DRAFT
TOXICOLOGICAL PROFILE FOR PARATHION

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

October 2014

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UPDATE STATEMENT

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

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Division of Toxicology and Human Health Sciences
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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 these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a 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 toxic 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. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov.
Follow the on-line instructions for submitting comments.

Written comments may also be sent to:
Agency for Toxic Substances and Disease Registry
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The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of 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. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs 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 is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Robin M. Ikeda, M.D., M.P.H.
Acting Assistant Administrator
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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:

Chapter 1	**How Can (Chemical X) Affect Children?**
Chapter 1	**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: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional material is available online at www.atsdr.cdc.gov:

Case Studies in Environmental Medicine—Case Studies are self-instructional publications designed to increase primary care provider's knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients.

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

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

Other Agencies and Organizations

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

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: (202) 245-0625 or 1-800-CDC-INFO (800-232-4636).

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.

Clinical Resources

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, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • 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 Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

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

1. Dr. Edward Levin, Psychology and Behavioral Sciences, School of Medicine, Duke University, Durham, North Carolina;

2. Dr. Falicia Edwards, Center for Environmental Health, College of Science, Engineering and Technology, Jackson State University, Jackson, Mississippi; and

3. Dr. Asa Bradman, Center for Environmental Research and Children's Health (CERCH), School of Public Health, University of California, Berkeley, Berkeley, California.

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

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

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 FOR PARATHION

Overview

We define a public health statement and show how it can help you learn about parathion.

Introduction

A public health statement summarizes information about a hazardous substance. The information is taken from a toxicological profile developed by the Agency for Toxic Substances and Disease Registry's (ATSDR's) Division of Toxicology and Human Health Sciences (DTHHS). A toxicological profile is a thorough review of a hazardous substance.

This toxicological profile examines parathion. This public health statement summarizes the DTHHS's findings on parathion, describes the effects of exposure to it, and describes what you can do to limit that exposure.

Parathion at hazardous waste sites

The U.S. Environmental Protection Agency (U.S. EPA) identifies the most serious hazardous waste sites in the nation. U.S. EPA then includes these sites the National Priorities List (NPL) and targets it for federal clean-up activities. U.S. EPA has found parathion in at least 21 of the 1,699 current or former NPL sites.

The total number of NPL sites evaluated for parathion is not known. But the possibility remains that as more sites are evaluated, the number of sites at which parathion is found may increase. However, this is not likely since parathion is no longer manufactured or used in the United States. This information is important; these future sites may be sources of exposure, and exposure to parathion may be harmful.

Why a parathion release can be harmful

When a contaminant 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. But such a release doesn't always lead to exposure. You can only be exposed to a contaminant when you come in contact with it. That contact—and therefore that exposure—can occur when you breathe, eat, or drink the contaminant, or when it touches your skin.

Even if you're exposed to parathion, you might not be harmed. Whether you are harmed will depend on such factors as the dose (how much), the duration (how long), and how you are exposed. Harm might also depend on whether you've been exposed to any other chemicals, as well as your age, sex, diet, family traits, lifestyle, and state of health.

A Closer Look at Parathion

Overview

This section describes parathion in detail and how you can be exposed to it.

What is parathion?

Parathion does not occur naturally in the environment. Parathion is the common name of a formerly used organophosphorus insecticide for the control of sucking and chewing insects and mites in a wide variety of crops.

The pure chemical is a pale-yellow liquid with a faint phenol-like odor. Technical parathion is a pale-yellow to dark-brown liquid.

How is parathion used?

Parathion was often repeatedly applied by fan or boom sprayers or by aircraft on a wide variety of orchard, row, and field crops.

It was sold under common trade names including Alkron, Folidol, E-605, Fostox E, Phoskil, SNP, Soprathion, Thiophos, and Vitrex.

Where is parathion found?

Parathion's previous production and use as a pesticide resulted in its release into the air, water, and soil.

Possible Sources	Outcome
Ambient and indoor air	Low levels of parathion may still be present in air samples, particularly in agricultural regions. When parathion was still being used as a registered pesticide in the United States, a range of ambient air concentrations of 0.017 to 0.089 micrograms per cubic meter ($\mu g/m^3$) were reported.
Surface water and groundwater	Parathion in the past was infrequently detected in water samples. Parathion was not detected in any surface water samples collected during 1999–2000 as part of the U.S. Geological Survey (USGS) National Water-Quality Assessment (NAWQA) Program, in which samples were collected from 34 sites located throughout the Yakima River Basin, Washington.
Agricultural soil	Low levels of parathion may still be present in soils where it was formerly used as an insecticide.

Other media (food and fish)	In a survey of U.S. produce conducted from 1989 to 1991, parathion was detected in 13 of 6,970 produce samples, including apples, grapefruit, lemons, limes, oranges, peaches, and strawberries. It was also detected in 2% of the Total Diet Study foods between 1984 and 1986. As parathion is no longer in use and it degrades in the environment, its frequency of detection in foods should be considerably lower.

How Parathion Can Affect Your Health

Overview

This section looks at how parathion enters your body and potential parathion health effects found in human and animal studies.

How parathion enters your body

Parathion can enter your body from the air, water, food, or soil.

Possible Sources	Possible Exposure Pathway
Air	If you breathe air containing parathion, you may absorb it into your body through the lungs.
Water and food	Parathion in food or water can be absorbed from the digestive tract.
Soil	If you touch soil contaminated with parathion or fruits or plants that have been sprayed with it, some small amount may enter the body through the skin.

Where parathion goes in your body

Once in the body, parathion distributes primarily to the liver where it is broken down into other chemicals (metabolites). Low levels of parathion and metabolites have been found also in other organs of exposed animals, including the kidneys, muscle, lung, and brain. Less parathion will reach the liver if it is inhaled or there is skin contact than if it is ingested.

How parathion leaves your body

Parathion is eliminated primarily via the excretion of metabolites in the urine. A small proportion of metabolites are eliminated through the feces. It can take several days to eliminate parathion from your body after a single exposure.

Parathion health effects

Parathion is a nerve poison, and works by stopping your nervous system from turning off, leading to overload so the rest of your body cannot function.

The health effects of parathion depend on how much parathion you are exposed to and the length of that exposure. Environmental monitoring data suggest that any parathion levels that the general public might encounter through contact with water, soil, or food are lower than levels that have caused health effects in animal studies.

Short-term exposure effects

People who ingested parathion either intentionally or in contaminated food, who were exposed during application of the pesticide to fields, or who entered areas that had been sprayed too soon after application of this substance suffered excessive eye watering and salivation, blurred vision, stomach crumps, diarrhea, difficulty breathing, tremors, and seizures, and some died.

The same types of effects have been observed in animals exposed briefly to high levels of parathion.

Long-term exposure effects

Studies of agricultural workers suggested that long-term exposure (i.e., years) to low-to-moderate amounts of parathion may be associated with allergic asthma and hearing loss. A study of Chinese male workers suggested that parathion may be associated with low sperm count. In all of these cases, the associations were weak and the subjects may have been exposed to other chemicals at the same time.

Animal studies have shown that eating parathion-contaminated food over long periods may cause occasional diarrhea and tremors.

Parathion and cancer

A study of agricultural workers suggested that exposure to parathion may be associated with increased risk of skin cancer. However, the evidence was not conclusive because it was based on a small number of cases. Parathion caused cancer of the adrenal cortex in rats.

The U.S. Department of Health and Human Services (DHHS) has not classified parathion as to its carcinogenicity.

The U.S. EPA has classified parathion as a Group C carcinogen (possible human carcinogen).

The International Agency for Research on Cancer (IARC) has placed parathion in Group 3 (not classifiable as to its carcinogenicity to humans).

See Chapters 2 and 3 for more information on health effects of parathion.

Children and Parathion

Overview

This section discusses potential health effects of parathion exposure in humans from when they're first conceived to 18 years of age, and how you might protect against such effects.

Exposure effects for children generally

Children who accidentally ate parathion or had skin contact with high amounts of parathion suffered the same effects seen in adults exposed to high amounts of parathion (excessive secretions, stomach cramps, diarrhea, tremors, and seizures).

No long-term exposure studies of children are available. However, studies of other similar pesticides found that long-term exposure might results in nervous system problems in children.

What about birth defects?

We do not know whether parathion can produce birth defects in children. A study of women from an agricultural community in California did not find an association between exposure to parathion and growth of the fetus. However, the study did not conclusively demonstrate specific exposure to parathion; it was only assumed based on the presence of a chemical in the urine that could have come from the breakdown of parathion or other substances in the body.

Studies in which pregnant rats and rabbits were given parathion by mouth did not find increases in birth defects.

How Can Families Reduce the Risk of Exposure to Parathion?

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

Production and use terminated

To prevent exposure and risk to the general population, the EPA terminated most production of parathion as of December, 2002, with the remaining production ending in 2003. The EPA also terminated the last registration for parathion products effective on December 21, 2006. Because of these actions and environmental degradation processes, it is likely that neither the general population nor workers are exposed to parathion in the United States.

Medical Tests to Determine Parathion Exposure

Overview

We identify medical tests that can detect whether parathion is in your body, and we recommend safe toxic-substance practices.

Parathion can be measured in blood and urine

Parathion and its breakdown products (metabolites) can be measured in blood and urine. However, the detection of parathion or its metabolites cannot predict the kind of health effects that might develop from that exposure. Because parathion and its metabolites leave the body fairly rapidly, the tests need to be conducted within days after exposure.

One of parathion's degradation products, *p*-nitrophenol, has been widely used to determine exposure to parathion. However, *p*-nitrophenol is also a breakdown product of a similar pesticide, methyl parathion, and a product used in the production of some medicines, like acetaminophen. So the presence of *p*-nitrophenol in your urine cannot be used to indicate exposure to parathion without information on possible sources of exposure.

Where known parathion exposure occurred, measurements of *p*-nitrophenol helped doctors and public health officials obtain reference values so that they could determine whether people had been exposed to higher amounts of parathion than were found in the general population.

For more information on the different substances formed by parathion breakdown and on tests to detect these substances in the body, see Chapters 3 and 7.

Federal Government Recommendations to Protect Human Health

Overview

One way the federal government promotes public health is by regulating toxic substances or recommending ways to handle or to avoid toxic substances.

The federal government regulates toxic substances

Regulations are enforceable by law. The U.S. EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that have adopted toxic substances regulations.

The federal government recommends safe toxic substance practices

The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) have made recommendations about toxic substances. Unlike enforceable regulations, these recommendations are advisory only.

Toxic substance regulations

Regulations and recommendations can be expressed as "not-to-exceed" levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

Some regulations and recommendations for parathion include:

Federal Organization	Regulation or Recommendation
U.S. Environmental Protection Agency (U.S. EPA)	The EPA does not regulate or provide guidelines for parathion in drinking water.
Food and Drug Administration (FDA)	The FDA does not regulate parathion in food or drugs.
Occupational Safety and Health Administration (OSHA)	OSHA set a legal limit of 0.1 milligrams per cubic meter (mg/m^3) for parathion in air averaged over an 8-hour work day.
National Institute for Occupational Safety and Health (NIOSH)	NIOSH has set a recommended limit of 0.05 mg/m^3 for parathion in air averaged over a 10-hour work day.

Additional Information

Overview

Where to find more information about parathion.

Who to contact

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.

Additional information from ATSDR

ATSDR can provide publically available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

Where to obtain toxicological profile copies

Toxicological profiles are also available online at www.atsdr.cdc.gov. For more information:

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or
- Write to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
1600 Clifton Road NE
Mailstop F-57
Atlanta, GA 30333

For-profit organizations should request final toxicological profile copies from:

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/

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2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PARATHION IN THE UNITED STATES

Parathion is an organophosphorus insecticide that was primarily used prior to 2006 for agricultural purposes and was released to the environment through spraying on a wide variety of agricultural crops and at agricultural sites. Once parathion is introduced into the environment, it may be degraded by atmospheric photooxidation and catalyzed by ozone or degraded by hydrolysis or biodegradation mediated by microorganisms found in most sediment, soils, and water. Parathion is not likely to migrate through the soil and into groundwater since it has little to no mobility in soils under varying conditions. Volatilization of parathion from water surfaces has been observed; however, minimal volatilization of parathion from soil surfaces has been reported due to binding. Data from limited studies suggest that bioconcentration of parathion does not occur to a significant extent in most aquatic organisms tested, and that it may be metabolized when it is accumulated.

Significant exposure of the general population to parathion is not likely at present, due to the ban on all uses in the United States. Parathion was formerly used as a widespread insecticide in agriculture. In 1991, parathion was registered as a restricted use insecticide and had been limited to use on nine crops. Due to the toxicity of this chemical, most production of manufacturing use products was cancelled effective as of September 2000 with the remainder cancelled in 2003. The production of end use products was slated to be terminated as of December 31, 2002, with the last legal use of this chemical and its products to be effective on October 31, 2003. The production and registration for the remaining end use products ended in 2006 (EPA 2006a).

When parathion was still used as a registered insecticide, general population exposure may have occurred through ingestion of contaminated food and inhalation. Ingestion of foods contaminated with small residues of parathion was the most likely route of exposure for the general population not living in areas where parathion was extensively used. Populations living within or very near areas of heavy agricultural parathion use would have had an increased risk of exposure to relatively larger amounts of parathion through dermal contact with contaminated plants, soils, or surface waters; by inhalation of the mist formed from the applied insecticide; or by ingestion of food-borne residues. Those likely to have received the highest exposures are those who were involved in the production, formulation, handling, and application of parathion, farm workers who enter treated fields prior to the passage of the appropriate restricted entry intervals, and workers involved in the disposal of parathion or parathion-containing

wastes. Dermal contact appears to have been the major route of exposure for workers. Inhalation of parathion in occupational settings depended on its volatility, the type of formulation used, and the application technique employed.

Children would have been expected to be exposed to parathion by the same routes that affect adults. Small children were more likely to come into contact with parathion residues that may have been present in soil and dust, due to increased hand-to-mouth activity and playing habits. Ingestion of foods contaminated with small residues of parathion was the most likely route of exposure for children. No data were located regarding parathion in breast milk; therefore, an adequate determination of the importance of this route of child exposure has not been made.

