecticides as the inhibition of target neural acetylcholinesterase arises from the metabolic activation of the parent compound. It is unique among organophosphates, however, since it is not possible to define an unequivocal LD_{50} for a given population of a test species. Preparations of malathion contain varying composition and amounts of impurities, many of which inhibit carboxylesterase and potentiate the toxicity of malathion (Lin et al. 1984b; Pellegrini and Santi 1972; Talcott et al. 1977, 1979c; Toia et al. 1980; Verschoyle et al. 1982). However, only isomalathion among the impurities inhibits human liver carboxylesterase (Talcott et al. 1979b). The existing literature is inadequate to describe the complex dynamics of malathion biotransformation following the initial exposure, but clearly, the toxicity of malathion is dependent upon the simultaneous reactions of the carboxylesterase hydrolyzing malathion/malaoxon and of the impurities inhibiting carboxylesterase. Conceivably, when impurities are low and carboxylesterase is very active, malaoxon may not build up to an effective level at the target as noted in the preceding section. The typical cholinergic mechanism of toxic action, however, likely accounts for the toxicity of most malathion formulations.

Inhibition of the target acetylcholinesterase by organophosphorus insecticides and other neurotoxic organophosphorus esters involves phosphorylation of the serine moiety at the active site of the enzyme, the reaction that parallels the acetylation during the normal hydrolysis of acetylcholine.

Besides the neural acetylcholinesterase, other serine hydrolases are also similarly inhibited. Most notably, acetylcholinesterase in the erythrocyte and cholinesterase (pseudocholinesterase) in serum are usually affected when the animal is exposed to a sufficient dose of malathion. Although the toxicological consequences of this inhibition are unknown, it is regarded as a useful marker of malathion exposure (see Section 3.8.2).

In the case of dimethyl phosphorus esters such as malathion, esterase inhibition by phosphorylation appears more reversible than in the case of their higher alkyl homologs. This is due to dephosphorylation rather than the true reversal of reaction, and represents a step in a series of displacement reactions in the hydrolysis of malaoxon by acetylcholinesterase (O'Brien 1967).

This step is sufficiently slow to suppress the normal action of acetylcholinesterase, but does occur at a measurable pace. For example, serum cholinesterase of New Zealand White rabbits was significantly

inhibited as early as 1 hour after being gavaged with 126 mg/kg of malathion, but showed a considerable recovery by the next day. Repeated dosings, however, caused a higher degree of inhibition with increased signs of poisoning (Machin and McBride1989). This indicates that there was a parallel effect on the neural acetylcholinesterase of the rabbits, and that there can be cumulative inhibition.

In organophosphorus insecticides with slower dephosphorylation, the use of nucleophiles such as pyridine aldoxime methiodide is a useful treatment of poisoning. In the case of dimethylphosphorus esters like malathion, the benefit seems unpredictable. In the fatal case of a 45-year-old man who ingested 50–90 mL of 50% malathion, for example, 3 grams of 2-pyridine aldoxime methochloride given within 3 hours when erythrocyte cholinesterase activity was <10% of normal, was not beneficial (Crowley and Johns 1966). In contrast, however, in an attempted suicide case of a 14-year-old boy who ingested 4 ounces of malathion and experienced severe cholinergic symptoms, cyanosis and coma, atropine treatment was not totally effective and pralidoxime chloride therapy was used. Within 5 minutes of intravenous infusion of 20 mL (500 mg) of this drug, restoration of muscle activities was noted. The boy recovered following repeated treatments with pralidoxime (Amos and Hall 1965). A poisoning victim may recover with only atropine without the use of oximes as was the case with a 10-year-old girl exposed to malathion apparently through dermal contact with a malathion formulation in the form of flakes and became semi-comatose (Parker and Chattin 1955).

Although dephosphorylation does occur with dimethyl phosphorus esters like malathion, the step may not be complete as it competes with another reaction called “aging”, representing demethylation of phosphorylated acetylcholinesterase (O’Brien 1967). Aging is observed as the change of phosphorylated acetylcholinesterase that is resistant to the action of forced dephosphorylation by nucleophilic agents like pyridine aldoxime methiodide, mentioned above.

In humans, inhibition of cholinesterases in RBCs and plasma is often a useful marker of exposure and inhibition of neural cholinesterase. In poisoning cases, blood cholinesterase seems to parallel the signs of poisoning. For instance, in the 1976 poisoning epidemic in Pakistan, blood cholinesterase activities were significantly lower in symptomatic workers than in those without symptoms, with signs of poisoning such as headache, blurred vision, or vomiting (Baker et al. 1978). The blood cholinesterase inhibition correlated well (r=-0.83) with the postspray cholinesterase activity, which was highest on Monday and fell as work progressed. Blood cholinesterase inhibition may occur in the absence of poisoning symptoms. In a study involving volunteers (Moeller and Rider 1962), oral administration of 0.11 mg malathion/kg/day for 32 days or 0.23 mg/kg/day for 47 days did not produce any significant depression of

plasma or RBC cholinesterase activity. However, administration of 0.34 mg malathion/kg/day for 56 days caused a maximum depression of 25% in plasma cholinesterase approximately 3 weeks after cessation of treatment. A similar depression in RBC cholinesterase was observed, but occurred later. No clinical manifestations of toxicity were noted throughout the study.

The high selective toxicity of malathion is due to its rapid hydrolysis by carboxylesterase in mammals and the general lack of this enzyme in most insect pests. This enzyme is inhibited by several of the impurities that accompany technical malathion as well as other organophosphorus esters including ethyl-p-nitrophenyl thionobenzenephosphonate (EPN) and triorthotolyl phosphate (TOTP). The effective dose of malathion preparations depends greatly on the carboxylesterase inhibition, which in turn is determined by the level of impurities. Experimental inhibition of most carboxylesterase by TOTP dramatically lowered acute LD_{50} of malathion preparations, from 1,600 to 20 mg/kg in one case and from 415 to 7.5 mg/kg in another (Main and Braid 1962) in male Sprague-Dawley rats.

3.5.3 Animal-to-Human Extrapolations

Malathion exerts most of its toxic effects through cholinergic disruption both in humans and in other mammalian species. Data obtained with rodent models are clearly relevant to humans as they share basic physiology both in the function of the nervous system and in the metabolic pathways. Because of these similarities, basic clinical signs of poisoning are similar in humans and in rodents when they are exposed to sufficient doses of malathion. In details, however, extrapolation of animal data to humans becomes difficult due mainly to differences in pharmakokinetics. The situation is exacerbated by the unique dependence of malathion toxicity on the degree of hydrolysis by carboxylesterases.

In humans, hepatic carboxylesterase activities appear similar to those in rat liver. Unlike rats, however, humans lack detectable levels of malathion carboxylesterase in the serum; the enzyme is also absent in human erythrocytes (Main and Braid 1962). Further confirmation of the general absence of malathion carboxylesterase in the serum of healthy humans was provided by Talcott et al. (1982). About 30% of blood donors had detectable levels of malathion carboxylesterase activity in serum, activity ranging from 0.1 to 7.2 units/mL; no relation to age, sex, or race was noted. Positive correlations between serum ALT and malathion carboxylesterase were noted among 46 hospital patients. In addition, the two enzymes in the serum of a patient hospitalized for acetaminophen poisoning were observed to rise and decline in parallel, with the peak being reached on day 4. These data suggest that the low level of malathion carboxylesterase found in some human serum is a reflection of liver damage. The lack of malathion

carboxylesterase in healthy human serum may underlie a significant deviation of pharmacokinetics from the rodent model (Talcott et al. 1982). These authors concur with clinical literature that safety of malathion to humans may have been overestimated by acute toxicity data on rats. It has been suggested that rats may not be a proper model and that another species with less extrahepatic carboxylesterase activity may be more appropriate (Talcott 1979).

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

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. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. However, appropriate terminology to describe such effects remains controversial. The terminology endocrine disruptors, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning endocrine disruptors. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as hormonally active agents. The terminology endocrine modulators has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view 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 chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

In recent years, concern has been raised that many pesticides and industrial chemicals are endocrine-active compounds capable of having widespread effects on humans and wildlife (Crisp et al. 1998; Daston et al. 1997; Safe et al. 1997). Particular attention has been paid to the possibility of these compounds mimicking or antagonizing the action of estrogen, and more recently, their potential anti-androgenic properties. Estrogen influences the growth, differentiation, and functioning of many target tissues, including female and male reproductive systems, such as mammary gland, uterus, vagina, ovary, testes, epididymis, and prostate. Thus far, there is no evidence that malathion is an endocrine disruptor in humans at the levels found in the environment.

A study following malathion spraying in the San Francisco Bay area found an increase in some anomalies at birth, but those that occurred most frequently than expected did not represent a biologically consistent pattern (Grether et al. 1987). A similar study of women who were pregnant during periods of malathion spraying to control an infestation by the Mediterranean fruit fly found no significant association between exposure to malathion and the incidence of spontaneous abortions, but there was a weak association between stillbirths and exposure accumulated up to 1 month before death as well as an increased incidence of gastrointestinal anomalies (Thomas et al. 1992). Exposure misclassification may have precluded drawing any firm conclusions in this report. An additional study of male workers exposed to malathion and several pesticides, including organochlorine pesticides, found decreased fertility among the workers, a higher percent of abortions and stillbirths among the wives of exposed males, and congenital defects in their offspring (Rupa et al. 1991b). The role of malathion, if any, cannot be determined. A case report described by Lindhout and Hageman (1987) discussed the possible association between dermal exposure of a pregnant women to a hair lotion containing malathion and the birth of a severely malformed child, but a causal link is difficult to establish. Decreased serum levels of ACTH, cortisol, and prolactin were reported in patients with severe intoxication following intentional ingestion of unspecified amounts of malathion (Güven et al. 1999). Transient alterations in thyroid hormones and TSH were also seen. The toxicological significance of these findings is unknown.

Increased pituitary gland weight and serum prolactin levels and decreased pituitary levels of prolactin were reported in male Wistar rats administered approximately 225 mg/kg/day of malathion for 6 days (Simionescu et al. 1977). An intermediate-duration study found congestion in the *zona reticularis* of the adrenal glands from rats treated by gavage with 10 mg/kg/day of malathion (94% pure) for 15 weeks (Ozmen and Akay 1993). Serum cortisol and aldosterone levels were increased at 10 mg/kg/day, but not at 100 mg/kg/day. Serum T_4, T_3, testosterone, and 17β-estradiol levels were not significantly affected by

treatment with malathion and there were no histopathologic changes in the thyroid in the treated animals (Ozmen and Akay 1993). The adrenal congestion reported in rats treated with malathion may be a nonspecific effect since hyperemia and petechial hemorrhages in some organs is not an uncommon finding following organophosphate intoxication. No such congestion was seen in the chronic studies with much larger doses (see below).

Chronic-duration studies in rats have not observed treatment-related gross or microscopic lesions in endocrine glands or reproductive organs (NCI 1978, 1979a), although increased relative and absolute thyroid and parathyroid weights were seen in female rats administered 415 mg/kg/day of malathion (97.1% pure) in the diet for 2 years (Daly 1996a); the NOAEL was 35 mg/kg/day. Similar lack of gross or microscopic alterations in endocrine organs were reported in a chronic study in mice, but an increased incidence of cystic endometrial hyperplasia was seen in mice administered 1,490 mg/kg/day malathion (95% pure) for 80 weeks (NCI 1978).

Studies in male rats have demonstrated that acute exposure to malathion (40 mg/kg/day) can produce transient testicular alterations such as a reduction in the number of Sertoli and Leydig cells (Krause 1977; Krause et al. 1976). A higher dose of 163 mg/kg/day of malathion (unspecified purity) damaged the seminiferous tubules and produced an abnormal pattern of Sertoli cells (Ojha et al. 1992). A considerably higher gavage dose of 1,950 mg/kg of malathion (95% pure) given once to 8-week-old male Wistar rats reduced the number of germinal layers and produced degeneration and necrosis of gonocytes in the seminiferous tubules during the first 3 days after dosing and it also caused systemic toxicity (Piramanayagam et al. 1996). Testicular effects were also reported in a 12-week study (Balasubramnian et al. 1987b). In general, these studies suffer from incomplete reporting of the results such that no firm conclusions can be drawn. Some studies have observed reduced number of implants in female rats at doses (500 mg/kg/day on Gd 6, 10, and 14) that also caused maternal toxicity (Prabhakaran et al. 1993), but no such effects were observed at even higher doses in another study in rats (800 mg/kg/day on Gd 6–15) (Lochry 1989). No effects on implantation were reported in rabbits treated with up to 100 mg/kg/day (Gd 6–18), but 50 mg/kg/day increased the mean number and percent resorptions (Siglin 1985). Exposure of rats to 50 mg/kg/day malathion for periods that included mating and gestation had no significant effects on reproductive parameters (Lechner and Abdel-Rahman 1984), and no significant effects on reproductive performance or fertility indices were seen in a 2-generation study in rats (Schroeder 1990). Dermal exposure of rabbits to up to 1,000 mg/kg/day of malathion for 21 days did not induce significant changes in weight or gross or microscopical alterations in the ovaries, testes, or epididymis (Moreno 1989).

Overall, the available studies do not suggest that malathion is an endocrine disruptor in humans or in animals.

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, whereas 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).

No studies were located that specifically addressed effects of exposure to malathion in children. Children could be exposed to malathion from food and drinking water, but these risks are low and not of concern. Greater concern exists from postapplication residential exposure to turf treatments, from other home and garden uses of malathion, and as bystanders from special uses of malathion in public health mosquito abatement control and the USDA's (U.S. Department of Agriculture) Boll Weevil Eradication Program. Because children spend more time outdoors than adults, they may be at a greater risk of exposure to malathion than nonoccupationally exposed adults by dermal contact with contaminated surfaces or by hand-mouth activity. Malathion is an organophosphate pesticide, and acute exposure to high amounts results in typical and easily recognizable signs of poisoning (Aaron and Howland 1998; Abou-Donia 1995; Ecobichon 1994; Taylor 1996). As detailed in Section 3.5.2, Mechanisms of Toxicity, the primary target of malathion toxicity is the nervous system and secondary ocular, exocrine glands, gastrointestinal, cardiovascular, and respiratory effects can be observed as a result of the excess acetylcholine at nerve terminals innervating tissues and organs from these systems. The most common manifestations of poisoning with organophosphates in general are increased salivation and lacrimation, miosis and blurred vision, nausea, vomiting, abdominal cramps and diarrhea, excessive bronchial secretions and dyspnea, bradycardia and low blood pressure, muscle fasciculations, muscle weakness in peripheral and respiratory muscles, and fatigue and mental confusion. Several reports have described these manifestations in children following oral poisoning with malathion (Ekin 1971; Healy 1959; Jušić and Milić 1978; Tuthill 1958) and dermal exposure (Parker and Chattin 1955; Ramu et al. 1973), and it does not appear that there

are significant differences in the responses between children and adults. A case report of aplastic anemia in a 12-year-old child following inhalation of malathion fumes after fumigation of a home was described by Reeves et al. (1981), but this case seems to be unique and there is no evidence that malathion was the causal agent. A population-based case-control study in California found no significant association between the use of household pesticides during pregnancy and the risk of pediatric brain tumors (Pogoda and Preston-Martin 1997).

It is not known whether or not children are more susceptible than adults to malathion toxicity. However, as previously mentioned, young animals are more susceptible to malathion than older animals. The single oral LD_{50} of 95% pure malathion in newborn male Wistar rats was 124.1 mg/kg, whereas in preweaning (14–16 days old) and adult (3–4 months) rats, LD_{50} values were 386.8 and 925.4 mg/kg, respectively (Lu et al. 1965). This difference was also observed for 4-day cumulative LD_{50} values (Lu et al. 1965). Similar findings were reported by Brodeur and DuBois (1967) and by Mendoza (1976) and Mendoza and Shields (1976, 1977) who also observed that the decrease in susceptibility more or less paralleled increases in the activities of esterases in various tissues. For example, using acetylthiocholine as substrate, a single dose of 8,000 mg/kg of malathion inhibited brain esterase by 85% in 18-day-old pups, while in 1-day-old pups, the same degree of inhibition was achieved with a dose of only 500 mg/kg (Mendoza and Shields 1977). More recent *in vitro* studies of Mortensen et al. (1998) showed that acetylcholinesterase activity in the rat brain increases during postnatal development and reaches a maximum at about 40 days of age, but the K_m, substrate profiles, and *in vitro* sensitivities to selected organophosphates were not different in young versus adult animals.

There is limited information regarding developmental effects of malathion in humans. A study of children born to women exposed to malathion via aerial spraying found some positive (and significant) associations for some anomalies, but the anomalies that occurred more frequently than expected did not represent a biologically consistent pattern (Grether et al. 1987). No significant association was found between low birth weight and increasing exposure to malathion. An additional study involving the same type of exposure found a statistically significant association between incidence of gastrointestinal anomalies in offspring and exposure to malathion during the second trimester of pregnancy (OR=4.14; CI=1.01, 16.6) (Thomas et al. 1992). No significant associations were observed for intrauterine growth retardation or other congenital defects reportable by the California Birth Defects Monitoring Program. García et al. (1998) compared paternal pesticide exposures between offspring with congenital malformations and controls. In a subgroup of 14 individuals exposed to malathion, regression analysis showed no significant associations with outcomes after adjusting for confounding factors. A case of a

woman who used a hair lotion containing 0.5% malathion during the 11th and 12th weeks of pregnancy and gave birth to a severely malformed child was described by Lindhout and Hageman (1987). The malformations resembled amyoplasia congenita, a condition in which skeletal muscle is almost completely replaced by fatty tissue. Although the causal link is difficult to establish, the mother and father were healthy and had two other children who were healthy. Studies in animals suggest that malathion is not a developmental toxicant at doses that do not induce maternal toxicity (Khera et al. 1978; Lochry 1989; Machin and McBride 1989a; Schroeder 1990; Siglin 1985). However, a study by Kalow and Marton (1961) found increased neonatal mortality (days 7 and 21 after birth) in rats following maternal exposure to 240 mg/kg/day malathion (95% pure) in the diet for at least 5 months starting before mating, but no information was provided regarding maternal effects.

There is no information regarding possible transgenerational effects of malathion in humans. A study in male mice treated with 300 mg/kg of malathion (>99% pure) intraperitoneally did not observe an increase in chromosome aberrations in spermatogonia (Degraeve and Moutschen 1984). In the same study, the investigators also conducted a dominant lethal mutation assay and found that the frequency of pre- and postimplantation fetal lethality was not significantly increased over the control level. Salvadori et al. (1988) treated male mice dermally with multiple doses of 500 mg/kg/day of commercial malathion (unspecified purity) and found a significant increase in chromosome aberrations in primary spermatocytes. Malathion (250 mg/kg/day) also produced an increase in univalent chromosomes (lacking centromeres). However, as mentioned in Section 3.3, the significance of results of Salvadori et al. (1988) has been questioned by some investigators.

There is no information regarding the pharmacokinetics of malathion in children or regarding the nutritional factors that may influence the absorption of malathion. A PBPK simulation of exposure to malathion during an urban pesticide application estimated that the highest dermally absorbed dose for adults and children (14–34 kg) were 1.3 and 0.4 mg, respectively (Dong et al. 1994). Analysis of urine samples from humans exposed to malathion suggests the involvement mainly of phase I metabolic enzymes in the biotransformation and elimination of malathion. The specific P-450 isozymes involved in phase I metabolism are not known, and thus, no conclusions can be drawn based on general differences in isozymes activities between adults and children. The hydrolysis of malathion/malaoxon to the biologically-inactive α-monoacids is catalyzed by carboxylesterases and at least in rats, the activities of these enzymes in various tissues increase postnatally, which explains in part the greater susceptibility of young animals to the acute toxicity of malathion compared to older ones (Brodeur and DuBois 1967; Lu et al. 1965; Mendoza 1976; Mendoza and Shields 1976, 1977). No information was located regarding

whether or not human carboxylesterases are developmentally regulated. One study was found reporting the presence of malathion in breast milk (5 ppb) from 1 of 11 Italian women with no known high exposure to malathion (Roggi et al. 1991). There is evidence in animals that it (or metabolites) can be transferred via breast milk to the offspring (Chhabra et al. 1993) and that it can cross the placenta (Machin and McBride 1989b; Mathews and Devi 1994).

Characteristic clinical signs and symptoms of cholinergic stimulation along with malathion metabolites in the urine constitute biomarkers of effect and exposure to malathion in children and in adults. No studies were located regarding interactions of malathion with other chemicals in children. No information was located regarding pediatric-specific methods for reducing peak absorption following exposure to malathion or reducing body burden. In addition to supporting therapy, treatment of organophosphate poisoning involves mainly administration of atropine to counteract the muscarinic effects and of pralidoxime to reactivate the acetylcholinesterase activity; appropriate dose adjustments for children are recommended (Aaron and Howland 1998; Carlton et al. 1998; Osmundson 1998).

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 malathion 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 malathion 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 3.8.2 "Populations That Are Unusually Susceptible".

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Malathion

The most specific biomarkers for exposure to malathion are the parent compound itself and metabolites in tissues and body fluids. However, because malathion is rapidly metabolized and eliminated (see Section 3.4), the parent compound may only be found in cases of acute exposure to considerable amounts of the pesticide (Faragó 1967; Jadhav et al. 1992; Morgade and Barquet 1982; Vasilić et al. 1999). Studies of the general population and occupational exposures have detected malaoxon dicarboxylic acid (DCA), malathion monocarboxylic acid (MCA), dimethyl phosphorothioic acid (DMPT), *O,O*-dimethyl phosphorodithioate (DMPDT), and *O,O*-dimethylphosphate (DMP) as the main metabolic products in samples of blood and urine. In a survey of almost 7,000 people from the U.S. population conducted during 1976–1980, about 1.1% was found to have quantifiable levels of MCA in the urine and <1% had quantifiable levels of DCA (Kutz et al. 1992). MacIntosh et al. (1999b) conducted a longitudinal study of 80 individuals from five contiguous counties in Maryland during 1995–1996 in which they measured DCA in up to six urine samples per individual at intervals of about 8 weeks over a 1-year period. They detected DCA in 6.6% of the samples, which was higher than what Kutz et al. (1992) reported; however,

the maximum concentration reported by Kutz et al. (1992), 250 μg/L, was 5 times higher than that found in the Maryland study, 51 μg/L.

A study of 5 workers and 16 residents exposed to malathion during a spraying operation in Haiti measured urinary MCA at various times after the operation (Warren et al. 1985). All of the subjects were tested on Friday after daily spraying during the week and again on Monday after the weekend; eight residents were tested 1 week later. The residents were not at home during the spraying, but returned home the Friday after the operation was completed. Urinary MCA levels ranged from 0.9 to 6.8 mg/L after the spraying week and from 0.047 to 0.13 mg/L after the weekend. Residents showed negligible levels of MCA when they returned home, but levels increased to 0.084–1.4 mg/L over the weekend. In eight residents who were tested 1 week after the operation, MCA ranged from negligible to 0.31 mg/L, suggesting that malathion and/or metabolites may be more persistent in the environment than it had been previously thought. A study of 19 agricultural workers (mixers and applicators) evaluated dermal exposure to malathion by monitoring urinary DMTP and DMDTP and also used a fluorescent tracer technique to monitor exposure (Fenske 1988). Urinary metabolites were monitored for 3 days following exposure. The results showed that applicators excreted 17% of the applied dose and mixers excreted 23%. Exposure was better correlated with excretion of metabolites for applicators (r=0.91) than for mixers (r=0.73). A more recent study of date dusters and harvesters in California showed that malathion metabolites could be detected in the urine as soon as 2–3 hours of work (Krieger and Dinoff 2000). On a molar basis, DMTP > MCA > DMP > DCA were the most prominent urinary metabolites. Samples of urine collected on Monday morning during mid-season had low or undetectable levels of MCA and DCA suggesting that malathion is quickly metabolized and eliminated in the urine.

3.8.2 Biomarkers Used to Characterize Effects Caused by Malathion

Diagnosis of organophosphate poisoning, including malathion, can be made by the presence of characteristic clinical signs and measurements of serum (plasma) cholinesterase and RBC acetylcholinesterase activities. Enzyme inhibition, however, is not specific for organophosphates since exposure to carbamate insecticides also results in cholinesterase inhibition. Nonspecific cholinesterase (pseudocholinesterase, butyrylcholinesterase) is present in myelin, liver, and plasma, whereas acetylcholinesterase is present in the central and peripheral nervous systems and in RBC. Plasma cholinesterase activity can be inhibited by 20–25% without significant physiological consequences (Abou-Donia 1995). Malathion is a stronger inhibitor of plasma cholinesterase than of RBC acetyl-cholinesterase (Maroni et al. 2000). Plasma cholinesterase regenerates at a more rapid rate than RBC

acetylcholinesterase, about 25% regeneration occurs in the first 7–10 days, and is regenerated by the liver in about 2 weeks (Abou-Donia 1995). After severe poisoning, plasma cholinesterase activity remains depressed for up to 30 days, which corresponds to the time that it takes the liver to synthesize new enzymes. Although a more sensitive indicator of exposure to organophosphates than RBC acetylcholinesterase, plasma cholinesterase is less specific since the levels may also be suppressed due to genetic factors and to a variety of conditions and diseases (Zimmerman and Henry 1984; Tafuri and Roberts 1987). The rate of decrease of RBC acetylcholinesterase correlates better with appearance of symptoms than the absolute value reached after exposure (Maroni et al. 2000). Reduction of RBC acetylcholinesterase after severe exposure lasts up to 100 days reflecting the time of production of new cells. RBC acetylcholinesterase 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 malathion (Midtling et al. 1985). Tafuri and Roberts (1987) proposed a classification of organophosphate poisoning as follows. Clinical signs and symptoms of intoxication may occur when plasma cholinesterase levels drop to below 50% of the normal value. Mild poisoning, with the patient still ambulatory, may occur when plasma 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 plasma cholinesterase levels <10% of normal.

Several methods for measuring RBC acetylcholinesterase and plasma cholinesterase are available (see Chapter 7). Baseline data are often collected for workers, preferably three values, but these data would not be available for environmentally exposed people. Inferences made by comparing values of exposed subjects with a reference population may be erroneous since values at the upper limit of the normal range may be 200% higher than those at the lowest one (Maroni et al. 2000). Therefore, it is useful to conduct a long-term sequential determination of cholinesterase activity to confirm enzyme inhibition (Coye et al. 1987). Plasma cholinesterase is preferred over RBC acetylcholinesterase since it recovers more quickly and an increase in activity is more likely to occur over shorter observation periods.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Studies on the influence of chlorinated hydrocarbons on the toxicity of malathion showed that treatment of rats with hexachlorobenzene (HCB) from before mating to postnatal day 18 significantly decreased the acute toxicity of malathion (99.3% pure) in 18-day-old pups (Mendoza and Shields 1976). The LD_{50} for malathion in the pups increased from 1,415 to 3,317 mg/kg in HCB-exposed pups. This was correlated with a markedly reduced inhibition by malathion of cholinesterases and carboxylesterases in different

organs. Townsend and Carlson (1981) examined the influence of a series of chlorinated and brominated benzenes on the toxicity of malathion (92% pure) in mice. Pretreatment of the mice orally for 7 days with the halogenated benzenes increased the LD_{50} for malathion (decreased toxicity), the greatest increase was seen with 1,2,4-tribromobenzene (from 1,370 to 2,053 mg/kg). In general, there was a good correlation between the effects on lethality and increases in in vitro carboxylesterase activity with malathion or malaoxon as substrate. Trisubstituted compounds were more protective than disubstituted, and brominated benzenes were more active than chlorinated ones. A study of combined application of hexachlorocyclohexane and malathion to the skin of guinea pigs for 30 days showed no significant influence of either chemical on morbidity or mortality induced by the other (Dikshith et al. 1987).

The influence of the pesticide carbaryl on the developmental toxicity of malathion in rats was examined by Lechner and Abdel-Rahman (1984). Doses of 50 mg/kg/day of malathion (unspecified purity) administered for 3 months prior to mating and during gestation caused no significant teratogenicity or embrytoxicity upon examination of Gd 20. The only significant effects of the combination were increases in the number of litters with resorptions and in the percentage of resorptions which were greater than expected from the simple addition of individual contributions. The same group of investigators also examined the effects of an equimolar malathion/carbaryl combination on liver microsomal enzyme activities (aminopyrine demethylase, aniline hydroxylase, nitrobenzoate reductase, and uridine diphosphate-glucuronyl transferase) in a 7-day study in rats (Lechner and Abddel-Rahman 1985). Treatment with malathion had no significant effect on the activities of any of the enzymes. Carbaryl significantly increased the activity of uridine diphosphate-glucuronyl transferase and the same extent of increase was seen in the group treated with the combination of pesticides. A further study by the same group on the effect on serum enzymes and glutathione in rats showed that treatment with malathion (50 mg/kg once or for 21 days) had no effect on serum transaminases, glutamic dehydrogenase, leucine aminopeptidase, or β-glucuronidase activities. Malathion did not significantly affect blood glutathione levels. Groups treated with the combination of malathion and carbaryl showed responses not significantly different than those seen with the individual pesticides.

Moeller and Rider (1962) conducted a controlled oral study with volunteers to examine the influence of EPN on malathion-induced cholinesterase activity inhibition. The pesticides were administered alone or in various combinations for up to 56 days. Administration of 0.11 mg malathion/kg/day for 32 days or 0.23 mg/kg/day for 47 days did not produce any significant depression of plasma or RBC cholinesterase activity or induce clinical signs. Malathion at 0.34 mg/kg/day for 56 days caused a maximum depression of 25% in plasma cholinesterase approximately 3 weeks after cessation of treatment. A similar

depression in RBC cholinesterase was observed, but occurred later. No clinical signs were seen in the volunteers. Malathion and EPN in combination seemed to have additive effects, but no potentiation was apparent. The influence of EPN on the acute toxicity of malathion was determined in rats and dogs (Frawley et al. 1957). Malathion doses were 0, 600, 800, 1,000, 1,250, 1,600, and 2,000 mg/kg. There were no deaths in rats with the 600 mg/kg dose and all (10) rats died with the 2,000 mg/kg dose. Typical cholinergic signs were seen before death. Deaths generally occurred several hours after dosing. The combination malathion/EPN in a ratio of 25/1 showed about a 10-fold potentiation of malathion alone. In dogs (malathion doses of 0, 25, 50, 100, 200, 500, 1,000, 2,000, and 4,000 mg/kg), there were no deaths with 2,000 or 4,000 mg/kg malathion alone and doses of 100 mg/kg or less of EPN were not lethal. However, a combination of 100 mg/kg malathion and 2 mg/kg EPN killed four out of four dogs, which suggested a potentiation factor of about 50-fold. Frawley et al. (1957) also studied the effect of malathion and the influence of simultaneous administration of EPN on blood cholinesterase activity in an 8-week feeding study in rats. No significant change in whole blood cholinesterase activity was observed by treatment with malathion alone. However, 500 ppm malathion (about 43.7 mg/kg/day) plus 25 ppm EPN (which caused moderate depression of cholinesterase activity) reduced cholinesterase activity to about 30% of pretreatment values during treatment. In a 12-week feeding study in dogs, plasma cholinesterase activity was not significantly altered by malathion (0, 25, 100, or 250 ppm), but the high dose caused about 20% inhibition in erythrocyte activity after 6 weeks of treatment. Simultaneous administration of EPN greatly potentiated the effect of malathion, particularly on erythrocyte cholinesterase. The high malathion dose with 50 ppm EPN caused a maximum inhibition of about 95% after 8 weeks of treatment, whereas 50 ppm EPN alone inhibited the enzyme by not more than 5%. Su et al. (1971) measured the effects of carboxylesterase inhibition on the toxicity of malathion by feeding rats organophosphate insecticides (EPN, parathion, Folex®, TOTP, Guthion®) for 1 week and then administering malathion intraperitoneally. All insecticides significantly increased the acute toxicity of malathion (reduced the LD_{50}) and the amount of increase was correlated with the inhibition of liver carboxylesterase (especially the enzyme that hydrolyzes diethylsuccinate), less with inhibition of serum carboxylesterase, and poorly with inhibition of brain, liver, and serum cholinesterase. Murphy and Cheever (1968) noted that administration of 10 ppm dioxathion in the diet for 30 days to rats or 30 ppm ronnel for 7 days did not significantly inhibit brain cholinesterase activity, but these diets greatly increased the inhibition of the enzyme by a single dose of malathion. Finally, equitoxic doses (based on the LD_{50} values) of aldrin and malathion or DDT plus malathion provided mutually protective action in rats, whereas synergistic effects (more than additive) were noted when 1/3 of the LD_{50} values of each chlordane, parathion, and malathion were administered to mice (Keplinger and Deichmann 1967).

The effects of metabolic enzyme inducers on the toxicity of malathion have been examined in several studies. For example, Brodeur (1967) observed that intraperitoneal administration of 50 mg/kg of phenobarbital (PB) to rats for 5 days before a single injection of malathion (unspecified purity) produced maximum protection against the inhibition of cholinesterase activity of malathion in brain, submaxillary gland, and serum; extension of the PB treatment for 25 days did not confer additional protection. The PB-induced reduction in anticholinesterase activity was paralleled by an increase in the intraperitoneal LD_{50} from 520 to 920 mg/kg. Further experiments showed that PB-induced resistance was due mostly to induction of a liver carboxylesterase and that inhibition of this enzyme by TOTP resulted in a complete loss of protection of PB against malathion (Brodeur 1967). In similar experiments in mice, three daily intraperitoneal treatments with 75 mg/kg of PB did not protect against the toxicity of malathion (unspecified purity); the control LD_{50} was 985 vs. 915 mg/kg in PB-pretreated mice (Menzer and Best 1968). No enzymatic assays were conducted in the latter study. In a more recent study, Ketterman et al. (1987) produced differential induction of cytochrome P-450-dependent monooxygenases, microsomal carboxylesterases, and cytosolic glutathione-S-transferases, all systems that metabolize malathion. PB (100 mg/kg) given on days 1, 4, 6, and 7 significantly induced cytochrome P-450 and carboxylesterase activity, and pretreatment with 2(3)-tert-butyl,-4-hydroxyanisole (BHA), which greatly induced glutathione-S-transferases, did not protect against malathion (98.5% pure) toxicity. Ketterman et al. 1987) suggested that the lack of protection may have been due to concurrent increases in both activating and detoxifying pathways.

In addition to studies of interactions with other chemicals, a few studies have examined the influence of malnutrition on the toxic effects of malathion. For example, Bulusu and Chakravarty (1984) reported that administration of a single oral dose of malathion to rats kept on a low protein diets for 3 weeks induced more severe liver effects than those seen in rats maintained on a normal diet and given malathion. This conclusion was based on the findings of greater decreases in liver AST and ALT activities and greater increases in liver β-glucuronidase activity in rats maintained on lower protein diets and given malathion than in rats kept on normal diets and administered malathion. The authors speculated that a combined effect of malathion and low protein diets on membranes allowed cytoplamic AST and ALT to leak into the plasm, whereas disruption of lysosome membrane caused β-glucuronidase to be released into the cytoplasm. Similar results regarding β-glucuronidase activity were reported in a study in which the rats were maintained on low protein diets and treated with malathion for 3 weeks (Bulusu and Chakravarty 1986). In rats, exposure to malathion during gestation days 6, 10, and 14 increased serum levels of cholesterol and triglycerides and the levels of cholesterol, triglycerides, and phospholipids in brain, liver, kidney, and uterus, and these effects were intensified in rats maintained on a low protein diet

(Prabhakaran and Devi 1993). In a study of similar design, the same group of investigators reported that a low protein diet plus malathion may have induced more severe embryotoxicity in rats than either treatment alone, but it is difficult to draw a definite conclusion from the data presented in the study (Prabhakaran et al. 1993).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to Malathion than will most persons exposed to the same level of malathion 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 malathion, or compromised function of organs affected by malathion. Populations who are at greater risk due to their unusually high exposure to malathion are discussed in Section 6.7, Populations With Potentially High Exposures.

Some of the most common signs and symptoms of organophosphate intoxication are bronchoconstriction and increased bronchial secretions; therefore, individuals with respiratory conditions such as asthma may be affected by exposure to malathion levels lower than would affect normal subjects. However, following aerial application of malathion in Santa Clara County, California, in 1981, a survey conducted to assess the acute health effects of the application found no significant increase in the number of asthma-related visits to a university medical school in the area; however, the authors cautioned that the numbers in the study may have been too small to provide definite conclusions (Kahn et al. 1992).

Anticholinergic agents have been recommended for the treatment of wide variety of conditions, but therapeutic uses have been established mainly in four areas: atony of the smooth muscle and the intestinal tract and urinary bladder, glaucoma, myasthenia gravis, and termination of the effects of competitive neuromuscular blocking agents (Taylor 1996). Any individual using anticholinergic agents for therapeutic purposes may be at risk of suffering an increase in unwanted side effects due to possible addition of effects if exposed to organophosphate pesticides.

Little information was located regarding possible polymorphism in enzymes involved in the metabolism or toxic actions of malathion. Talcott et al. (1982) evaluated malathion carboxylesterase activity in 143 human blood serum samples and found an activity range that spanned almost two orders of magnitude (0.1–7.2 units/mL), but found no remarkable age-, sex-, or race-related activity differences. Without providing further details, Abou-Donia (1995) indicated that a genetically determined low level of

plasma cholinesterase is present in about 3% of the population, and therefore, these individuals are particularly sensitive to the effects of organophosphate pesticides.

As detailed in Section 3.9, subjects exposed to other pesticides that also inhibit carboxylesterase activity, enzyme responsible for the detoxification of malathion in mammalian species, may be at higher risk of exceeding thresholds for the manifestation of adverse effects when exposed simultaneously to malathion.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to malathion. 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 malathion. 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 organophosphate pesticides:

Goldfrank LR, Flomenbaum NE, Lewin NA, et al., eds. 1998. Goldfrank's toxicologic emergencies. 6th ed. Stamford, CT: Appleton and Lange.

Haddad LM, Shannon MW, Winchester JF, eds. 1998. Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: WB Saunders Company.

Viccellio P, Bania T, Brent J, et al., eds. 1998. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers.

3.11.1 Reducing Peak Absorption Following Exposure

The following information was extracted from the books listed above; specific chapters were written by Aaron and Howland (1998), Carlton et al. (1998), and Osmundsen (1998). Following dermal contamination with organophosphates, most texts recommend washing the skin with copious amounts of soap and water, which may be followed by a second washing with ethyl alcohol. Ocular exposures should have copious eye irrigation with normal saline or lactated Ringer's solution (Aaron and Howland 1998). Contaminated clothing including leather garments should be destroyed. After oral ingestion, activated charcoal is recommended for many organophosphates, although Carlton et al. (1998) note that it may lack efficiency with some organophosphates such as for malathion. Osmundsen (1998) points out that Ipecac should not be used for organophosphate poisoning. Cathartics may be unnecessary as

intestinal motility is greatly increased. Gastric lavage may be performed with the care to prevent aspiration, as organic solvent vehicles may precipitate pneumonitis. Treatment of inhaled organophosphates is mostly supportive as respiratory distress is a common effect of poisoning; intubation may be necessary to facilitate control of secretions.

3.11.2 Reducing Body Burden

No information was located regarding reducing the body burden of malathion, or organophosphates, following exposure. As mentioned in Section 3.4, malathion is eliminated relatively rapidly, such that short-term exposures will not result in accumulation of the pesticide.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The following information has been extracted from the texts listed above. Administration of atropine and pralidoxime (2-PAM) seems to be a universally accepted treatment for organophosphate poisoning. It should be mentioned, however, that glycopyrrolate, a quaternary ammonium compound, has also been used instead of atropine (Bardin and Van Eeden 1990). Unlike atropine, glycopyrrolate does not cross the blood-brain barrier and, therefore, has fewer central nervous system effects. Atropine is a competitive antagonist at muscarinic receptor sites and since it crosses the blood-brain barrier, it also treats the central nervous system effects. Atropine is particularly helpful in drying excessive secretions especially from the tracheobronchial tree. Atropine does not antagonize nicotinic effects; therefore, 2-PAM is needed for treatment of muscle weakness and respiratory depression. Most texts recommend an initial dose of 1–2 mg for an adult and 0.05 mg/kg for children, preferably by the intravenous route. This may be repeated every 15–30 minutes until signs of atropinization occur. 2-PAM is a quaternary amine oxime that can reverse the phosphorylation of acetylcholinesterase and thereby restore activity. It may also prevent continued toxicity by detoxifying the organophosphate molecule and has an anticholinergic effect (Carlton et al. 1998). 2-PAM and other oximes function by nucleophilic attack on the phosphorylated enzyme; the oxime-phosphonate is then split off, leaving the regenerated enzyme. 2-PAM should be administered as soon as the diagnosis is made. The initial dose is 1–2 g for adults and 25–50 mg/kg for children administered intravenously over 30–60 minutes. The dose can be repeated in 1 hour and then every 8–12 hours until clinical signs have diminished and the patient does not require atropine. Some patients may require multiple doses, as enzyme regeneration depends on plasma levels of the

organophosphate. A 2-PAM serum level of 4 µg/L is suggested as the minimum therapeutic threshold. 2-PAM is considered a very safe drug with few side effects.

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 malathion 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 malathion.

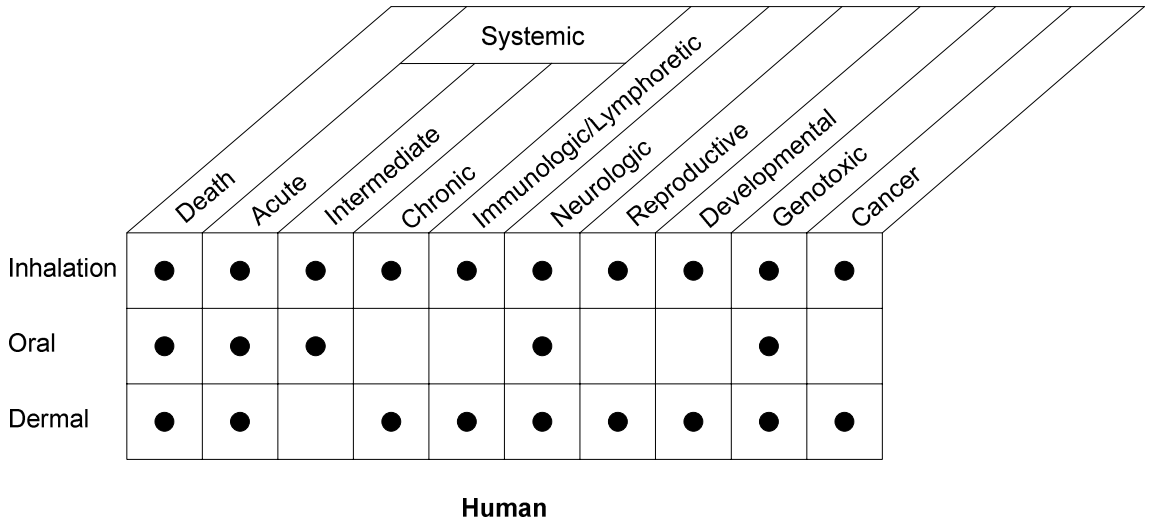
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean 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 Malathion

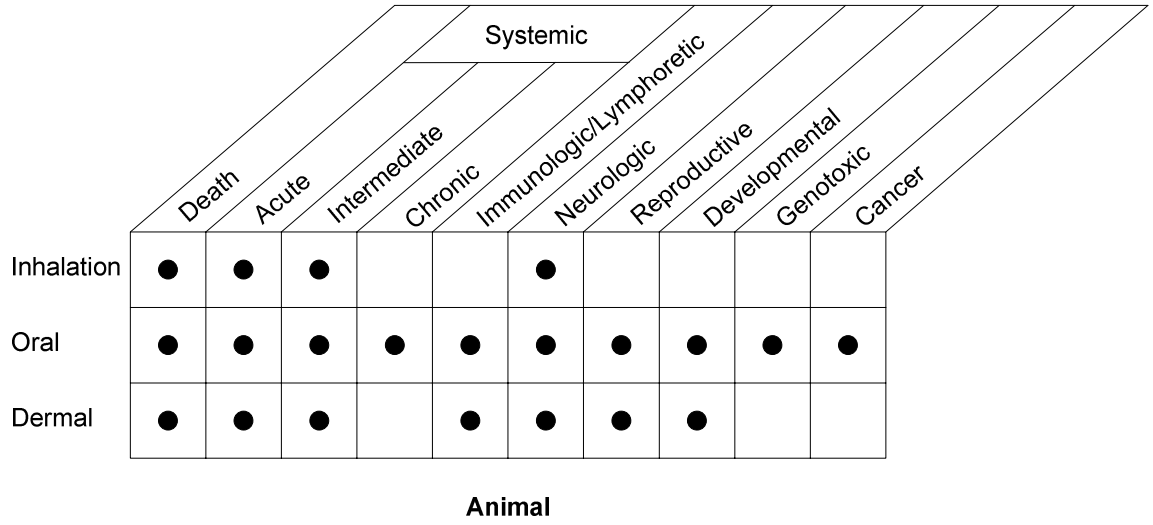
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to malathion are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of malathion. Each dot in the figure indicates that one or more 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 (Agency for Toxic Substances and Disease Registry 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.

As shown in Figure 3-5, there seems to be a fairly complete database on the effects of malathion in humans exposed by inhalation and dermal routes. However, most of this information is derived from

Figure 3-5. Existing Information on Health Effects of Malathion



Human



Animal

● Existing Studies

studies in which subjects were exposed during the manufacture of the material or during application (as applicators or bystanders), situations that involve inhalation and dermal exposure and generally unknown exposure levels. Furthermore, few inhalation and dermal studies provided information specifically for malathion. A single study of controlled inhalation exposure to malathion was available. The oral database is much more limited and consists mainly of case reports of accidental or intentional ingestion of high amounts of malathion formulations. This provided a considerable amount of data on acute systemic and neurological effects, less intermediate data, and no chronic data. No information was located regarding reproductive, developmental, or cancer effects in humans following oral exposure to malathion.

In animals, the studies available for review provided information on systemic, immunologic, neurologic, reproductive, developmental, genotoxic, and cancer effects following oral administration of malathion. It should be mentioned, however, that information on many systemic end points was lacking from the oral studies. No studies were available on chronic systemic effects by the inhalation and dermal routes of exposure, regarding reproductive, developmental, genotoxic, or cancer following inhalation exposure, and regarding genotoxic and cancer effects after dermal exposure.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Limited acute inhalation data specific for malathion were provided by Reeves et al. (1981), Golz (1959), and Albright et al. (1983). Reeves et al. (1981) reported the case of a 12-year-old girl who died from aplastic anemia 6 months after exposure to malathion. Golz (1959) conducted a controlled inhalation study in volunteers and reported nasal and eye irritation within 5–10 minutes of exposure to 85 mg/m^3 of a malathion aerosol; no effects were reported at 21 mg/m^3. Albright et al. (1983) described the case of a 65-year-old man who developed transient renal insufficiency with massive proteinuria 3 weeks after spraying intensively with malathion. Only one study was available with acute inhalation data in animals. In this study, four out of six rabbits died 24 hours after a 6-hour exposure to 128 mg/m^3 of malathion aerosol generated from a formulation containing 6% malathion and a fuel oil mixture (Weeks et al. 1977). However, there were no deaths among rabbits exposed to 123 mg/m^3 generated from a 95% pure malathion formulation, an exposure concentration that induced a 38% inhibition of RBC cholinesterase activity. An exposure concentration of 65 mg/m^3 was a NOAEL and was used to derive an acute inhalation MRL. Acute oral data in humans come almost exclusively from case reports of accidental or intentional ingestion of high amounts of malathion formulations. Many cases resulted in deaths following ingestion of estimated doses of malathion between 350 and 2,000 mg/kg (Faragó 1967; Jušić and Milić 1978; Morgade and Barquet 1982; Namba et al.

1970; Zivot et al. 1993). Almost all cases presented the typical signs and symptoms of cholinergic stimulation (Amos and Hall 1965; Choi et al. 1998; Crowley and Johns 1966; Dive et al. 1994; Jušić and Milić 1978; Monje Argiles et al. 1990; Namba et al. 1970; Tuthill 1958; Zivot et al. 1993).

Acute oral studies in animals provided information regarding death (Lu et al. 1965; Mendoza 1976; Talcott et al. 1977; Umetsu et al. 1977; Weeks et al. 1977), systemic effects (Krause 1977; Krause et al. 1976; Lox 1983; Ojha et al. 1992; Piramanayagam and Manohar 2002; Piramanayagam et al. 1996; Simionescu et al. 1977), immunological effects (Casale et al. 1983; Rodgers et al. 1986; Rodgers and Xiong 1996, 1997b, 1997d), neurological effects (Casale et al. 1983; Ehrich et al. 1993; Mathews and Devi 1994; Vijayakumar and Selvarajan 1990; Weeks et al. 1977), reproductive effects (Krause et al. 1976; Lochry 1989; Ojha et al. 1992; Prabhakaran et al. 1993; Siglin 1985), and developmental effects (Khera et al. 1978; Lochry 1989; Machin and McBride 1989a, 1989b; Mathews and Devi 1994). Although there appears to be an extensive database from animal studies, the quality of many studies precludes their use for risk assessment. Some of the limitations include poor reporting of the results and/or only one dose level tested. Well-conducted studies by Rodgers and colleagues identified the lowest effects levels for immunological alterations in mice (degranulation of mast cells) administered 0.1 mg malathion/kg/day for 14 days (Rodgers and Xiong 1997d). An additional study from this series found increased serum histamine levels in rats and mice after a single dose of 10 mg/kg (Rodgers and Xiong 1997b); the NOAEL was 1 mg/kg. The physiological significance of these immunological effects is unknown and should be addressed in further studies in which the animals are challenged with pathogens. Therefore, it seems inappropriate at this time to base an acute oral MRL on subtle immunological alterations of unknown physiological significance. Worth noting also is a relatively low LOAEL of 4.4 mg/kg (the only dose level tested) for decreased hematocrit and platelet counts in rats administered the pesticide once by gavage in water (Lox 1983). It is interesting that an intermediate-duration study by Lox and Davis (1983), also in rats given malathion in the drinking water, reported hematological and hepatic effects at very low doses (see below) not seen in any other gavage or feeding study. Therefore, additional studies should compare the effects of malathion on a wide range of end points given in water with those after administration mixed with food. The study design should clarify the role of the administration vehicle. The physiological significance of the LOAEL of 4.4 mg/kg from the Lox (1983) study is unknown and not appropriate for MRL derivation.

Acute dermal data in humans include a report by Ramu et al. (1973) who described a fatality among a group of children who had their hair washed with a solution containing 50% malathion in xylene. Typical signs and symptoms of cholinergic stimulation were seen among the most severely intoxicated children.

Parker and Chattin (1955) also described a case of a 10-year-old girl who had neurological manifestations of poisoning after having extensive dermal contact with a malathion formulation in the form of flakes. Also, laboratory studies in volunteers showed that a single exposure to 10% malathion (95% pure) induced contact sensitization in almost half of the subjects, and that 0.1 and 0.01% concentrations of 99.3% malathion were able to evoke positive responses in previously sensitized individuals (Milby and Epstein 1964). Information on effects of malathion after acute dermal exposure in animals was limited a study of lethality in rats (Gaines 1960), a study of delayed-type hypersensitivity in mice (Cushman and Street 1983), and a report on subtle immunological alterations in rats and mice following a single dermal application of malathion (Rodgers and Xiong 1997c). Qualitative data (no dose level) on RBC and plasma cholinesterase were also available from a study in dogs (Vestweber and Kruckenberg 1972). Although the information available does not suggest that the toxicity of malathion is route-dependent, further well-conducted acute dermal studies seem necessary to establish dose-response relationships for a range of end points. This is important because considerable dermal exposure to malathion can occur for the residential handler and during post-application events. Furthermore, under certain exposure scenarios such as following aerial application of malathion over urban areas, dermal doses may be orders of magnitude higher than inhalation doses (Marty et al. 1994).

Intermediate-Duration Exposure. Few intermediate-duration studies were located that described health effects in humans specifically exposed to malathion. However, it is reasonable to assume that many of the studies on cohorts exposed occupationally to malathion, or to pesticides in general, described in Section 3.2, included subjects who may have been exposed for intermediate durations. Limited information is available from a controlled inhalation study in volunteers that identified a NOAEL of 85 mg/m^3 for body weight and neurological effects (cholinesterase activity) (Golz 1959); subjects were exposed to malathion aerosols 2 hours/day for 42 days. Limited data were also located in the studies available regarding effects in animals exposed to malathion in the air. A 13-week study in rats reported hyperplastic changes in the epithelium from the upper respiratory tract following intermittent exposure to 100 mg/m^3 of malathion aerosol and significant reduction in RBC cholinesterase activity at 450 mg/m^3 and higher (Beattie 1994). The LOAEL of 100 mg/m^3 was used to derive an intermediate inhalation MRL for malathion.

A study in humans administered malathion in capsules for up to 56 days identified a NOAEL of 0.34 mg/kg/day for hematological and renal effects; this dose level also constituted a LOAEL for neurological effects (plasma and RBC cholinesterase activity) (Moeller and Rider 1962). The NOAEL for neurological effects was 0.23 mg/kg/day and was used as the basis for derivation of an intermediate-

duration oral MRL. Studies in animals provided information on lethality (NCI 1978, 1979a), systemic effects (Desi et al. 1976; Foster 1968; Krause et al. 1976; Lox and Davis 1983; Ozmen and Akay 1993), immunological effects (Banerjee et al. 1998; Desi et al. 1978; Rodgers and Xiong 1997c), neurological effects (Desi et al. 1976, 1978; Fischer 1988; Husain et al. 1987; Lamb 1994b), and reproductive and developmental effects (Balasubramanian et al. 1987a, 1987b; Kalow and Marton 1961; Krause et al. 1976; Lechner and Abdel-Rahman 1984; Ozmen and Akay 1993; Schroeder 1990). Of special interest is a 60-day study by Lox and Davis (1983), which reported hepatocyte degeneration in rats at the very low dose of approximately 0.15 mg/kg/day of malathion (99% pure) in drinking water (1 ppm in water). This is one of the few studies in which malathion was administered in the drinking water. Since no liver histopathology was described in any other intermediate-duration oral study with much higher malathion doses either in the food or by gavage, the findings of Lox and Davis (1983) should be interpreted with caution until such results can be replicated. Also of interest is the finding of increased peritoneal macrophage function in mice treated for 90 days with 0.1–10 mg/kg/day by gavage (Rodgers and Xiong 1997c). However, as Rodgers and Ellefson (1992) pointed out, the physiological significance of the magnitude of this effect is unknown. An additional 28-day immunological study in mice reported that doses as low as 0.018 mg/kg/day of commercial-grade malathion increased the primary immune response to immunization with SRBC (Johnson et al. 2002). Dermal data in animals were limited to information on lethality (Dikshith et al. 1987), systemic effects (Boyes et al. 1999; Moreno 1989), and neurological effects (Boyes et al. 1999; Dikshith et al. 1987; Moreno 1989). Results regarding systemic effects after dermal exposure were insufficient to construct dose-response relationships, but additional studies may not be necessary since malathion is rapidly degraded in the environment and long-term dermal exposure is not expected to occur for the general population or for people living near waste sites.

Chronic-Duration Exposure and Cancer. Limited information was found regarding health effects in humans after chronic-duration exposure to malathion. Information on effects of chronic exposure is derived mostly from studies of workers in which both the inhalation and dermal routes of exposure play significant roles. It should also be noted that although occupational exposure is generally assumed to be chronic, for some types of occupations (i.e., pesticide applicators), exposures are usually seasonal, involving only a few weeks or months per year. A study of workers exposed to organophosphates (not only malathion) for up to 29 years found a higher frequency of respiratory tract infections among the workers than in controls (Hermanowicz and Kossman 1984). The authors also observed marked impairments of neutrophil chemotaxis and significantly decreased neutrophil adhesion among the workers. A study at a pesticide manufacturer (primarily malathion) found an inverse relationship between hemoglobin concentration and duration of employment (Singaravelu et al. 1998). Studies of workers

exposed to several pesticides have also documented inhibition of plasma and RBC cholinesterase, clinical signs, and neurophysiological alterations (Baker et al. 1978; Ernest et al. 1995; Peedicayil et al. 1991; Stålberg et al. 1978). A study of pesticide applicators also investigated the possible role of organophosphate insecticides and retinal degeneration, but a definite conclusion could not be reached (Kamel et al. 2000). Information is lacking on potential effects of long-term, low-level exposure to malathion on many end points. This information can only be obtained from evaluation of cohorts exposed only to malathion, but data from subjects exposed to a limited number of organophosphates would also be helpful. No studies were located that evaluated the effects of chronic inhalation or dermal exposure in animals, but because malathion is relatively rapidly degraded in the environment, no such exposures are expected to occur for the general population or for people living near waste sites. Several long-term bioassays have been conducted in rats and mice that provided information on noncancer effects (death, systemic, and neurological effects) (Daly 1996a; NCI 1978, 1979a; Slauter 1994). The lowest LOAEL was 29 mg malathion/kg/day for 29% inhibition of plasma cholinesterase in male Fischer-344 rats in a study by Daly (1996a); the NOAEL was 2 mg/kg/day and was used to derive a chronic oral MRL.

Several studies have examined the possible association between occupational exposure to pesticides and certain types of cancer, particularly non-Hodgkin's lymphoma (NHL) and leukemia. However, because workers are usually exposed to multiple pesticides, it is difficult to establish associations with specific pesticides. Still, information relevant to malathion is available in some of these studies. Exposure to malathion was associated with increased risk of NHL in a study of men in Iowa and Minnesota (Cantor et al. 1992), of women in Nebraska (Zahm et al. 1993), and of men in Canada (McDuffie et al. 2001). A retrospective cohort study of 32,600 employees of a lawn care company found no specific association between deaths due to NHL and exposure to malathion (Zahm 1997) and neither did a study of pesticide users from Iceland (Zhong and Rafnsson 1996). The study of men in Iowa and Minnesota also found an elevated risk of leukemia in men who used malathion as an animal insecticide for >10 days/year (Brown et al. 1990). A slight non-significant increased risk for multiple myeloma was observed among farmers who used malathion in an additional study among men in Iowa, but failure to use protective equipment was not associated with increased risk (Brown et al. 1993). In spite of some positive associations, there is no clear evidence that exposure to malathion causes cancer in humans. As previously mentioned, the magnitude of the excesses is generally small, exposure assessment is unreliable, and mixed exposure always occurs.

Malathion has been tested in oral bioassays conducted in rats (two strains) (Daly 1996a; NCI 1978, 1979a) and mice (NCI 1978; Slauter 1994). The metabolite, malaoxon, also has been tested in rats (Daly 1996b; NCI 1979b) and mice (NCI 1979b). No clear evidence of carcinogenicity for malathion was found in the bioassays conducted by NCI (NCI 1978, 1979a), but there was evidence of liver carcinogenicity in female Fischer-344 rats in the Daly (1996a) study and in male and female $B3C6F_1$ mice in the Slauter (1994) study. In the two positive studies, evidence of carcinogenicity occurred at doses that were considered excessive (EPA 2000a, 2000b). There was no evidence of carcinogenicity for malaoxon in rats or mice (Daly 1996b; NCI 1979b), but upon reevaluation of the NCI (1979b) study, NTP concluded that there was equivocal evidence of carcinogenicity for male and female Fischer-344 rats based on reinterpretation of C-cell neoplasms of the thyroid (Huff et al. 1985). Further bioassays do not seem necessary.