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

2.2 SUMMARY OF HEALTH EFFECTS

Parathion is an organophosphate pesticide of relatively high acute toxicity compared to other organophosphates. Signs and symptoms of acute toxicity are typical of those induced by organophosphate insecticides as a group. With the current state of knowledge, the great majority of systemic effects observed following exposure to parathion are due to the action of its active metabolite, paraoxon, on the nervous system, or are secondary to this primary action. Paraoxon inhibits the enzyme, acetylcholinesterase (AChE), at the various sites where the enzyme is present in the nervous system: the central nervous system, the sympathetic and parasympathetic divisions of the autonomic nervous system, and the neuromuscular junction. Inhibition of AChE results in accumulation and continuous action of the neurotransmitter acetylcholine at postsynaptic sites. Information regarding effects of parathion in humans is derived mainly from cases of accidental or intentional ingestion of parathion, studies of workers involved in the manufacture of parathion, studies of agricultural workers, members of the general population, and a few controlled exposure studies with volunteers. Oral ingestion or dermal absorption of high amounts of parathion resulted in typical signs and symptoms of organophosphate intoxication, including reduced plasma and red blood cell cholinesterase activity, excessive bronchial secretions, respiratory distress, salivation, pinpoint pupils, bradycardia, abdominal cramps, diarrhea, tremor, fasciculations, and possibly death.

Limited data are available regarding health effects in humans exposed to parathion other than neurological effects. Evaluations of participants in the Agricultural Health Study (AHS) have suggested weak associations between exposure to parathion and allergic asthma, hearing loss, and cutaneous melanoma. The AHS, sponsored by the National Institute of Health (NIH 2014), is a prospective cohort study of nearly 90,000 private pesticide applicators (mostly farmers), their spouses, and commercial pesticide applicators in Iowa and North Carolina. Parathion was one of multiple pesticides involved in the evaluations. The AHS is a collaborative effort involving the National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), and the EPA. Results from the AHS also showed no significant association between exposure to parathion and wheezing, non-allergic asthma, and neurobehavioral function (memory, motor speed and coordination, sustained attention, verbal learning, and visual scanning and processing). Two population-based, case-control studies did not find a significant association between exposure to parathion and Parkinson's disease. A small study of Chinese workers exposed to parathion and methamidophos reported sperm alterations in workers compared to unexposed subjects; however, the small sample size (only 20 workers) renders the results uncertain at best. A study of Latina women living in an agricultural community in California did not find significant associations between several measures of *in utero* exposure to parathion and fetal growth. That study, however, assessed exposure to parathion by measuring urinary *p*-nitrophenol, which could have been produced by exposure to chemicals other than parathion. Studies in animals support the human data and confirm that the main target of parathion toxicity is the nervous system. Exposure levels were not available in the studies mentioned above. Very few studies that evaluated reproductive and developmental effects of parathion in animals were available for review. An intermediate-duration oral study in rats reported that doses of 2.6 mg parathion/kg/day (only dose tested and in the lethal range estimate for human adults) induced testicular tubular atrophy, necrotic spermatogenic cells, and enlargement of the interstitial space of the tested. Oral chronic-duration studies in rats exposed to up to 4.4 mg parathion/kg/day or in mice exposed to up to 27.6 mg parathion/kg/day did not find gross or microscopic alterations in the reproductive organs. Parathion was not embryotoxic or teratogenic in rats and rabbits following repeated oral administration of up to 1 and 0.3 mg parathion/kg/day, respectively, during gestation. An additional study in rats reported that pups exposed during gestation and lactation showed alterations in the electrocardiograms (EKGs) (i.e., decreased rate of atrial depolarization and ventricular repolarization) on postnatal day 25 even with the lowest maternal dose tested, 0.01 mg parathion/kg/day. Since this is not a developmental end point routinely tested in standard developmental studies, it would be helpful to try to replicate these results to determine if they are developmental in nature. A series of studies in which neonatal rats were administered subcutaneous doses of parathion that

did not induce significant inhibition of AChE reported alterations in the development of neurotransmitter systems, neurobehavior, and metabolic dysregulation that were evident at later times up to adulthood.

Parathion increased the incidence of adrenal gland adenomas and carcinomas in Osborne-Mendel rats in a dietary bioassay. Parathion induced immunosuppression in mice in acute oral studies; the lowest dose to do so was 1.5 mg parathion/kg/day. However, none of these studies challenged the mice with an external agent to evaluate whether resistance to infection was compromised. Evidence suggested that cholinergic stimulation played a major role in parathion-induced plaque-forming cell response. Parathion also increased the sensitivity to allergens in mice at the relatively low dose of 0.15 mg parathion/kg/day. The investigators suggested that the effects may involve alterations in the number of helper and cytotoxic T-cells, in levels of T_H1 and T_H2 cytokines, and in gene expression in lymph nodes. Chronic-duration studies in rats and mice did not find gross or microscopic alterations in lymphoreticular organs. In general, little systemic toxicity was reported in the animal studies available for review. Mild liver histopathology was reported in rats in a 90-day gavage study. The chronic-duration oral studies available for review did not find gross or microscopic alterations in the liver, kidneys, heart, or lungs from rats or mice. Neurotoxicity is the main effect of parathion 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 parathion intoxication are typical of organophosphate poisoning. Parathion through its active metabolite, paraoxon, inhibits the enzyme AChE and thus prevents 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, sufficient 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.

Death generally occurs due to respiratory failure attributed to excessive tracheobronchial and salivary secretions, nicotinic paralysis of the diaphragm and respiratory muscles and depression of central nervous system respiratory centers.

The signs and symptoms described above have been documented in almost all of the cases of accidental or intentional ingestion or dermal exposure to high amounts of parathion. Estimates of lethal doses range from about 2 to 13 mg/kg in adults and from 0.1 to 1.3 mg/kg in children. Studies that measured cholinesterase levels showed significant decreases in both red blood cell AChE and plasma cholinesterase levels. In general, plasma cholinesterase activity can be inhibited by 20–25% without significant physiological consequences. Red blood cell AChE activity can be reduced 20–25% without manifestation of clinical signs. A decrease of 40% is a danger signal for overexposure, and a depression of ≥60% is an indication for removal from the exposure site to prevent overt poisoning. Studies also have shown that the rate of decrease of red blood cell AChE correlates better with the appearance of symptoms than the absolute value reached after exposure. Red blood cell AChE better reflects the AChE content in the central nervous system than plasma cholinesterase. In a study of multiple cases of severe oral intoxication, red blood cell cholinesterase was depressed 78%. In another study of six cases of severe oral poisoning with parathion, red blood cell cholinesterase activity was reduced to <10% of normal in all cases. In workers exposed to high amounts of parathion primarily by dermal contact during the synthesis and handling of various parathion formulations, and who suffered severe symptoms, red blood cell cholinesterase activity reached 11–22% of normal. In two fatal cases of oral poisoning, inhibition of brain AChE was found to be regionally selective. Measurements done within 32 hours of death showed the biggest decreases (65–80%) in the cerebellum, some thalamic nuclei, and the cortex. Moderate decreases of 10–30% were reported in the *substantia nigra* and basal ganglia; no significant changes were seen in the white matter. Studies in volunteers exposed orally to parathion indicate that repeated doses of approximately 0.1 mg parathion/kg may result in reductions of red blood cell AChE activity of <20% and no adverse clinical signs. Application of approximately 100 mg to the hand and forearm of volunteers for 2 hours during 5 consecutive days resulted in maximal inhibition of red blood cell AChE of 14%, and no clinical signs were observed. As detailed in Section 3.2, numerous studies in animals exposed to parathion by any route have shown inhibition of plasma, red blood cell, and brain cholinesterase activities.

A condition that has been reported in humans as a consequence of acute exposure to high amounts of some organophosphate pesticides 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. Single cases due to specific exposure to parathion have been reported. In a report of 68 cases of acute exposure to parathion, 7 developed intermediate syndrome (10.3%).

A serious neurological effect of some organophosphate pesticides is delayed neurotoxicity. Organophosphorus pesticide-induced neuropathy (OPIDN) is a neurodegenerative disorder characterized by a delayed onset of prolonged ataxia and upper motor neuron spasticity. The lesion is a central-peripheral distal axonopathy caused by a Wallerian-type degeneration of the axon, followed by myelin degeneration of the central and peripheral nervous systems. A few cases of parathion-induced delayed neuropathy have been described.

2.3 MINIMAL RISK LEVELS (MRLs)

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

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 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.

Inhalation MRLs

An acute-duration inhalation MRL was not derived for parathion. Adequate human data were not available. Hartwell et al. (1964) exposed two volunteers to various formulations of heated parathion dust or liquid technical parathion for periods of 30 minutes and measured red blood cell AChE activity. However, the concentrations of parathion to which the subjects were exposed were not determined. An acute-duration study that identified no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) for neurological end points including red blood cell AChE activity and clinical signs in rats and dogs was available for review; the exposure period was 4 hours for both species (NIOSH 1974). Red blood cell AChE activity was the most sensitive end point in both species and, since it is a valid neurological end point in the absence of brain AChE data, could be considered for MRL derivation. However, studies of cholinesterase inhibition have shown that it takes approximately 21–28 days for inhibition of cholinesterase activity to reach a steady state and that values obtained in single dose or short-duration studies carry great uncertainty (EPA 2001, 2006). This also translates into an apparent lack of dose-response, particularly at the low exposure levels. For example, in the NIOSH (1974) study with parathion, 24 hours after exposure to 0.035, 0.206, 0.235, 0.825, 0.905, 1.21, or 2.17 mg/m^3 parathion aerosol, red blood cell AChE activity in male rats was inhibited 7, 8, 28, 17, 8, 11, and 30%, respectively. Examination of the extent of red blood cell AChE inhibition across time gives a similar picture. For example, in male rats, exposure to 0.235 mg/m^3 parathion aerosol resulted in 0, 23, 14, 0, and 26% inhibition at 4, 24, 48, 168, and 336 hours after exposure ceased, respectively. In dogs, the lowest exposure level tested (0.153 mg/m^3) resulted in levels of red blood cell AChE activity 62.1, 49.3, 44.0, 71.6, and 58.0% of normal at 4 hours, 24 hours, 48 hours, 7 days, and 14 days after exposure, respectively. For these reasons, and also based on data collected on enzyme inhibition for a great number of organophosphate pesticides that suggest that AChE inhibition data obtained in single-dose or short-duration studies carry great uncertainty (EPA 2006), as indicated above, an acute-duration inhalation MRL was not derived for parathion. However, since the lowest acute-duration inhalation LOAEL is 0.153 mg/m^3, the intermediate-duration inhalation MRL of 20 ng/m^3 (see below) is protective of acute effects.

- An MRL of 20 ng/m^3 has been derived for intermediate-duration inhalation exposure (15–364 days) to parathion based on adverse neurological effects in rats.

The only quantitative information regarding long-term exposure of humans to parathion in air is from a study of 13 workers at an industrial plant that manufactured concentrated parathion as well as dusts containing various concentrations of parathion (Brown and Bush 1950). Only one of these workers was

unexposed to parathion. The exact duration of exposure was not known. Parathion was measured in air at different operations. The maximum concentration determined was 0.8 mg/m^3 and the estimated average was about 0.2 or 0.3 mg/m^3. Due to the rotation of personnel, the 12 exposed subjects had only intermittent contact with parathion-contaminated air until July 1949, when production ceased. Therefore, it was impossible to determine exactly what the total exposure had been. Analyses of blood from five subjects who provided successive blood samples over a 6-month period showed a decrease in plasma cholinesterase activity. However, the changes in red blood cell cholinesterase activity were less conclusive. The investigators noted that probably the most significant finding was the fact that measurements of cholinesterase activities conducted 5 months after the plant had stopped manufacturing parathion showed a marked increase in activities in almost all cases. The information presented in this study is inadequate for MRL derivation.

Although only one intermediate-duration study provided information regarding effects of parathion in animals, the study was considered adequate for derivation of an intermediate-duration MRL (NIOSH 1974). The study monitored clinical signs and plasma cholinesterase and red blood cell AChE activities in male Sprague-Dawley rats and in male beagle dogs exposed whole-body to aerosolized technical parathion.

Groups of male rats (20/group) were exposed to 0, 0.01, 0.1, or 0.74 mg parathion/m^3 7 hours/day, 5 days/week for 6 weeks. Blood samples obtained from 71 rats were assayed for red blood cell and plasma cholinesterase and served as baseline controls. Ten rats per exposure group and control group were sacrificed at various times during the exposure period and during a 6-week post-exposure period to collect blood samples. The rats were observed for clinical signs and were weighed before blood sampling and sacrifice. No clinical signs were seen in rats exposed to 0.01 or 0.1 mg parathion/m^3. Some rats in the high-concentration group showed signs of parathion toxicity, including tremors and ataxia. Blood collected from the high-dose group after the last exposure showed no significant alteration in hematocrit. Body weight was not significantly altered by exposure to parathion. In the low-exposure group, red blood cell AChE activity was maximally decreased by approximately 30% on exposure weeks 4 and 5; no data were available for week 3. On exposure week 6, red blood cell AChE activity in the low-exposure group had recovered to 97.3% of control levels. In the mid-exposure group, the maximum decrease in red blood cell AChE was 43% and occurred on week 1. During the rest of the exposure period, red blood cell cholinesterase activity was 60–70% of pretest levels, suggesting that a steady state had been achieved. Red blood cell AChE activity during the first and second week of the post-exposure period was 82 and 84.4% of controls, indicating that recovery was in progress. In the high-exposure group, red blood cell

AChE activity achieved its maximal depression on week 5 of exposure, reaching 15% of controls. In general, enzyme activities recovered during the 6-week post-dosing period. Changes in plasma cholinesterase activity paralleled red blood cell changes, but recovered faster and significantly exceeded controls starting the first week post-exposure. Since the exposure level of 0.1 mg parathion/m^3 induced a level of depression of red blood cell AChE activity that appeared to achieve steady state at approximately 60–70% of controls during exposure, this exposure concentration constitutes a less serious LOAEL for neurological effects in rats; the exposure concentration of 0.01 mg parathion/m^3 is a NOAEL.

Male beagle dogs (6/group) were exposed to parathion aerosol at concentrations of 0, 0.001, 0.01, or 0.2 mg/m^3 7 hours/day, 5 days/week for 6 weeks and were held for an additional 6-week post-exposure period. Blood samples obtained from the dogs at various times during the exposure and post-exposure periods were assayed for red blood cell AChE and plasma cholinesterase. Blood samples were taken pre-exposure so that each dog served as its own control. No clinical signs were observed in the dogs. Exposure to parathion did not affect body weight gain in the dogs. No significant effects on red blood cell AChE activity were observed at the low-exposure level. Exposure to 0.01 mg parathion/m^3 reduced red blood cell AChE activity by 21% by the end of the second week of exposure, but levels recovered to 86% of pre-exposure values by the third week of exposure and to 100% of pretest levels during the remaining of the exposure period. In the high-exposure group, red blood cell AChE activity was reduced between 26 and 46% during the first 5 weeks of exposure and inhibition reached a maximum of 41% of pre-exposure levels on week 6 of exposure. Slow recovery was evident during the post-exposure period, with complete recovery at 6 weeks in dogs exposed to 0.20 mg/m^3. Plasma cholinesterase activity was inhibited to a greater extent during the exposure period, but seemed to recover faster during the post-exposure period. Based on the fact that red blood cell AChE activity was depressed over 20% (21%) only on week 2 of exposure in the 0.01 mg/m^3 group, this exposure level is considered a NOAEL for neurological effects in dogs in an intermediate-duration study; the LOAEL is 0.2 mg/parathion/m^3.

Since only means without deviation parameters were reported for red blood cell AChE values, dose-responses using the benchmark dose approach cannot be constructed to estimate points of departure from the rat and dog data. Therefore, a NOAEL/LOAEL approach will be used and the NOAEL of 0.01 mg parathion/m^3 for red blood cell AChE in rats is the point of departure for MRL derivation. Although the NOAEL is the same in both species, the data in rats are preferred over dogs based on the fact that a lower LOAEL was established, there were 20 rats per group versus 6 dogs per group, and more extensive data regarding cholinesterase inhibition have been collected in rats than in dogs. In any case, the data in dogs support the findings in rats.

Although NIOSH (1974) stated that particle size was determined by the use of a Rochester cascade impactor, no data regarding droplet size were located in the report available for review. In the absence of droplet size data, a dosimetric adjustment cannot be performed to estimate a human equivalent concentration. Therefore, the MRL is derived by applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the duration-adjusted NOAEL (0.01 mg/m^3 x 7 hours/24 hours x 5 days/7 days x 1/100). This yields an intermediate-duration inhalation MRL of 20 ng/m^3 for parathion.

A chronic-duration inhalation MRL was not derived for parathion. No chronic-duration inhalation studies in humans or animals exposed to parathion were located. It is possible that in the study of workers exposed to parathion conducted by Brown and Bush (1950) summarized above, some workers could have been exposed for over a year.

Oral MRLs

An acute-duration oral MRL was not derived for parathion for the reasons discussed below. Data regarding inhibition of red blood cell AChE activity in short-term studies, including a 5-day exposure study in volunteers (Morgan et al. 1977), were not considered for MRL derivation for the reasons previously discussed regarding an acute-duration inhalation MRL for parathion. The decision is based on the fact that studies of cholinesterase inhibition have shown that it takes approximately 21–28 days for inhibition of cholinesterase activity to reach a steady state, and that values obtained in single-dose or short-duration studies carry great uncertainty. In addition to data on blood cholinesterase activity, intermediate-duration oral studies in animals provided information on systemic effects (mostly body weight), developmental effects, and effects on the immune system. Acute oral developmental studies in rats and rabbits reported NOAEL values of 1 and 0.3 mg parathion/kg/day, respectively, the highest doses tested (Renhof 1984, 1985). A study in mice identified a relatively low LOAEL of 0.15 mg parathion/kg/day for increased sensitivity to allergens (Fukuyama et al. 2011); that dose was the lowest dose tested. Another study from the same group of investigators found that mice dosed with 1.5 mg parathion/kg/day for 5 days exhibited decreased IgM antibody plaque-forming cells in response to sheep red blood cell (SRBC) antigen; the NOAEL was 0.15 mg parathion/kg/day (Fukuyama et al. 2012). Other studies had reported similar effects, but had tested higher doses (Casale et al. 1983, 1984; Kim et al. 2005; Wiltrout et al. 1978). The plaque-forming cell assay is a widely used test of immuno-competence, specifically humoral-mediated immunity, and has been shown to be a sensitive target of toxicity. The end

point has been used to derive MRLs for various chemicals (Abadin et al. 2007) and could have been considered for derivation of an acute-oral MRL for parathion. However, as explained below, an intermediate-duration oral study in humans (Rider et al. 1969) identified a LOAEL of 0.11 mg parathion/kg/day and a NOAEL of 0.09 mg parathion/kg/day for red blood cell AChE inhibition. The NOAEL of 0.09 mg parathion/kg/day is lower than the LOAEL for increased sensitivity to allergens (0.15 mg/kg/day) and decreased humoral-mediated immunity (1.5 mg/kg/day) identified in the Fukuyama et al. (2011, 2012) studies. Because human data are preferred over animal data, and because an intermediate-duration oral MRL based on the human NOAEL would be protective of the immunological effects reported in the acute-duration studies in mice, the immunological data are not used for derivation of an acute-duration oral MRL for parathion.

- An MRL of 0.009 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to parathion based on neurological effects in humans.

Two intermediate-duration oral studies in volunteers provide information on red blood cell AChE activity in humans during exposure to parathion. The first study identified a NOAEL of 0.1 mg parathion/kg/day (the highest dose tested) for red blood cell AChE activity in female volunteers administered the pesticide orally for 6 weeks; no further information regarding red blood cell AChE was provided (Edson 1964). The second human study identified a NOAEL of approximately 0.09 mg parathion/kg/day for red blood cell AChE activity in male volunteers administered the pesticide in a capsule for 30 days (Rider et al. 1969). The intermediate-duration oral studies in animals provide information on body weight, neurological effects, and reproductive and developmental effects. The lowest LOAEL for neurological effects was 0.047 mg parathion/kg/day for a 25% inhibition of red blood cell AChE in dogs in a 24-week dietary study; the NOAEL was 0.021 mg/kg/day (Frawley and Fuyat 1957). In another study in dogs, doses of 0.5 mg parathion/kg/day in a capsule reduced red blood cell AChE activity 25–58% during a 6-week treatment period followed by a 6-week recovery period; the NOAEL was 0.1 mg/kg/day (NIOSH 1974). Two studies in rats dosed for several weeks identified LOAELs of 0.1 mg parathion/kg/day for red blood cell AChE; the NOAELs were 0.024 and 0.05 mg parathion/kg/day (Ivens et al. 1998; NIOSH 1974). An intermediate-duration oral study in monkeys identified a LOAEL of 0.1 mg parathion/kg/day (the only dose tested) for altered auditory detection behavior; no measurements of enzyme activities were conducted in this study (Reishchl et al. 1975). The only developmental study available for review reported a considerably lower LOAEL of 0.01 mg parathion/kg/day (the lowest dose tested) for altered EKGs in 24-day-old pups from rats dosed from day 2 of gestation through day 15 of lactation (Deskin et al. 1979). Since this is not a developmental end point routinely tested in guideline developmental studies, it would be helpful to try to replicate these results before it could be considered for MRL derivation.

The available intermediate-duration oral studies suggest that in humans, rats, and dogs, significant inhibition (>20%) of red blood cell AChE activity occurs with repeated doses ≥0.1 mg parathion/kg/day. In the Frawley and Fuyat (1957) study, red blood cell AChE activity was depressed approximately 25% in dogs dosed 0.047 mg parathion/kg/day for 12 weeks, but appeared to increase to near 90% of pretest values on week 16 of exposure. Another study in dogs showed that a constant inhibition of the enzyme of >20% could be achieved only with repeated doses of 0.5 mg parathion/kg/day (NIOSH 1974). Since utilizing human data will reduce the uncertainty over using animal data, the study of Rider et al. (1969) in volunteers is selected for derivation of an intermediate-duration oral MRL for parathion.

In the Rider et al. (1969) study, five male volunteers were administered 3, 4.5, 6, or 7.5 mg parathion/day in a capsule (0.04, 0.06, 0.09, and 0.11 mg/kg/day assuming 70 kg body weight) for approximately 30 days; two additional subjects served as controls. Although not explicitly stated in the paper, it appears that all of the subjects were exposed to all of the doses. In a pretest period of 30 days, blood was collected to establish baseline levels of plasma cholinesterase and red blood cell AChE. The subjects were also monitored during a post-test period of about 30 days. At the beginning of the pretest period, routine blood counts, urinalysis, and prothrombin time were performed, and these were repeated at the end of each test period. Doses of 0.04 or 0.06 mg parathion/kg/day did not affect the levels of either enzyme. Administration of 0.09 mg parathion/kg/day caused a slight depression of plasma cholinesterase (data not provided). Doses of 0.11 mg parathion/kg/day induced a 27% decrease in the plasma enzyme in one subject on day 4. On day 9, two subjects showed 36 and 32% inhibition of the plasma enzyme. On day 16, the levels of plasma cholinesterase in these two subjects were 50 and 52% of pretest levels, and parathion dosing was discontinued. In the other three subjects, plasma cholinesterase levels were 97, 82, and 69% of pretest levels. On day 16, the mean levels of plasma cholinesterase in the five exposed subjects was reduced by 28% from the control value. In two subjects who received parathion during 35 days, the lowest plasma cholinesterase levels were 86 and 78% of their pretest values. Red blood cell AChE activity in the three subjects who discontinued the parathion dosing achieved maximal inhibition levels of 63, 78, and 86% of pretest levels. In the two subjects who completed the test period, there was no significant effect on red blood cell AChE activity. By the end of the post-test period, both enzymes had returned to pretest levels. No information was provided regarding blood counts, urinalysis, or prothrombin test results. Based on a >20% inhibition of red blood cell AChE activity in two out of five subjects for 16 days, the dose of 0.11 mg parathion/kg/day is a LOAEL for neurological effects; the next lower dose, 0.09 mg parathion/kg/day, is a NOAEL. Benchmark dose analysis cannot be performed because the data were not presented as means plus or minus a measure of dispersion such as standard

deviation or standard error of the mean. The intermediate-duration oral MRL for parathion is derived by dividing the NOAEL of 0.09 mg parathion/kg/day by an uncertainty factor of 10 (to account for human variability); this yields an MRL of 0.009 mg parathion/kg/day (9 µg/kg/day).

A comparison of the intermediate-duration inhalation (20 ng/m^3) and oral (9,000 ng/kg/day) MRLs for parathion suggests that there may be a relatively large difference (perhaps as large as 3 orders of magnitude) in the exposure dose between these two route-specific MRLs. This could be due, in part, to differences in study design, as well as species- and route-specific differences in parathion toxicokinetics and toxicodynamics. For example, dose spacing in the rat inhalation study resulted in a 10-fold difference between the NOAEL and the LOAEL, compared to a 0.12-fold difference in the human oral study—a difference equivalent to almost 2 orders of magnitude. The lack of absorption data in humans and rats for the inhalation and oral routes of exposure and limited species-specific toxicodynamics data preclude making a direct comparison of MRL values. Although our understanding of the differences in rat and human toxicokinetics to parathion is as yet incomplete, the currently available information indicates that both of these MRLs should be adequately protective of human health.

A chronic-duration oral MRL was not derived for parathion. No chronic-duration oral studies with parathion in humans were located, and the available animal studies were inadequate for MRL derivation. In an early dietary study in rats, administration of up to approximately 1.7 mg parathion/kg/day for 365 days did not induce adverse clinical signs (Barnes and Denz 1951). Histological examination of the major organs and tissues from 14 out of 70 rats did not show treatment-related alterations. In another chronic-duration study, exposure of rats to up to 4.4 mg parathion/kg/day or of mice to up to approximately 27.6 mg parathion/kg/day did not result in gross or microscopic alterations in the brain (NCI 1979). In the NCI (1979) study, the investigators noted that during the first half of the second year, clinical signs among dosed rats appeared at a low or moderate incidence, and during the second half of the year, they increased. However, no quantitative data were presented. In addition, the investigators mentioned that by week 60 of the study, all high-dose male mice (approximately 27.6 mg parathion/kg/day) showed signs of hyperexcitability, but no data were shown. Furthermore, none of these studies monitored AChE activity.

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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 parathion. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

Many of the systemic effects observed following exposure to parathion 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 paraoxon (the active metabolite of parathion) of AChE at nerve terminals from the central, peripheral somatic, and autonomic divisions of the nervous system. Inhibition of AChE 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 AChE. AChE inhibition is a biochemical feature common to all organophosphate pesticides.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death,

or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

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

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

Individuals who work with parathion are potentially exposed through inhalation of aerosols or dusts and through dermal contact. Minor oral exposure may also occur since inhaled materials can be swallowed through hand-to-mouth activities or deposited in the oral mucosa and either directly absorbed or swallowed. However, the specific contribution of each route of exposure is difficult to determine, especially in cases in which it is not known whether or not the workers were using protective clothing and/or respirators. Because technical parathion has relatively low vapor pressure, it is unlikely that workers would be subjected to saturated air for prolonged periods of time. On the other hand, agricultural

workers, particularly thinners and harvesters, had extensive contact between the fruit and their hands and less extensive contact between their arms and other parts of their body and the foliage (Milby et al. 1964; Quinby and Lemmon 1958). Therefore, studies of agricultural workers and other studies of humans in which no specific mention is made regarding which exposure route prevailed are summarized in Section 3.2.3, Dermal Exposure. 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

Among 30 deaths that occurred in children due to parathion exposure in Florida from 1956 through 1964, one was due to inhalation of parathion powder (Eitzman and Wolfson 1967); in this lethal case, the time from contact of a hospital to death was 7 hours. Inhalation may have contributed to three additional deaths (Eitzman and Wolfson 1967).

A 1-hour LC_{50} of 137 mg/m^3 was calculated for technical parathion in female Sprague-Dawley rats (EPA 1978). All rats exhibited typical signs of cholinesterase inhibition, including salivation, lacrimation, exophthalmos, defecation, urination, and muscle fasciculations. An additional study reported a 4-hour LC_{50} of 84 mg/m^3 in male Sprague-Dawley rats exposed to technical-grade parathion (NIOSH 1974). Tremors, convulsions, and death occurred at concentrations ≥50 mg/m^3, but not at ≤35 mg/m^3. No lethality was observed in groups of four male beagle dogs exposed to up to 37.1 mg/m^3 aerosolized technical parathion for 4 hours followed by an observation period of 14 days (NIOSH 1974).