A recent review of the literature on pesticides and cancer by Zahm et al. (1997) identified several areas where data gaps exist. First, improvements in exposure assessment in epidemiologic studies are needed. Also, there is a need for validity and reliability studies of recall of pesticide use both for occupationally and nonoccupationally exposed populations. In addition, efforts should continue to try to gain access to information on inert ingredients of pesticide formulations since inert components are not necessarily biologically inert. Another data gap identified is the lack of studies on migrant and seasonal farm workers who often start exposure at an early age. The mechanism of malathion-induced carcinogenicity in animals is not known, but it does not appear to involve mutagenicity. Additional studies investigating noncholinergic mechanism of malathion toxicity and how these may potentially by involved in malathion carcinogenicity would be valuable.

Genotoxicity. The genotoxicity of malathion has been investigated in many studies. Of four studies that monitored humans exposed to malathion occupationally or by intentional ingestion of malathion formulations, two found increased chromosomal aberrations in peripheral lymphocytes and micronuclei (Singaravelu et al. 1998; van Bao et al. 1974), whereas the remaining two found no evidence of micronuclei or chromosomal aberrations (Titenko-Holland et al. 1997; Windham et al. 1998). The majority of the studies in animals were conducted in mice and showed that malathion has the capacity to produce chromosomal changes, including chromosomal aberrations and micronuclei in bone marrow (Abraham et al. 1997; Amer et al. 2002; Dulout et al. 1982, 1983; Giri et al. 2002; Kumar et al. 1995). However, a negative effect for chromosomal aberrations in mouse bone marrow was reported by Degraeve and Moutschen (1984) and a weak positive effect was reported by Dzwonkowska and Hubner (1986) in hamster bone marrow. Effects on germ cells have been mixed. No chromosomal aberrations

were reported in mouse spermatogonia by Degraeve and Moutschen (1984) and tests for dominant lethal mutation also were negative in that study. In contrast, Salvadori et al. (1988) reported chromosomal aberrations in mouse spermatogonia and Hoda et al. (1993) noticed a decrease in meiotic index in primary spermatocytes of mice treated with malathion. A study in *Drosophila* also showed a positive dominant lethal mutation (Kumar et al. 1995).

In general, the results from standard gene mutation tests in bacteria did not show mutagenicity with or without activation or gave a weak positive response (Pednekar et al. 1987; Shiau et al. 1980; Wong et al. 1989). Results from *in vitro* studies in mammalian cells, including human lymphocytes, showed that malathion appeared to produce cytogenetic damage as evidenced by chromosomal aberrations and sister chromatid exchanges (Balaji and Sasikala 1993; Garry et al. 1990; Nicholas et al. 1979; Nishio and Uyeki 1981; Pluth et al. 1996, 1998; Sobti et al. 1982; Walter et al. 1980). There is weak evidence of *in vitro* interaction of DNA bases by malathion (Wiaderkiewicz et al. 1986).

Although it appears that malathion has been tested for genotoxicity in a wide variety of systems, the results have been mixed largely because of the different experimental designs and different malathion formulations tested. Studies in vitro should always monitor cell viability to clearly distinguish genetic effects from cytotoxicity. Also, it would be important to know the composition of the malathion mixture to be tested and to test each one of the components since humans are likely to be exposed to technical mixtures rather than to pure malathion. Additional studies are also necessary to examine the interaction of malathion and DNA. Continued studies on genomic sequence analysis combined with reverse transcription polymerase chain reaction (PCR) amplification of lymphocytes from malathion exposed subjects may be able to identify a mutation spectrum that may be fairly specific for malathion and that could eventually be used as a biomarker of exposure.

Reproductive Toxicity. Limited information was located regarding reproductive effects in humans following exposure to malathion. A study of pregnant women exposed during periods of malathion spraying in California found a moderate association between stillbirths and certain exposure variables, but these associations were not consistent or statistically significant and, therefore, were attributed to chance (Thomas et al. 1992). An additional study of males involved in the mixing and spraying of a variety of organophosphates and insecticides found a significantly higher percent of stillbirths and abortions compared to unexposed couples, and also lower fertility among exposed males (Rupa et al. 1991b). However, the role of malathion, if any, is impossible to determine. No studies were located on reproductive effects of malathion in humans exposed orally or dermally.

No information was available regarding reproductive effects in animals following inhalation exposure to malathion. Acute studies in male animals, mainly rats, administered malathion orally have reported transient alterations in spermatogenesis and alterations in the seminiferous tubule epithelium (Krausse 1977; Krausse et al. 1976; Ojha et al. 1992; Piramanayagam et al. 1996), but none of these studies assessed reproductive function. A 12-week gavage study also reported reversible testicular alterations in rats given 45 mg/kg/day malathion (Balasubramanian et al. 1987b), but no morphological alterations were seen in the reproductive organs from male rats or mice in chronic bioassays (NCI 1978, 1979a). An intermediate-duration dermal study in male and female rabbits did not observe any significant gross or microscopic alterations in the reproductive organs following application of up to 1,000 mg/kg/day of malathion 6 hours/day, 5 days/week for 3 weeks (Moreno 1989). Malathion was not a reproductive toxicant when administered to females at doses that did not induce maternal toxicity (Lechner and Abdel-Rahman 1984; Mathews and Devi 1994; Prabhakaran et al. 1993; Siglin 1985). A 2-generation study in rats found no significant effects on reproductive performance, fertility indices, and gestation length (Schroeder 1990). The only significant finding in a chronic bioassay was an increased incidence of cystic endometrial hyperplasia in mice treated with approximately 1,490 mg/kg/day of malathion for 80 weeks (NCI 1978). The overall evidence in animals suggests that malathion is not a reproductive toxicant, but the less than optimal quality of some studies do not allow drawing a firm conclusion. The issue of testicular toxicity should be further explored in studies in animals exposed at various ages including exposure in utero and later tested for reproductive performance. Also, studies examining standard semen and sperm parameters in adult animals would provide valuable information. These studies should be conducted by the oral route of exposure since this route is the most relevant for exposure of the general population and there is no evidence suggesting that the toxicity of malathion is route-specific.

Developmental Toxicity. Data on developmental effects of malathion in humans are limited. Two studies conducted in California after aerial spraying of malathion did not find consistent or significant developmental effects in the offspring from women who were pregnant during the spraying (Grether et al. 1987; Thomas et al. 1992). Some positive associations were found in the former study between exposure and some anomalies, but no biologically consistent pattern was observed. Thomas et al. (1992) found a significant association for gastrointestinal anomalies and second trimester exposure, but the gastrointestinal tract is completely developed by the second trimester. An additional study of paternal exposure to malathion found no significant association between exposure and congenital malformations (García et al. 1998). No information was found regarding developmental effects in humans following oral exposure to malathion. The only data after dermal exposure are from Lindhout and Hageman (1987),

who discussed a possible association between the use of a hair lotion containing malathion by a woman during weeks 11 and 12 of pregnancy and the birth of a severely malformed child. However, a causal link is difficult to establish.

No information was located regarding developmental effects in animals following inhalation or dermal exposure to malathion. Transfer of malathion (and/or metabolites) to the fetus through the placenta and via maternal milk has been demonstrated indirectly (Chhabra et al. 1993; Mathews and Devi 1994). Oral studies in rats and rabbits have not shown embryotoxicity (Khera et al. 1978; Lochry 1989; Machin and McBride 1989a; Siglin 1985) or showed embryotoxicity at doses that also caused maternal toxicity (Prabhakaran et al. 1993). However, reduced fetal weight and crown-rump length were seen in mice in a study that provided no information on maternal effects (Asmatullah et al. 1993). A study by Kalow and Martin (1961) found increased neonatal mortality in rats treated for at least 5 months before pregnancy, but again, no information was presented on maternal effects, which seriously weakens the evidence. In a 2-generation study, the only developmental effect noticed was a decrease in body weight gain in pups from the F1A and F2B litters during the lactation period at parental doses of 394 mg/kg/day of malathion for males and 451 mg/kg/day for females, with corresponding NOAELs of 131 and 153 mg/kg/day (Schroeder 1990). No teratogenic effects of malathion were reported in the studies evaluated (Khera et al. 1978; Lechner and Abdel-Rahman 1984; Lochry 1989; Prabhakaran et al. 1993; Schroeder 1990; Siglin 1985). Although most of the data suggest that malathion is not a developmental toxicant, there is still uncertainty regarding whether effects could occur at doses not causing maternal toxicity, largely because of limitations of experimental design or reporting in some studies. Therefore, a well-designed study is warranted. In addition, a developmental neurotoxicity study in rats in which pups are tested at various ages after being exposed in utero and/or via maternal milk would fill a data gap. The oral route should be preferred to complement the existing information and because there is no evidence that the toxicity of malathion is route-specific.

Immunotoxicity. There is some information suggesting that exposure to malathion may affect the immune system in humans. Albright et al. (1983) described a case of possible immune complex nephropathy in a man who developed transient renal insufficiency with massive proteinuria after spraying intensively with malathion. Impairment of neutrophil chemotaxis was observed among a group of workers exposed to organophosphate pesticides, including malathion, for 0.1–29 years (Hermanowicz and Kossman 1984). Malathion was shown to be a contact sensitizer in a laboratory study with volunteers (Milby and Epstein 1964). A case of immediate IgE reaction to malathion and another of irritant reaction to malathion and to the bait was described among subjects who developed dermatitis following aerial

application of malathion in Southern California (Schanker et al. 1992). No delayed hypersensitivity was seen among these cases. Another study of subjects in Southern California following aerial spraying of malathion found no significant increases in the number of visits for allergic problems to hospital emergency departments during the application period compared with the prespray period or the corresponding period the previous year (Kahn et al. 1992). No information was located regarding immunological effects in humans following oral exposure to malathion.

Studies in animals suggest that malathion can induce both immune enhancement and immune depression at noncholinergic dose levels. A number of studies conducted by Rodgers and colleagues showed that malathion stimulated immune cell function. For example, relatively low (1–2 mg/kg) single oral or dermal doses of malathion (>99% pure) increased serum histamine levels in rats and mice (Rodgers and Xiong 1997b). Daily oral dosing for 14 days with 1 mg/kg/day of malathion stimulated macrophage function in mice (Rodgers and Xiong 1997d). Immunosuppressive effects were reported mostly in repeated dosing studies. Mice administered malathion in the diet for 3–12 weeks showed alterations in both humoral immune function and cell mediated immunity (Banerjee et al. 1998). Immune suppression was also seen in rats and rabbits exposed to malathion for intermediate-duration periods (Banerjee et al. 1998). Cell mediated suppression was also observed in mice administered malathion for 90 days at 1 and 10 mg/kg/day, but cell mediated enhancement was seen at 0.1 mg/kg/day (Rodgers and Xiong 1997c). Enhancement of antibody production was reported in female mice treated with 0.018 mg/kg/day in a 28-day study (Johnson et al. 2002). The available studies in animals indicate that malathion modulates immune parameters at relatively low doses, but further research is needed to determine whether these observed responses place the animals at increased risk when challenged with pathogens. Rodgers and Ellefson (1992) suggested that malathion-induced mast cell degranulation may be due to inhibition of an esterase on the cell surface; therefore, further research should explore this possibility. The immune enhancing properties of malathion may be relevant for people with autoimmune disease as their condition may aggravate if exposed to malathion. As suggested by Rodgers and Xiong (1997b), it is also possible that the immune enhancement by malathion may be related to reports of possible contact hypersensitivity (Milby and Epstein 1964) or skin rashes and irritation after malathion applications for pest control (CDHS 1991; Schanker et al. 1992).

Neurotoxicity. Information in both humans and animals indicates that the nervous system is the main target of malathion-induced toxicity following acute exposure by any route. This is particularly evident after exposure to high doses of malathion, as has occurred, for example, in cases of accidental or intentional ingestion of malathion formulations (Choi et al. 1998; Dive et al. 1994; Jušić and Milić 1978,

Lee and Tai 2001; Matsukawa et al. 1997; Monje Argiles et al. 1990; Namba et al. 1970; Ramu et al. 1973). As an organophosphate pesticide, malathion inhibits the activity of the enzyme acetylcholinesterase as well as that of plasma cholinesterase. The inhibition of acetylcholinesterase at various levels within the nervous system produces a characteristic set of signs and symptoms including respiratory distress, bradycardia, increased bronchial secretions, excessive salivation, lacrimation, pupillary constriction, fasciculations, abdominal cramps, and diarrhea (Aaron and Howland 1998; Carlton et al. 1998; Osmundson 1998). Most of these signs and symptoms have been observed in the cases listed above. In addition, abnormal electromyographic findings were reported in some studies of documented ingestion of malathion (Crowley and Johns 1966; Dive et al. 1994; Monje Argiles et al. 1990). A study of controlled administration of malathion in capsules to volunteers identified a NOAEL and LOAEL for inhibition of plasma cholinesterase of 0.23 and 0.34 mg/kg/day, respectively (Moeller and Rider 1962), and these findings were used to derive an intermediate oral MRL for malathion. Studies of workers exposed to several pesticides have also documented inhibition of plasma and RBC cholinesterase, and in some cases, the degree of enzyme inhibition has been correlated with the presence or absence of clinical signs (Ernest et al. 1995; Peedicayil et al. 1991; Stålberg et al. 1978). Information is lacking on potential effects of long-term, low-level exposure to malathion as well as on potential long-term effects of acute high exposure to malathion. This information can only be obtained from evaluation of cohorts exposed only to malathion, but data from subjects exposed to a few organophosphates would also be helpful.

Studies in animals support the findings in humans. In addition to measurements of cholinesterase activity, a few studies have examined the effects of malathion on neurobehavioral parameters. An acute study that tested a functional observation battery in rats reported increased motor activity 21 days after a single gavage dose of 2,000 mg/kg of malathion (88% pure) (Ehrich et al. 1993), whereas a similarly designed study found decreased motor activity 14 days after dosing with 2,000 mg/kg malathion (96.4% pure) (Lamb 1994a). Similar inconsistencies were seen between two 90-day feeding studies (Desi et al. 1976; Lamb 1994b). Further studies are needed to clarify these inconsistencies. Chronic-duration studies have reported inhibition of plasma and RBC cholinesterase activity in both rats (Daly 1996a) and mice (Slauter 1994) and body tremors in female mice after 70 weeks of dosing with approximately 2,980 mg/kg/day of malathion (NCI 1978). Should additional chronic studies be conducted, microscopic examination of nervous tissues from both peripheral and central nervous system may be conducted. Also, a subgroup of animals could be tested for possible subtle neurobehavioral alterations of long-term, low-level exposure. Finally, pilot studies should be designed to evaluate possible neurodevelopmental effects of gestational and lactational exposure to malathion.

Epidemiological and Human Dosimetry Studies. Information on the health effects of malathion in humans is derived from case reports of accidental or intentional exposure to malathion (Choi et al. 1998; Crowley and Johns 1966; Dive et al. 1994; Faragó 1967; Jušić and Milić 1978; Monje Argiles et al. 1990; Morgade and Barquet 1982; Namba et al. 1970; Ramu et al. 1973; Tuthill 1958; Zivot et al. 1993), epidemiological studies (Grether et al. 1987; Kahn et al. 1992; Thomas et al. 1992), studies of exposure to multiple pesticides including malathion (Brown et al. 1990, 1993; Cantor et al. 1992; Ernest et al. 1995; Hermanowicz and Kossman 1984; Peedicayil et al. 1991; Rupa et al. 1991b; Stålberg et al. 1978; Zahm 1997; Zahm et al. 1993), and controlled exposure studies (Golz 1959; Milby and Epstein 1964; Moeller and Rider 1962). The most likely identifiable subpopulations exposed to malathion are pesticide applicators, farm workers, individuals involved in the production of malathion, and individuals exposed in homes after residential application. Well-designed epidemiological studies of exposed workers and follow-up evaluations of cohorts from the general population who may have been exposed during aerial application of the pesticide are needed. Specific assessment of cancer risks and examination of the effects of malathion on the nervous system and immune systems are needed. The nervous system is a known target of acute exposure, but little is known on possible long-term effects of acute exposure. Malathion seems to have modulatory effects on the immune system of animals at noncholinergic dose levels. Therefore, evaluation of the immune status of exposed humans would be important. Studies in animals have shown that impurities in malathion formulations play an important role in the toxicity of malathion and have inherent toxicity themselves. Identification of impurities and inert ingredients in commercial formulations as well as potential levels of exposure seems indicated.

Biomarkers of Exposure and Effect.

Exposure. Malathion metabolites (MCA, DCA, DMPT, DMPDT) have been measured in the urine from the general U.S. population and from workers exposed to the pesticide (Fenske 1988; Krieger and Dinoff 2000; Kutz et al. 1992; MacIntosh et al. 1999b; Warren et al. 1985). In the general population, MCA was the most abundant and was found in only a small percentage of the samples (Kutz et al. 1992; MacIntosh et al. 1999b). Since malathion does not seem to accumulate in the body, the presence of malathion metabolites in the general population probably reflects continuous background exposure via the food rather than isolated exposures to significant amounts. Additional studies of the general population correlating malathion metabolite levels with health status as well as with dietary habits would provide useful information for risk characterization and risk assessment.

Suggestive evidence of malathion-induced specific mutations in human T-lymphocytes exposed *in vitro* was presented by Pluth et al. (1996, 1998). Further studies on this issue are needed to establish dose-

response relationships, to test other organophosphates to determine specificity, and to test cells from occupationally and accidentally (or intentionally) exposed subjects.

Effect. There are no biomarkers of effect specific for malathion. As an organophosphate pesticide, malathion in sufficient amounts, produces typical signs and symptoms of cholinergic stimulation. Plasma and RBC cholinesterase levels are widely used as biomarkers of exposure to organophosphates, but alone, their levels do not predict whether adverse health effects will occur except in cases of significant inhibition (Maroni 2000). Because baseline data for plasma and RBC 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.

Absorption, Distribution, Metabolism, and Excretion. Among the areas of absorption, distribution, metabolism, and excretion, the greatest data needs seem to lie in metabolism. The most unique feature of malathion toxicokinetics (i.e., the extremely rapid hydrolysis at the carboxylester linkages) is still poorly understood. Since carboxylesterase activities are the major determinant of the malathion and malaoxon levels *in vivo*, many aspects of this enzyme need to be studied. Although it is known that carboxylesterase exists in more than one form, details remain unknown. The question of whether the same carboxylesterase hydrolyze both malathion and malaoxon is still unanswered. It is also unknown whether the reported variable α/β ratio of monocarboxylic acid metabolites is due to the variation in the enzyme or to variable contributions of different isozymes.

Less urgent toxicologically, but relevant, is the nature of the enzyme that yields dicarboxylic acid from either of the monocarboxylic acids. Beyond the isozyme question, kinetic data on these enzymes would also contribute to our understanding of toxicokinetics. Knowledge of K_m and V_{max} values of isozymes in various organs would greatly facilitate construction of useful PBPK models. Though the importance of malaoxon in the acute toxicity of malathion is unquestionable, generation, distribution, and metabolism of malaoxon has been little studied. This likely reflects the technical difficulty imposed by the overwhelmingly active carboxylesterase that prevents quantitation or even detection of malaoxon. Such difficulties may be overcome by inhibiting carboxylesterase *in vitro* as was demonstrated by the increase in cytochrome P-450 binding of malathion and malaoxon in the presence of bis-(p-nitrophenyl)phosphate, a carboxylesterase inhibitor (Stevens and Greene 1973). *In vivo* studies of distribution and metabolism may also benefit from similar strategies. Suppression of carboxylesterase in Sprague-Dawley rats *in vivo* has been accomplished with TOTP.

Defining the source of malaoxon responsible for the acute neurotoxicity of malathion will be critical to our understanding of human hazards. The source may not be a single organ (as was discovered for parathion) (Nakatsugawa 1992). Although the detoxification of malathion is mainly set by carboxylesterase, other biotransformation enzymes assume a much greater role when carboxylesterase is suppressed. Since the suppression occurs to varying degrees with all commercial formulations, there is also a need to define the nature and significance of the phosphatases and GSH S-transferase involved in the metabolism of malathion and malaoxon. Human hazards from malathion will be better understood through further studies of absorption of malathion. Here again, studies of absorption in isolation from the influence of carboxylesterase may reveal clearer data. In addition, relationships between physical properties such as partition coefficients and absorption of chemicals were explored in early literature without clear conclusions. The reported lack of clear correlation in early literature (Ahdaya et al. 1981; Shah et al. 1981), for example, may need to be reexamined. The technique employed seems inadequate to estimate such physical parameters accurately, relying on near-background level counts to estimate the concentration in the oil phase. More reliable partition coefficients have been published. Meaningful distribution studies may only be possible when better metabolic data and techniques have been secured. When the levels of malathion and malaoxon are obscured by the rapid metabolism, more data on just the distribution of both the parent insecticide and metabolites would reveal little additional information.

Comparative Toxicokinetics. Absence of carboxylesterase in human blood is a conspicuous departure from the rat model, which has most often been employed. Comparative studies involving volunteers, rats, mice, and perhaps other mammals may reveal useful patterns. Interestingly, fairly wide differences between rats and mice are already apparent. Umetsu et al. (1977) tested the acute oral toxicity of malathion samples in female Sprague-Dawley rats and Swiss white mice fasted 6 hours before dosing. For a technical malathion, the LD50 for the rat was 1,500 mg/kg and for mice was similar at 1,850 mg/kg. For a 99.3% pure malathion, the LD50 values were 9,500 mg/kg for rats and 3,000 mg/kg for mice. For a sample purified by recrystallization, the respective values were 12,500 and 3,600 mg/kg. Comparison seems valid since all tests were done during the course of a single study using the same source of animals. Comparative data for metabolism, particularly for carboxylesterases in various tissues in various species against malathion and malaoxon will contribute greatly to our understanding of potential toxic effects on humans.

Methods for Reducing Toxic Effects. There is good information on the procedures used to limit absorption and to interfere with the mechanism of action of organophosphates, including malathion, after acute exposures (Aaron and Howland 1998; Carlton et al. 1998; Osmundsen 1998). 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. Information on the effects of malathion in children is derived mainly from case reports of accidental ingestion of high amounts of commercial formulations (Ekin 1971; Healy 1959; Jušić and Milić 1978; Tuthill 1958) and cases of dermal exposure (Parker and Chattin 1955; Ramu et al. 1973). In all of these cases, exposure to malathion resulted in the characteristic signs and symptoms of organophosphate poisoning: increased salivation and lacrimation, miosis, nausea, vomiting, abdominal cramps and diarrhea, excessive bronchial secretions and dyspnea, bradycardia and low blood pressure, and muscle fasciculations. One fatality occurred among the cases described by Ramu et al. (1973). A case report of aplastic anemia in a 12-year-old child following inhalation of malathion fumes after fumigation of a home was described by Reeves et al. (1981), but this case seems to be unique; besides, there is no evidence that malathion was the causal agent. These case reports suggest that there are no significant differences in the responses between children and adults. Studies in animals have shown that young animals are more susceptible to the toxicity of high doses of malathion and that this is related to activities of esterases in various tissues (Brodeur and DuBois 1967; Lu et al. 1965; Mendoza 1976; Mendoza and Shields 1976, 1977).

Data on developmental effects of malathion in humans are limited. Two studies conducted in California after aerial spraying of malathion did not find consistent or significant developmental effects in the offspring from women who were pregnant during the spraying (Grether et al. 1987; Thomas et al. 1992). An additional study of paternal exposure to malathion found no significant association between exposure and congenital malformations (García et al. 1998). Most animal data suggest that malathion is not a developmental toxicant when administered at doses that are not maternally toxic (Khera et al. 1978; Lochry 1989; Machin and McBride 1989a; Schroeder 1990; Siglin 1985). However, some uncertainty still remains, largely because of limitations of experimental design or reporting in some studies. Therefore, a well-designed developmental study would be useful. Also, as previously mentioned, a developmental neurotoxicity study in rats in which pups are tested at various ages after being exposed *in utero* and/or via maternal milk would fill a data gap. There is no evidence that malathion has hormone-like effects.

There are no adequate data to evaluate whether pharmacokinetics of malathion in children are different from adults. There is no information to evaluate whether metabolism of malathion is different in children than in adults since the specific P-450 enzymes involved in the metabolism are not known. Only one report was found regarding levels of malathion (or metabolites) in human milk (Roggi et al. 1991). There is evidence in animals that it (or its metabolites) can be transferred via breast milk to the offspring (Chhabra et al. 1993) and that it can cross the placenta (Machin and McBride 1989b; Mathews and Devi 1994). Further information on the dynamics of malathion and metabolites during pregnancy and lactation would be useful.

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 malathion. There are no data on the interaction of malathion with other chemicals in children. Studies in animals have suggested that malnutrition, as may occur among some sectors of the general population, may exacerbate the toxicity of malathion (Bulusu and Chakravarty 1984; Prabhakaran and Devi 1993). Further studies on children from undernourished populations should be conducted to explore this issue. The information available indicates that methods to reduce peak absorption of malathion and to interfere with the mechanism of action used for intoxication in adults are applicable to children.

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

The following ongoing studies concerning health effects associated with malathion have been identified in the Federal Research in Progress (FEDRIP 2002) database.

Dr. R.L. Carr at the Mississippi State University has proposed to determine the effects on behavior and neurochemical function in animals exposed to chronic low levels of malathion and other insecticides. Laboratory rats will be exposed at birth and continue until weaning, a critical time of central nervous system development. The research is sponsored by the U.S. Department of Agriculture.

Dr. H.P. Misra at the Virginia Polytechnic Institute plans to investigate the mechanism of potential genotoxicity of malathion and pesticide mixtures in immune cells *in vitro*. Specific studies include (1) induction of apoptotic cell death by pesticides, (2) the role of p38 MAP kinase and NF-kappa B in

mediating the toxic effects as a consequence of oxidative stress, and (3) the persistence of DNA damage induced by inhibition of repair enzymes. The cells used will be splenocytes and thymocytes from C57B1/6 mice. The research is sponsored by the U.S. Department of Agriculture.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

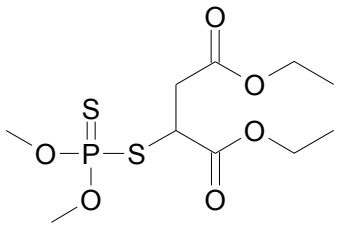
Information regarding the chemical identity of malathion is located in Table 4-1.

Malathion is manufactured in the United States as a technical-grade concentrate that is >90% pure malathion and contains approximately 5% of impurities consisting largely of reaction byproducts and degradation products. As many as 14 impurities have been identified in technical-grade malathion. The identities of the impurities and their percent (w/w) in technical grade malathion were found to be as follows: S-1,2-ethyl-*O,S*-dimethyl phosphorodithioate (isomalathion; 0.2%), S-1,2-bis(ethoxycarbonyl)-ethyl-*O,O*-dimethyl phosphorothioate (malaxon; 0.1%), diethylfumarate (DEF; 0.9%), *O,S,S*-trimethyl phosphorodithioate (0.003–1.2%), *O,O*,S-trimethyl phosphorothioate (0.04%), *O,O,S*-trimethyl phosphorodithioate (1.2%), *O,O,O*-trimethyl phosphorothioate (0.45%), diethylhydroxysuccinate (0.05%), ethyl nitrite (0.03%), diethyl mercaptosuccinate (0.15%), diethyl methylthiosuccinate (1.0%), *O,O*-dimethylphosphorothioate (0.05%), diethyl ethylthiosuccinate (0.1%), and sulfuric acid (0.05%). Malathion is formulated as an emulsifiable concentrate (EC), a dust (D), a wettable powder (WP), a ready-to-use (RTU) liquid, and a pressurized liquid. The quantity of active ingredient (ai) in EC and RTU formulations is variable and can contain up to 82 and 95%, respectively (Brown et al. 1993b; EPA 2001a).

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of malathion is located in Table 4-2.

Table 4-1. Chemical Identity of Malathion

Characteristic	Information	Reference
CAS Nomenclature	Diethyl[(dimethoxyphosphino -thioyl)thio]butanedioate	CAS 2001
Common name	Malathion	Howard and Neal 1992
Synonym(s)	1,2-Di(ethoxycarbonyl)ethyl *O,O*-dimethyl phosphorodithioate	Howard and Neal 1992
Registered trade name(s)	Cekumal Fyfanon® Malixol® Maltox®	Farm Chemicals Handbook 2000 Howard and Neal 1992 Farm Chemicals Handbook 2000 Howard and Neal 1992
Chemical formula	$C_{10}H_{19}O_6PS_2$	Howard and Neal 1992
Chemical structure	 Butanedioic acid, [(dimethoxyphosphinothioyl) thio]-, diethyl ester (malathion)	
Identification numbers:		
CAS registry	000121-75-5	Howard and Neal 1992
NIOSH RTECS	WM8400000	HSDB 2001
EPA hazardous waste		
OHM/TADS		
DOT/UN/NA/IMCO	NA 2783; Malathion	HSDB 2001
shipping	665	HSDB 2001
HSDB		
NCI		

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 Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substance

Table 4-2. Physical and Chemical Properties of Malathion

Property	Information	Reference
Molecular weight	330.36	Howard and Neal 1992
Color	Colorless liquid (pure form)	Matsumura 1985
	Deep brown to yellow	Budavari 1996; NIOSH 1997
Physical state	Liquid	Matsumura 1985
Melting point	2.9 °C	Budavari 1996
Boiling point	156–157 °C	Budavari 1996
Boiling point pressure	0.7 torr	
Density:		
at 25 °C	1.23 g/cm^3	Budavari 1996
Odor	Garlic-like	NIOSH 1997
	Mercaptan	Farm Chemicals Handbook 1999
Odor threshold:		
Water 60 °C	1.0 mg/L	Fazzalari 1978
Air	13.5 mg/m^3 (low) and 13.5 mg/m^3 (high)	Ruth 1986
Solubility:		
Water at 20 °C	145 mg/L	
Organic solvent(s)	Miscible with alcohols, esters, ketones, ethers, aromatics, and vegetable oil; limited solubility in paraffin hydrocarbons	Tomlin 1997 Budavari 1996
Partition coefficients:		
Log K_{ow}	2.36	Hansch et al. 1995
Log K_{ow}	2.89	Chiou et al. 1977; Freed et al. 1978
Log K_{oc}	3.25	Buyuksonmez 1999
Vapor pressure		
at 25 °C	5.03x10^{-6} torr	Watanabe 1993
at 30 °C	3.38x10^{-6} torr	SRC 2000
at 25 °C	7.9x10^{-6} torr	Kim et al. 1984
Henry's law constant (25 °C)	4.9x10^{-9} atm m^3/mol	Fendinger et al. 1990
Autoignition temperature	No data	
Flashpoint	163 °C[a]	Farm Chemicals Handbook 1989
Flammability limits	No data	
Conversion factors[b]	No data	
Explosive limits	Containers of malathion may explode in a fire	U.S. Coast Guard 1984–1985

[a]Pensky-Martens closed cup test
[b]The conversion factor for ppm to mg/m^3 is: ppm = (mg/m^3) (24.45 L/mole)/(g/mole).

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

5.1 PRODUCTION

The organophosphorus insecticide, S-1,2-di(ethoxycarbonyl)ethyl *O,O*-dimethyl phosphorodithioate (common chemical name: malathion), is commercially produced in the United States and abroad. Malathion is not known to occur as a natural substance (IARC 1983). It is produced commercially by the reaction of phosphorus pentasulfide (P_2S_5) with methanol in toluene solvent to produce an intermediate, dimethylphosphorodithioic acid (DMPDT), and a byproduct, hydrogen sulfide (H_2S) (Sittig 1980). The DMPDT intermediate is isolated and then reacted with either diethylfumarate or diethylmaleate. The crude material is then stripped of solvent, washed, and filtered to produce technical-grade malathion.

Malathion was first commercially produced in the United States in 1950 by American Cyanamid Chemical Company (USTC 1953) and was first registered in the United States in 1956. Manufacturing rights were transferred to Cheminova Agro, Inc. in 1991 (EPA 1999). Production volume data were not located for the 1950s and 1960s. The production of malathion was estimated to be 24 million pounds in 1972 (Santodonato 1985; von Rumker et al. 1974) and 30 million pounds in 1978 (IARC 1983). No recent production volume data are available for malathion.

As of 1999, there were 63 pesticide formulators of malathion for the United States markets. The 63 formulators produce approximately 235 products that contain malathion. Some of the products contain other active ingredients, such as methoxychlor (EPA 1999). Table 5-1 lists the production year, number of facilities, the state where each facility is located, and the range (in pounds) for each domestic manufacturer that reported the production or formulation of malathion in 2000 (TRI00 2002). Manufacturers are required to report Toxics Release Inventory (TRI) data to satisfy EPA requirements. The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

5.2 IMPORT/EXPORT

Data for import for 1977 and export volumes of malathion are limited. Import volumes reported were 6,457 pounds for light (USITC 1978) and 143,260 pounds for 1982 (SRI 2000); no recent import volume

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	1	10,000	99,999	12
GA	3	100,000	999,999	2, 3, 4, 7, 9
IA	1	10,000	99,999	7
MO	2	100,000	99,999,999	7, 9
MS	1	100,000	999,999	7
TX	3	10,000	999,999	9, 12

Source: TRI00 2002

[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
14. Process Impurity

data are available. In 1978, U.S. exports of malathion were estimated to be 11,020,000 million pounds (SRI 2000).

5.3 USE

Malathion is a nonsystemic broad-spectrum organophosphorus (OP) contact, stomach, and respiratory insecticide and acaricide effective by direct contact, oral ingestion,and inhalation exposure that is used in agriculture and horticulture applications (HSDB 2001). Malathion is applied to a wide variety of crops including alfalfa, apple, apricot, asparagus, avocado, barley, bean (succulent and dry), beets (garden, table, and sugar), blackberry, blueberry, boysenberry, broccoli, cabbage, carrot, cauliflower, celery, chayote, cherry, clover, corn, cotton, cucumber, date dewberry, eggplant, potato, fig, flax, garlic, gooseberry, grape, grapefruit, guava, hay grass, hops, horseradish, kale, kohlrabi, kumquat, leek, lemon, lettuce, lime, loganberry, macadamia nut, mango, melon, mint, mushroom, mustard greens, nectarines, oats, okra, onion, orange, pea, peach, pear, pecan, pepper, pineapple, pumpkin, radish, raspberry, spinach, wheat, squash, strawberry, tangerine, tomato, walnut, watermelon, wild rice, and yam crops. Malathion may also be used for an indoor stored commodity treatment and in empty storage facilities for barley, corn, oats, and wheat (EPA 2000d). It is also used by homeowners for ornamental flowering plants, ornamental lawns, ornamental turf, vegetable gardens, and fruit trees; at golf courses for ornamental flowers, shrubs, and trees; at Christmas tree plantations; and around uncultivated nonagricultural areas, outdoor garbage dumps, intermittently flooded areas, irrigation and sewage systems, pastures, and range land. Malathion is also used to control ectoparasites of cattle (Budavari 1996), flies, and human head and body lice (nonFIFRA pharmaceutical use). It is also used in regional pest eradication programs to control boll weevil, medfly (USDA), and mosquito (EPA 2000d). Malathion is generally applied as a spray using conventional ground or air equipment, and application rates depend on use (von Rumker et al. 1974).

Data for the domestic use of malathion by volume was estimated to be 16.2 million pounds in 1972, and 2–3 million pounds in 1995 and 1996 (EPA 2000e). The estimated total average use of malathion in the United States is 16.7 million pounds as the active ingredient. Of the 16.7 million pounds, approximately 12 million pounds of active ingredient are used on agricultural crops and 90% of the 12 million pounds is used on cotton to control boll weevil (USDA); approximately 0.5 million pounds are used around buildings, roads, and ditches; approximately 0.3 million pounds are applied to post harvest corn, wheat, and oats; approximately 800,000 pounds are used for medfly control (USDA); and approximately 472,000 pounds are used to control mosquitos (EPA 2000d). Other sources state that the total amount of

malathion used in 1994 in the United States was 3,377,681 pounds (Gianessi and Anderson 1997), with 782,434 pounds in California (Annual Pesticide Use Report 1996)

5.4 DISPOSAL

Incineration in a furnace equipped with an afterburner and a scrubber is the recommended method of disposal for malathion (Sittig 1985). If incineration is not an available option, malathion may be disposed of by absorbing in vermiculite, dry sand, earth, or a similar material and then then being buried at a designated landfill site (Mackison 1981). Only small amounts of malathion may be land filled (United Nations 1985). Waste water treatment technologies using biological treatment and reverse osmosis have been investigated for malathion (EPA 1982).

Another method of disposal that has been suggested for malathion is molten salt combustion using potassium chloride. This process is attractive because the destruction of malathion is >99% and the products of combustion can be used as a fertilizer (United Nations 1985).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Malathion has been identified in at least 21 of the 1,623 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2003). However, the number of sites evaluated for malathion is not known. The frequency of these sites can be seen in Figure 6-1. All of the 1,623 sites are located within the United States; none of the sites are located in the Commonwealth of Puerto Rico.

Malathion is an insecticide used for agricultural and nonagricultural purposes that is released to the environment primarily through spraying on agricultural crops and at agricultural sites, spraying for home and garden use, and spraying for public health use in both urban/residential and nonresidential areas; the insecticide is also released to the environment using fogging equipment. Once malathion is introduced into the environment, it is degraded by atmospheric photooxidation, hydrolysis, or biodegradation mediated by microorganisms found in most sediment, soils, and water. The oxon degradate of malathion, malaoxon, which is more toxic than malathion, is formed from the oxidation of malathion and may also be present as an impurity in the parent compound. Malathion and malaoxon can be transported from the site of application by precipitation, fog, and wind to other areas. Malathion is moderately mobile to very highly mobile in soils, creating the potential for it to move through the soil profile and into groundwater. However, because degradation of malathion occurs rapidly in the environment, the potential for malathion movement into groundwater is generally not significant and leaching of the chemical into groundwater is usually not observed. Volatilization of malathion from ground surfaces following aerial applications has been observed. Data from limited studies suggest that bioconcentration of malathion does not occur to a significant extent in most aquatic organisms tested because it is rapidly metabolized. Malathion is not widely dispersed or persistent in the environment, but is detected frequently in foods. Residue amounts of malathion have been detected in air, water, soil, fish, and agricultural crops consumed as food.

The general population is not likely to be exposed to large amounts of malathion. Some exposure to residues of malathion is possible, however, as many studies show that malathion has been detected in foods and atmosphere samples. Populations living within or very near areas of heavy malathion use would have an increased risk of exposure to relatively larger amounts of malathion through dermal contact with contaminated plants, by inhalation of the mist formed from the applied insecticide, or by

Figure 6-1. Frequency of NPL Sites with Malathion Contamination

ingestion of water or food-borne residues. Also at increased risk of exposure are persons utilizing malathion for extensive home and garden use, particularly if they consume contaminated, unwashed backyard produce. Those likely to receive the highest levels of exposure are those who are involved in the production, formulation, handling, and application of malathion, as well as farm workers who enter treated fields prior to the passage of the appropriate restricted entry intervals. Dermal contact appears to be the major route of exposure, while ingestion may also be an important route of exposure. Inhalation has not been shown to be a significant route of exposure to malathion.

6.2 RELEASES TO THE ENVIRONMENT

Malathion has been released to the environment mainly as a result of its use as an insecticide on food and feed crops, noncrop agricultural use, home and garden use, and public health use (for medfly and mosquito control). It is also released as a result of USDA special program usage such as the USDA Boll Weevil Eradication Program, which accounts for approximately 90% of malathion agricultural crop usage (EPA 2000a). Additionally, malathion is used as a pharmaceutical for humans. It is applied in the environment mainly by aerial, ground spraying, or fogging equipment, but is also used in bait type formulations (i.e., applied to food baits). The annual use of malathion in 1994 was reported to be 3,377,681 pounds, of which 782,434 pounds were used in the state of California (Wilson et al. 1997). There are no known natural sources of the compound. Malathion has been identified in at least 21 of the 1,623 hazardous waste sites on the NPL (HazDat 2003).

According to recent Toxics Release Inventory (TRI) data, malathion was discharged to air from four processing sites and to water from one processing site in the United States in 2000; no releases to soil were reported for that year (TRI00 2002). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

6.2.1 Air

As a result of its use as an insecticide on cotton, sod/turf, ornamentals, berries, fruit trees, vegetables, and other crops; its use in regional pest eradication programs, including public health use for medfly quarantine and mosquito abatement; its noncrop agricultural site use; and its outdoor home and garden use, malathion is released directly to the atmosphere during application. It is applied primarily by

spraying from aircraft or from ground spray or fogging equipment (EPA 2000a). Aerial application of malathion to agricultural fields and to residential or other target areas releases the insecticide to the air.

Following repeated aerial applications of malathion, at a target rate of 23.8 mg/m^2, to urban/residential areas (1,500 km^2) of southern California between August 1989 and July 1990 to eradicate Mediterranean fruit flies (Medflies), the California Department of Food and Agriculture (CDFA) Environmental Monitoring Branch measured the mass deposition, air concentrations, and selected water concentrations of malathion and its primary oxidation product, malaoxon (Bradman et al. 1994). The mean mass deposition of the malathion (originally released to the air; for the first application only) at a target rate of 23.8 mg/m^2 was 22.1 mg/m^2, with a range of 1.7–53.7 mg/m^2 (Bradman et al. 1994). Following the release to air, the maximum mean concentrations (averaged for three sites) of malathion and malaoxon in the air were 61.6 ng/m^3 at 24 hours and 48.1 ng/m^3 at 24–48 hours, respectively (Brown et al. 1993b).

Malathion may also be released into the air as a result of volatilization from crop surfaces. As a result of summertime agricultural use in the Central Valley in California, malathion was released to the air by volatilization and was transported to higher elevation regions of the Sierra Nevada Mountains (LeNoir et al. 1999). In a study of the air, rain, and surface water associated with a subestuary of the Chesapeake Bay estuarine drainage system (in the Patuxent River watershed), which includes 57,000 km^2 of agricultural cropping areas, malathion was present in 30% of the air samples and 50% of the rain samples (used to determine wet deposition flux) collected in the spring and summer of 1995 (Harman-Fetcho et al. 2000).

No data were found on releases to the atmosphere from production facilities and disposal sites. Based on a measured Henry's law constant of 4.89×10^{-9} atm/m^3 mol (Fendinger and Glotfelty 1990) and a measured vapor pressure of 3.38×10^{-6} mm Hg (USDA Pesticide Property Database), it is considered unlikely that malathion will be released to the air to any significant extent as a result of volatilization from either moist or dry soil surfaces or water surfaces at disposal sites.

Malathion was detected in air at 1 of the 1,623 current or former NPL sites where malathion has been identified in some environmental medium (HazDat 2003).

The most recent TRI data indicate that 11 sites in the United States processed malathion in 2000 (TRI00 2002). The total of reported releases to air was 3,094 pounds, representing 99.7% 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.

6.2.2 Water

Malathion can potentially be released to surface waters by direct application; storm runoff from sprayed fields or urban/residential areas; atmospheric deposition following aerial application (wet deposition from rain and fog water); waste water releases from formulation, manufacturing, or processing facilities; and spills.

Malathion has been released to shoreline beaches and surface waters in adjacent coastal marshes on the eastern coast of central Florida for mosquito control using aerial spraying and truck-mounted (ultra-low volume; ULV) equipment (Clark et al. 1993).

Malathion has been detected in three rivers, which are the three largest tributaries to the Chesapeake Bay (Foster and Lippa 1996). Malathion was collected in 6–16% of the water samples collected from the Susquehanna, Potomac, and James Rivers in 1992–1993; mean aqueous concentrations of malathion in the three rivers were 6, 12, and 7 ng/L, respectively. Annual loads of malathion from the three respective tributaries to the Chesapeake Bay were determined to be 8–86, 3–25, and 3–18 kg/year, respectively (Foster and Lippa 1996).

Malathion has been released to surface waters as a result of wet deposition following volatilization from crop surfaces and transport through the atmosphere. Reportedly as a result of summertime agricultural use in the Central Valley in California, and following volatilization from crop surfaces and transport through the atmosphere, malathion was released to surface waters by wet deposition in higher elevation regions of the Sierra Nevada Mountains; malathion was not detected in any of the dry deposition samples (LeNoir et al. 1999). Malathion was detected in the surface waters transecting the Central Valley to the Sierra Nevada Mountains at aqueous concentrations of 65–83 ng/L; the compound was not detected in surface water samples collected from the two highest (of eight) elevations studied. In a study of the air, rain, and surface water associated with a sub-estuary of the Chesapeake Bay estuarine drainage system (in the Patuxent River watershed), which includes 57,000 km^2 of agricultural cropping areas, the total wet deposition flux of malathion in the spring and summer of 1995 was determined to be 5,200 ng/m^2 (in the 200 mm of rain that fell during the study period; Harman-Fetcho et al. 2000). The wet deposition flux of

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

	Reported amounts released in pounds per year[a]							
State[b]	Number of facilities	Air[c]	Water	Under-ground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
AR	1	1	No data	No data	No data	1	No data	1
GA	3	41	5	No data	No data	46	18	64
IA	1	539	No data	No data	No data	539	No data	539
MO	2	2,818	No data	No data	No data	2,818	No data	2,818
MS	1	250	0	No data	No data	250	No data	250
TX	3	255	5	No data	0	260	250	510
Total	11	3,904	10	No data	0	3,914	268	4,182

Source: TRI00 2002

[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).

malathion for the 24 measured rain events ranged from 8 to 1,800 ng/m^2; malathion was detected in only 50% of the collected samples.

No information was found in the literature on the release of malathion to water by spillage, or on waste water releases from formulation, manufacturing, or processing facilities. In a study of pesticides in storm water runoff in the Sacramento River Basin in California, malathion was not detected; however, the limit of detection for the compound was 35 ng/L (Domagalski 1996).

Malathion has been detected in surface water at 4 of the 1,623 current or former NPL sites where malathion has been identified in some environmental medium (HazDat 2002). Malathion has been detected in groundwater at 7 of the 1,623 current or former NPL sites where malathion has been identified in some environmental medium (HazDat 2003).

The most recent TRI data indicate that 11 sites in the United States processed malathion in 2000 (TRI00 2002). The total of reported releases to water was 10 pounds, representing 0.26% 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.

6.2.3 Soil

Malathion is primarily released to soils through direct deposition of spray droplets, which reach the soil surface following aerial spraying, ground spraying, and fogging applications. These releases to soil may occur following applications that are either made directly to soil (public health use in residential areas) or to crops. Releases to soil may also occur as a result of wet deposition of malathion. Approximately 12.5 million pounds of malathion are applied to agricultural crops annually in the United States, with approximately 90% of it applied through the USDA Boll Weevil Eradication Program (EPA 2000a). In 1997, over 10 millions pounds of malathion were released to areas of Texas and Alabama for this purpose (EPA 2000a). In the four counties closest to Sequoia National Park in California's Central Valley, 28,683 kg of malathion were applied to approximately 900,000 acres of harvested cropland in 1995, with the peak release period occurring in March (McConnell et al. 1998). Additionally, approximately 0.5 and 3.4 million pounds are released to soil annually through applications to both agricultural sites (e.g., roads, ditches, and near buildings) and nonagricultural sites (medfly and mosquito control, golf courses, home and garden use), respectively (EPA 2000a).

Following repeated aerial applications of malathion, at a target rate of 23.8 mg/m^2, to urban/residential areas (1,500 km^2) of southern California between August 1989 and July 1990 to eradicate medflies, the CDFA Environmental Monitoring Branch measured the mass deposition, air concentrations, and selected water concentrations of malathion and its primary oxidation product, malaoxon (Bradman et al. 1994). Mass deposition of malathion ranged from 1,100 to 2,413 µg/ft^2; mass deposition of malaoxon ranged from 2.9 to 6.0 µg/ft^2 (Brown et al. 1993b). Based on measured values of mass deposition, daily malathion and malaoxon residue levels in soil were estimated for a single application. Based on a mixing depth of 1 cm, soil concentrations of the parent and its oxon degradate were estimated as 1.4 and 0.01 µg/g, respectively; based on a mixing depth of 0.1 cm, the corresponding estimated concentrations in soil were 14.1 and 0.10 µg/g (Bradman et al. 1994).

Malathion may also be released to the soils by improper handling of pesticide formulations during processing or handling, including from spills or the usage of poor storage and containment practices. In a study of 49 randomly chosen agrichemical facilities located throughout Illinois, malathion was detected in soil samples at 6 of the 18 sites that handled the compound (Krapac et al. 1995). Malathion was detected in 11 of the soil samples from the six sites, at a mean concentration of 125 µg/kg (ppm) and at a concentration range of 31–690 µg/kg; the common range of detections was 22–100 µg/kg.

Malathion has been detected in soil at 11 of the 1,623 current or former NPL sites where malathion has been identified in some environmental medium (HazDat 2003). Malathion has been detected in sediment at 4 of the 1,623 current or former NPL sites where malathion has been identified in some environmental medium (HazDat 2003).

The most recent TRI data indicate that 11 sites in the United States processed malathion in 2000 (TRI00 2002); no releases to soil were reported for that year (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.

6.3 ENVIRONMENTAL FATE

The malathion released to the atmosphere can be transported back to surface water and soil by wet deposition (Harman-Fetcho et al. 2000; McConnell et al. 1998). Malathion that is released to the atmosphere can also be transformed by indirect photolysis to its oxygen analog, malaoxon, by oxidation with photochemically produced hydroxyl radicals (Howard 1991).

In surface waters, malathion degrades by hydrolysis and microbially mediated biodegradation (Mulla et al. 1981). Hydrolysis is considered to be the predominant degradation process, and occurs more rapidly at alkaline pHs, while the compound is stable to hydrolysis at acidic pHs (Wolfe et al. 1975). Malathion appears to be relatively stable to direct aqueous photolysis, but may be transformed in the water by indirect photolysis. Adsorption to sediment and suspended particulate matter is not expected to be a significant factor in the fate of the compound in the environment.

In soil and sediments, the major degradation process of malathion is microbially mediated biodegradation, which occurs mainly through enzyme-catalyzed hydrolysis (Mulla et al. 1981). The predominant pathway for the biodegradation of malathion has been reported to be carboxylesterase activity (Laveglia and Dahm 1977). Malathion degrades rapidly in soil, with reported half-lives ranging from hours to approximately 1 week (Gibson and Burns 1977; Howard 1991; Konrad et al. 1969). Half-life values in soil of 3–7 days have been reported for the degradate malaoxon (Bradman et al. 1994). Based on limited data, malathion does not appear to photodegrade on soils (Chukwudebe et al. 1989; EPA 2000a). Little malathion appears to volatilize from soil (EPA 2000a) and, while malathion is moderately to highly mobile in soils (EPA 2000a), leaching of malathion through the soil and into groundwater is unlikely due to the rapid degradation of the compound in the environment.

6.3.1 Transport and Partitioning

Data indicate that malathion may be transported in the air following application to either agricultural or urban/residential areas (LeNoir et al. 1999; Majewski et al. 1998). Malathion may be transported in the atmosphere as a vapor or adsorbed onto particulate matter (Bossan et al. 1995). In a review paper, Mulla et al. (1981) stated that the occurrence of malathion in the atmosphere is generally localized. However, in a non-U.S. study of malathion adsorbed to fly ash (particulate matter), Bosson et al. (1995) determined that adsorbed malathion is photodegraded when exposed to irradiation of >290 nm for up to 1.5 hours, but does not degrade when adsorbed to kaolin. These study results indicate that malathion adsorbed to kaolin may be transported over long distances, while malathion adsorbed to fly ash will be rapidly photodegraded and, therefore, will not be transported far in the atmosphere (Bosson et al. 1995). Additionally, malathion has been detected in the fog of remote pristine areas, indicating that long-range transport may occur under some conditions (Rice 1996).

Transport of malathion residues in air may follow aerial applications or result from spray drift or postapplication volatilization; however, the latter source may not be significant for this compound. The

Henry's law constant for malathion is 4.89×10^{-9} atm/m^3 mol (Fendinger and Glotfelty 1990), indicating a low potential for volatilization from either moist soil or water. The vapor pressure of malathion is 3.38×10^{-6} mm Hg (USDA/ARS Pesticide Properties Database), indicating a low potential for volatilization of the compound from dry soil surfaces. Data provided in the EPA Reregistration Eligibility Decision (RED) for malathion indicate that the compound did not appreciably volatilize (≤5.1% in 16 days) from a silt loam soil when applied in three different formulations to soil samples at various moisture contents (EPA 2000a). In a study of malathion volatilization from dry quartz sand, the compound was not observed to volatilize (Mulla et al. 1981). However, several researchers have suggested the possibility of the volatilization of malathion from nonnatural surfaces, such as metals, plastic playground equipment, cement, and paved areas, based on mass deposition study data (Bradman et al. 1994; Brown et al. 1993b).

Based on the results of several studies, malathion may be removed from the atmosphere by wet deposition (Harman-Fetcho et al. 2000; McConnell et al. 1998). Dry deposition of malathion does not appear to occur; the compound is generally present in the atmosphere in a vapor phase rather than as a particulate, although it may exist adsorbed to particulate matter (Bossan et al. 1995; Mulla et al. 1981). Malathion and its oxon degradate, malaoxon (also present in the parent compound as an impurity), have both been detected in the water phase of fog (Rice 1996). Malathion has been observed in fogwater collected from pristine remote areas, indicating that it may be transported away from locations of use (Rice 1996).

The water solubility of malathion is relatively high from an environmental fate perspective, at 145 mg/L (25 °C), leading to a high potential for its transport in surface water and groundwater (Mulla et al. 1981). Additionally, malathion generally does not adsorb significantly to soils, leading to a high potential for its leaching through soils and into groundwater. However, the actual presence of malathion in water will also depend on the persistence of the compound, which is generally longer at acidic pHs. Data from several studies summarized in a review paper indicate that malathion has been detected in both surface water and groundwater, and that its presence may be attributed to either direct application or contamination from indirect sources (Mulla et al. 1981). Based on information contained in a database for pesticides in groundwater that was compiled by EPA from monitoring data available for 1971–1991, malathion was detected in a total of 12 wells in three states (California, Mississippi, and Virginia), at concentrations ranging from 0.007 to 6.17 µg/L; monitoring data were reported for a total of 3,252 wells (EPA 1992).

Malathion has been observed to be very highly mobile to highly mobile in sandy loam, sand, loam, and silt loam soils, with Freundlich K_d values of 0.83–2.47 (EPA 2000a). However, the corresponding K_{oc} values (151–183) for the four soils indicate that malathion may also be classified as moderately mobile in the soils. At the concentrations (not reported) tested in the batch equilibrium study, the soil adsorption isotherms were found to be linear, indicating that adsorption was independent of concentration (EPA 2000a). It is noted, however, that malathion is rapidly degraded in the soil, with a half-life of <1 week (Mulla et al. 1981). Therefore, despite the potentially high mobility of the compound in soil, leaching of malathion through the soil into groundwater may not be a significant factor affecting the fate of the compound in the environment.

Although data on the mobility of malathion in U.S. soils were relatively scarce in the literature, adsorption of malathion has been shown to be related to the soil organic matter content as well as the cation exchange capacity of the soil clay fraction. MacNamara and Toth (1970) reported that in a laboratory study of the adsorption of malathion to three clay mineral systems (kaolinite, illite, and montmorillonite) and a humic acid system, greater adsorption was observed in the humic acid system relative to the clay mineral systems. Among the clay mineral systems, the adsorption of malathion increased with the increasing cation exchange capacity of the soils; adsorption did not appear to be correlated with pH. These researchers also demonstrated that the adsorption of malathion was greater in soils with greater amounts of soil organic matter, and that the destruction of the soil organic matter fraction of soils led to decreased adsorption; the pH of the soil:solution test systems (pH 4.5– 6.7) was not observed to be correlated with adsorption (MacNamara and Toth 1970). Studies conducted on non-U.S. soils have also demonstrated that the adsorption of malathion is significantly correlated to the soil organic matter or organic carbon contents, with greater adsorption observed in soils with higher organic matter or organic carbon contents (Bell and Tsezos 1987; Khan and Khan 1986; Sujatha and Chacko 1991).

The bioconcentration factor (BCF) for malathion in aquatic organisms has been reported for several types of organisms. In a review, Howard (1991) reported malathion BCF values of 7.36 for lake trout, 29.3 for Coho salmon, a range of 150–1,917 (mean of 869) for white shrimp (*Paneaeous setiferus*), and a range of 200–1,667 (mean of 959) for brown shrimp (*P. azkecus*); malathion did not bioconcentrate in a freshwater fish (Motsugo; *Pseudorasbora parva*). In a Japanese study, it was reported that malathion bioconcentrated in the freshwater fish willow shiner (*Gnathopogon caerulescens*) with a mean BCF of 34.4 (Tsuda et al. 1989).

In the EPA RED for malathion, BCF values ranging from 23 to 135 were reported for whole bluegill sunfish, while a range of 4.2–18 was reported for the edible tissue of the fish (EPA 2000a). These results, reported to EPA by the malathion registrant, and those reported in Howard (1991) do not clearly indicate whether bioconcentration in aquatic organisms is an important fate process for malathion that would allow for the potential for biomagnification of malathion residues in the food chain. However, it was also reported to EPA that 96 and 73% of the malathion residues depurated from the whole and edible fish tissues, respectively, during a 14-day depuration period. Additionally, residue analysis indicated that the parent compound was partially metabolized in the fish, with 33.3–35.9% of the residues present as the degradate malathion monocarboxylic acid and 5.7% of the residues present as 1 of 22 other compounds including malathion dicarboxylic acid, malaoxon, demethyl malathion, monoethylfumarate, and oxalacetic acid (EPA 2000a). Additionally, in a review paper, Niimi (1987) reported that the half-life of malathion in the muscle tissue of carp was 1 day. These data indicate, despite the apparent tendency of malathion to partition into the tissues of aquatic organisms, that the potential for biomagnification in the food chain is likely to be low because malathion appears to be metabolized by the aquatic organisms.

No data were found in the literature on the partitioning of malathion into and within plants.

6.3.2 Transformation and Degradation

In general, malathion is degraded in the environment through two main pathways, activation and degradation (Mulla et al. 1981). Activation of the compound involves oxidative desulfuration, yielding the degradate malaoxon, a cholinesterase inhibitor with greater toxic properties than its parent compound. Activation may be achieved by photooxidation, chemical oxidation, or biological activation, the latter of which occurs enzymatically through the activity of mixed function oxidases (Mulla et al. 1981). Degradation of malathion occurs through both chemical and biological means, with hydrolysis being the most important pathway for each (Konrad et al. 1969). Biological degradation through the hydrolytic pathway is mainly achieved through the enzymatic activity of carboxylesterases and phosphatases, and to a lesser extent through the activity of reductase (Laveglia and Dahm 1997; Mulla et al. 1981). Malathion may also be degraded through des- or dealkylation of the *O*-methyl or *O*-ethyl groups, mediated by a phosphatase/mixed-function oxidase system (Laveglia and Dahm 1977; Mulla et al. 1981).