The LC_{50} values in female rats in the EPA (1978) study and in male rats in the NIOSH (1974) study are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The highest NOAEL values 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 hepatic, renal, endocrine, dermal, or ocular effects in humans or animals after inhalation exposure to parathion.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL: Less Serious (mg/m³)	LOAEL: Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	1 hr				137 F (1-hour LC50)	EPA 1978	
2	Rat (Sprague-Dawley)	4 hr				84 M (LC50)	NIOSH 1974	
Systemic								
3	Rat (Sprague-Dawley)	4 hr	Resp	35 M	50 M (respiratory difficulties)		NIOSH 1974	
			Gastro			26.1 M (diarrhea in 15/34 rats)		
4	Rat (Wistar)	1 hr	Resp		63 M (increased lung resistance after provocation test)		Pauluhn et al. 1987	No increase in lung resistance in the absence of provocation test
Neurological								
5	Rat (Sprague-Dawley)	4 hr			5.4 M (50% inhibition of RBC cholinesterase)	50 M (tremors in 8/34 rats)	NIOSH 1974	
6	Dog (Beagle)	4 hr			0.015 M (56% Inhibition RBC cholinesterase)	3.4 M (62% inhibition RBC cholinesterase)	NIOSH 1974	No apparent clinical signs.

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Table 3-1 Levels of Significant Exposure to Parathion - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Systemic								
7	Rat (Sprague-Dawley)	6 wk 5 d/wk 7 hr/d	Hemato	0.74 M			NIOSH 1974	Hematology NOAEL is for hematocrit on week 6.
			Bd Wt	0.74 M				
8	Dog (Beagle)	6 wk 5 d/wk 7 hr/d	Bd Wt	0.2 M			NIOSH 1974	
Neurological								
9	Rat (Sprague-Dawley)	6 wk 5 d/wk 7 hr/d		0.01[b] M	0.1 M (35-40% decrease RBC cholinesterase during exposure)	0.74 M (85% decrease RBC cholinesterase on week 5)	NIOSH 1974	
10	Dog (Beagle)	6 wk 5 d/wk 7 hr/d		0.01 M	0.2 M (59% reduced RBC cholinesterase on week 6)		NIOSH 1974	

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

b Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.00002 mg/m3 for parathion; the MRL was derived by dividing the duration-adjusted NOAEL by an uncertainty factor of 100 (10 for animal-to-human extrapolation and 10 for human variability).

Bd Wt = body weight; d = day; F = female; Gastro = gastrointestinal; Hemato = hematological;hr = hour; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; RBC = red blood cell; Resp = respiratory; wk = week

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

Acute (≤14 days)

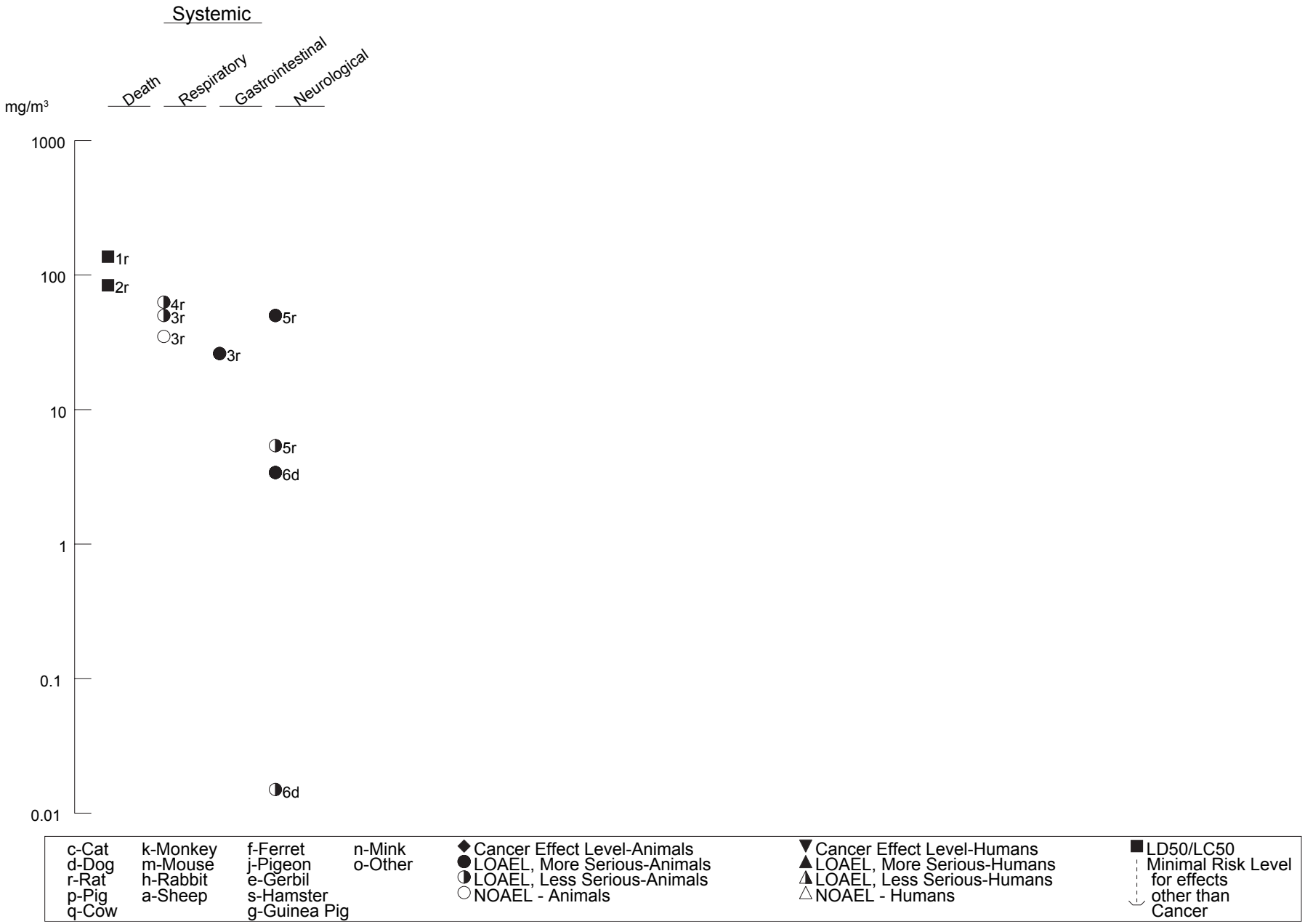

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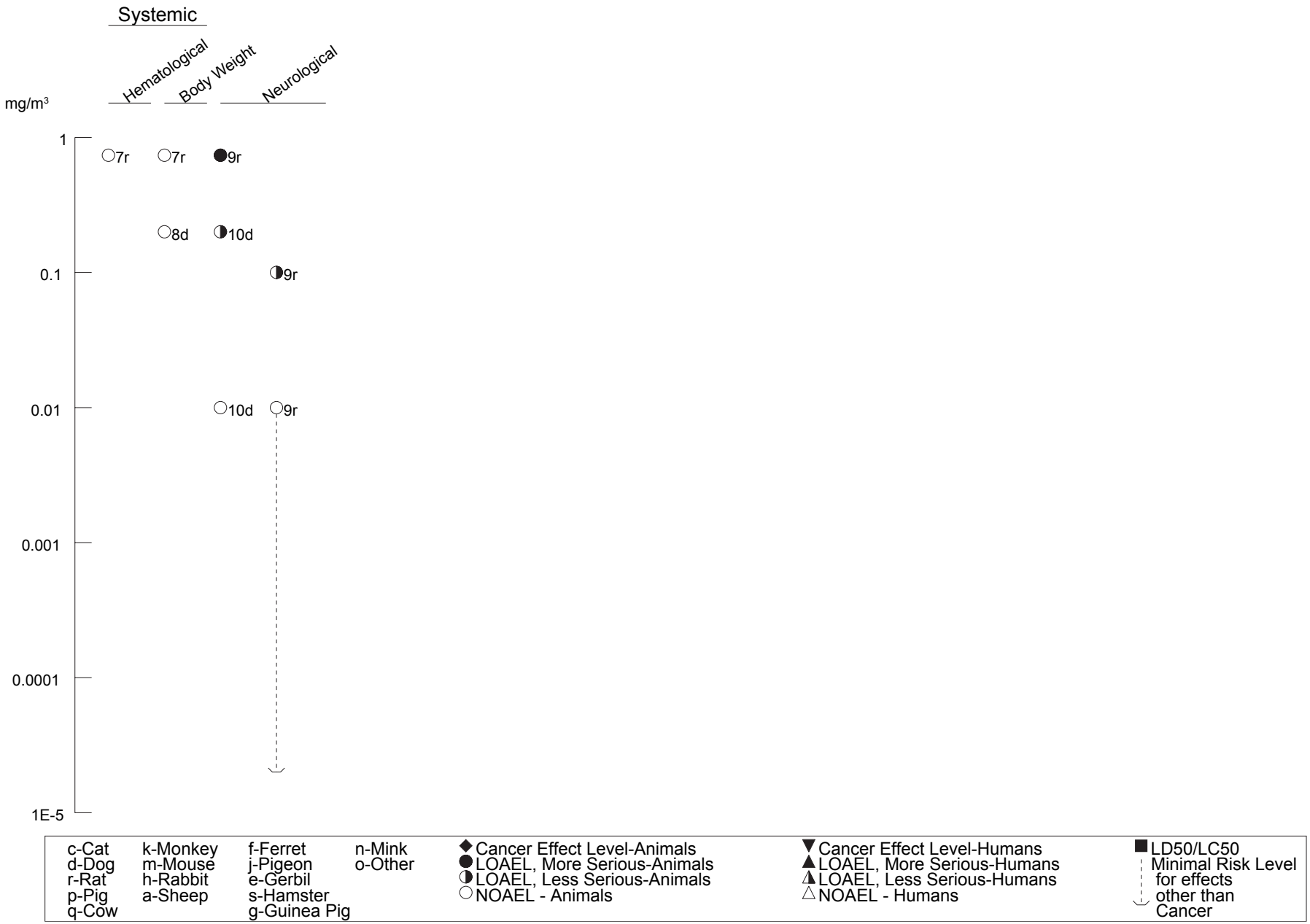
Figure 3-1 Levels of Significant Exposure to Parathion - Inhalation *(Continued)*

Intermediate (15-364 days)



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Respiratory Effects. Male Sprague-Dawley rats exposed to 50 mg/m^3 parathion aerosol for 4 hours showed respiratory difficulties; no such effect was observed at 35 mg/m^3 (NIOSH 1974). A study that examined the effects of technical-grade parathion on lung function in male Wistar rats reported that nose-only exposure to 63 mg/m^3 (the only concentration tested) aerosolized parathion did not affect basal lung resistance (Pauluhn et al. 1987). However, airway resistance was increased after a provocation test with acetylcholine.

Cardiovascular Effects. No explicit information regarding cardiovascular effects in animals was located in the limited number of inhalation studies available, most likely because cardiovascular end points were not monitored. Toxic doses of parathion high enough to induce a cholinergic crisis typically also affect heart rate and blood pressure, usually inducing hypertension.

Gastrointestinal Effects. Diarrhea was reported in 15 out of 34 male Sprague-Dawley rats exposed to 26.1 mg/m^3, the lowest concentration tested, technical parathion aerosol for 4 hours (NIOSH 1974). Gastrointestinal symptoms, such as nausea, abdominal pain and cramps, are commonly reported by humans after high exposure to parathion.

Hematological Effects. The only relevant information in the inhalation studies in animals available is that hematocrit was not altered in male Sprague-Dawley rats after exposure to 0.74 mg/m^3 (the highest concentration tested) technical parathion aerosol 7 hours/day, 5 days/week for 6 weeks (NIOSH 1974).

Musculoskeletal Effects. The available inhalation studies in animals do not provide any information regarding musculoskeletal effects following exposure to parathion. Muscle fasciculation tremors that occur following high exposure to parathion are of neurological origin and are discussed below in Section 3.2.1.4.

Body Weight Effects. Body weight was not affected in male Sprague-Dawley rats or male beagle dogs exposed to concentrations of 0.74 and 0.2 mg/m^3, respectively, of technical parathion aerosol (the highest concentrations tested) 7 hours/day, 5 days/week for 6 weeks (NIOSH 1974).

3.2.1.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological and lymphoreticular effects in humans or animals following inhalation exposure to parathion.

3.2.1.4 Neurological Effects

Limited information regarding neurological effects in humans comes from two studies that assessed changes in red blood cell cholinesterase in subjects during exposure to parathion. The first study assessed the activity of plasma and red blood cell cholinesterase among workers at an industrial plant that manufactured concentrated parathion as well as dusts containing various concentrations of parathion (Brown and Bush 1950). Parathion was measured in air at different operations. The maximum concentration determined was 0.8 mg/m^3 and the estimated average was about 0.2 or 0.3 mg/m^3. The cohort consisted of 13 workers; only 1 worker was an unexposed person. No further data were provided regarding the study group. Due to the rotation of personnel, the 12 exposed subjects had only intermittent contact with parathion-contaminated air until July 1949, when production ceased. Therefore, the investigators noted that it was impossible to determine exactly what the total exposure had been. Analyses of blood from five subjects who provided successive blood samples over a 6-month period showed a decrease in plasma cholinesterase activity. However, the changes in red blood cell cholinesterase activity were less conclusive. The investigators noted that probably the most significant finding was the fact that measurements of cholinesterase activities conducted 5 months after the plant had stopped manufacturing parathion showed a marked increase in activities in almost all cases.

In the second study, two volunteers were exposed to various formulations of heated parathion dust or liquid technical parathion for periods of 30 minutes (Hartwell et al. 1964). The concentrations of parathion to which the subjects were exposed were not determined. Exposure to dusts heated to 82°F (~28°C) did not immediately reduced red blood cell cholinesterase activity, but it did so (15–20%) 7 hours after exposure began; levels returned to pre-exposure levels after 20 hours. Exposure to dust heated to 120°F (~49°C) reduced red blood cell cholinesterase activity (19%) in one subject immediately after exposure. A second exposure 24 hours later reduced the enzyme activity to 78% of pre-exposure levels. Exposure of one subject to vaporized technical parathion at 105°F (~41°C) had no significant effect on red blood cell cholinesterase; however, when the subject was exposed to the chemical at 120°F (~49°C) for 3 consecutive days, only the second exposure reduced the enzyme activity (29%) following exposure, and pre-exposure levels were achieved 20 hours later. No *p*-nitrophenol was detected in the urine after exposures at 82°F (~28°C), and only small amounts were detected at the higher temperatures.