6.3.2.1 Air

Pesticides may be transformed and degraded in the atmosphere due to photolysis and by reaction with ozone, hydroxyl, and nitrate radicals. Very little definitive information was found in the literature on the transformation and degradation of malathion in air. Bradman et al. (1994) stated that both malathion and malaoxon are unstable in the atmosphere and that reported half-lives for the two compounds in air range from a few hours to 1 day; however, a review of the original papers cited in Bradman et al. (1994) do not directly support this statement for malathion and malaoxon specifically (Atkinson et al. 1989; Goodman et al. 1988). In a review paper, Mulla et al. (1981) stated that although the effects of light (including ultraviolet [UV] radiation) on both malathion and its degradate malaoxon have been studied, little is understood of the transformation of the parent to malaoxon through photolysis. Howard (1991) reported an estimated atmospheric photooxidation half-life of 1.5 days based on the reaction of malathion with photochemically produced hydroxy radicals. Based on the scarce data available in the literature, it appears that malathion degradation in the atmosphere occurs mainly due to indirect photolysis (photo-oxidation) rather than resulting from direct photolysis. In a photodegradation study of malathion exposed to natural sunlight and UV irradiation (maximum wavelength of 360 nm) as thin films on glass, the compound was relatively stable to sunlight and exhibited only slight degradation (16%) by 25 hours under UV light; none of the six degradates were present at >0.01% (Chukwudebe et al. 1989). In a non-U.S. study of malathion adsorbed to fly ash (particulate matter), Bossan et al. (1995) determined that adsorbed malathion is photodegraded when exposed to irradiation of >290 nm for up to 1.5 hours, but does not degrade when adsorbed to kaolin. Malathion on fly ash decreased by up to 70% of the adsorbed compound following 40 minutes of irradiation. However, the study authors attributed the degradation of malathion on fly ash to the presence of metals and metal oxides in the fly ash.

6.3.2.2 Water

Malathion in water undergoes chemical and microbial degradation. The rate and extent of its degradation is dependent on the chemical and physical properties of the water system, particularly temperature and the solution pH, in addition to the composition of the microbial population present in the system.

Malathion is degraded rapidly by hydrolysis at more alkaline pH levels, but is stable to hydrolysis at acidic pHs (Wolfe et al. 1975, 1977). In a review paper, Mulla et al. (1981) noted that malathion was instantaneously degraded by hydrolysis at pH 12; had a half-life of approximately 1 day at pH 11; was

rapidly degraded at pHs 9 and 7.7, with respective half-lives of approximately 12–24 hours and >3 days; did not degrade at pH ≤6.2 by 3 days; and was hydrolytically stable in acidic solution (pH >2). A half-life of 6.21 days has been reported for malathion at pH 7 (EPA 2000a). Wolfe et al. (1975) reported a half-life of >1 year at pH 4. Chapman and Cole (1982) reported half-lives of 18 weeks at pH 4.5, 5.8 weeks at pH 6.0, 1.7 weeks at pH 7.0, and 0.53 weeks at pH 8.0. In an unpublished study submitted to EPA, malathion was observed to degrade to some extent at pH 5, with approximately 20% degradation by 28 days (EPA 2000a). These data indicate that, in general, under conditions typically encountered in the environment, where pH is commonly 5–9, hydrolysis is expected to be a significant fate process at all but the more acidic pH levels (i.e., pH 5 and 6).

It has been demonstrated that temperature also has an effect on the hydrolysis of malathion. The rate of hydrolysis of malathion has been reported to increase by a factor of 4 (4X) for each 10 °C increase in temperature (Mulla et al. 1981). A half-life of 1.3 days at pH 7.4 has been reported for malathion at a temperature of 37.5 °C, with a corresponding half-life of 10.5 days reported for that pH when the temperature was decreased to 20 °C (Freed et al. 1979a). It has also been demonstrated that the temperature of the water system has an effect on the hydrolysis products at alkaline pHs (Wolfe et al. 1975, 1977). Observed hydrolysis products included malathion monoacids, *O,O*-dimethyl-phosphorodithioic acid, and diethyl fumarate. Wolfe et al. (1975, 1997) reported that two competing processes, carboxyl ester hydrolysis and *O,O*-dimethyl phosphorodithioic acid elimination, were occurring, with the former process being favored at lower temperatures. These researchers also reported that the α-monoacid was more prevalent than the β-monoacid (85:15), and that malathion monoacids are approximately 18 times more stable than the parent compound under similar alkaline conditions. Under alkaline conditions, the potential degradate malathion diacid was determined to be approximately 200 times more stable than the parent compound under similar alkaline conditions (Wolfe et al. 1975).

A study on the oxidation of malathion to malaoxon in oxygen-saturated water under acidic conditions demonstrated that oxidation by molecular oxygen is not a significant fate process in the environment (Wolfe et al. 1975, 1977). Malathion was stable in oxygen-saturated water under acidic conditions for up to 2 weeks.

Malathion may also be transformed in the water by indirect photolysis, but appears to be relatively stable to direct photolysis based on the limited data available in the literature. Wolfe et al. (1975) demonstrated that malathion was photolytically stable in distilled water (pH 6) when exposed to irradiation with wavelengths of >290 nm, but degraded with an observed first half-life of 16 hours in natural water

obtained from the Suwannee River which contained "a large amount of colored materials." It is assumed that the referenced "colored materials" are derived from humic acids which, as known photosensitizers, can contribute to indirect photolysis in water systems. Aside from the early studies referenced here, very little other information on the photolysis of malathion in water was found in the literature. In a non-U.S. study, the rapid degradation of malathion in natural (estuarine) water exposed to ambient sunlight and temperature was reported; the half-life of malathion in estuarine water from the Ebre Delta area of Spain was 4.4–4.9 days (LaCorte et al. 1995). The contribution of photolysis to the overall degradation rate for the compound was not determined. In a study of malathion in river water, sea water, and groundwater in Hawaii, Miles and Takashima (1991) found that although degradation was rapid (mean half-life of 4.7 days), photodegradation and biodegradation of the compound were not important; degradation proceeded mainly by an elimination reaction. Based on these data, the direct photolysis of malathion in water is not an important fate process.

Microbial degradation of malathion in water has been studied in different types of water. A study was conducted to determine the degradation rate of malathion at 20 °C in sterile (autoclaved; pH 8.20) and unsterile (pH 8.05) filtered seawater and in a seawater/sediment (pH 7.3–7.7) microcosm (Cotham and Bidleman 1989). Reported half-lives were 3.3 days in sterile seawater, 2.4 days in unsterile seawater, and 2 days in the seawater/sediment microcosm. When the values determined for the seawater systems were normalized to pH 8.0, the half-life of malathion was approximately twice as long in sterile seawater, at 5.3 days, as in unsterile seawater (half-life of 2.6 days; Cotham and Bidleman 1989). These researchers noted that the more rapid degradation in the seawater/sediment system relative to the unsterile seawater system, which had a higher pH (leading to more rapid hydrolysis), indicates that microbial activity or interaction of malathion with the sediment was a contributing factor (in addition to hydroxide-catalyzed hydrolysis) to the degradation of the compound. Half-lives of 92–96 hours for malathion (1 mg/L) in seawater were reported by Bourquin (1977); significant malathion degradation was not observed in sterile seawater. Degradation products observed in the study were malathion monocarboxylic acid and malathion dicarboxylic acid; malaoxon was not detected as a degradation product.

In a study of the degradation of malathion by isolated salt-marsh microorganisms, 11 of the 15 bacterial cultures were able to degrade malathion as a sole carbon source and the remaining 4 were able to degrade malathion by cometabolism when 0.2% peptone was added as an additional source of carbon (Bourquin 1977). An isolated salt-marsh fungus was unable to degrade malathion without the addition of 0.2% peptone. The study author attributed the degradation of malathion by bacterial cultures to a carboxylesterase system that leads to the formation of the mono- and dicarboxylic acids, and a delayed

demethylation reaction that leads to the formation of demethyl-malathion. Delayed phosphatase activities leading to phosphorylated derivatives, which act as cholinesterase inhibitors in fish, were also cited (Bourquin 1977). Complete mineralization of malathion was observed to be more rapid (initial appearance of CO_2 at 2 versus 7 days) with a mixed microbial culture than with the individual cultures.

A study was conducted to determine the ability of fungi to degrade malathion in aquatic environments using a species of fungus (*Aspergillus oryzae*) isolated from a freshwater pond (Lewis et al. 1975). Although the study authors stated that the rate of transformation of malathion in the lab could not be extrapolated to the field, it was determined, based on comparisons with data obtained previously, that malathion was degraded 5,000 times more rapidly by bacteria versus the fungus. The main degradate of the fungal degradation of malathion, β-malathion monoacid, was the same degradate produced by bacterial degradation of malathion (Lewis et al. 1975).

6.3.2.3 Sediment and Soil

In soils and sediments, microbial degradation (mainly through enzyme-catalyzed hydrolysis) and hydrolysis are important degradation processes for malathion. Studies have demonstrated that this is particularly true at higher pH values and soil moisture contents (Miles and Takashima 1991). Malathion degrades rapidly in soil, with reported half-lives in soil ranging from hours to approximately 1 week (Gibson and Burns 1977; Howard 1991; Konrad et al. 1969). Bradman et al. (1994) reported a range of half-life values of <1–6 days for malathion and 3–7 days for malaoxon in soil based on data obtained from the literature. Miles and Takashima (1991) reported respective half-lives of 8.2 and 2 hours for malathion in Hawaiian soil in the laboratory and the field.

In a review paper, Mulla et al. (1981) reported that biological degradation of malathion proceeds mainly through hydrolysis catalyzed by enzyme systems including carboxylesterases and phosphatases; malathion is also degraded by des- or dealkylation by means of phosphatase or mixed-function oxidase (MFO) enzyme systems. In a review paper on the degradation of organophosphorus insecticides in soil, Laveglia and Dahm (1977) stated that the predominant pathway for the biodegradation of malathion is carboxylesterase activity. Degradates observed in studies of the microbial degradation of malathion include malathion monoacid, malathion dicarboxylic acid, potassium dimethyl phosphorothioate, potassium dimethyl phosphorodithioate, and demethyl phosphorodithioate (Mulla et al. 1981). Other potential malathion degradates resulting from biodegradation by individual species of microorganisms

include malaoxon, inorganic phosphate, thiophosphate, monomethyl phosphate, dimethyl phosphate, and diethyl maleate (Laveglia and Dahm 1977).

Konrad et al. (1969) observed a more rapid initial degradation of malathion in sterile soils than in an inoculated aqueous system in which malathion did not undergo biodegradation until after a 7-day lag period, indicating that actual biodegradation of the compound requires acclimation by the microbial population. In a study on the degradation of malathion in sterile and nonsterile soils, these researchers also found that the degradation rate of malathion was more rapid in soils that exhibited more rapid initial adsorption of the compound (Konrad et al. 1969). The study authors concluded that the degradation of malathion in soil is directly related to the adsorption of the compound to the soil surfaces, which serves to catalyze the degradation process and allows for almost immediate degradation of the compound. Based on the results of the study, the researchers also concluded that (direct) biodegradation by soil microorganisms does not play an important role in malathion degradation in soils (Konrad et al. 1969). Other researchers have also concluded that the degradation of malathion in soil is mainly due to exoenzymes in some soils, and is a combination of microbial metabolism; exoenzyme activity, particularly in the organic matter fraction of the soil; and hydrolysis (Gibson and Burns 1977).

In a study on the cometabolism of malathion in soil, Merkel and Perry (1977) found that the presence of certain cosubstrates (alkanes and 1-alkenes) increased the rate of malathion biodegradation in soil from a tobacco field and sediment from an estuary of the Neuse River in North Carolina. Compared with a control (unamended system), the addition of 1-heptadecene and n-heptadecane each increased the rate (2–3 times) of metabolically produced $^{14}CO_2$ in the soil system; acetate, succinate, pyruvate, and citrate did not effectively serve as cosubstrates for the oxidation of malathion in either of the soils studied.

Data on the photodegradation of malathion on soil were scarce in the available literature. In a photodegradation study of malathion exposed to natural sunlight and UV irradiation (maximum wavelength of 360 nm) as thin films on glass, the compound was relatively stable to sunlight and exhibited only slight degradation (16%) by 25 hours under UV light; none of the degradates were present at >0.01% (Chukwudebe et al. 1989). In the EPA RED for malathion, a photodegradation on soil half-life of 173 days was reported for a pH 6.5 sandy loam soil (EPA 2000a). Based on these limited data, photodegradation on soil is not likely to be a significant fate process for malathion in the environment.

6.3.2.4 Other Media

Limited data were found on the degradation of malathion in or on plants. In a Canadian study conducted to determine the persistence of malathion on strawberry plots, malathion decreased rapidly in strawberry flowers and immature fruits (Bélanger et al. 1990). In the first year of the study, malathion decreased to 2.7% of the initial concentration within 2 days of application and was 1.5% within 7 days; in the second study year, malathion decreased to 4.35% of the initial concentration by 3 days. Mulla et al. (1981) reported that degradation of malathion in plants, as in soil and water, occurs mainly by means of hydrolysis at the P-S bond; carboxylesterase-mediated hydrolysis is also of great importance.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

In a study conducted in the fall of 1991 to determine the individual concentrations of 23 commonly used indoor pesticides, including malathion, in indoor ambient air and dust, air samples were collected from two rooms each of seven homes in New Jersey at two heights, 25 and 75 cm, to represent the breathing space of a child while crawling and standing, respectively, and dust samples were collected from vacuum cleaners (Roinestad et al. 1993). Malathion was not detected (respective detection limits of 1 and 50 ng/m^3) in the air or dust collected from any of the seven homes.

A study was conducted to determine the presence of 10 pesticides, including malathion, in the ambient air of the storage rooms (5 of which were located in buildings separate from the offices) and offices of 10 commercial pest control firms in North Carolina during the summer (August) and winter (February) of 1993; an inventory taken in February 1993 indicated that 5 of the 10 companies had malathion in storage at that time (Wright et al. 1996). Malathion was detected in 23 of the samples, at a mean concentration of 0.77 µg/m^3 and at a range of 0.02–3.57 µg/m^3, with the maximum concentration found during the summer in an office of a company in which the offices and storage rooms were located in one building. The compound was detected in the air of both offices and storage rooms during both the summer and winter, including in the air of a storage room that did not have malathion listed on the inventory.

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. Malathion, which is used minimally for

agricultural purposes within the 40-km zone near the river, was detected at all 10 sampling times during the 10-day study; the highest levels of detection corresponded with the major metropolitan areas near or along the sampling route. The maximum concentration (0.25 ng/m^3 detection limit) of malathion was 4.6 ng/m^3 (near New Orleans, Louisiana), with a range of 0.14–4.6 ng/m^3; the median concentration was 0.23 ng/m^3 (Majewski et al. 1998).

A review of published data was conducted to determine the presence of pesticides in atmospheric fog in both agricultural and nonagricultural areas of the United States (Rice 1996). The presence of malathion has been reported most frequently in the San Joaquin Valley of California during the dormant spraying season (January–February) when dense fog events occur frequently in the California's Central Valley. Reported concentrations of malathion plus malaoxon (in a 1:0.9 ratio) in atmospheric fog over agricultural areas have ranged from 0.07 to 8.7 µg/L, with the maximum concentration observed in Monterey, California in January 1985; concentrations of 0.14–0.30 and 0.90–3.0 µg/L have been reported for malathion and malaoxon, respectively, for nonagricultural areas of Monterey, California. Concentrations of <0.0032 µg/L have been reported for malathion in fog over the Bering/Chukchi Sea, a pristine remote ecosystem (Rice 1996).

A study was conducted to determine the wet deposition of current-use pesticides, including malathion, in the Sierra Nevada Mountain Range in the Central Valley of California in the winter and spring of 1995 and 1996; rain and snow samples were collected from two sites in Sequoia National Park (SNP) and one site in the Lake Tahoe Basin (McConnell et al. 1998). In the four counties closest to Sequoia National Park in California's Central Valley, 28,683 kg of malathion were applied to approximately 900,000 acres of harvested cropland (mainly cotton) in 1995, with the peak release period occurring in March. Malathion was detected in 53% of the collected wet deposition samples from SNP, at <0.046–24 ng/L in samples from the lower SNP elevation and <0.045–6 ng/L in samples from the higher SNP elevation; malathion was present at <0.046–18 ng/L in the Lake Tahoe Basin samples.

Following repeated aerial applications of malathion, at a target rate of 23.8 mg/m^2, to urban/residential areas (1,500 km^2) of southern California between August 1989 and July 1990 to eradicate medflies, the CDFA Environmental Monitoring Branch measured the mass deposition, air concentrations, and selected water concentrations of malathion and its primary oxidation product, malaoxon (Bradman et al. 1994). The mean mass deposition of the malathion originally released to the air (during the first application only) at a target rate of 23.8 mg/m^2 was 22.1 mg/m^2, with a range of 1.7–53.7 mg/m^2 (Bradman et al. 1994). The mean concentration of malathion in the air was 25.1 ng/m^3 during the aerial spraying period,

increased to a maximum of 61.6 ng/m^3 within 24 hours of spraying, and was 3.3 ng/m^3 within 96–120 hours of spraying (Brown et al. 1993b). The mean concentration of malaoxon in the air was 5.4 ng/m^3 during the spraying, was a maximum of 48.1 ng/m^3 within 24–48 hours of spraying, and was 4.5 ng/m^3 within 96–120 hours of spraying (Brown et al. 1993b).

6.4.2 Water

Several studies have been conducted to determine the presence and concentration of malathion in runoff waters as well as in surface waters of various river basins in agricultural areas of the United States. Malathion was not detected (detection limit of 35 ng/L) in storm water runoff (from rice fields and fruit orchards) within the Sacramento River Basin, California, following a storm event in January 1994 (Domagalski 1996). In a study of pesticides in the streams of an agricultural and an urban area of Colorado, conducted from April 1993 to April 1994, 25 water samples were collected each from the Lonetree Creek Basin near Greely, Colorado (an agricultural land-use area), and the Cherry Creek Basin (urban area) near Denver, Colorado; 2 of the samples in the agricultural area and 7 of the samples in the urban area were collected during storm runoff events (Kimbrough and Litke 1996). Malathion was not detected (detection limit of 0.014 µg/L) in the water samples from the agricultural area, but was present in approximately 30% of the samples from the urban area, at a maximum concentration of 0.16 µg/L; statistical analysis of the data indicated that concentrations of malathion were significantly higher in the storm runoff event samples than in the nonstorm samples.

In a study of pesticide fluxes in nine surface water bodies of the Mississippi River Basin, the concentrations of 26 pesticides, including malathion, were monitored between May 1991 and March 1992 at nine sites, including three sites on the Mississippi River and six sites located near the mouths of major tributaries of the Mississippi (Larson et al. 1995). Malathion was detected (detection limit of 0.005 µg/L) at only two of the eight sites for which data were reported. In the White River Basin, the malathion flux as percentage of the total agricultural usage of malathion (0.98 metric tonnes or 980 kg) in the river basin was 0.12% (1.18 kg); in the Missouri River Basin, the malathion flux was <0.01% (8.5 kg) of the total agricultural usage (85 metric tonnes or 85,000 kg) in the river basin.

A study was conducted in 1990 to determine the presence of pesticides and polycyclic aromatic hydrocarbons (PAHs) in the subsurface and microlayers of the Winyah Bay and North Inlet in South Carolina; samples were collected at seven locations every 2 months during the year-long study (Kucklick and Bidleman 1994). Malathion, used for mosquito control in the populated areas of coastal South

Carolina, was detected (detection limit of 0.5 ng/L) in the subsurface water at a maximum mean concentration of 32 ng/L, with a range in individual samples of below the limit of detection to 47 ng/L. In the surface microlayer (top ≤1 mm) samples, malathion was detected at a maximum mean concentration of 32 ng/L, with a range in individual samples of below the limit of detection to 57 ng/L.

Monitoring studies have been conducted to determine the presence of numerous pesticides, including malathion, in groundwater in the United States. In a review of pesticides in groundwater monitoring data in the literature, Ritter (1990) reported that malathion occurrence in groundwater from normal agricultural use was reported in the literature for only one state. In a database of pesticides in groundwater that was compiled by EPA from data available for 1971–1991, results indicated that malathion was detected in a total of 12 wells in three states (California, Mississippi, and Virginia) at concentrations ranging from 0.007 to 6.17 μg/L; monitoring data were reported for a total of 3,252 wells (EPA 1992). Forty-one land-use studies were conducted in 1993–1995 at a total of 1,034 agricultural and urban sites representing 20 major hydrologic basins throughout the United States to assess the occurrence of 46 pesticides, including malathion, in shallow groundwater for the National Water-Quality Assessment (NAWQA) program; 31 of the studies were in agricultural areas and 10 were in urban areas (Kolpin et al. 1998). Malathion was detected (detection limit of 0.005 μg/L) at 0.2% of all sites, with detection frequencies of 0.4% for sites where corn and alfalfa growth accounted for >20% of the crops grown there, and 1.7% for sites where orchards or vineyards accounted for >50% of the crops (Kolpin et al. 1998).

6.4.3 Sediment and Soil

To estimate soil concentrations following an aerial application of malathion, at a target rate of 23.8 mg/m^2, to urban/residential areas (1,500 km^2) of southern California between August 1989 and July 1990 for the eradication of medflies, mass deposition data for malathion and its primary oxidation product, malaoxon, were obtained from the CDFA Environmental Monitoring Branch (Bradman et al. 1994). Based on measured values of mass deposition, daily malathion and malaoxon residue levels in soil were estimated for a single application using two sample mixing depths. Based on a mixing depth of 1 cm, soil concentrations of the parent and its degradate were estimated as 1.4 and 0.01 μg/g, respectively; based on a mixing depth of 0.1 cm, the corresponding estimated concentrations in soil were 14.1 and 0.10 μg/g (Bradman et al. 1994).

In a study of 49 randomly chosen agrichemical facilities located throughout Illinois, malathion was detected in soil samples at 6 of the 18 sites that handled the compound (Krapac et al. 1995). Malathion

was detected in 11 of the soil samples from the six sites (a total of 822 samples were collected from the 18 total sites in the study), at a mean concentration of 125 µg/kg (ppb) and at a concentration range of 31–690 µg/kg; the common range of detections was 22–100 µg/kg.

No monitoring data were found in the available literature for malathion detections in sediment.

6.4.4 Other Environmental Media

Monitoring studies have been conducted to determine the presence of malathion residues in/on food and feeds. Malathion residues were present, at 0.05–>2.0 ppm, in 249 of the 19,851 samples of food and animal feeds tested by the FDA in fiscal years 1982–1986; the selection of test samples was not random, but was geared toward choosing samples most likely to contain pesticide residues based on various factors (Luke et al. 1988). The malathion degradate malaoxon was detected in only two of the samples. In an FDA monitoring study of organohalogen and organophosphorus pesticide residues in 545 domestic surveillance samples of mixed feed rations conducted during fiscal years 1989–1994, malathion was the most commonly detected pesticide, occurring in 425 of the samples (in trace amounts in 53 of those samples) and accounting for approximately 53% of all pesticide residues detected (Lovell et al. 1996). Malathion was detected in the samples at a concentration range of 0.006–4 ppm, with a median concentration of 0.098 ppm. In a study conducted in 1977 to determine malathion residues on and in oranges following low-volume (100 gal/ac) and dilute applications (1,500 gal/ac) to orange trees in California, malathion residues on and in unwashed whole fruits were below the then current residue tolerance levels of 8 ppm (Carman et al. 1981). In the edible portion (pulp) of the fruits, malathion residues were 0.01–0.03 ppm 7 days after treatment and <0.01 ppm 30 days after treatment; the authors stated that the results indicated that the majority of the residues were present in or on the orange rinds.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

There are insufficient data to determine the potential daily inhalation and dermal exposure levels for the general population, although estimates of daily exposure to malathion in air at two U.S. sites have been reported (Whitmore et al. 1994). Based on the results of that study and on the information presented in Sections 6.3 and 6.4, exposure levels for the general population are likely to be low by these routes. Inhalation exposure is not considered to be important for the general population, with the possible exception of those individuals living in or near areas where malathion is frequently sprayed or those

individuals using a low pressure handwand for mosquito and household pesticide control (EPA 2000a). Since malathion is adsorbed through the skin, dermal contact is a more relevant pathway, compared with inhalation, for the general population, and may be of even greater importance for those who apply malathion for home and garden use. Dermal exposure to malathion for the general population may also be more important for persons living near sites where malathion is sprayed for public health usage or where off-target drift from Boll Weevil Eradication Programs occurs (EPA 2000a). However, dermal contact is most likely to occur in people who are occupationally exposed to malathion.

As part of the National Health and Nutrition Examination Survey (NHNES II) conducted in 1976–1980, urine specimens from 6,990 people living in the United States were analyzed for selected pesticide residues to determine the occurrence of pesticide body burden residues in the general population and to estimate the extent of human exposure to pesticides in the general U.S. population. Residues of malathion monitored in the study included malathion dicarboxylic acid (DCA) and malathion alpha-monocarboxylic acid (MCA). The degradates MCA and DCA were detected in samples from 1.1% and 0.5% of the 6,990 study participants, respectively, at a maximum concentrations of 970 ng/mL (ppb) and 250 ng/mL, respectively (Kutz et al. 1992). Based on the results of the study, it was estimated that 1,800,000 and 800,000 persons in the general U.S. population would have quantifiable MCA and DCA in their urine samples, indicating recent exposure to malathion (Kutz et al. 1992).

In a study of selected pesticide metabolites in urine, conducted in Maryland for a single year during 1995–1996, MacIntosh et al. (1999a) found the malathion metabolite DCA in 6.6% of 347 samples, at a maximum concentration of 51.0 µg/L (and 51.0 µg/g creatinine).

In a study conducted to determine human exposure to selected pesticides in drinking water, conducted in Maryland during 1995–1996, MacIntosh et al. (1999b) did not find malathion above the limit of detection (0.043 µg/L) in any of the drinking water samples.

In the EPA's Non-Occupational Pesticide Exposure Study conducted at two U.S. sites (Jacksonville, Florida and Springfield/Chicopee, Massachusetts) during 1986–1988, it was determined that 17–32% of the Jacksonville population was exposed to detectable levels of malathion in the indoor air during the three sampling seasons (summer, spring, winter) utilized at that site; 0–4% of the population was exposed to malathion in the outdoor air and 11–15% of the population was exposed to malathion in their personal space air (Whitmore et al. 1994). The maximum concentrations of malathion in the indoor air in Jacksonville for the three seasons ranged from 14.9 to 20.8 ng/m^3; maximum concentration ranges for the

outdoor air and the personal space air were 0–0.3 and 9.2–16.8 ng/m^3, respectively. At the Massachusetts site, 0–2% of the population was found to be exposed to malathion in the indoor air during the two sampling seasons (spring and winter) utilized at that site; 0–5% of the population was exposed to malathion in the outdoor air and 0–4% of the population was exposed to malathion in their personal space air (Whitmore et al. 1994). Measurements conducted in spring showed a mean concentration of malathion in the indoor air at the Massachusetts site of 5.0 ng/m^3, a mean of 0.8 ng/m^3 was detected outdoors, and 0.5 ng/m^3 was found in personal air space; no malathion was detected in winter. Mean daily air exposure estimates were determined for each of the two sites so that the values could be compared with dietary exposure estimates; the respective mean air exposure estimates for the Florida and Massachusetts sites were 232 and 8 ng/day (Whitmore et al. 1994). Based on dietary exposure estimates made using data from FDA Total Diet Studies and dietary recall questionnaires, it was determined that dietary exposure to malathion residues was much greater than exposure to residues in air for the populations of both the Florida and Massachusetts sites. Dietary exposure to malathion residues for the periods 1982–1984, 1986–1987, and 1987 ranged from 4,510 to 4,701 ng/day for the Florida site population, and was 4,625 ng/day for the Massachusetts site population in 1982–1984 (Whitmore et al. 1994). These results indicate that the inhalation route of malathion exposure is much less important than the ingestion route for the general populations of the two sites studied.

In an assessment of exposure to malathion and malaoxon in areas of southern California that had received aerial applications of malathion for public health purposes, adult, infant, and child exposures through dermal and inhalation routes were estimated and compared with a select dietary exposures (including backyard vegetables and soil); estimates of the various exposures were made for both average and high-end exposure scenarios. In general, estimated exposures to malathion residues increased with the extent of outdoor activity and with higher levels of consumption of backyard vegetables (Marty et al. 1994). The most important routes of exposure for adults were dermal exposure and ingestion exposure from consumption of contaminated, unwashed backyard vegetables, with respective estimated doses of 1–246 and 30–80 µg/kg/day; the estimated inhalation dose for adults was only 0.01–0.1 µg/kg/day (Marty et al. 1994).

The FDA Total Diet Studies (formerly referred to as Market Basket Studies) examine food for levels of pesticides. Estimates are then made of the mean intake of a pesticide per unit body weight (in µg/kg/day) using the amounts of pesticides found in foods and food consumption patterns; target groups include 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. Malathion was the second most frequently detected pesticide in

the study conducted during June 1984–April 1986 (Gunderson et al. 1995a), occurring in 22% of the samples, and was the most frequently detected pesticide in the study conducted during July 1986–April 1991, occurring in 20% of the samples (Gunderson et al. 1995b). For the period June 1984–April 1986, the mean daily intake estimates for malathion were 0.1333 µg/kg/day for the 6–11 months group, 0.2548 µg/kg/day for the 2 years group, 0.0835 µg/kg/day for the 14–16 years female group, 0.1159 µg/kg/day for the 14–16 years male group, 0.0699 µg/kg/day for the 25–30 years female group, 0.0796 µg/kg/day for the 25–30 years male group, 0.0615 µg/kg/day for the 60–65 years female group, and 0.0719 µg/kg/day for the 60–65 years male group (Gunderson et al. 1995a). For the period July 1986–April 1991, the mean daily intake estimates for malathion were 0.1139 µg/kg/day for the 6–11 months group, 0.2184 µg/kg/day for the 2 years group, 0.0686 µg/kg/day for the 14–16 years female group, and 0.0965 for the µg/kg/day 14–16 years male group, 0.0598 µg/kg/day for the 25–30 years female group, 0.0704 µg/kg/day for the 25–30 years male group, 0.0567 µg/kg/day for the 60–65 years female group, and 0.0645 µg/kg/day for the 60–65 years male group (Gunderson et al. 1995b). FDA Total Diet Studies conducted in 1979–1980 and 1980–1982 estimated the average daily exposure to malathion was 14.0 µg/day (Gartrell et al. 1985) and 16.8 µg/day, respectively (Gartrell et al. 1985).

Based on an EPA risk assessment of malathion conducted, in part, using the Dietary Exposure Evaluation Model (DEEM), acute dietary exposure to malathion (plus malaoxon) from food is not a concern for the majority (95^{th} exposure percentile) of the U.S. population (EPA 2000a). Based on a calculated acute population adjusted dose (aPAD), at which no adverse health effects would be expected using the safety factor prescribed in the Food Quality Protection Act (FQPA), the population subgroup with the highest acute dietary exposure (at 38% of the aPAD) is children aged 1–6 (EPA 2000a). For chronic dietary exposure, the population subgroup with the highest exposure (at 1.6% of the cPAD) is also children aged 1–6. However, values of <100% of the aPAD or cPAD are not considered to be of concern (EPA 2000a). The reported aPAD and cPAD values were 0.5 mg/kg/day (500 µg/kg/day) and 0.024 mg/kg/day (24 µg/kg/day), respectively. Based on these values and the results of the FDA's Total Diet Studies, dietary exposure to malathion from food is also not important for the general population. EPA also determined that dietary risk of malathion exposure from drinking water was not important for the general population (EPA 2000a).

Exposure of the general population to higher concentrations of malathion 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 malathion through contact with contaminated waste site media.

NIOSH estimated that approximately 19,170 U.S. workers, employed in 18 occupations excluding farm work, are potentially exposed to malathion in occupational settings; of these, an estimated 1,909 are females (NIOSH 1981). Occupational exposure to malathion is mainly through the dermal route, but may also occur through inhalation. The OSHA workplace air environmental limit for malathion is 15 mg/m^3 (NIOSH 2001).

Agricultural workers and commercial applicators may also be exposed to malathion through occupational practices. Farm worker protection measures include routine cholinesterase monitoring of blood samples; similar monitoring is required in many states for commercial applicators who apply organophosphate insecticides (Fenske and Leffingwell 1989). For many crops, the restricted entry intervals for workers to enter fields treated with malathion following application are generally short (<1 day) relative to reentry intervals for other organophosphate pesticides (Swift 1976), although restricted entry intervals for certain activities such as hand pruning or harvesting of crops are often longer (0–6 days; EPA 2000a).

In a Department of Commerce monograph on human exposure to malathion in the workplace, Santodonato et al. (1985) reported that the number of U.S. workers exposed during (initial) production of malathion is limited since production of the chemical was limited at that time to a single corporation (American Cyanamid), but increases greatly at the formulation stage since numerous companies utilize malathion in formulated products; the production of these products requires activities such as loading, blending/mixing, and packaging. While production of malathion is no longer limited to a single corporation, it is still not widely spread.

Exposure levels for workers are affected by the type of work activity being conducted at the time of the exposure (Santodonato et al. 1985; Swift 1976). In a study of the exposure of formulating plant workers to ethion and malathion, the exposure to malathion of workers employed in various activities was determined; worker categories included mixers, baggers, and stackers (Wolfe et al. 1978). For all categories combined, the potential exposure to malathion was determined to be 150 mg/hour for the dermal route and 1.29 mg/hour via inhalation. For the dermal route, however, exposure was approximately 5–6 times greater for baggers (244 mg/hour) compared with either mixers or stackers (40–50 mg/hour). For the inhalation route, potential exposure to malathion was also much greater for baggers (2.19 mg/hour) than for mixers (0.05 mg/hour) or stackers (0.50 mg/hour). None of the exposure levels identified in the study were considered to represent a very great hazard to the formulating plant workers (Wolfe et al. 1978).

Several researchers have found that worker exposure to malathion for a variety of activities (e.g., application operations, harvesting, field observation, formulating operations) using various formulation types (e.g., spray, dust, aerosol) is greater via the dermal route than through inhalation (Culver et al. 1956; Culver et al. 1956; Durham and Wolfe 1962; Jegier 1964; Lin and Hee 1998; Wolfe et al. 1978, 1967). Based on data reported in the literature, Santodonato et al. (1985) reported mean dermal exposures during malathion spraying of 2–67 mg/hour, and mean airborne concentrations of 0.6–6 mg/m^3, indicating a lower potential for exposure via inhalation relative to the dermal route. In a review of worker exposure data, Durham and Wolfe (1962) reported that exposure rates for workers applying malathion as an aerosol (liquid sprays) were 6.6 mg/70-kg man/hour via the dermal route and 0.3 mg/70-kg man/hour via inhalation.

In a study of the persistence of pesticides on the hands of occupationally exposed workers, malathion was found to persist on the hands of three of eight farmers occupationally exposed to malathion; it was also found to persist for at least 7 days on the hands of a home gardener who grew fruits and vegetables treated with the compound, which was applied by the gardener without the use of protective gloves (Kazen et al. 1974). In the study, malathion was not detected on the hands of three nonoccupationally exposed workers.

In a study of occupational exposure to flea control products, including malathion, among pet handlers in California, Ames et al. (1989) found that not only the workers who applied the products, but also others (nonapplicators) who worked at the facilities where the products were used, were exposed to the chemicals. Of the 200 workers considered to be nonoccupationally exposed based on their duties, 31 of the workers reported that they were exposed to malathion in the workplace.

In a study of malathion permeation through the gloves of workers exposed to the compound, Lin and Hee (1998) reported that the highest potential for exposure was associated with worker dermal contact with pure and technical-grade malathion and the emulsifiable concentrate formulations; these formulations generally contain 30–91% (w:w) malathion. Dermal exposure to malathion varied with the type of protective gloves worn by the workers in the study, with greater protection provided by Viton and Silver Shield gloves, and the least protection provided by nitrile gloves; for the first two types of gloves, exposure following permeation through the gloves was <0.02 mg, while permeation through the latter type of glove ranged from <0.02 to 283 mg (Lin and Hee 1998). Differences in permeation mass and time of breakthrough for the nitrile gloves was related to the carrier (e.g., *m*-xylene, distilled water) in the

formulated malathion product. These data indicate that in addition to the formulation type of the malathion product utilized and the activity performed by the worker, the type of protective materials or equipment used will affect the potential worker exposure levels.

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 within the general population living in areas far from where malathion is sprayed are not likely to be exposed to high levels of malathion. An exception to this may be at homes where malathion is used extensively for home and garden use, particularly if inappropriately high application rates (relative to label recommendations) are utilized and if backyard vegetables are not washed prior to consumption. Children playing on turf following the application of malathion by means of a handgun sprayer may be exposed to malathion via the dermal route at levels high enough to cause concern (EPA 2000a).

For those children living in areas where malathion is sprayed for public health use or at homes where malathion is used extensively, children within the general population are likely to be exposed to malathion in the same ways that adults are, including through contact with sprayed plants, soil, or other surfaces; breathing contaminated air; eating contaminated foods; or drinking contaminated water. Additionally, small children are more likely than adults to be in close contact with yard dirt or playground dirt, lawns, and indoor (carpet) dust. Malathion residues bound to soil or dust particles in carpets or on bare floors may present an exposure route for infants and toddlers through dermal contact and oral ingestion. Children are known to participate in frequent hand-to-mouth activity and to have a tendency to put foreign objects into their mouths. As a result of this behavior, children may ingest malathion present

in soil and dust or through direct transfer of the chemical from their skin to their mouths. Children are also lower to the ground than adults and something that may exist at arm or hand level for an adult may be at mouth level for a child.

Approximately 16–20% of the annual malathion use in the United States is attributed to general agricultural use, while 59–61% is attributed to use by the USDA in eradication programs (EPA 2000a). Approximately 0.5 million pounds of malathion are released to soil annually just through applications to agricultural sites (e.g., roads, ditches, and near buildings); this value excludes other agricultural uses (i.e., crops; EPA 2000a). 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, contact with pesticide spray drift, or from playing in the fields near where malathion has been sprayed. Dermal exposure is expected to be the most likely route of exposure once the pesticide has been applied, although oral ingestion through the direct transfer caused by hand-to-mouth activity or consumption of unwashed produce treated with malathion is also likely. Malathion is moderately to highly mobile in soil, however, indicating that it does not readily adsorb to soil particles. Additionally, it breaks down rapidly in soils, as does the primary oxidation product, malaoxon. Thus, the level of exposure that children will have to malathion is dependent on the time that has passed since the application of the compound. Also, exposure to certain levels of malathion or its residues does not mean that the compounds will be bioavailable at those levels. No U.S. data were found on exposure or body burden measurements made on children.

Approximately 3.4 million pounds of malathion are released to soil annually through applications to nonagricultural sites; this includes malathion use for medfly and mosquito control, golf courses, and home and garden use (EPA 2000a). Malathion has been sprayed over large areas for public health usage, to eradicate medflies and to control mosquito populations; approximately 8–15% of the malathion used annually in the United States is attributed to public health use (EPA 2000a). This practice may lead to exposure of malathion to children through dermal contact and ingestion when they play on treated soil surfaces or in contaminated sand boxes and perform the frequent hand-to-mouth activity common in children. To estimate exposure concentrations following repeated aerial applications of malathion to urban/residential areas (1,500 km^2) of southern California for the eradication of medflies, mass deposition data for malathion and its primary oxidation product, malaoxon, were obtained from the CDFA Environmental Monitoring Branch (Bradman et al. 1994). Based on measured values of mass deposition, malathion and malaoxon exposure concentrations (acute and chronic) were estimated for typical and high or upper bound exposure levels. Estimated malathion acute and chronic exposure concentrations for a typical exposure for the top 0.1-cm depth of soil were 14.7 and 4.9 mg/g, respectively; the corresponding

values for malaoxon were 0.10 and 0.03 mg/g (Bradman et al. 1994). For outdoor surfaces, potentially including playground equipment, estimated malathion acute and chronic exposure concentrations for a typical exposure were 22.0 and 7.3 mg/g, respectively; the corresponding values for malaoxon were 0.15 and 0.05 mg/g (Bradman et al. 1994).

Malathion is widely used for residential (i.e., home and garden) purposes; approximately 10% of the malathion used annually in the United States is attributed to home and garden use (EPA 2000a). Children may be exposed to malathion used in the home or garden, or to malathion tracked into the home from outside by themselves or other household members. A Minnesota study monitored the urinary metabolite level of commonly used pesticides including malathion in 102 children, ages 3–13 years. The intrachild urinary metabolite levels were found to be greater than the detection limit 46% of the time for malathion (Adgate et al. 2001). In a nine-home pilot study to assess monitoring methods for use in determining pesticide exposure to children aged 6 months to 5 years old, malathion was not detected in any of the nine homes; however, the study authors indicated that the lack of detections may have been due to analytical limitations for the 7 of 30 targeted pesticides, including malathion, which were not detected in any of the homes (Lewis et al. 1994).

Children may be exposed to malathion brought into the home by parents or other household members who are occupationally exposed. Malathion residues may be present on the skin, hair, clothing items and shoes of workers employed in industries, such as agriculture, where malathion is used or at sites where malathion is manufactured or formulated. Exposure to children may occur through dermal contact with contaminated items. Because children are likely to be in close contact with carpet or floors, transfer of contaminated dirt from work shoes to carpeting provides a means of exposure. Respiratory exposure from contact with occupationally exposed workers is not likely to be significant.

In a study of pesticide exposure to children in the home in rural areas, samples of house dust were analyzed from a day care center and 10 homes, 5 of which were also the home of at least one farm worker (currently working in the field) and 8 of which reported home pesticide use (Bradman et al. 1997). While malathion was detected in one nonfarmworker home, at a concentration of 1.60 μg/g and a loading of 2.40 $\mu g/m^2$, it was not detected in any of the homes with a farmworker as a resident. Malathion was also not detected in the day care center.

Children may be exposed to malathion and its residues in the foods that they eat. In an early (1963–1967) study of pesticide residues in prepared baby foods in the United States, the average malathion

concentration was below the limit of detection (0.005 ppm); however, the pesticide was only monitored in a limited number of samples (Lispcomb 1968). In an FDA Total Diet Study conducted in 1980–1982 to determine the dietary intake of selected pesticides for infants and toddlers, the estimated average daily intakes of malathion residues were determined based on pesticide residue concentrations found in 11 food groups (Gartrell et al. 1986). The estimated average daily intake of malathion from infant diets was 1.45 μg/day; malathion was found in the grain and cereal products and the oil and fats food groups at concentrations of 0.008–0.158 ppm. The estimated average daily intake of malathion from toddler diets was 2.64 μg/day; malathion was found in the grain and cereal products, fruit and fruit juices, oil and fats, sweets and adjuncts, and beverages food groups at concentrations of less than the limit of quantification (LOQ)–0.24 ppm. Data on the weight-adjusted intake of malathion by infants and toddlers were determined based on the results of the FDA Total Diet Studies for fiscal years 1978–1981/1982 (Gartrell et al. 1986). The reported weight-adjusted intakes of malathion ranged from 0.126 to 0.331 μg/kg body weight/day for infants and were 0.193–0.299 μg/kg body weight/day for toddlers for the four study years.

Quantitative estimates of the exposure of infants and children to pesticides have been reported in the results of FDA Total Diet 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 malathion per unit body weight were made for the 6–11 months age group, 2 year age group, and the 14–16 years female and 14–16 years male age group. For the period June 1984–April 1986, the estimates were 0.1333 μg/kg/day for the 6–11 months group, 0.2548 μg/kg/day for the 2 year group, 0.0835 μg/kg/day for the 14–16 years female group, and 0.1159 μg/kg/day for the 14–16 years male group (Gunderson et al. 1995a). The daily intake values for the 6–11 months group and the 2 year group were similar to the values determined in the FDA Total Diet Study for the same period of time in 1982–1984 (Gunderson et al. 1995a). For the period July 1986–April 1991, the mean daily intake estimates were 0.1139 μg/kg/day for the 6–11 months group, 0.2184 μg/kg/day for the 2 year group, 0.0686 μg/kg/day for the 14–16 years female group, and 0.0965 for the μg/kg/day 14–16 years male group (Gunderson et al. 1995b). Malathion residues were not detected in any of the samples of infant formula (milk-based without iron, canned, ready-to-serve) analyzed in the study (Gunderson et al. 1995b).

The FDA Total Diet Study results for fiscal years 1985–1991 include estimates of pesticide residue intakes associated with 33 types of representative infant foods, infant formula, and adult foods eaten by infants and children (e.g., raw and processed fruits, fruit juices, milk, peanut butter) that have been prepared for consumption (Yess et al. 1993). Malathion residues were found in infant foods at maximum levels of 0.001–0.008 ppm in cereals, combination meat or poultry dinners, fruits/fruit juices, and

vegetables; malathion residues were not detected in samples of infant formulas. Malathion was detected in adult foods eaten by infants and children at maximum concentrations of 0.004 ppm in grape juice, 0.0005–0.0009 ppm in milk (including processed/canned and fluid), and 0.40 ppm in peanut butter.

The FDA Regulatory Monitoring Program analyzes surveillance samples of whole, unwashed, unpeeled foods that may be eaten by infants/children to determine pesticide concentrations in 10,000 domestic and imported food samples (Yess et al. 1993). During the fiscal years 1985–1991, malathion was detected in domestic samples at a maximum concentration of 0.12 ppm in apples (in 7 of 2,464 samples) and 0.036 ppm (in 9 of 862 samples) in oranges. In imported samples, malathion was detected at maximums of 0.60 ppm in bananas (in 10 of 1,097 samples), 0.02 ppm in orange juice (in 1 of 64 samples), and 0.25 ppm in oranges (in 32 of 474 samples). Based on an EPA risk assessment of malathion conducted, in part, using the Dietary Exposure Evaluation Model (DEEM), acute dietary exposure to malathion (plus malaoxon) from food is not a concern for children aged 1–6 (EPA 2000a). Based on a calculated acute population adjusted dose (aPAD), at which no adverse health effects would be expected using the safety factor prescribed in the Food Quality Protection Act (FQPA), the population subgroup with the highest acute dietary exposure (at 38% of the aPAD) and the highest chronic dietary exposure (at 1.6% of the cPAD) is children aged 1–6 (EPA 2000a). However, values of <100% of the aPAD or cPAD are not considered to be of concern (EPA 2000a). The reported aPAD and cPAD values were 0.5 mg/kg/day (500 μg/kg/day) and 0.024 mg/kg/day (24 μg/kg/day), respectively. Based on these values and the results of the FDA's Total Diet Studies, dietary exposure to malathion from food is not considered to be important for children aged 1–6.

A potential source of exposure in infants is the presence of malathion in breast milk. Malathion was detected in breast milk (5 ppb) from 1 of 11 Italian women from the general population on the 5th day postpartum, but was not detected by the 11th day (Roggi et al. 1991).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The populations most at risk for exposure to relatively high levels of malathion are field workers who go into sprayed areas, particularly before the prescribed restricted entry intervals have passed. Also at greater risk for potentially high exposures are occupationally exposed workers who do not use adequate protective equipment that is appropriate for the type of malathion product being utilized. People who live in or near areas where malathion is sprayed for public health uses and those who consume unwashed

backyard vegetables treated with malathion may also be exposed to higher levels of the chemical relative to the general population.

In an assessment of exposure to malathion and malaoxon in areas of southern California that had received aerial applications of malathion for public health purposes estimates of the various exposures were made for both average and high-end exposure scenarios. In general, estimated exposures to malathion residues increased with the extent of outdoor activity and with higher levels of consumption of backyard vegetables (Marty et al. 1994). The most important routes of exposure for adults were dermal exposure and ingestion exposure from consumption of contaminated, unwashed backyard vegetables, with respective estimated doses of 1–246 and 30–80 µg/kg/day (Marty et al. 1994).

It has been reported that malathion was oxidized to malaoxon following its release in 1990 in the Los Angeles Basin of California for control of the Mediterranean fruit fly; concentrations of malaoxon in air were greater than those of parent malathion (Wolfe and Sieber 1993). Because malathion is less toxic in the parent (thiono) form than in its oxon form, exposure to malathion residues are potentially more harmful in situations that favor the formation of the degradate malaoxon. Such a case may occur when a dust formulation is utilized on plant or tree leaves, which allows for the formation of a catalytic surface where oxidation to malaoxon may take place, particularly in the presence of a high level of atmospheric oxidant such as ozone and in times of low humidity; these conditions are thought to be favorable to the buildup of the oxon (Wolfe and Sieber 1993). These data indicate that the restricted entry intervals that do not account for such cases may lead to higher potential exposures to workers who enter a field with such conditions too early after spraying.

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 malathion 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 malathion.

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 malathion are sufficiently well characterized to allow assessment of the environmental fate of the compound to be made (Budavari 1996; Buyuksonmez 1999; Chiou et al. 1977; Fazzalari 1978; Freed et al. 1979a; Hansch et al. 1995; Howard and Neal 1992; Kim et al. 1984; Matsumura 1985; Ruth 1986; Tomlin 1997; Watanabe 1993).

Production, Import/Export, Use, Release, and Disposal. Malathion is commercially produced in the United States and abroad. Malathion has been commercially produced in the United States since 1950. No production volume data were located for the 1950s and 1960s; production was estimated to be 24 million pounds in 1972 (Santondonato et al. 1985; von Rumker et al. 1974) and 30 million pounds in 1983 (IARC 1983). Recent production volume data for the United States were not located. Data on import volumes are limited; import volumes for 1977 were 6,457 pounds (USITC 1978) and 143,260 pounds in 1982 (SRI 2000). U.S. exports of malathion were estimated to be 11,020,000 pounds in 1978 (SRI 2000). More current information on the production volume, import, and export of malathion is needed to make and accurate assessment of the potential for human exposure to the pesticide.

Releases to air, land, and water occur primarily through the use of malathion as an insecticide. The media of most importance for human exposure are 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 2000, became available in June of 2000. This database is updated yearly and provides a list of industrial production facilities and emissions.

The recommended methods of disposal of malathion are incineration in a furnace equipped with an afterburner and a scrubber (Sittig 1985). If incineration is not an option, malathion may be disposed of by absorbing in vermiculite, dry sand, earth, or similar material and then burying in a designated landfill (Mackison 1981). Only small amounts of malathion may be land filled (United Nations IRPTC 1985). Waste water treatment technologies have been investigated for malathion using biological treatment and

reverse osmosis (EPA 1982). Another method of disposal that has been suggested for malathion is combustion in molten potassium chloride. The destruction of malathion is 99% and the products of combustion can be used as a fertilizer (United Nations IRPTC 1985).

Environmental Fate. There is a lack of data on the degradation (fate and persistence) of malathion in soil under both aerobic and anaerobic acidic conditions, as well as on the degradation of malathion on dry surface soils where hydrolysis is less likely to occur. Further studies with malathion are needed to assess these particular situations. Monitoring data for pesticide disposal and other hazardous waste sites are also lacking and would be useful in determining the prevalence of malathion residues at these sites. As very little definitive information was found in the literature on the transformation and degradation of malathion in air, additional studies are needed on this topic, including on the transformation of the parent to malaoxon through photolysis and on the subsequent degradation of malaoxon. Several researchers have suggested the possibility of the volatilization of malathion from nonnatural surfaces, such as metals, plastic playground equipment, cement, and paved areas, based on mass deposition study data (Bradman et al. 1994; Brown et al. 1993b). More information is needed on the potential volatilization of malathion from nonnatural surfaces such as pavements and playground equipment. Additionally, information is needed on the potential for photodegradation of malathion and malaoxon on such surfaces in order to characterize the fate of malathion in the environment when it is used over widespread areas for public health purposes. Information on the physical properties and the fate and persistence of the malathion degradate malaoxon (which is also present in malathion as an impurity) would be particularly useful in assessing the human health risks from malathion use, as the oxon is considered to be more toxic than the parent compound (EPA 2000a).

Bioavailability from Environmental Media. Malathion can be absorbed following inhalation or dermal contact with contaminated media, and by ingestion of contaminated water or food, particularly of unwashed backyard vegetables (Bradman et al. 1994; Brown et al. 1993b; Durham and Wolfe 1962; EPA 2000a; Kutz et al. 1992; MacIntosh et al. 1999a; Whitmore et al. 1994). Dermal contact with malathion present in soil or on treated crops and ingestion of malathion present on backyard vegetables or soil particles are exposure routes that may be of concern. No information was found in the available literature on the bioavailability of malathion following ingestion of soil or dermal contact with contaminated media; such data are needed to determine potential exposures to humans.

Food Chain Bioaccumulation. The majority of the data available on the bioaccumulation of malathion suggest that, while malathion may be bioconcentrated, it is rapidly metabolized or depurated

from the tissue of aquatic organisms and is, therefore, not likely to be biomagnified in the food chain such that it would pose human exposure threats (EPA 2000a; Howard 1991). However, bioconcentration factor data available in the literature did not definitively show that such a concern would be unfounded. Additional data to verify (or refute) the assumption that food chain bioaccumulation of malathion is not an important fate process would be helpful in assessing human exposure risks from ingestion of contaminated fish or other aquatic organisms. Data on the uptake and potential concentration of malathion residues by plants were not found in the literature. Because malathion is utilized for home garden purposes, there is a potential for malathion to be taken up by vegetable and other produce plants. Although malathion is water soluble, malathion residues incorporated into the plants may be difficult to remove through washing or other food preparation processes and the consumption of such may provide a route for exposure. Additional data are needed on the ability of food plants to uptake malathion residues from the soil or through aboveground plant parts that come into contact with the insecticide through direct application.

Exposure Levels in Environmental Media. Malathion has been detected in the ambient air (Bradman 1994; Brown et al. 1993b; Majewski et al. 1998; Wright et al. 1996), precipitation (McConnell et al. 1998), fog (Rice 1996), surface water (Kimbrough and Litke 1996; Kucklick and Bidleman 1994; Larson et al. 1995), groundwater (EPA 1992; Ritter 1990), soil (Krapac et al. 1995), and in/on food and feeds (Carman et al. 1981; Lovell et al. 1996; Luke et al. 1988). Estimates of human intake of malathion have been made for ingestion of foodstuffs (EPA 2000a; Gartrell et al. 1985, 1986; Gunderson et al. 1995a, 1995b). Limited estimates of dermal and inhalation exposure have been made for the general population (Marty et al. 1994; Whitmore et al. 1994). Improved estimates of exposure from air, water, and soil as well as from treated nonnatural surfaces (such as pavements, sidewalks, and playground equipment) are needed to assess human exposure to malathion, particularly for exposures resulting from home and garden use and public health uses. Estimates of exposure to malaoxon, the production of which is favored in the environment under some conditions, are particularly important for assessing the human health risks related to malathion use. Information concerning concentrations of malathion in the air, water, and soil at the NPL hazardous waste sites known to be contaminated with malathion are needed to assess the exposure of populations living in the vicinity of these sites.

Exposure Levels in Humans. The malathion residues malathion dicarboxylic acid (DCA) and malathion alpha-monocarboxylic acid (MCA) may be detected in human urine samples following recent exposure to malathion (Fenske and Leffingwell 1989; Kutz et al. 1992; MacIntosh et al. 1999a). These compounds are specific for malathion when there is a history of exposure. Limited studies have been

conducted to determine the occurrence of pesticide body burden residues in the general population and to estimate the extent of human exposure to pesticides in the general U.S. population (Kutz et al. 1992); to determine the exposure of human populations at two U.S. sites to malathion via dermal and inhalation routes and compare these with estimated dietary exposure in the same populations (Whitmore et al. 1994); to determine malathion exposure to adults, infants, and children in areas receiving aerial applications of malathion for public health purposes (Marty et al. 1994); and to determine exposure levels in occupationally exposed persons (Ames et al. 1989; Lin and Hee 1998; Wolfe et al. 1978). However, a population that is potentially exposed to malathion through home and garden use of the compound also exists. Within occupationally exposed populations, subgroups of persons who may be exposed to higher levels of malathion exist; these include workers who don't wear adequate protective materials/equipment and workers who may enter too early into treated areas that have conditions favorable to the buildup of malaoxon. Information on the body burdens and intake of malathion residues for these populations and subgroups would be useful in assessing the exposure levels of persons with potentially high exposures to malathion. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. The exposure of children to malathion through ingestion of foodstuffs eaten by infants and children has been estimated fairly extensively for various age groups including infants, toddlers, and teenagers (EPA 2000a; Gunderson et al. 1995a, 1995b), and weight-adjusted intakes have been calculated (Gartrell et al. 1986). However, only limited studies have been conducted to estimate the extent of the exposure of children to malathion residues through dermal and inhalation pathways or through the ingestion of contaminated soil (Bradman et al. 1994). Data on the body burden measurements of malathion made on children are needed to determine exposures to children, particularly to those children living in or near areas where malathion is sprayed for public health purposes or used in the home and garden. Also, additional studies on the exposure of children to malathion on natural outdoor surfaces such as fields and turf, and on nonnatural outdoor surfaces such as sidewalks and playground equipment in areas where malathion is widely sprayed are necessary to determine the health risks to children living in such areas. Studies are also needed to determine breast milk contamination by malathion in order 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 malathion were located. This chemical 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 malathion.

6.8.2 Ongoing Studies

Information on ongoing studies related to the physical and chemical properties; the production, use, release, and disposal; the environmental fate and exposure; and the bioavailability of malathion was scarce. The Federal Research in Progress (FEDRIP 2002) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. With the exception of one study being funded by the U.S. Geological Survey (USGS), all of the studies identified in the FEDRIP database are being funded by the USDA. The majority of the studies identified in the database abstracts that mentioned malathion tend to be for research that deals with identifying alternative compounds, including chemically based alternatives and biopesticides, that are of lower risk or safer to use compared with malathion. Other studies focus on finding improved methods of application, which would lead to the safer, more accurate, and more timely application of pesticides, including malathion. Related studies focused on studying aspects of the boll weevil, a target pest for which malathion is used in USDA eradication programs, in order to find more environmentally sound and more cost effective ways (including decreased usage of pesticides) of achieving the goal of boll weevil eradication. The use of ultra-low volume (ULV) applications for control of boll weevils or mosquitoes are mentioned in several of the research abstracts, as is the implementation of integrated pest management (IPM) programs. Some of the studies focus on the use of safer and more efficacious biological and chemical compounds to be used for the control of riceland mosquito populations that have exhibited a high tolerance to malathion.

A literature search in an additional database identified a few studies related to the use, disposal, exposure, and environmental fate of malathion.

Researchers at Mississippi State are conducting a study funded by Agricultural Research Service (ARS)/USDA to identify methods to improve the efficiency of the production of channel catfish in aquaculture. Because malathion use (as ULV applications) for boll weevil eradication in the local study

area is potentially problematic for the catfish industry, the study includes experiments intended to determine the bioaccumulation of malathion in catfish tissue. Additional experiments in the study focus on the malathion degradation in aquarium and pond water.

Scientists at the University of Hawaii are conducting research funded by Cooperative State Research, Education, and Extension Service (CSREES)/USDA to help in obtaining minor use and specialty use pesticide clearances and to assist in the maintenance of current pesticide registrations. Proposed uses for individual pesticides are evaluated and prioritized based on several factors including safety to man, non-target organisms and the environment. Uses being studied for malathion include application of the insecticide on multiple fruit, nut, and vegetable crops as well as ornamentals.