Typical cholinergic signs were observed in acute toxicity studies with parathion in rats. Exposure of male Sprague-Dawley rats for 4 hours induced tremors and convulsions and eventually death (NIOSH 1974). The ED_{50} for red blood cell cholinesterase (exposure concentration that caused 50% inhibition) was 5.4 mg/m^3. The ED_{50} for tremors and convulsions were 73.7 and 110.6 mg/m^3, respectively. Exposure of groups of four male beagle dogs for 4 hours to up to 37.1 mg/m^3 parathion aerosol did not induce acute cholinergic signs; however, the lowest concentration tested, 0.015 mg/m^3, reduced red blood cell cholinesterase activity by 56% 48 hours after exposure, while 3.4 mg/m^3 inhibited the enzyme by 62% (NIOSH 1974).

In an intermediate-duration study, male Sprague-Dawley rats were exposed to 0.01, 0.1, or 0.74 mg/m^3 parathion aerosol 7 hours/day, 5 days/week for 6 weeks (NIOSH 1974). No clinical signs were seen in rats in the low- or mid-concentration groups. Some rats in the high-concentration group showed signs of parathion toxicity, but quantitative information was not available. The maximum decrease in red blood cell cholinesterase in the low-concentration group was approximately 30% and occurred on weeks 4 and 5. In the mid-concentration group, the maximum decrease in red blood cell cholinesterase was 43% and occurred on week 1. During the rest of the exposure period, red blood cell cholinesterase activity was 60–70% of pretest levels. In the high-concentration group, red blood cell cholinesterase activity was decreased 85% on week 5. In general, activities recovered during a 6-week post-dosing period. Groups of male beagle dogs were exposed in a similar manner to 0.001, 0.01, or 0.2 mg/m^3 parathion aerosol (NIOSH 1974). No information was provided regarding clinical signs in the dogs. No significant effects on levels of red blood cell cholinesterase were observed at the low exposure level. Exposure to 0.01 mg/m^3 parathion reduced red blood cell cholinesterase by 21% by the end of the second week of exposure. Red blood cell levels recovered and were <20% reduced the rest of the study. Exposure to 0.2 mg/m^3 parathion reduced red blood cell cholinesterase by 59% by the end of week 6 of exposure. Data regarding red blood cell AChE inhibition in rats were used to derive an intermediate-duration inhalation MRL for parathion.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-1 and Figure 3-1.

No information was located regarding the following effects after inhalation exposure to parathion:

3.2.1.5 Reproductive Effects
3.2.1.6 Developmental Effects
3.2.1.7 Cancer

3.2.2 Oral Exposure

3.2.2.1 Death

Severe parathion poisoning can lead to death if not treated. Severe poisoning is generally characterized by unconsciousness, marked miosis and loss of pupillary reflex to light, muscle fasciculations, flaccid paralysis, secretions from the mouth and nose, moist rales in the lungs, respiratory difficulty and cyanosis, and serum cholinesterase levels <10% of normal value (Namba et al. 1971). If untreated patients poisoned with parathion are alive 24 hours after the onset, they usually recover (Namba et al. 1971). Death generally occurs due to respiratory failure attributed to excessive tracheobronchial and salivary secretions, nicotinic paralysis of the diaphragm and respiratory muscles and depression of central nervous system respiratory centers (Abou-Donia 1995).

There are numerous reports of deaths involving adults and children following ingestion of either a commercial parathion formulation or food prepared with contaminated components such as contaminated flour. Selected studies that reported multiple deaths are briefly summarized below; additional references can be found in those reports and in review articles (i.e., Gallo and Lawryk 1991).

Wishahi et al. (1958) reported that 8 out of 22 children who consumed parathion contaminated food in Egypt died. All fatal cases fell rapidly into a coma and died from respiratory failure 4–9 hours after the onset of symptoms. In a similar case of consumption of contaminated food, 17 out of 79 people died in Jamaica (Diggory et al. 1977). Deaths occurred within 6 hours of poisoning as a result of respiratory arrest. Postmortem examinations conducted in two cases showed pulmonary edema with intra-alveolar hemorrhage; no other significant gross findings were noted. In yet another report of ingestion of contaminated food, 14 out of 49 people exposed died in Sierra Leone (Etzel et al. 1987). Eitzman and Wolfson (1967) reported that 30 children died in the state of Florida from 1945 through 1964 due to exposure to parathion; 16 of the deaths resulted from ingestion of the pesticide. Six children ingested the parathion from improper containers such as a soft drink bottle. Another group of six children obtained the parathion from the floor or windowsill where it had been placed to kill roaches. The majority of the children were dead on arrival to the emergency room and the remainder died within 3 hours. Estimates of

lethal doses range from about 2 to 13 mg/kg in adults (assuming 70 kg body weight) and from 0.1 to 1.3 mg/kg in children (Gallo and Lawryk 1991). However, Gallo and Lawryk (1991) also indicate that there have been reports of patients who survived after ingesting 20,000–40,000 mg parathion and that prompt treatment with oximes can save some patients who have ingested as much as 50,000 mg parathion. In addition to potentially unreliable estimates, whether or not proper treatment was implemented after poisoning and how fast this was done probably impacted the outcome and contributed to the wide range of lethal doses reported for parathion in humans.

Several studies provide information regarding death in animals following oral exposure to parathion. Oral LD_{50} values of 14 and 7.9 mg/kg were reported in male and female Sprague-Dawley rats, respectively (EPA 1978). In another study with technical parathion in Sprague-Dawley rats, the 24-hour LD_{50} in males was 6.8 mg/kg, no deaths occurred at 4 mg/kg, and all rats in the group (n=10) dosed with 10 mg/kg died within 2 hours (NIOSH 1974). Gaines (1960) reported oral LD_{50} values of 13 and 3.6 mg/kg in male and female Sherman rats, respectively. To determine whether LD_{50} values underwent seasonal variations, Gaines and Linder (1986) conducted bimonthly determinations in male and female Sherman rats over a period of 1 year. The LD_{50} values ranged from 6.9 to 11.0 mg/kg in males and from 3.0 to 3.4 mg/kg in females, suggesting that LD_{50} values were little affected by the time of the year that the tests were conducted. Pasquet et al. (1976) reported 10-day LD_{50} values of 16 and 6 mg/kg for technical parathion in male and female CD rats, respectively. The results of these studies also suggested that female rats are more sensitive to the acute effects of parathion than male rats. Signs of poisoning reported in some of these studies included muscle fasciculation, excessive salivation, lacrimation, tremors, diarrhea, and involuntary urination. In a developmental study, administration of 1 mg parathion/kg/day to a group of 25 pregnant Wistar rats on gestation days 6 through 15 resulted in 13 deaths; no deaths occurred with 0.3 mg parathion/kg/day (Renhof 1984). The exact time of death was not indicated, but it was before the study termination on gestation day 20 (Renhof 1984). Deaths were attributed to respiratory and circulatory failure.

In a 6-week dietary study with technical parathion in Osborne-Mendel rats, two out of five males dosed approximately 14 mg parathion/kg/day died within 2 weeks and two out of five females dosed with approximately 7.6 mg parathion/kg/day died during the first week of the study (NCI 1979). No males dosed with 7 mg/kg/day or females dosed with 3.8 mg/kg/day died during the study.

In an intermediate-duration study in albino rats, feeding the animals a diet that provided approximately 5.3 mg parathion/kg/day (76.8% active ingredient) 6 days/week resulted in 24 out of 72 rats dying within

3 weeks of starting the experiment; the exact times of death were not specified (Barnes and Denz 1951). The 5.3 mg/kg/day dose was the lowest dose tested. In a group dosed with approximately 7.9 mg/kg/day, 59 out of 72 rats died within 27 days in the study. In a group dosed with approximately 10.5 mg/kg/day group, 65 out of 72 rats died in the first 19 days of the study.

A 36% mortality rate was reported among male C57BL/6N mice 2 days after receiving a single gavage dose of 16 mg technical parathion/kg (Casale et al. 1983). Mild to severe signs of toxicity, including tremors, muscle fasciculation, and excessive salivation, began 1–2 hours after dosing and lasted for 4–7 hours. In a 6-week dietary study with $B6C3F_1$ mice, all five males dosed with approximately 58 mg technical parathion/kg/day and four of the five females dosed with approximately 62 mg parathion/kg/day died during the second week of the study (NCI 1979). Doses of approximately 29 and 31 mg/kg/day were not lethal to males or females, respectively.

In male beagle dogs (4/group), the 24-hour LD_{50} for technical parathion administered in a capsule was 8.27 mg/kg (NIOSH 1974). No deaths occurred at 2.5 mg/kg; all dogs administered doses of 20 mg/kg died.

Reliable oral LD_{50} values and lethal doses are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

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

Respiratory Effects. Commonly reported respiratory signs and symptoms occurring after oral exposure to parathion include excessive bronchial secretions, rhinorrhea, wheezing, edema, tightness of the chest, bronchospasms, bronchoconstriction, cough, and dyspnea. In cases of fatal intoxication in children described by Wishahi et al. (1958), hyperpnea was the earliest manifestation of respiratory failure, which in turn was the direct cause of death. Shallow respiration and pulmonary edema were reported in similar cases described by Eitzman and Wolfson (1967). Among 246 cases of acute parathion poisoning reported by Tsachalinas et al. (1971), 92 had increased bronchial secretions and 33 developed lung edema. Among 79 cases of intoxication due to ingestion of contaminated food in Jamaica, dyspnea was reported in the more severe cases (Diggory et al. 1977); deaths occurring in this study were due to respiratory arrest. Postmortem examination of 17 fatalities showed pulmonary edema and intra-alveolar

Table 3-2 Levels of Significant Exposure to Parathion - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (G)				14 M (LD50) 7.9 F (LD50)	EPA 1978	
2	Rat (Sherman)	once (GO)				13 M (LD50) 3.6 F (LD50)	Gaines 1960	
3	Rat (Sherman)	once (GO)				6.9 M (LD50) 3 F (LD50)	Gaines and Linder 1986	
4	Rat (Osborne-Mendel)	1 wk ad libitum (F)				14 M (2/5 deaths on week 2) 7.6 F (2/5 deaths on week 1)	NCI 1979	
5	Rat (Sprague-Dawley)	once (GO)				6.83 M (24-hour LD50)	NIOSH 1974	
6	Rat (CD)	once (G)				16 M (10-day LD50) 6 F (10-day LD50)	Pasquet et al. 1976	
7	Rat (Wistar)	10 d Gd 6-15 1 x/d (GW)				1 F (13/25 deaths)	Renhof 1984	
8	Mouse (C57BL/6N)	once (GO)				16 M (36% mortality rate)	Casale et al. 1983	

Table 3-2 Levels of Significant Exposure to Parathion - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
9	Mouse (C57BL/6N)	once				16 M (20% lethality)	Casale et al. 1984	
10	Mouse (B6C3F1)	2 wk ad libitum (F)				58 M (5/5 deaths on week 2) 62 F (4/5 deaths on week 2)	NCI 1979	
11	Dog (Beagle)	once (C)				8.27 M (24-hour LD50)	NIOSH 1974	
Systemic								
12	Rat (Long- Evans)	once (GO)	Bd Wt	4 M		7 M (9.7% body weight loss)	Moser 1995	
13	Rat (Wistar)	10 d Gd 6-15 1 x/d (GW)	Bd Wt	0.3 F		1 F (56% reduced weight gain during treatment)	Renhof 1984	1 mg/kg/day also caused lethality.
14	Mouse (BALB/c)	once (GO)	Hepatic	16 F			Kim et al. 2005	Hepatic NOAEL is for serum AST and ALT activities.
			Bd Wt	16 F				
15	Mouse (Swiss-Webster)	5 d 1 x/d (GO)	Bd Wt	5.3 M			Thomas and Schein 1974	

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Table 3-2 Levels of Significant Exposure to Parathion - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
16	Mouse (BALB/c)	8 d 1x/d (GO)	Bd Wt			2.2 F (20% reduction in body weight)	Wiltrout et al. 1978	
Immuno/ Lymphoret								
17	Mouse (C57BL/6N)	once (GO)			16 M (suppressed IgM PFC response)		Casale et al. 1983	Dose also caused lethality.
18	Mouse (C57BL/6N)	once		4 M	16 M (suppressed IgM response to SRBC)		Casale et al. 1984	The high dose also caused lethality.
19	Mouse CBA/J	5 d 1 x/d (GO)			0.4 F (increased response to allergens)		Fukuyama et al. 2010	
20	Mouse (BALB/c)	5 d 1 x/d (GO)			0.15 F (increased sensitivity to allergens)		Fukuyama et al. 2011	
21	Mouse C3H/HeN	5 d 1 x/d (GO)		0.15 F	1.5 F (decreased SRBC-specific IgM response in blood)		Fukuyama et al. 2012	
22	Mouse (BALB/c)	once (GO)		4 F	16 F (suppressed antibody response to SRBC)		Kim et al. 2005	

Table 3-2 Levels of Significant Exposure to Parathion - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
23	Mouse (BALB/c)	8 d 1x/d (GO)			2.2 F (suppressed humoral immune response)		Wiltrout et al. 1978	A 20% loss in body weight occurred at 2.2 mg/kg/day
Neurological								
24	Human NA	5 d 1 x/d (F)		0.028			Morgan et al. 1977	NOAEL is for clinical signs and RBC cholinesterase activity.
25	Monkey (Cynomolgus)	once (GO)			2 (50% depression of RBC cholinesterase)		Elkner et al. 1991	
26	Monkey (Rhesus)	once		0.5 M	1 M (abolished performance of a learned task)		Reiter et al. 1975	
27	Rat (Long- Evans)	once (GO)		4 M	7 M (altered neurological functions)		Moser 1995	
28	Rat (Sprague-Dawley)	once (GO)		4 M		5 M (tremors in 10/10)	NIOSH 1974	
29	Rat (Sprague-Dawley)	once (GO)		0.35 M	0.7 M (27.4% inhibition of RBC cholinesterase)	5.6 M (69.7% inhibition of RBC cholinesterase)	NIOSH 1974	

Table 3-2 Levels of Significant Exposure to Parathion - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
30	Rat (Sprague-Dawley)	once (GO)			2.8 M (56% inhibiton RBC cholinesterase 4 hours after dosing)		NIOSH 1974	
31	Rat (CD)	once (G)			1.1 F (50% inhibition of RBC cholinesterase)		Pasquet et al. 1976	Percent inhibition 24 hours after dosing.
32	Rat (Wistar)	10 d Gd 6-15 1 x/d (GW)		0.3 F		1 F (tremors in 8/25 rats)	Renhof 1984	1 mg/kg/day also caused lethality.
33	Mouse (C57BL/6N)	once (GO)				16 M (tremors, fasciculations)	Casale et al. 1983	Dose also caused lethality.
34	Mouse (Swiss-Webster)	once (G)			6 M (impaired learning of a passive avoidance task)		Reiter et al. 1973	
35	Dog (Beagle)	once (C)		2.5 M		6.3 M (tremors, ataxia, convulsions)	NIOSH 1974	
36	Dog (Beagle)	once (C)			0.5 M (29% inhibition of RBC cholinesterase)	2.5 M (64% inhibition of RBC cholinesterase)	NIOSH 1974	

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Table 3-2 Levels of Significant Exposure to Parathion - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
37	Dog (Beagle)	once (C)				2.5 M (64% inhibition of RBC cholinesterase 24 hours after dosing)	NIOSH 1974	
Reproductive								
38	Mouse (Swiss-Webster)	5 d 1 x/d (GO)		5.3 M			Thomas and Schein 1974	NOAEL is for testis and prostate weight and metabolism of testosterone.
Developmental								
39	Rat (Wistar)	10 d Gd 6-15 1 x/d (GW)		1 F			Renhof 1984	NOAEL is for standard developmental parameters.
40	Rabbit (Himalayan)	13 d Gd 6-18 1 x/d (GW)		0.3 F			Renhof 1985	NOAEL is for standard developmental parameters.
INTERMEDIATE EXPOSURE								
Death								
41	Rat (albino)	3 wk 6 d/wk (F)				5.3 (24/72 deaths within 3 weeks)	Barnes and Denz 1951	
Systemic								
42	Rat (NS)	90 d 1 x/d (GO)	Hepatic		2.6 M (mild liver histopathology)		Dikshith et al. 1978	
			Renal	2.6 M				

Table 3-2 Levels of Significant Exposure to Parathion - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
43	Rat (Wistar)	4-15 wk ad libitum (F)	Bd Wt	0.55 F			Ivens et al. 1998	
44	Rat (Osborne-Mendel)	6 wk ad libitum (F)	Bd Wt	3.8 F		7.6 F (body weight reduced 24%)	NCI 1979	
45	Rat (Sprague-Dawley)	6 wk 5 d/wk (GO)	Bd Wt	0.25 M			NIOSH 1974	
46	Mouse (B6C3F1)	6 wk ad libitum (F)	Bd Wt		29 M (body weight reduced 14%)		NCI 1979	
47	Dog (Beagle)	60 d 1 x/d (C)	Bd Wt	0.794			Atkinson et al. 1994	
48	Dog (Beagle)	6 wk 5 d/wk (C)	Bd Wt	0.5 M			NIOSH 1974	
Neurological								
49	Human (NA)	25-70 d 5 d/wk (NS)		0.1 F			Edson 1964	NOAEL is for RBC cholinesterase activity.

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Table 3-2 Levels of Significant Exposure to Parathion - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
50	Human (NA)	30 d 1 x/d (C)		0.09[b] M	0.11 M (22 and 37% reduced RBC cholinesterase in 2/5 subjects)		Rider et al. 1969	
51	Monkey Squirrel	148 d 1 x/d (C)			0.1 M (increased variability in hearing thresholds)		Reishchl et al. 1975	
52	Rat (albino)	3 wk 6 d/wk (F)				5.3 (fasciculations, tremors)	Barnes and Denz 1951	Dose also caused lethality.
53	Rat (NS)	90 d 1 x/d (GO)			2.6 M (50% reduced brain cholinesterase)		Dikshith et al. 1978	
54	Rat (Wistar)	4-15 wk ad libitum (F)		0.024 M	0.1 M (36-39% reduced RBC cholinesterase)	0.4 M (>80% reduced RBC cholinesterase)	Ivens et al. 1998	
55	Rat (Osborne-Mendel)	364 d ad libitum (F)				3.5 F (generalized body tremors)	NCI 1979	
56	Rat (Sprague-Dawley)	6 wk 5 d/wk (GO)		0.05 M	0.1 M (22% inhibition of RBC cholinesterase on week 4)		NIOSH 1974	

Table 3-2 Levels of Significant Exposure to Parathion - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
57	Dog (Beagle)	60 d 1 x/d (C)		0.794			Atkinson et al. 1994	NOAEL is for ocular function.
58	Dog Mixed breed	24 weeks ad libitum (F)		0.021	0.047 (25% reduced RBC cholinesterase)		Frawley and Fuyat 1957	
59	Dog (Beagle)	6 wk 5 d/wk (C)		0.1 M	0.5 M (25-58% inhibition of RBC cholinesterase)		NIOSH 1974	
Reproductive								
60	Rat (NS)	90 d 1 x/d (GO)			2.6 M (tubular atrophy in testes)		Dikshith et al. 1978	
Developmental								
61	Rat (CD)	34 d Gd 2-21 Ld 1-15 (GO)			0.01 (altered EKG in pups)		Deskin et al. 1979	

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Table 3-2 Levels of Significant Exposure to Parathion - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
62	Rat (albino)	365 d 6 d/wk (F)	Resp	1.7			Barnes and Denz 1951	NOAELs are for organs histopathology.
			Cardio	1.7				
			Gastro	1.7				
			Hepatic	1.7				
			Renal	1.7				
			Endocr	1.7				
			Bd Wt	1.7				
			Other	1.7				
63	Rat (Osborne-Mendel)	80 wk ad libitum (F)	Resp	4.4 M			NCI 1979	NOAELs are for organ histopathology. Hematological NOAEL is for bone marrow.
			Cardio	4.4 M				
			Gastro	4.4 M				
			Hemato	4.4 M				
			Musc/skel	4.4 M				
			Hepatic	4.4 M				
			Renal	4.4 M				
			Endocr	4.4 M				
			Dermal	4.4 M				

Table 3-2 Levels of Significant Exposure to Parathion - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
64	Mouse (B6C3F1)	62-80 wk ad libitum (F)	Resp	27.6			NCI 1979	NOAELs are for organ histopathology. Hematology NOAEL is for bone marrow.
			Cardio	27.6				
			Hemato	27.6				
			Musc/skel	27.6				
			Hepatic	27.6				
			Renal	27.6				
			Endocr	27.6				
Immuno/ Lymphoret								
65	Rat (albino)	365 d 6 d/wk (F)		1.7			Barnes and Denz 1951	NOAEL is for histopathology of lymphoreticular organs.
66	Rat (Osborne-Mendel)	80 wk ad libitum (F)		4.4 M			NCI 1979	NOAEL is for histopathology of the spleen and lymph nodes.
67	Mouse (B6C3F1)	62-80 wk ad libitum (F)		27.6			NCI 1979	NOAEL is for histopathology of the spleen and lymph nodes.

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Table 3-2 Levels of Significant Exposure to Parathion - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
68	Rat (albino)	365 d 6 d/wk (F)		1.7			Barnes and Denz 1951	NOAEL is for clinical signs and brain histopathology.
Reproductive								
69	Rat (albino)	365 d 6 d/wk (F)		1.7			Barnes and Denz 1951	NOAEL is for histopathology of ovaries and testis.
70	Rat (Osborne-Mendel)	80 wk ad libitum (F)		4.4 M 3.5 F			NCI 1979	NOAEL is for histopathology of the sex organs.
71	Mouse (B6C3F1)	62-80 wk ad libitum (F)		27.6			NCI 1979	NOAEL is for histopathology of the sex organs.
Cancer								
72	Rat (Osborne-Mendel)	80 wk ad libitum (F)				2.2 M (CEL:adrenal cortical adenoma or carcinoma)	NCI 1979	Comparison is between low-dose group and pooled controls.

a The number corresponds to entries in Figure 3-2.

b Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.009 mg/kg/day for parathion; the MRL was derived by dividing the NOAEL by an uncertainty factor of 10 (for human variability).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; Hemato = hematological; IgM = immunoglobulin M; Immuno/Lymphoret = immunological/lymphoreticular; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NA = not applicable; NOAEL = no-observed-adverse-effect level; NS = not specified; PFC = plaque-forming cells; RBC = red blood cell; Resp = respiratory; SRBC = sheep red blood cell; x = time(s); wk = week(s)

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

Acute (≤14 days)

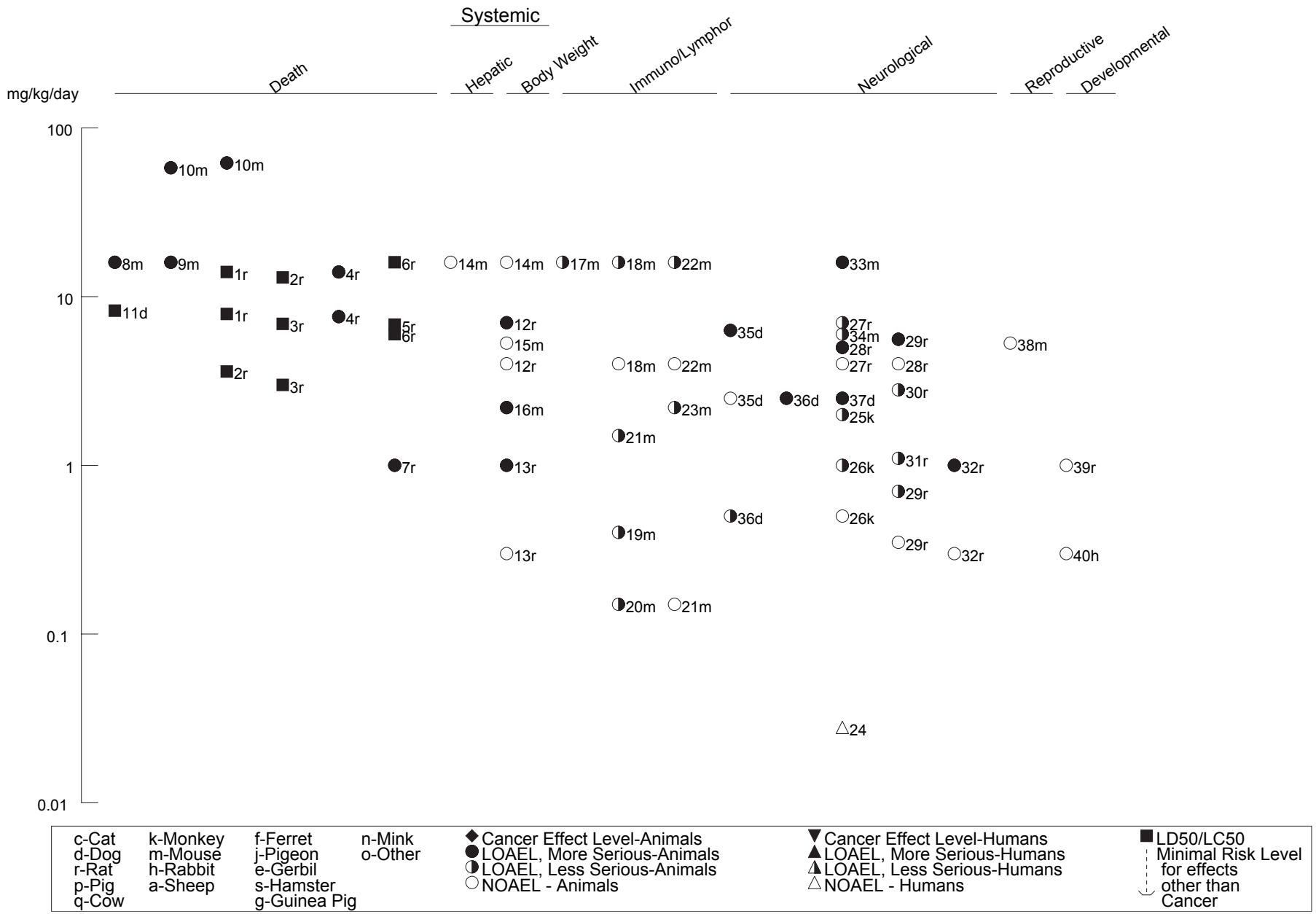

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Figure 3-2 Levels of Significant Exposure to Parathion - Oral *(Continued)*

Intermediate (15-364 days)