Scientists at Cornell University are conducting research funded by CSREES/USDA to elucidate mechanisms of degradation and identify degradation products of various pesticides using various analytical methods. The main objective of the study is to develop a new kinetic model that will allow the researchers to evaluate the Anodic Fenton Treatment system, a newly developed technology for degrading/mineralizing pesticides and pesticide wastes (such as rinsate). The study will include the assessment of the toxicity, at both the molecular and cellular level, of the post-treatment aqueous effluent.

Researchers at the University of Maryland are measuring the concentrations of pesticides including malathion and combustion-derived polycyclic aromatic hydrocarbons in the air and water of the Chesapeake Bay. The object of the study is to understand the transport processes as well as the chemical-biological mechanisms that influence pesticide volatilization and transport. This includes studying the impacts of deposited volatiles and development of means to reduce volatile emissions. The study will also include an evaluation of the spatial and temporal trends in atmospheric transport and deposition of pesticides and combustion-derived chemicals to the Chesapeake Bay.

Scientists at the Connecticut Agricultural Experiment Station will examine pesticide exposure through non-dietary routes at commercial agricultural operations, public facilities, and in the home environment. The potential routes of non-dietary exposure to be examined include: dermal exposure by touching and handling contaminated items; non-dietary ingestion arising from hand to mouth contact with contaminated surfaces; continuous dermal exposure as a result of wearing contaminated clothing; and respiratory exposure from the inhalation of airborne contaminants.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring malathion, its metabolites, and other biomarkers of exposure and effect to malathion. 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

In mammals, malathion is metabolized by hydrolytic cleavage of one or both succinate esters and by hydrolysis of the succinate moiety from the dialkylthiophosphate (see Section 3.4.3, Metabolism). The primary metabolites found in biological fluids following exposure to malathion are malathion dicarboxylic acid (DCA) and malathion monocarboxylic acid (MCA). The DCA and MCA carboxylic acids represent more than 80% of the total metabolites excreted in urine. In addition, smaller amounts of two other metabolites, *O,O*-dimethyl phosphorothionate (DMTP) and *O,O*-dimethyl phosphorodithioate (DMDTP), are also found. Metabolites may also arise from malaoxon, a metabolite of malathion.

The principal method used for the detection of malathion and metabolites in biological samples is gas chromatography (GC) using an electron capture detector (ECD), a nitrogen/phosphorous detector (NPD), a flame photometric detector (FPD) in phosphorous mode, or a mass spectroscopy detector (MS). The detection of malathion using GC-flame-ionization-dection (FID) is reported to have low sensitivity and results are generally not reproducible (Lin and Hee 1998). Confirmation of GC analysis is typically accomplished using gas chromatography with mass spectroscopy (GC-MS). The preparation of samples for GC analysis typically involves sample extraction with an organic solvent (e.g., hexane or diethyl ether) and purification of the extract (e.g., by column chromatography or further extraction). The major metabolites of malathion, DCA and MCA, require derivativization prior to GC analysis.

Exposure to organophosphorous pesticides is generally assessed by monitoring:blood cholinesterase (ChE) inhibition and urinary metabolite excretion. Assay of blood cholinesterase activities is the most common and reliable biological indicator of human exposure to organophosphorous pesticides (OPs). The OPs inhibit acetylcholinesterase (AChE) in red blood cells (RBCs) and pseudocholinesterase (PChE) in serum or plasma. Depending upon the degree of exposure, type of OPs, and AcChE/PChE, the reduction in PChE and AChE activity can last for several days. Malathion and its activated product, malaxon, are not good inhibitors of cholinesterases. Several analytical methods have been developed to determine AChE and PChE in blood. Results obtained from the methods are generally comparable, but differ widely in accuracy, sensitivity, and precision. Analytical methods for the detection of metabolites of malathion in urine are more sensitive than those used to determine AChE and PChE in blood. Because of the increase in sensitivity, the methods are capable of revealing exposures that may be insufficient to bring about a toxic response. However, since alkyl phosphates such as malathion are rapidly metabolized in the body and their metabolites are excreted in urine within a short time (24–36 hours), urine samples for analysis must be collected quickly. Table 7-1 summarizes the analytical methods used to detect malathion and its metabolites as well as cholinesterase activity in biological tissues and fluids.

Malathion has been determined in human serum using a hexane extraction procedure and detection using GC-FPD (Fournier and Sonnier 1978). It was necessary to perform serum assays within 48 hours of patient exposure since malathion is quickly hydrolyzed in human tissues. The limit of detection was reported as 0.2 mg/L.

The quantity of malathion, DCA, and MCA in rat and human urine has been measured using GC-FPD (Bradway and Shafik 1977). Sample preparation required an extensive clean-up procedure involving extraction with diethyl ether, centrifugation, acidification, and additional extractions. The extracted DCA and MCA was then derivatized by ethylation or methylation and purified by column chromatography on silica gel using an ethyl acetate/benzene eluent. The percent recoveries for MCA and DCA from samples of rat urine were 99–104% for MCA and 98–101% for DCA. The lowest limits of detection in rat and human urine were 0.005 mg/L for MCA and 0.002 mg/L for DCA; the detection limits were found to be dependent upon detector sensitivity and the presence of interfering peaks in the GC. This procedure is commonly used, but difficulties have been reported with extraction and derivativization (Ito et al. 1979). Significant background interference in GC analysis can occur when inorganic phosphates are present (Moody et al. 1985). Derivatives of DMTP and DMDTP have been measured in human urine using GC-FPD in phosphorous mode (Fenske and Leffingwell 1989). Urine samples were subjected to alkaline hydrolysis to convert DCA and MCA to DMTP and DMDTP, which were derivatized with

Table 7-1. Analytical Methods for Determining Malathion or Biomarkers of Exposure in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human blood	Collection of blood samples, 0.1 M phosphate buffer (pH=8.0)	Spectrophotometer (at 410–412 nm)	No data	No data	Ellman et al. 1961
Human blood	Collection of blood samples, tris(hydroxymethyl)aminomethane, sodium chloride, HCl, centrifuge	Colorimeter analysis (at 412 nm)	No data	No data	Knaak et al. 1978
Blood	Microtiter assay using acetylthiocholine, AChE, Ellman assay reaction mixture	Microtiter assay; absorbance measurement (at 405 nm)	No data	No data	Doctor et al. 1987
Human serum	Extraction with hexane	GC-FPD	0.001 mg/L	No data	Fournier and Sonnier 1978
Human urine	Extract with diethyl ether, centrifuge, acidify, extract with hexane, alkylate with BF_3-methanol, purify on silica gel (elution with benzene/ethyl acetate	GC-FPD	0.002 mg/L (DCA) 0.005 mg/L (MCA)	98–101% for DCA 98–104% for MCA	Bradway and Shafik 1977
Human urine	Hydrolysis of MCA and DCA with 1.0 N KOH, 90 □C, 4 hours, extraction with hexane, derivatization with PFBB	GC-FPD (phosphorous mode)	0.014 mg/L (DMTP) 0.025 mg/L (DMDTP)	88% (total malathion) 120% (DMTP) 70% (DMDTP)	Fenske and Leffingwell 1989
Human urine	Solid-phase extraction, methanolic HCl extraction, derivatization with diazomethane,	Isotope dilution Ion Trap GC-MS	6.5 ng/mL (DCA) 4.4 ng/mL (MCA)	106–114% (DCA) 50–60% (MCA)	Draper et al. 1991
Human urine	Acidify to pH 3.7, extract twice with CH_2Cl_2/diethyl ether (1:4), centrifuge and concentrate	Isotope dilution HPLC/MS/MS	0.5 µg/L (DCA)	75%	Baker et al. 2000; Beeson et al. 1999

DCA = malathion dicarboxylic acid; DMDTP = *O,O*-dimethyl phosphorodithionate; DMTP = *O,O*-dimethyl phosphorothionate; FPD = flame photometric detection; GC = gas chromatography; HCl = hydrochloric acid; HPLC = high performance liquid chromatography; KOH = potassium hydroxide; M = Molar; MCA = malathion monocarboxylic acid; MS = mass spectrometry; PFBB = pentafluorobenzyl bromide

pentafluorobenzyl bromide. However, the procedure is not specific for malathion since DMTP and DMDTP are common to several types of organophosphorous insecticides. The detection limits were 0.014 mg/L for DMTP and 0.025 mg/L for DMDTP. Ion-exchange resins and anion-exchange solid-phase extraction have been used to isolate metabolites of malathion from urine (Lores and Bradway 1977; Muan and Skare 1989). The MCA, DCA, DMDTP, and DMTP metabolites were derivatized with diazomethane and assayed using GC-nitrogen-phosphorus-detection (NPD). A detection limit of 2 µg/mL for each metabolite was reported. A later modification of this procedure utilized isotope dilution ion trap GC-MS to detect the diazomethane derivatives to improve the detection limits. The lowest limits of detection for DCA and MCA were 0.006 and 0.004 mg/L, respectively.

A recent method for identifying and quantifying malathion diacid in urine samples collected from nonoccupationally exposed populations utilizes isotope dilution high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS); the method has the advantage of not requiring derivatization of DCA (Baker et al. 2000; Beeson et al. 1999). Using this method, urine samples are acidified (10% sulfuric acid) to a pH of 3.7 and extracted with methylene chloride and ethyl ether (1:4). The organic extracts are combined and concentrated for HPLC injection and MS/MS analysis. The analytical limit of detection was 0.0005 mg/L and the recovery was 75%. The advantages of this technique are the high specificity and sensitivity that are achieved by chromatographically separating out unwanted contaminants that could interfere with the mass analysis and the use of isotope dilution to correct for sample recoveries.

The most commonly used assay for determining ChE activity is that of Ellman et al. (1961). In this method, RBCs are suspended in a buffer (e.g., 10 µL blood in 6 mL of 0.1 M phosphate buffer). For assay of only RBC ChE, the suspension is treated with quinidine sulfate to inhibit PChE. Total esterase activity is determined in the samples with no addition of quinidine sulfate. The production of thiocholine formed in the hydrolysis of acetylthiocholine is measured by coupling of the reactive thiol with 5,5'-dithio-bis(2-nitrobenzoate) (DTNB) to give a thionitrobenzoate (TNB). The TNB is a yellow anion and its formation can be measured spectrophotometrically. The production of TNB is rapid and the concentration of DTNB used in the assay does not inhibit the enzyme. Absorbance is typically measured at 410–412 nm, but other wavelengths have been used. Because a nonlinear reaction of the thiol reagent with reduced glutathion of RBCs is possible, a sample blank is required. This method has been adapted to assay cholinesterase in other tissues such as lung, brain, liver, stomach, heart, and muscle. An adaptation of the Ellman assay is a microtiter assay method for AChE that has been developed by Doctor et al. (1987). The AChE samples to be assayed are added to microtiter plates and enzymatic hydrolysis is

initiated by adding Ellman reaction mixture (DTNB). The hydrolysis reaction is terminated by the addition of an AChE inhibitor (1,5-bis(4-allyldimethylammoniumphenyl)-pentan-3-one dibromide. The absorbance of the microtiter can be measured continuously by reader at 405 nm filter.

Several modified versions of the Ellman assay have been developed, including an automated procedure that is used by the State of California to monitor exposure of field workers (Knaack et al. 1978). In this method, samples of whole blood and plasma are diluted with tris(hydroxymethyl)aminomethane (0.05 Molar) and sodium chloride (0.114 Molar) buffer adjusted to pH 7.7 with hydrogen chloride. The samples are centrifuged at 1,600 rpm for 4 minutes to separate RBCs from plasma, which are then analyzed for esterase activity using a continuous flow Technicon Analyzer. Prediluted whole blood or plasma samples are passed through a 37 °C dry bath incubator for 1.17 minutes. The sample is then passed through a 12-inch dialyzer equipped with a Type C membrane and the released thiocholine is passed through a solution of DTNB color reagent. The thiocholine DTNB mixture is sent to a delay coil for color development prior to being passed through a 15x1.5 mm flow cell.

7.2 ENVIRONMENTAL SAMPLES

The principal method that is used to analyze environmental samples for malathion is GC. Detectors that are used include FPD in phosphorous mode, ECD, and MS. Another method that has also been used successfully is GC with tandem ion trap MS/MS. Table 7-2 summarizes the analytical methods used to detect malathion and its metabolites in environmental samples.

Malathion has been detected in air using GC equipped with FPD and a nitrogen-phosphorous detector and with GC-MS. The lowest limit of detection reported was in the 0.5–1.0 ng/m^3 range. Several methods of sample collection have been reported and include collection on resin and filter paper (Brown et al. 1993b), a combined filter-sorbent tube sampler (OSHA Versatile sampler; Kennedy et al. 1994), a glass wool-Tenax TA tube (Roinestad et al. 1993), a polyethylene-backed adsorbent paper (Brown et al. 1991), and air samplers equipped with Ortho 42 tubes (Wright et al. 1996). Sample preparation typically involves desorption of analytes from the tubes using an organic solvent (e.g., acetone, acetone-toluene, and acetone-hexane-toluene) (Brown et al. 1993b). Recoveries were reported to be in the 90–100% range. The 100% recovery of malathion was reported by Kennedy (1994) during a study of indoor household air. Sample preparation was accomplished by desorption of malathion from a collection tube

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (indoor)	Adsorption onto sample tube containing 25 mg TENAX TA and desorption with acetone	GC-MS with chemical ionization	1.0 ng/m^3	100%	Roinestad et al. 1993
Air	Collection on glass cartridges containing XAD-2 resin, extract with acetone	GC-FPD (in phosphorous mode)	No data	No data	Brown et al. 1993
Air	Adsorption on OVS, desorption with acetone-toluene (1:9)	GC-FPD (in phosphorous mode)	0.05 µg/mL	94%	Kennedy et al. 1994
Air (indoor)	Brian Model Air Sampler (Ortho 42 tubes), extract with toluene:hexane:acetone (1.0:0.5:0.5)	GC with NPD and GC-FPD (in phosphorous mode)	No data	90%	Wright et al. 1996
Water	Extracted with hexane	GC-FPD	0.06 µg/L	117%	Zweig and Devine 1969
Water	Adsorption onto a macroreticular resin (Amberlite XAD-2), desorb with acetone-hexane (15:85)	GC-NPD (or GC-FID)	20 pg (0.02 ng/L)	96–103%	Label et al. 1979
Water	Absorption into a microfiber (SPME), desorb directly in GC injector	GC-NPD	0.04 ng/mL (40 ng/L)	No data	Beltran et al. 1998
Water	Adsorption onto a macroreticular resin (Amberlite XAD-2), desorption with diethyl ether, concentrate, hydrolyze to DMDTP, complex with Bi(III), and extract with CCl_4	Colorimetric	0.023 mg/L	95%	Clark and Qazi 1980
Water	SFE-CO_2+0.3 mL methanol, 50 °C, 350 bar	GC-MS	No data	85%	Barnabas 1994
Water	SPE elution with methylene chloride-methanol (80:20)	GC-MS (ion trap)	0.12 µg/L	51%	Eitzer and Chevalier 1999
Soil	Soxhlet extraction with acetone-hexane	GC-ECD	No data	79%	Kramer et al. 1999
Soil	Microwave assisted extraction with acetone-hexane	GC-ECD	No data	75%	Kramer et al. 1999
Soil	Subcritical water extraction with deionized water	GC-ECD	No data	9%	Kramer et al. 1999
House dust	Soxhlet extraction with 6% diethyl ether in *n*-hexane	GC-ECD; GC-MS	50–1,500 ng/g	75%	Lewis et al. 1994

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
House dust	Soxhlet extraction with 6% diethyl ether in *n*-hexane	GC-FPD (or NPD) and GC-MS	50 ppb	92%	Bradman et al. 1997
Handwipe (children)	Wiping hands with sterile gauze with propanol, extract with diethyl ether in *n*-hexane	GC-FPD	50 ppb	92%	Bradman et al. 1997
Soil	SFE-CO_2+5% methanol, 50 °C, 250 bar, 15 minute static, 30 minute dynamic	GC-MS	No data	76.3–96.7%	Camel 1997
Food (grains)	SFE-CO_2, 40 °C, 450 bar, dynamic	GC-FPD	No data	>80%	Camel 1997
Food (fruits, vegetables, and milk)	Extract with acetonitrile-ethanol (95:5, v/v), SPE (Envi-Carb) using acetonitrile-toluene (3:1, v/v)	GC with tandem ion trap MS/MS	ppb	No data	Sheridan and Meola 1999
Fruit	Extract the flower or fruit with acetone, partition with water/hexane, column chromatography on Florisil using 20% acetone in hexane (v/v)	GC/ECD	0.0005 ppm (0.05 ppb)	>95%	Belanger et al. 1990
Potato	SFE-CO_2, 60 °C, 320 bar, 2 minute static, 10 minute dynamic	GC-MS	No data	72–94%	Camel 1997
Vegetable, fruit	Extraction with ethyl acetate	GC-FPD (phosphorous mode) and GC-MS	5–20 µg/kg	105%	Aguera 1993
Edible fat	SFE (CO_2-3% acetonitrile; 60 °C; 27.58 Mpa) column chromatography on florisil	GC-FPD (phosphorous mode)	No data	80–85%	Hopper 1999
Milk (whole, skim, infant formula)	Extraction with acetone-acetonitrile, centrifuge, partition with dichloromethane/water, solid phase extraction with acetonitrile, chromatography on a C18 (SPE) cartridge	GC-FPD (phosphorous mode)	No data	86–103%	Erney 1995

DMDTP = *O,O*-dimethyl phosphorodithionate; ECD = electron capture detector; FID = flame ionization detector; FPD = flame photometric detection; GC = gas chromatography; LC = liquid chromatography; MS = mass spectrometry; NaCl = sodium chloride; NPD = nitrogen/phosphorus detector; OSHA = Occupational Safety and Health Administration; OVS = OSHA versatile sample; SFE = supercritical fluid extraction; SFE-CO_2 = supercritical fluid extraction with carbon dioxide; SPE = solid phase extraction; SPME = solid-phase micro extraction; ppb = parts per billion; ppm = parts per million; v/v = volume/volume

using acetone. The solution was concentrated and analyzed using GC-MS with chemical ionization (Kennedy et al. 1994). The limit of detection was reported as 0.5 ng/m^3.

In water, malathion can be analyzed using colorimetric analysis, GC-FPD, GC-NPD, and GC-MS. The isolation of malathion from water generally requires sample extraction followed by purification of the extract to remove substances that may interfere with detection methods. Several methods have been developed for the extraction of malathion from water samples involving extraction with an organic solvent (Zweig and Devine 1969); collection on a resin column followed by elution with an organic solvent (Clark and Qazi 1979; LeBel et al. 1979); and solid-phase extraction and elution with an organic solvent (Eitzer and Chevalier 1999). Beltran et al. (1998) demonstrated that solid-phase micro extraction (SPME) can be used to identify organophosphorous pesticides in water samples without the use of organic solvents. Organophosphorous compounds can be extracted from water onto a polymeric (polydimethylsiloxane or polyacrylate) collection filter according to their affinity for the filter coating and are subsequently thermally desorbed from the coating directly in the GC injector. The limit of detection for malathion was 0.04 ng/mL (Beltran et al. 1998). In another study, the mean percent recovery of malathion from water using SPME was found to be very low, suggesting that the technique may require further investigation to optimize partitioning of pesticides to the collection fiber (Kramer et al. 1999). Supercritical fluid extraction (SFE), a process using carbon dioxide liquified above 31 °C at high pressure, provides efficient extraction of pesticides and their metabolites in a variety of matrices without the use of large quantities of organic solvents (Camel 1997). A modified SFE using methanol-CO_2 was used to obtain recoveries of 84.6% for malathion from water (Barnabas et al. 1994).

Analytical analysis of soils, sand, sediments, and indoor house dust has been performed using GC-ECD, GC-FPD, GC-NPD, and GC-MS; analysis of food, milk (whole and infant formula), and edible fat has been accomplished using GC-FPD, GC-ECD, GC-MS, and tandem GC-MS/MS. Sample preparation methods vary widely since extraction and cleanup methods are dependent upon the sample matrix. For soils and sediments, soxhlet extraction is the standard extraction technique used in most EPA methods (Smith 1994). Pesticide residues in house dust have been determined using soxhlet extraction (6% diethyl ether in hexane). Recoveries of malathion were reported to be 75–92% with a limit of detection of 0.05–1.5 mg/ng (Bradman et al. 1997; Lewis et al. 1994). In a recent study of organophosphorous pesticides, Kramer et al. (1999) examined various extraction techniques and compared their percent recoveries. For malathion, soxhlet extraction was found to have slightly higher recoveries (79%; average of three extractions) than microwave assisted extraction (75%; average of five extractions). Standard

procedures for the extraction of milk and fat involve the complete extraction of the fat and extensive cleanup by column chromatography on Florisil prior to analysis (AOAC 1990; FDA 1999). To simplify these procedures, Erney (1995) developed a method that utilizes solid-phase extraction for the cleanup. Using this method, recoveries of 86–103% were obtained for malathion in whole and skim milk, and in infant formula (Erney 1995). In a recent study, SFE was used successfully to extract organophosphorous pesticides from edible fats. Although the method was determined to be less effective than standard procedures for the recovery of some analytes, the recovery of malathion was 80–85% (Hopper 1999). The use of GC with ion trap mass spectrometry (MS/MS) has been investigated by Sheridan and Meola (1999) for analysis of food matrices. Because MS/MS is highly selective, it is capable of making clear compound identification of even complex matrixes at the parts-per-billion range and is less susceptible to interfering coextractives than selective detectors (e.g., ECD and FPD). Using GC-MS/MS, malathion was detected in strawberries at 0.01 ppm. In contrast, detection of malathion using a selective detector was 0.009 ppm (Sheridan and Meola 1999).

Analysis of handwipe samples taken from children has been accomplished using GC-FPD or GC-NPD. Detection limits were reported as 50 ppb (μg/L) with an average recovery of 92% (Bradman et al. 1997).

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 malathion 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 malathion.

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.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Organophosphate pesticides, such as malathion, inhibit cholinesterases. Methods exist for the measurement of erythrocyte and plasma cholinesterase levels (EPA 1980d; Nabb and Whitfield 1967). However, there are some problems with the reliability of these methods 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 (Zimmerman and 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.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods exist to measure low levels of malathion in air (Brown et al. 1993b; Kennedy et al. 1994; Roinestad et al. 1993; Wright et al. 1996); water (Beltran et al. 1998; Clark and Qazi 1979; Eitzer and Chevalier 1999; LeBel et al. 1979; Zweig and Devine 1969); soil; carpet dust; milk; infant formula; fats and oils; and foods (Bradman et al. 1997; Erney 1995; Hopper 1999; Kramer et al. 1999; Lewis et al. 1994; Sheridan and Meola 1999). These methods can be used to identify potentially contaminated media that may be sources of human exposure. Several analytical methods exist for the detection of malathion. Gas chromatography coupled with sensitive phosphorous detectors and GC-MS are the most commonly used methods of detection. The detection limit is typically in the low parts-per-billion for air (Kennedy et al. 1994), water (Eitzer and Chevalier 1999) and soil; carpet dust; milk; infant formula; and foods (Bradman et al. 1997; Lewis et al. 1994; Sheridan and Meola 1999). Studies are needed to investigate improved methods of isolation from complex matrixes, selectivity of detection, precision, and accuracy.

7.3.2 Ongoing Studies

No information was located concerning ongoing studies for improving methods of analysis of malathion metabolites, or other biomarkers of exposure and effect for malathion in biological materials.

8. REGULATIONS AND ADVISORIES

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

ATSDR has derived an acute inhalation MRL of 0.2 mg/m^3 for malathion based on a NOAEL of 65 mg/m^3 for inhibition of erythrocyte cholinesterase activity in rabbits (Weeks et al. 1977). The LOAEL was 123 mg/m^3. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for the protection of sensitive human groups). A conversion factor was used to adjust from intermittent exposure to continuous exposure (6/24hours).

ATSDR has derived an intermediate inhalation MRL of 0.02 mg/m^3 for malathion based on a LOAEL of 100 mg/m^3 for upper respiratory tract effects in rats (Beattie 1994). An uncertainty factor of 1,000 was used (10 for animal to human extrapolation, 10 for the use of a LOAEL, and 10 for the protection of sensitive human groups). A conversion factor was used to adjust from intermittent exposure to continuous exposure (5/7x6/24 hours).

ATSDR has derived an intermediate oral MRL of $2x10^{-2}$ mg/kg/day for malathion based on a NOAEL of 0.23 mg/kg/day for inhibition of plasma and red blood cell cholinesterase activities in humans (Moeller and Rider 1962). The LOAEL was 0.34 mg/kg/day. An uncertainty factor of 10 was used for the protection of sensitive human groups.

ATSDR has derived a chronic oral MRL of $2x10^{-2}$ mg/kg/day for malathion based on a NOAEL of 2 mg/kg/day for inhibition of plasma and red blood cell cholinesterase activities in male rats administered malathion in the diet for 2 years (Daly 1996a). The LOAEL was 29 mg/kg/day. An uncertainty factor of 100 was used (10 for extrapolation from animal to humans and 10 for the protection of sensitive populations).

EPA (IRIS 2003) has derived an RfD of $2x10^{-2}$ mg/kg/day for malathion based on a NOAEL 0.23 mg/kg/day for inhibition of plasma and red blood cell cholinesterase activities in humans (Moeller and Rider 1962). The LOAEL was 0.34 mg/kg/day. An uncertainty factor of 10 was used for the protection of sensitive human groups.