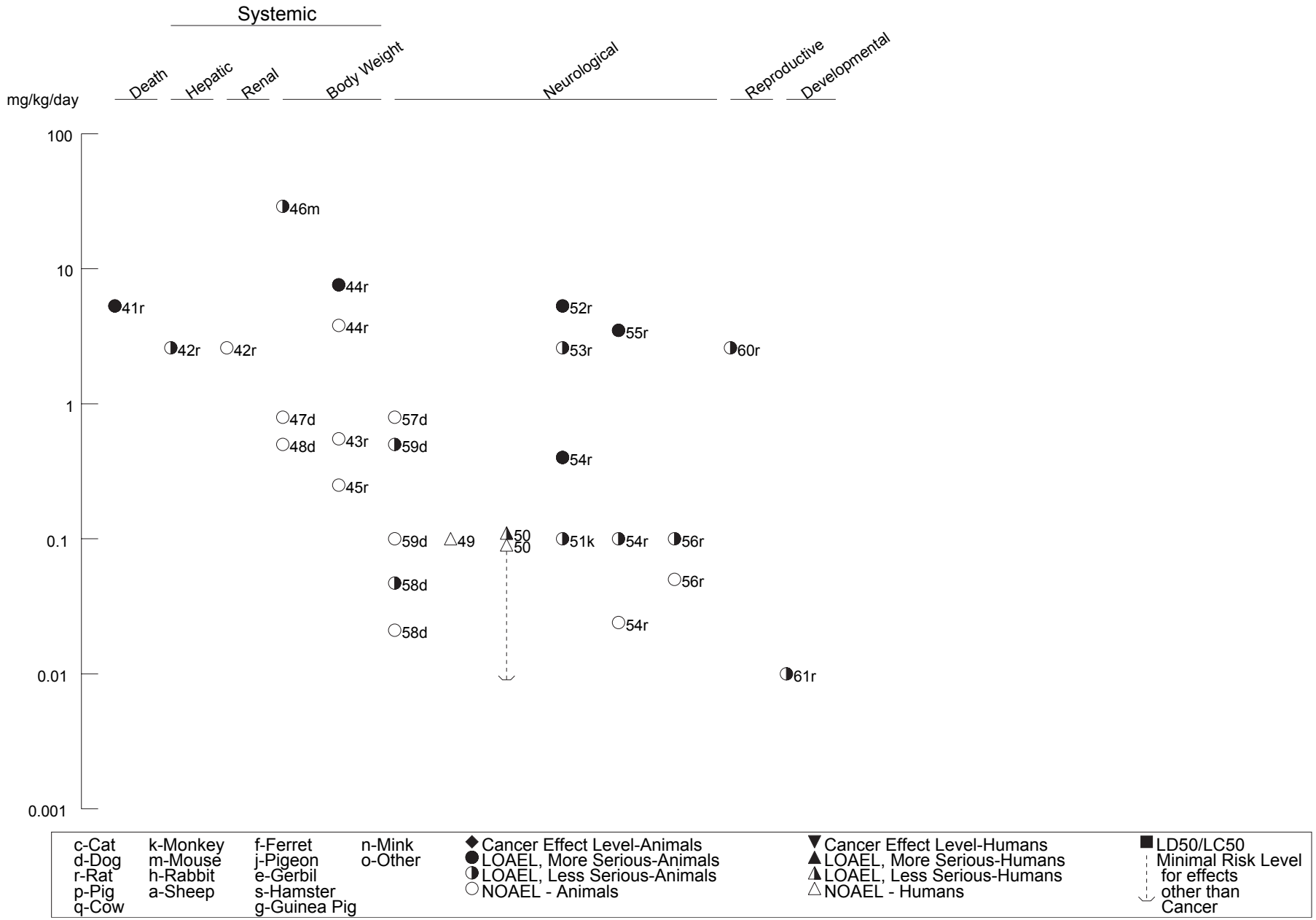

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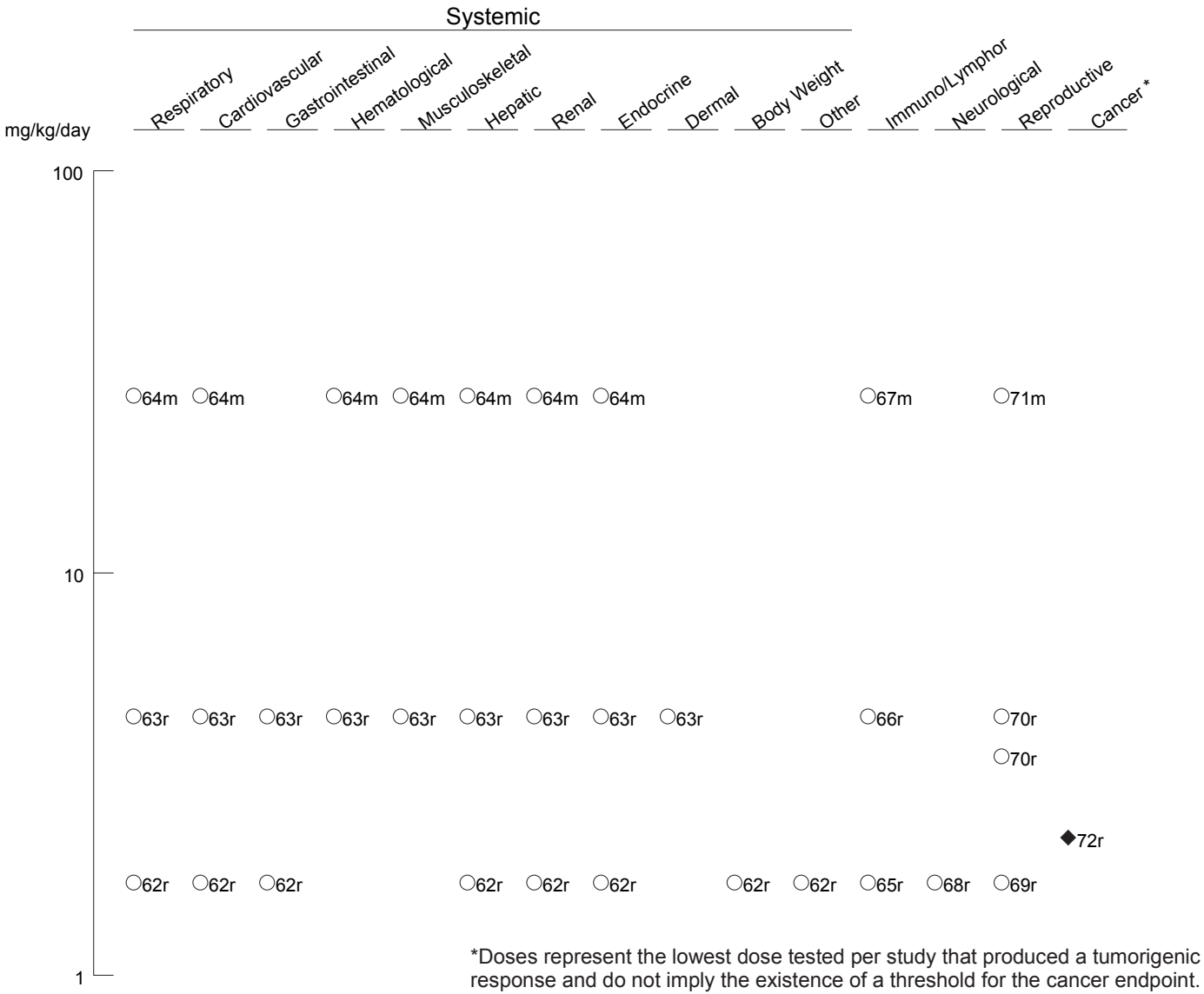
Figure 3-2 Levels of Significant Exposure to Parathion - Oral *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat d-Dog r-Rat p-Pig q-Cow	k-Monkey m-Mouse h-Rabbit a-Sheep	f-Ferret j-Pigeon e-Gerbil s-Hamster g-Guinea Pig	n-Mink o-Other	◆ Cancer Effect Level-Animals ● LOAEL, More Serious-Animals ◑ LOAEL, Less Serious-Animals ○ NOAEL - Animals	▼ Cancer Effect Level-Humans ▲ LOAEL, More Serious-Humans ◭ LOAEL, Less Serious-Humans △ NOAEL - Humans	■ LD50/LC50 Minimal Risk Level for effects other than Cancer

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hemorrhage in two of them. Edema of the lungs and bronchospasms were reported in a study of 68 cases of acute poisoning in China (He et al. 1998). Similar findings were reported in multiple cases of intoxication due to consumption of contaminated food in Sierra Leone (Etzel et al. 1987).

Chronic exposure of rats to up to 4.4 mg parathion/kg/day or of mice to up to 27.6 mg parathion/kg/day did not result in gross or microscopic alterations in the respiratory tract (Barnes and Denz 1951; NCI 1979).

Cardiovascular Effects. Inhibition of AChE can result in overstimulation of muscarinic and nicotinic receptors, both of which play a role in the control of blood pressure and heart rate. Therefore, individuals acutely poisoned with parathion can present with tachycardia or bradycardia and hypertension or hypotension. Six of eight fatal cases of children described by Wishahi et al. (1958) developed shock and two of them developed hypertension; hypertension was also reported in cases that survived. One of the cases studied by Lankisch et al. (1990) developed high blood pressure and tachycardia 1 week after ingesting parathion; the other case was in shock (no blood pressure measurable) on admission to the emergency room. Hypotension and bradycardia were seen among the children who died as described by Eitzman and Wolfson (1967). Bradycardia and hypertension were prevalent in a study of 246 acute poisonings in Greece (Tsachalinas et al. 1971). Among 79 cases of acute poisoning via contaminated food studied by Diggory et al. (1977), bradycardia was reported in the most severe cases. Circulatory insufficiency and bradycardia were seen in four out of six cases of acute poisoning studied by Eyer et al. (2003). Bradycardia was also reported in other single cases of poisoning (i.e., De Jager et al. 1981; Nisse et al. 1998).

Chronic exposure of rats to up to 4.4 mg parathion/kg/day or of mice to up to 27.6 mg parathion/kg/day did not result in gross or microscopic alterations in the heart (Barnes and Denz 1951; NCI 1979).

Gastrointestinal Effects. Nausea, vomiting, abdominal tightness, swelling and cramps, diarrhea, tenesmus, and fecal incontinence are typical signs and symptoms of acute intoxication with organophosphorus pesticides. Nausea, vomiting, and cramps have been reported in numerous studies of multiple and single cases of poisoning that included children and adults (i.e., Diggory et al. 1977; Eitzman and Wolfson 1967; Etzel et al. 1987; He et al. 1998; Hoffman and Papendorf 2006; Tsachalinas et al. 1971; Wishahi et al. 1958). Severe poisoning can rapidly induce loss of consciousness; therefore, information regarding gastrointestinal effects in these cases may not be available. In addition, some

reports only state that the victim suffered a cholinergic crisis without detailing specific signs and symptoms.

Diarrhea has been reported in animals in studies of acute toxicity of parathion. Diarrhea is neurological in origin and results from stimulation of parasympathetic autonomic post-ganglionic fiber innervating smooth gastrointestinal musculature. Chronic exposure of rats to up to 4.4 mg parathion/kg/day or of mice to up to 27.6 mg parathion/kg/day did not result in gross or microscopic alterations in the gastrointestinal tract (Barnes and Denz 1951; NCI 1979).

Hematological Effects. Very few reports of humans exposed orally to parathion provide information regarding hematological effects following oral exposure to parathion. In most cases, it is unknown whether hematological tests were conducted following poisoning with parathion or, if conducted, the results were unremarkable and were not discussed in the report. Leukocytosis was reported in one of the six cases described by Eyer et al. (2003), in a case described by Nisse et al. (1998), and in two cases described by Lankisch et al. (1990). Leukocytosis may occur secondary to increased catecholamine release from the adrenal medulla triggered by acetylcholine released by preganglionic fibers (Osmundson 1998). Effects on red blood cell cholinesterase are discussed in Section 3.2.4, Neurological Effects.

No information was located in the studies available regarding hematological effects in animals following oral exposure to parathion, except for lack of alterations in bone marrow from rats exposed to up to 4.4 mg parathion/kg/day and mice exposed to up to 27.6 mg parathion/kg/day in chronic-duration studies (Barnes and Denz 1951; NCI 1979).

Musculoskeletal Effects. Acute intoxication with parathion results in tremors, muscle fasciculations, and convulsions. These are signs of hyperstimulation of both nicotinic and muscarinic receptors in the central nervous system and of nicotinic receptors at the neuromuscular junction. Denervation potentials were recorded in the anterior tibial and gastrocnemius muscles and in the small hand muscles from a subject who developed polyneuropathy (see Section 3.2.2.4) after ingesting a large amount of parathion (De Jager et al. 1981). The subject had been in a coma for 7 weeks and the recordings were made 54 days after the poisoning. Denervation potentials were still seen in the anterior tibial muscles 1 year after poisoning. In another case of polyneuropathy, electromyography (EMG) of both anterior tibial muscles showed profuse fibrillations without voluntary motor unit potentials present several weeks after poisoning (Besser et al. 1993). Thenar EMG showed only few fasciculations with reduced recruitment. Microscopic examination of the quadriceps and deltoid muscles from a subject who

developed intermediate syndrome (see Section 3.2.2.4) after ingesting parathion showed small groups of atrophic fiber and mild fiber type grouping in the former (De Bleecker et al. 1992). Endplate staining for AChE and nonspecific esterase was absent in both muscles. Microscopic examination of the intercostal muscle 35 days after the poisoning showed a fair number of atrophic angulated fibers. Muscle potentials of reduced amplitude were reported in another study of cases that developed intermediate syndrome after ingestion of parathion (He et al. 1998).

Chronic-duration studies did not report gross or microscopic alterations in skeletal bone from rats exposed to up to 4.4 mg parathion/kg/day through the diet or in bone from mice similarly exposed to up to 27.6 mg parathion/kg/day (Barnes and Denz 1951; NCI 1979).

Hepatic Effects. No information was located regarding hepatic effects in humans following oral exposure to parathion. It is reasonable to assume that laboratory tests conducted in poisoned individuals may have included tests for liver function. Therefore, the lack of explicit information probably reflects the fact that liver function is usually not affected, except in the most severe cases in which death is due to multiorgan failure, as in, for example, cases described by Eyer et al. (2003).

Administration of a single dose of 16 mg parathion/kg, the highest dose tested, to Balb/c mice did not significantly alter alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or the liver content of reduced glutathione 4 days after dosing (Kim et al. 2005). However, these parameters were altered by parathion in mice pretreated with phenobarbital, indicating that metabolic activation plays a role in parathion-induced hepatotoxicity. In an intermediate-duration study, daily treatment of male rats by gavage with 2.6 mg parathion/kg/day (only dose level tested) for 90 days resulted in mild changes in the liver consisting of hepatocyte swelling, congestion of blood vessels of the portal triads, and mild proliferation of fibroblasts around the bile ducts (Dikshith et al. 1978). Chronic exposure of rats to up to 4.4 mg parathion/kg/day or of mice to up to 27.6 mg parathion/kg/day did not result in gross or microscopic alterations in the liver (Barnes and Denz 1951; NCI 1979).

Renal Effects. As with hepatic effects, renal failure seems to develop in severe cases of poisoning with parathion that ultimately result in death (i.e., Eyer et al. 2003).

Treatment of male rats by gavage with 2.6 mg parathion/kg/day, the only dose level tested, for 90 days did not induce microscopic alterations in the kidneys (Dikshith et al. 1978). Chronic exposure of rats to

up to 4.4 mg parathion/kg/day or of mice to up to 27.6 mg parathion/kg/day did not result in gross or microscopic alterations in the kidneys (Barnes and Denz 1951; NCI 1979).