Table 8-1. Regulations and Guidelines Applicable to Malathion

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 3[a]	IARC 2001
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV-TWA[b]	10 mg/m^3	ACGIH 2000
NIOSH	REL (TWA) IDLH	10 mg/m^3 250 mg/m^3	NIOSH 2001
OSHA	PEL (8-hour TWA) General industry (total dust)	15 mg/m^3	OSHA 2001a 29CFR1910.1000 Table Z-1
	PEL (8-hour TWA) Construction industry (total dust)	15 mg/m^3	OSHA 2001b 29CFR1926.55 Appendix A
	PEL (8-hour TWA) Shipyard industry (total dust)	15 mg/m^3	OSHA 2001c 29CFR1915.1000 Table Z
b. Water			
DOT	Marine pollutant		DOT 2001a 49CFR172.101 Appendix B
EPA	Drinking water guideline	0.2 mg/L	HSDB 2001
	Health advisories 1 Day (10-kg child) 10 Day (10-kg child) DWEL Lifetime	 0.2 mg/L 0.2 mg/L 0.7 mg/L 0.1 mg/L	EPA 2000c
	Pesticide chemicals—effluent limitations for BPT		EPA 2001a 40CFR455.20(b)
	Water programs—designation of hazardous substance		EPA 2001b 40CFR116.4
	Water programs—determination of reportable quantity Reportable quantity	 100 pounds	EPA 2001c 40CFR117.3

Table 8-1. Regulations and Guidelines Applicable to Malathion

Agency	Description	Information	References
NATIONAL *(cont.)*			
c. Food			
EPA	Methyl eugenol combination (pesticide) residue tolerances of agricultural commodities; ratio of parts of methyl eugenol to technical malathion is 3:1; eugenol and malathion maximum dosage per application per acre	28.35 g methyl eugenol and 9.45 g malathion	EPA 2001d 40CFR180.1067
	Pesticides—where residues from two or more chemicals in the same class are present in or on a raw agricultural commodity, the tolerance for the total of such residues shall be the same as that for the chemical having the lowest numerical tolerance in this class, unless a higher tolerance level is provided		EPA 2001e 40CFR180.3(e)(5)
	Pesticides—tolerances for residues (ppm)		EPA 2001f 40CFR180.111
	Alfalfa	135	
	Almond hulls	50	
	Almonds	8	
	Almonds, shells	50	
	Apples	8	
	Apricots	8	
	Asparagus	8	
	Avocados	8	
	Barley (grain)	8	
	Beans	8	
	Beets (tops)	8	
	Beets (sugar, roots)	1	
	Beets (sugar tops)	8	
	Birdsfoot trefoil (forage and hay)	135	
	Blackberries	8	
	Blueberries	8	
	Boysenberries	8	
	Carrots	8	
	Cattle (fat, meat byproducts, meat)	4	
	Chayote (fruit and roots)	8	
	Cherries	8	
	Chestnuts	1	
	Clover	135	
	Corn, forage and grain	8	
	Corn, fresh (including sweet)	2	
	Cottonseed	2	

Table 8-1. Regulations and Guidelines Applicable to Malathion

Agency	Description	Information	References
	Pesticides—tolerances for residues (ppm)		
	Cowpea (forage and hay)	135	
	Cranberries	8	
	Cucumbers	8	
	Currants	8	
	Dates	8	
	Dewberries	8	
	Eggplants	8	
	Eggs (from application to poultry)	0.1	
	Figs	8	EPA 2001f
	Filberts	1	40CFR180.111
	Flax seed	0.1	
	Flax straw	1	
	Garlic	8	
	Goats (fat, meat byproducts, meat)	4	
	Gooseberries	8	
	Grapefruit	8	
	Grapes	8	
	Grass (including hay)	135	
	Guavas	8	
	Hogs (fat, meat byproducts, meat)	4	
	Hops	1	
	Horseradish	8	
	Horses (fat, meat byproducts, meat)	4	
	Kumquats	8	
	Leeks	8	
	Lemons	8	
	Lentils	8	
	Lespedeza (hay and straw)	135	
	Lespedeza (seed)	8	
	Limes	8	
	Loganberries	8	
	Lupine (seed)	8	
	Macadamia nuts	1	
	Mangos	8	
	Melons	8	
	Milk, fat (from application to dairy cows)	0.5	
	Mushrooms	8	
	Nectarines	8	
	Oats (grain)	8	
	Okra	8	
	Onions (including green tops)	8	
	Oranges	8	
	Papayas	1	
	Parsnips	8	
	Pesticides—tolerances for		

Table 8-1. Regulations and Guidelines Applicable to Malathion

Agency	Description	Information	References
	residues (ppm)		
	Passion fruit	8	
	Peaches	8	
	Peanut (forage and hay)	135	
	Peanuts	8	
	Pears	8	
	Peas	8	
	Peavine (including hay)	8	
	Pecans	8	
	Peppermint	8	EPA 2001f
	Peppers	8	40CFR180.111
	Pineapple	8	
	Plums	8	
	Potatoes	8	
	Poultry (fat, meat byproducts, meat)	4	
	Prunes	8	
	Pumpkins	8	
	Quinces	8	
	Radishes	8	
	Raspberries	8	
	Rice (grain and wild)	8	
	Rutabagas	8	
	Rye (grain)	8	
	Safflower (seed)	0.2	
	Salsify (including tops)	8	
	Shallots	8	
	Sheep (fat, meat byproducts, meat)	4	
	Sorghum (forage and grain)	8	
	Soybeans (dry and succulent)	8	
	Soybeans (forage and hay)	135	
	Spearmint	8	
	Squash (summer and winter)	8	
	Strawberries	8	
	Sunflower seeds	8	
	Sweet potatoes	1	
	Tangerines	8	
	Tomatoes	8	
	Turnips (including tops)	8	
	Vegetables (leafy, including Brassica)	8	
	Vetch (hay and straw)	135	
	Vetch (seed)	8	
	Walnuts	8	
	Wheat (grain)	8	
USDA	Agriculture—labeling of treated seed shall not be deemed harmful when present at a rate less than indicated	8 ppm	USDA 2001 7CFR201.31a

Table 8-1. Regulations and Guidelines Applicable to Malathion

Agency	Description	Information	References
NATIONAL *(cont.)*			
d. Other			
ACGIH	BEI—organophosphorus cholinesterase inhibitors (cholinesterase activity in red cells)	70% of individual's baseline	ACGIH 1999
ACGIH	Carcinogenicity classification	A4[c]	ACGIH 2000
DOT	Superfund—reportable quantity	100 pounds	DOT 2001b 49CFR172.101 Appendix A
EPA	RfD	$2x10^{-2}$ mg/kg/day	IRIS 2001
	NPDES—permit application testing requirements; toxic pollutants and hazardous substances required to be identified by existing dischargers if expected to be present		EPA 2001g 40CFR122 Appendix D Table V
	Standards for hazardous waste TSD facilities—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		EPA 2001h 40CFR265 Appendix VI
	Superfund—reportable quantity	10 pounds	EPA 2001i 40CFR302.4
	Toxic chemical release reporting; Community Right-to-Know—effective date	01/01/95	EPA 2001j 40CFR372.65
STATE			
Regulations and Guidelines:			
a. Air			
Alaska	Air contaminant standard		BNA 2001
	Total dust	10 mg/m^3	
	Respirable fraction	5 mg/m^3	
California	Airborne contaminant		BNA 2001
Colorado	Standards applicable to surface water		BNA 2001
	Human health based (water supply)	140 µg/L	
	Aquatic life based (chronic)	0.1 µg/L	
Connecticut	HAP—hazard limiting value		BNA 2001
	8 Hours	200 µg/m^3	
	30 Minutes	1,000 µg/m^3	
Hawaii	Air contaminant (PEL-TWA)		BNA 2001
	Total dust	10 mg/m^3	

Table 8-1. Regulations and Guidelines Applicable to Malathion

Agency	Description	Information	References
STATE *(cont.)*			
Idaho	Toxic air pollutant		BNA 2001
	OEL	10 mg/m^3	
	EL	$6.67x10^{-1}$ pounds/hour	
	AAC	0.5 mg/m^3	
Illinois	Toxic air contaminant		BNA 2001
Kentucky	TAL	40 mg/m^3	BNA 2001
	Average time	8 hours	
	Significant levels	$2.551x10^{-3}$ pounds/hour	
Michigan	Air contaminant (PEL-TWA)		BNA 2001
	Total dust	15 mg/m^3	
	Occupational air contaminant		BNA 2001
	MAC	15 mg/m^3	
Montana	Occupational air contaminant[b]	15 mg/m^3	BNA 2001
New Hampshire	Toxic air pollutant		BNA 2001
	OEL	10 mg/m^3	
New Jersey	Toxic air pollutant		BNA 2001
	OEL	10 mg/m^3	
	Emissions	$6.67x10^{-1}$ pounds/hour	
New York	Dangerous air contaminant		BNA 2001
	TLV[b]	15 mg/m^3	
	Total dust		BNA 2001
	Transitional limits (PEL)[b]	15 mg/m^3	
	Final rule limits (TWA)[b]	10 mg/m^3	
North Carolina	General industry standards		BNA 2001
	Total dust	10 mg/m^3	
Oregon	Air contaminant	10 mg/m^3	BNA 2001
South Carolina	Toxic air emissions		BNA 2001
	MAC	100 $\mu g/m^3$	
Texas	TLV[b]	15 mg/m^3	BNA 2001
Washington	Air contaminant (TWA)		BNA 2001
	Total dust	10 mg/m^3	
	Toxic air pollutant		BNA 2001
	ASIL (24-hour average)	33 $\mu g/m^3$	
b. Water			
Alaska	Water quality standards—toxic substance		BNA 2001
Arizona	Drinking water guideline	140 µg/L	HSDB 2001
	Groundwater protection list		BNA 2001
California	Drinking water guideline	160 µg/L	HSDB 2001
Connecticut	Water pollution control—hazardous substance		BNA 2001
Delaware	Surface water quality standards—toxic substance		BNA 2001
	Fresh (chronic)	0.1 µg/L	
	Marine (chronic)	0.1 µg/L	

Table 8-1. Regulations and Guidelines Applicable to Malathion

Agency	Description	Information	References
STATE *(cont.)*			
Florida	Drinking water guideline	140 µg/L	HSDB 2001
	Surface water quality criteria		BNA 2001
	Potable water supply	0.1 µg/L	
	Shellfish propagation or harvesting	0.1 µg/L	
	Predominantly fresh waters	0.1 µg/L	
Georgia	Hazardous site response—groundwater criteria concentration	0.2 mg/L	BNA 2001
Hawaii	Water quality criteria		BNA 2001
	Freshwater (chronic)	0.1 µg/L	
	Saltwater (chronic)	0.1 µg/L	
Kansas	Surface water quality criteria		BNA 2001
	Aquatic life (chronic)	0.1 µg/L	
	Agriculture (livestock)	100 µg/L	
Maine	Drinking water guideline	40 µg/L	HSDB 2001
	Private water systems		BNA 2001
	Maximum exposure guideline	0.04 mg/L	
	Action level	0.02 mg/L	
Massachusetts	Environmental toxicity values		BNA 2001
	Freshwater (chronic)	0.1 µg/L	
	Marine (chronic)	0.1 µg/L	
Minnesota	Water quality standards		BNA 2001
	Drinking water supply	200 µg/L	
	Groundwater	200 µg/L	
	Protection of aquatic life	0.1 µg/L	
Nebraska	Standards for water quality		BNA 2001
	Aquatic life (chronic)	0.1 µg/L	
	Water quality standards for wetlands		BNA 2001
	Aquatic life (chronic)	0.1 µg/L	
Nevada	Standards for toxic materials applicable to designated waters		BNA 2001
	Aquatic life	0.1 µg/L	
New Hampshire	Water quality criteria		BNA 2001
	Fresh (chronic)	0.1 µg/L	
	Marine (chronic)	0.1 µg/L	
New Jersey	Groundwater quality criteria	200 µg/L	BNA 2001
	PQL	5 µg/L	
New York	Groundwater quality standards		BNA 2001
	MAC	7.0 µg/L	
Ohio	Surface water quality standards		BNA 2001
	Outside mixing zoning average	0.1 µg/L	

Table 8-1. Regulations and Guidelines Applicable to Malathion

Agency	Description	Information	References
STATE *(cont.)*			
Oklahoma	Surface water quality criteria		BNA 2001
	Fish and wildlife propagation (chronic)	0.1 µg/L	
Oregon	Water quality		BNA 2001
	Fresh (chronic)	0.1 µg/L	
	Marine (chronic)	0.1 µg/L	
South Dakota	Surface water—toxic pollutant		BNA 2001
Texas	Water quality		BNA 2001
	Freshwater (chronic)	0.01 µg/L	
Utah	Water quality—hazardous substances required to be identified by existing dischargers if expected to be present		BNA 2001
Virginia	Criteria for surface water		BNA 2001
	Freshwater (chronic)	0.1 µg/L	
	Saltwater (chronic)	0.1 µg/L	
Wyoming	Water quality criteria		BNA 2001
	Aquatic life (chronic)	0.1 µg/L	
c. Food		No data	
d. Other			
Alabama	Standards for hazardous waste TSD facilities—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 2001
Arizona	Soil remediation levels		BNA 2001
	Residential	1,300 mg/kg	
	Non-residential	14,000 mg/kg	
Arkansas	Standards for hazardous waste TSD facilities—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 2001
California	Chemicals required to have been tested for potential to cause cancer or reproductive toxicity, but which have not been adequately tested as required (data requirements)	Oncogenicity	BNA 2001
	Hazardous substance		BNA 2001
	Pesticide field worker safety—restricted entry intervals		BNA 2001
	Citrus	1 day	
	Grapes	1 day	
	Peaches/nectarines	1 day	
	Pesticide registration—active ingredients		BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Malathion

Agency	Description	Information	References
STATE *(cont.)*			
Colorado	Standards for hazardous waste TSD facilities—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 2001
Delaware	Standards for hazardous waste TSD facilities—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 2001
	Reportable quantity	100 pounds	BNA 2001
Florida	Toxic substance in the workplace		BNA 2001
Georgia	Hazardous site response—regulated substance		BNA 2001
Illinois	Standards for hazardous waste TSD facilities—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 2001
Louisiana	Standards for hazardous waste TSD facilities—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 2001
Maine	Identification of hazardous waste —hazardous constituent		BNA 2001
	Screening standards for beneficial use (waste concentration)	2,000 mg/kg dry weight	BNA 2001
Massachusetts	Containers adequately labeled pursuant to federal law		BNA 2001
	Human health based toxicity values (chronic oral RfD)	$2.0x10^{-2}$ mg/kg/day	BNA 2001
	Oil and hazardous material		BNA 2001
Michigan	Identification and listing of hazardous waste		BNA 2001
Minnesota	Toxic pollutant and hazardous substance		BNA 2001
Mississippi	Packaging dates for malathion	Must mark all retail containers with a code or batch number from which the date of packaging may be determined	BNA 2001
Nebraska	Standards for hazardous waste TSD facilities—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 2001
	Pesticide classes	Class III[d]	BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Malathion

Agency	Description	Information	References
STATE *(cont.)*			
New Jersey	Hazardous substance		BNA 2001
New York	Pesticide control—use of chemicals for the control or elimination of aquatic insects	Not to exceed 0.5 pounds/acre (active ingredient)	BNA 2001
	Reportable quantity		BNA 2001
	Air	100 pounds	
	Land/water	1 pound	
South Carolina	Standards for hazardous waste TSD facilities—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 2001
Tennessee	Standards for hazardous waste TSD facilities—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 2001
Texas	Risk-based exposure limits—soil dermal contact		BNA 2001
	Gastrointestinal absorption factor	$5.00x10^{-1}$	
	Dermal absorption factor	$1.00x10^{-1}$	
Washington	Hazardous substance required to be identified by existing dischargers if expected to be present		BNA 2001
	Standards for hazardous waste TSD facilities—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 2001
West Virginia	Hazardous substance required to be identified by existing dischargers if expected to be present		BNA 2001
	RfD	$2.00x10^{-2}$ mg/kg/day	BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Malathion

Agency	Description	Information	References
STATE *(cont.)*			
Wyoming	Standards for hazardous waste TSD facilities—compounds with Henry's law constant less than 0.1 atm m^3/mol (at 25 °C)		BNA 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]Class III: oral LD50 greater than 900 mg/kg^{-1}

AAC = acceptable ambient concentrations; ACGIH = American Conference of Governmental Industrial Hygienists; ASIL = acceptable source impact levels; BEI = biological exposure index; BNA = Bureau of National Affairs; BPT = best practical technology; CFR = Code of Federal Regulations; DOT = Department of Transportation; DWEL = drinking water equivalent level; EL = emissions level; EPA = Environmental Protection Agency; HAP = hazardous air pollutant; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; IRIS = Integrated Risk Information System; MAC = maximum allowable concentration; NIOSH = National Institute of Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; OEL = occupational exposure limit; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation level; REL = recommended exposure limit; RfD = oral reference dose; TAL = threshold ambient limits; TLV = threshold limit value; TSD = treatment, storage, and disposal; TWA = time-weighted average; USDA = United States Department of Agriculture

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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 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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 LEVELS 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.

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 agency wide 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 NE, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Malathion
CAS Number: 121-75-5
Date: March 20, 2003
Profile Status: Final Draft Post Public
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 2h
Species: Rabbits

Minimal Risk Level: 0.2 [ ] mg/kg/day [X] mg/m^3

Reference: Weeks MH, Lawson MA, Angerhofer RA, et al. 1977. Preliminary assessment of the acute toxicity of malathion in animals. Arch Environ Contam Toxicol 6:23-31.

Experimental design: The purpose of the study was to compare the acute effects of two different malathion aerosols on the activity of plasma and erythrocyte (RBC) cholinesterase from rabbits. Groups of male New Zealand rabbits (6/exposure level) were exposed for 6 hours to 0 (chamber air), 6, 34, 65, or 123 mg malathion/m^3 as an aerosol generated from a technical malathion formulation (95% pure). Blood was collected at 10 minutes, 24 hours, 72 hours, and 7 days postexposure for determination of cholinesterases activities. Tissues were also removed for histopathological examination. In a parallel experiment, rabbits were similarly exposed to aerosols generated from a formulation containing 6% malathion and a fuel oil mixture. The malathion concentration in the air in the latter case was 0 (controls), 8, 24, 30, 66, or 128 mg/m^3.

Effects noted in study and corresponding doses: There were no signs of toxicity or deaths in the group exposed to 95% technical malathion. Exposure to 128 mg/m^3 aerosol generated from the 6% formulation resulted in four out of six rabbits dying 24 hours after exposure. Exposure to the highest concentration of the 95% formulation inhibited plasma cholinesterase by 37% 24 hours postexposure and 41% 72 hours postexposure. No other significant differences were seen. RBC cholinesterase was inhibited by 38, 48, and 48% by the high exposure concentration at 24 hours, 72 hours, and 7 days postexposure, respectively. Exposure to the aerosol generated from the 6% formulation resulted in 38% inhibition of plasma cholinesterase with the 66 mg/m^3 concentration 72 hours after exposure and 71% inhibition with the 128 mg/m^3 concentration 10 minutes postexposure. With this formulation, RBC cholinesterase was inhibited 61 and 46% with the 128 mg/m^3 concentration 10 minutes and 24 hours, respectively, postexposure. Without providing any further details, the authors stated that exposure to malathion caused no histopathological alterations in the organs examined (not specified).

Exposure concentration and end point used for MRL derivation: 65 mg/m^3; NOAEL for neurological effects (inhibition of RBC cholinesterase activity).

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration:
A human equivalent concentration was not determined due to lack of information on the size distribution of the aerosol particles in the study.

Was a conversion used from intermittent to continuous exposure?
Yes, 6/24.

Other additional studies or pertinent information that lend support to this MRL: Malathion is an organophosphate pesticide and as such, its main target of toxicity is the nervous system (Abou-Donia 1995; Ecobichon 1994; Koelle 1994; Taylor 1996). Within the nervous system, malathion and its active metabolite, malaoxon, inhibit acetylcholinesterase, the enzyme that terminates the action of the neurotransmitter acetylcholine. The effects of malathion have been well documented in studies in animals and also in humans, although in the latter case, mostly from case reports of accidental or intentional ingestion of high amounts of malathion. A 42-day controlled-exposure study in volunteers reported nasal and eye irritation after 5–10 minutes of exposure to 85 mg/m^3 malathion (Golz 1959); subjects were exposed 2 hours/day. Neither plasma nor RBC cholinesterase activities were significantly altered during the study.

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Malathion
CAS Number: 121-75-5
Date: March 20, 2003
Profile Status: Final Draft Post Public
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 4r
Species: Rat

Minimal Risk Level: 0.02 [ ] mg/kg/day [X] mg/m^3

Reference: Beattie G. 1994. A 13-week toxicity study of aerolized malathion administered by whole body inhalation exposure to the albino rat: Lab project No: 90729. Unpublished study prepared by Product Safety Assessment, Bio-Research Labs, Ltd. MRID 43266601.

Experimental design: Groups of male and female Sprague-Dawley rats (15/sex/exposure level) were exposed whole body to malathion (96.4% pure) aerosols at concentrations of 0 (air control), 100, 450, or 2010 mg/m^3 6 hours/day, 5 days/week, for 13 weeks. Rats were monitored for clinical signs and body weight changes. At termination, gross necropsies were conducted, and tissues (unspecified in the summary available) were processed for microscopical evaluation. Cholinesterase activity was determined in plasma, red blood cells (RBC), and brain.

Effects noted in study and corresponding doses: There were no malathion-related effects on survival, body weight, or food intake. Adverse clinical signs consisting of urogenital staining, excessive salivation, and ungroomed fur were seen mostly in the high-exposure group, but also occurred sporadically in the other exposed groups. I appears that histopathological treatment-related alterations were restricted to the respiratory epithelium. Exposure-concentration-related lesions in the nasal cavity and the larynx of both sexes were seen. The lesions in the nasal cavity consisted of slight to moderate degeneration and/or hyperplasia of the olfactory epithelium. The lesions in the larynx consisted of epithelial hyperplasia with squamous keratization seen in some rats. The effects on cholinesterase activities were concentration-related and effects on females seemed more pronounced than in males. Plasma cholinesterase activity was decreased 30 and 70% in the mid-level and high-level females, respectively. RBC cholinesterase activity was decreased 22% and 27% in mid-level males and females, respectively, and 43 and 44% in high-level males and females, respectively. Brain cholinesterase activity was decreased 41% in high-level females.

Exposure concentration and end point used for MRL derivation: 100 mg/m^3; LOAEL for respiratory effects (hyperplasia of the olfactory epithelium and of the larynx epithelium).

[] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 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?
Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: A human equivalent concentration was not determined due to lack of information on the size distribution of the aerosol particles in the summary of the study available.

Was a conversion used from intermittent to continuous exposure?
Yes, 5/7 x 6/24.

Other additional studies or pertinent information that lend support to this MRL: Malathion is an organophosphate pesticide and as such, its main target of toxicity is the nervous system (Abou-Donia 1995; Ecobichon 1994; Koelle 1994; Taylor 1996). A 42-day controlled-exposure study in volunteers exposed to up 85 mg/m^3 malathion 2 hours/day reported no signs of toxicity during the study except for occasional nose and eye irritation 5–10 minutes into the exposure session (Golz 1959). No significant changes in plasma or RBC cholinesterase activities were seen throughout that study.

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Malathion
CAS Number: 121-75-5
Date: March 20, 2003
Profile Status: Final Draft Post Public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 72
Species: Humans

Minimal Risk Level: 0.02 [X] mg/kg/day [ ] ppm

Reference: Moeller HC, Rider JA. 1962. Plasma and red blood cell cholinesterase activity as indications of the threshold of incipient toxicity of ethyl-p-nitrophenyl thionobenzenephosphorate (EPN) and malathion in human beings. Toxicol Appl Pharmacol 4:123-130.

Experimental design: A three-phase study was conducted in humans. In the first phase, five male volunteers were administered daily capsules containing malathion (purity not reported) in corn oil that provided an approximate dose of 0.11 mg malathion/kg/day for 32 days. In the second phase, which started 3 weeks after the first phase had terminated, five male volunteers received daily capsules with malathion providing about 0.23 mg malathion/kg/day for 47 days. In the third phase, five new subjects received approximately 0.34 mg malathion/kg/day for 56 days. Plasma and red blood cell (RBC) cholinesterase was determined twice weekly before, during, and after administration of malathion. Routine blood counts and urinalyses were conducted at the end of each study period.

Effects noted in study and corresponding doses: Administration of 0.11 mg malathion/kg/day for 32 days or 0.23 mg/kg/day for 47 days did not produce any significant depression of plasma or RBC cholinesterase activity, nor did it alter blood counts or urinalyses, or induce clinical signs. In phase three, 0.34 mg malathion/kg/day for 56 days caused a depression of about 10% in plasma cholinesterase activity during treatment and a maximum depression of about 25% approximately 3 weeks after cessation of treatment. RBC cholinesterase activity did not appear to be significantly affected during treatment, but was depressed also by about 25% 3–4 weeks after treatment with malathion ceased. No clinical signs were seen in the volunteers.

Dose and end point used for MRL derivation: 0.23 mg/kg/day; NOAEL for neurological effects (inhibition of plasma and RBC cholinesterase activities).

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 10 for extrapolation from humans to animals
[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 dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Malathion is an organophosphate pesticide and as such, its main target of toxicity is the nervous system (Abou-Donia 1995; Ecobichon 1994; Koelle 1994; Taylor 1996). Within the nervous system, malathion and its active metabolite, malaoxon, inhibit acetylcholinesterase, the enzyme that terminates the action of the neurotransmitter acetylcholine. The effects of malathion have been well documented in studies in animals and also in humans, although in the latter case, mostly from case reports of accidental or intentional ingestion of high amounts of malathion. The study by Moeller and Rider (1962) was the only available study of controlled ingestion of malathion in humans for review. Most of the studies in animals, while supporting the human data, have been conducted with higher dose levels of malathion.

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Malathion
CAS Number: 121-75-5
Date: March 20, 2003
Profile Status: Final Draft Post Public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 95r
Species: Rat

Minimal Risk Level: 0.02 [X] mg/kg/day [ ] ppm

Reference: Daly I. 1996a. A 24-month oral toxicity/oncogenicity study of malathion in the rat via dietary administration: Final Report: Lab Project Number:90-3461:J-11 90-3641 Unpublished study prepared by Huntington Life Sciences. MRID 43942901.

Experimental design: Groups of male and female Fischer-344 rats (90/sex/dose level) were administered malathion (97.1%) in the diet at levels of 0, 50/100, 500, 6,000, or 12,000 ppm for 2 years. The lowest dietary concentration was reduced from 100 to 50 ppm because of inhibition of RBC cholinesterase activity. The mean intakes of malathion estimated by the investigator were approximately 0, 2, 29, 359, or 739 mg malathion/kg/day to males and 0, 3, 35, 415, or 868 mg/kg/day to females. Ten rats/sex/group were sacrificed at 3 and 6 months primarily for ocular tissue evaluation. Additional sacrifices were conducted at 12 months for more complete assessments. End points evaluated included clinical signs, body weight, food consumption, hematology and clinical chemistry, and gross and microscopical appearance of main tissues and organs.

Effects noted in study and corresponding doses: Administration of malathion significantly increased mortality in males at 6,000 ppm and in both sexes at 12,000 ppm. Body weight gain was reduced both in males and females at the two highest exposure levels, but food intake was not decreased. Hemoglobin, hematocrit, mean corpuscular volume (MCV), and mean cell hemoglobin were also reduced at the two highest dietary levels of malathion in both males and females. Absolute and relative liver and kidney weights were increased in males and females from the 6,000 and 12,000 ppm groups. Relative absolute thyroid and parathyroid weights were increased in males at 6,000 ppm at 12 months and in females at 6,000 and 12,000 ppm at termination. At 24 months, at the 500 ppm malathion dietary level (29 mg/kg/day for males, 35 mg/kg/day for females), plasma cholinesterase activity was reduced 29 and 18% in males and females, respectively, RBC cholinesterase was reduced 17 and 27%, respectively, and brain cholinesterase was reduced 3 and 1%, respectively. At the 6,000 ppm level, plasma cholinesterase in males and females was reduced 64 and 61%, respectively, and brain cholinesterase was reduced 21 and 18%, respectively. No significant reduction in enzyme activities was observed at the lowest dietary level of malathion, 2 mg/kg/day for males and 3 mg/kg/day for females.

Dose and end point used for MRL derivation: 2 mg/kg/day; NOAEL for neurological effects (inhibition of RBC cholinesterase activity).

[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, conversions from dietary ppm to mg/kg/day doses were done by the study author.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Malathion is an organophosphate pesticide and as such, its main target of toxicity is the nervous system (Abou-Donia 1995; Ecobichon 1994; Koelle 1994; Taylor 1996). Within the nervous system, malathion and its active metabolite, malaoxon, inhibit acetylcholinesterase, the enzyme that terminates the action of the neurotransmitter acetylcholine. The effects of malathion have been well documented in studies in animals and also in humans, although in the latter case, mostly from case reports of accidental or intentional ingestion of high amounts of malathion. No data were located regarding effects of chronic oral exposure to malathion in humans. Few additional long-term studies have been conducted with malathion in rats and mice (NCI 1978, 1979a; Slauter 1994), but the one by Daly (1996a) used the widest dose range. The studies conducted by NCI (1978, 1979a) did not measure cholinesterase activities. An 18-month dietary study in mice identified a NOAEL of approximately 20 mg/kg/day for plasma and RBC cholinesterase inhibition (Slauter 1994), and this was the highest NOAEL below a LOAEL. However, ATSDR's policy and guidance for MRL derivation is to always use the most sensitive species and the database indicates that rats are more sensitive than mice for malathion.

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, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. 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 → **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 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
					↓		
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

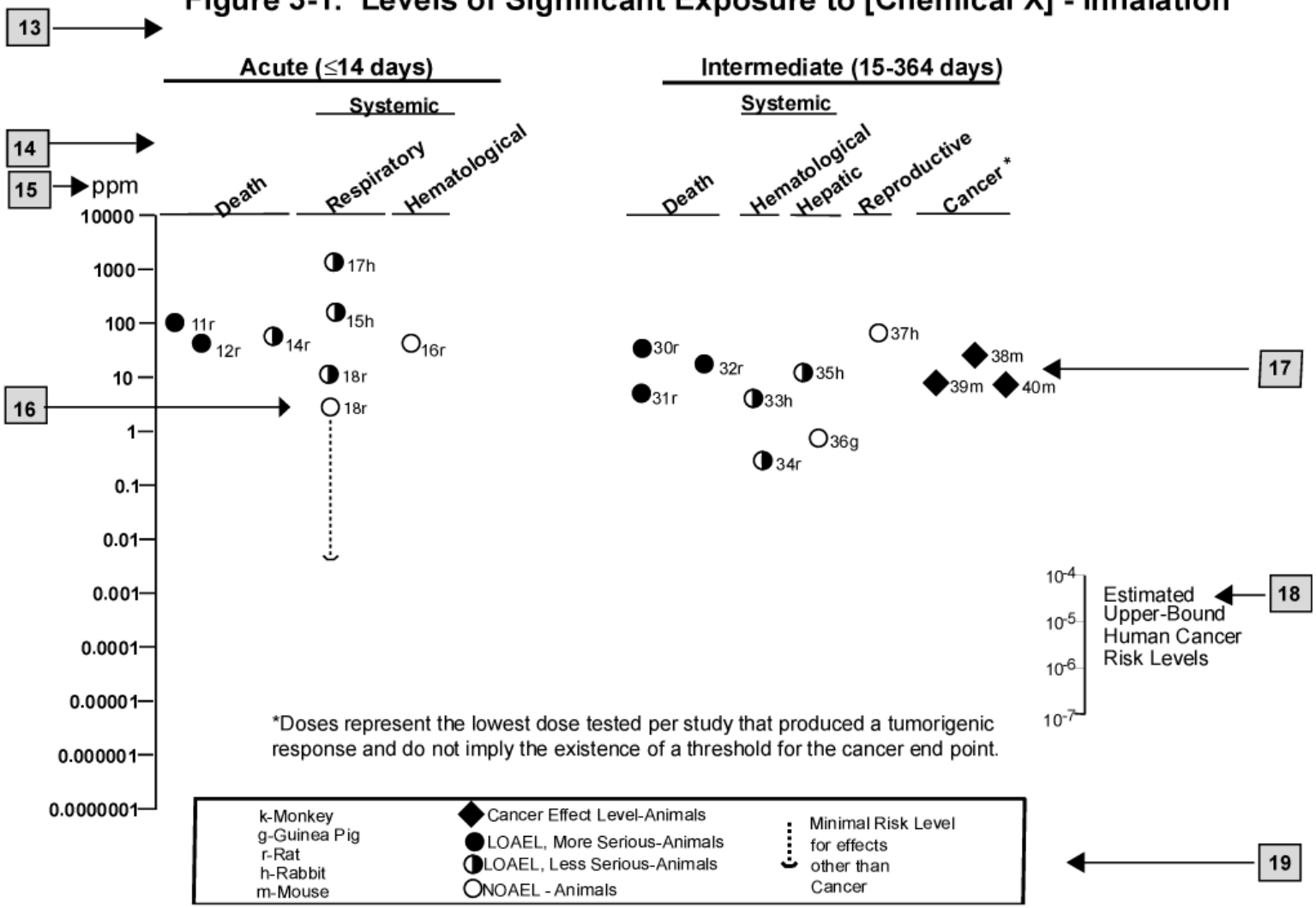
12 →

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

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-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

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotranferase
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
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
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
FR	*Federal Register*
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
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
LDH	lactic dehydrogenase
LH	luteinizing hormone
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

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
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
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
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
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
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
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
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
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized 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 carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	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