Endocrine Effects. No information was located regarding endocrine effects in humans following oral exposure to parathion. However, effects such as tachycardia, hypertension, and hyperglycemia, which have been reported in some cases of acute poisoning with parathion, may have been due in part to stimulation of the adrenal medulla by pre-ganglionic autonomic fibers.

No information was located in the available literature regarding endocrine effects in animals following oral exposure to parathion.

Dermal Effects. No information was located regarding dermal effects in humans following oral exposure to parathion.

Chronic dietary exposure of Osborne-Mendel rats to up to 4.4 mg parathion/kg/day or B6C3F$_1$ mice to up to 27.6 mg parathion/kg/day did not induce microscopic alterations in the skin (NCI 1979). No further information was located in the available literature.

Ocular Effects. Miosis and loss of pupillary reflexes resulting from the excess acetylcholine on parasympathetic autonomic post-ganglionic nerve fibers are typically seen in individuals acutely poisoned with parathion (see Section 3.2.2.4, Neurological Effects).

No information was located regarding ocular effects in animals following oral exposure to parathion.

Body Weight Effects. Effects on body weight would not be expected in humans following acute intoxication with parathion.

Acute-, intermediate-, and chronic-duration studies provide information regarding body weight in animals following oral exposure to parathion. In general, information regarding food consumption was not provided. In male Long-Evans rats, a single gavage dose of 7 mg parathion/kg induced a 9.7% reduction in body weight in 24 hours; this dose also caused tremors and gait changes (Moser 1995). In Balb/c mice, a single gavage dose of 16 mg parathion/kg did not affect body weight over a 4-day observation period (Kim et al. 2005), but 2.2 mg parathion/kg administered by gavage to female Balb/c mice for 8–13 days induced a 20% reduction in body weight (Wiltrout et al. 1978).

In intermediate-duration studies, the lowest LOAEL was 7.6 mg parathion/kg/day, a dose that induced a 24% decrease in body weight in female Osborne-Mendel rats following 6 weeks of dietary exposure (NCI 1979); the NOAEL was 3.8 mg parathion/kg/day. Mice appeared to be less sensitive, as doses of 31 mg parathion/kg/day in the diet for 6 weeks did not significantly affect the mean body weight of female $B6C3F_1$ mice, but 29 mg parathion/kg/day reduced body weight in males by 14% (NCI 1979). In a 6-week study in beagle dogs, 0.5 mg parathion/kg/day administered in a capsule 5 days/week did not significantly affect body weight (NIOSH 1974).

NCI (1979) reported that Osborne-Mendel rats fed a diet that provided approximately 4.4 mg parathion/kg/day to males and 3.5 mg/kg/day to females for 80 weeks had generally lower body weight than controls, but quantitative data were not provided. A similar observation was noted regarding male $B3C6F_1$ mice dosed with 27.6 mg parathion/kg/day for 62 weeks, but not in females receiving the same dose for 80 weeks (NCI 1979).

Metabolic Effects. No specific information was located regarding metabolic effects in humans following oral exposure to parathion. However, effects secondary to adrenal medulla stimulation, such as hyperglycemia, would not be unexpected. In addition, alterations in acid/base balance such as metabolic acidosis may be expected in severely poisoned subjects, particularly those exhibiting renal failure.

No information was located in the available literature regarding metabolic effects in animals following oral exposure to parathion.

Other Systemic Effects. Painless acute hemorrhagic pancreatitis was reported in two out of nine cases of acute parathion intoxication described by Lankisch et al. (1990). The investigators discussed the possibility that the condition was due to parathion-induced increase of pancreatic intraductal pressure and stimulation of pancreatic secretion.

3.2.2.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological and lymphoreticular effects in humans following oral exposure to parathion.

A limited number of studies in animals have shown that oral exposure to parathion can affect immune function. Administration of eight doses of 2.2 mg parathion/kg/day to female BALB/c mice immunized on day 9 induced a statistically significant suppression of the humoral immune response in terms of plaque-forming cells per spleen 4 days after immunization (Wiltrout et al. 1978). In similar studies, Casale et al. (1983, 1984) showed that a single gavage dose of 16 mg parathion/kg, which induced severe cholinergic signs and caused some lethality in C57BL/6N mice, significantly suppressed the primary IgM response. However, when the mice received multiple lower doses of parathion, which produced no cholinergic signs, the primary IgM response was not suppressed. The results of additional experiments with arecoline, a cholinomimetic agent, suggested that cholinergic stimulation played a major role in parathion-induced suppression of the plaque-forming cells response. Kim et al. (2005) also reported that a single dose of 4 or 16 mg parathion/kg suppressed the antibody response to immunization with SRBCs in female Balb/c mice; no significant effects were reported at 1 mg/kg. More recently, Fukuyama et al. (2012) also showed that exposure to 1.5 mg parathion/kg/day for 5 days significantly decreased the SRBC-specific IgM response in blood from female C3H/HeN mice; no significant effect was seen at 0.15 mg parathion/kg. The IgM plaque-forming cell response to SRBC in splenocytes showed a decreasing trend, but the differences from the control were not statistically significant. In addition, parathion did not decrease the total cell counts in the spleen. Finally, the 1.5 mg/kg dose significantly decreased the ratio, but not the number, of IgM-positive lymphocytes and germinal center-positive B-lymphocytes in splenocytes.

Studies in mice have also shown that pretreatment with 0.4 mg parathion/kg/day (the lowest dose tested) for 5 days increased the response to allergens such as 2,4-D-butyl and eugenol (Fukuyama et al. 2010). Both agents were classified as moderate sensitizers after pretreatment with vehicle, corn oil, and as strong sensitizers after pretreatment with parathion. In a subsequent study, the same group of investigators showed that pretreatment with parathion (0.15 mg/kg/day, the lowest dose tested) aggravated T_H1- and T_H2-type allergy (Fukuyama et al. 2011). According to the investigators, the mechanism for these effects may involve alterations in the number of helper and cytotoxic T-cells, in levels of T_H1 and T_H2 cytokines, and in gene expression in lymph nodes. Since T_H1- and T_H2-helper cells direct different immune pathways, alteration of their normal ratio may result in an unbalanced immune response to a challenge. Excessive proinflammatory responses due to overactivation of T_H1-type cytokines may lead to uncontrolled tissue damage, whereas excess T_H-2 responses will counteract the T_H-1-mediated microbicidal action.

Long-term dietary studies in Osborne Mendel rats and B6C3F$_1$ mice dosed with up to approximately 4.4 and 27.6 mg parathion/kg/day, respectively, did not find gross or microscopic alterations in the spleen or lymph nodes (NCI 1979).

The highest NOAEL values and all LOAEL values from each reliable study for immunological and lymphoreticular effects in each species and duration category are recorded in Table 3-2 and Figure 3-2.

3.2.2.4 Neurological Effects

Information regarding neurological effects in humans is available from reports of intentional or accidental ingestion of formulations of the pesticide, ingestion of food accidentally contaminated with parathion, and studies in volunteers.

In a short communication, Edson (1964) reported that oral administration of up to approximately 0.1 mg parathion/kg/day 5 days/week for 25–70 days did not result in adverse clinical signs in a small group of volunteers. However, it did reduce red blood cell cholinesterase activity by 16% when administered to four females for 6 weeks. At this time, whole blood cholinesterase was inhibited 33% and plasma cholinesterase was inhibited 37%. No further information was provided. In another study of controlled oral exposure in five volunteers, administration of approximately 0.11 mg parathion/kg/day for about 20 days resulted in red blood cell cholinesterase levels reduced to 63, 78, and 86% of pretest levels and dosing was discontinued (Rider et al. 1969). In two subjects who completed the test period of 30 days, there was no significant effect on red blood cell cholinesterase. By the end of a 30-day post-test period, red blood cell cholinesterase activity had returned to pretest levels. No significant depression of red blood cell cholinesterase occurred in any subject who received doses ≤0.09 mg parathion/kg/day. No explicit information was provided regarding clinical signs. In a study that examined the urinary excretion of parathion metabolites, administration of 1 or 2 mg parathion (0.014 or 0.028 mg/kg/day assuming 70 kg body weight) to four volunteers for 5 consecutive days did not cause any symptoms or signs of parathion intoxication, nor did it alter red blood cell or plasma cholinesterase activities (Morgan et al. 1977). Data from the Rider et al. (1969) study regarding red blood cell AChE inhibition were used to derive an intermediate-duration oral MRL for parathion.

Subjects who ingested food contaminated with parathion usually show the typical signs and symptoms caused by inhibition of acetyl cholinesterase. For example, Diggory et al. (1977) reported that 79 persons were acutely poisoned by parathion in Jamaica in 1976 following consumption of contaminated wheat

flour. Signs and symptoms began 10 minutes to 4 hours after a meal; 17 people died. Severe cases had double vision, pinpoint pupils, muscle fasciculations, and convulsions. Mean red blood cell cholinesterase activity measured in nine patients 5 days from the onset of illness was 78% depressed. Measurements done in 50% of the patients on day 31 showed that red blood cell cholinesterase activity was still depressed by 47%. Similar findings were reported by Etzel et al. (1987) in 49 persons from Sierra Leone acutely poisoned following ingestion of bread baked with parathion contaminated flour, 14 of whom died. Most common signs and symptoms included loss of consciousness, excess sweating and salivation, muscle twitching, and convulsions. Tsachalinas et al. (1971) examined 246 cases following acute poisoning with parathion in Greece. Although not explicitly indicated, it appeared that most cases were due to consumption of contaminated food. Neurological signs and symptoms recorded included miosis and muscle cramps and spontaneous contractions. No data regarding cholinesterase activities were provided in the Etzel et al. (1978) or Tsachalinas et al. (1971) reports.

More recently, Eyer et al. (2003) studied the toxicokinetics of parathion in six acute oral poisoning cases and provided information regarding neurological effects and levels of red blood cell cholinesterase activity. Two of the subjects presented to the emergency room with cholinergic signs; red blood cell cholinesterase activity measured in one of them was reduced to <10% of normal. The other four subjects were unconscious when they arrived at the emergency room. Red blood cell cholinesterase activity in one of them was 3% of normal, whereas no activity could be detected in two of them. In all of the subjects, administration of obidoxime was able to reactivate the enzyme to some degree. Worth noting is the fact that estimates of the amount of parathion absorbed in four subjects (0.31, 0.13, 0.36, and 1.15 g) based on measurements of *p*-nitrophenol in the urine were more than 2 orders of magnitude lower than estimated from anecdotal reports of the amount ingested.

Data regarding brain AChE activity following intoxication with parathion is available in a study by Finkelstein et al. (1998). The investigators employed a computerized method of quantitative histochemical analysis to measure levels of the enzyme in the brain of a man and a woman who died following intentional ingestion of parathion. Brains from two subjects who died of unrelated causes were used as matched controls. In all cases, the postmortem delay did not exceed 32 hours. The results of the enzyme analysis showed that inhibition of brain AChE by parathion was regionally selective. Relative to controls, the biggest decreases (65–80%) occurred in the cerebellum, some thalamic nuclei, and the cortex. Moderate decreases of 10–30% were seen in the *substantia nigra* and basal ganglia; no significant changes were seen in the white matter. Macroscopic observation of the parathion-exposed brains showed

slight diffuse edematous changes; no other gross abnormalities were detected. Brain congestion and edema were also observed in fatal cases of children described by Wishahi et al. (1958).

A condition that has been reported infrequently in humans as a consequence of acute exposure to high amounts of parathion 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, is thought to be due to persistent cholinesterase inhibition leading to combined pre- and post-synaptic impairment of neuromuscular transmission, and was first described by Senanayake and Karalliedde (1987) in a study of organophosphorus pesticides other than parathion. De Bleecker et al. (1992) described the first case due to acute parathion exposure. The syndrome was characterized by respiratory paresis, weakness in the territory of several motor cranial nerves, and weakness of proximal limb and neck flexor muscles, and persisted for 3 weeks. During this time, cholinesterase activity remained markedly depressed. Serial EMGs with repetitive nerve stimulation suggested a combined pre- and post-synaptic disorder of neuromuscular transmission. Among 68 cases of acute exposure to parathion studied by He et al. (1998), 7 developed intermediate syndrome (10.3%). Nisse et al. (1998) also described a case of intermediate syndrome following acute exposure to parathion. Besser et al. (1993) described a case of intermediate syndrome in a subject who later developed delayed neuropathy (see below).

Very few cases of parathion-induced delayed neuropathy have been described. Organophosphorus pesticide-induced delayed neuropathy (OPIDN) is a neurodegenerative disorder characterized by a delayed onset of prolonged ataxia and upper motor neuron spasticity (Abou-Donia 1995; Abou-Donia and Lapadula 1990; Johnson 1975). The lesion is a central-peripheral distal axonopathy caused by a Wallerian-type degeneration of the axon, followed by myelin degeneration of the central and peripheral nervous systems. De Jager et al. (1981) described the case of a man who ingested an estimated 150 g of parathion and became comatose. He was treated for the acute cholinergic crisis, but remained in a coma for 7 weeks. Upon recovering from the coma, he had flaccid paralysis of both legs and weakness of the muscles of both hands. The patient gradually recovered but after 3 months, there were still marked muscle wasting and weakness of dorsiflexors and plantar flexors of the feet. Besser et al. (1993) described an additional case of severe intoxication with coma, cholinergic crisis, and intermediate syndrome. After gradually recovering over a 28-day period, the patient complained of numbness and weakness in his feet and hands. Clinical examination showed signs of severe, symmetrical, distal sensorimotor polyneuropathy. The patient was unable to stand and walk. Gradual recovery was observed

during the next 5 weeks, more completely in the hands than in the feet. Eventually, the patient was able to walk without assistance, but distal weakness persisted in the legs.

Results from studies in animals support the findings in humans. The available studies provide information regarding enzyme activities, clinical signs, and neurobehavioral end points.

The lowest LOAEL for a >20% inhibition of red blood cell cholinesterase activity in an acute-duration study was reported in male beagle dogs administered a single dose of 0.5 mg parathion/kg in a capsule (NIOSH 1974). That dose inhibited the enzyme by 29% 24 hours after dosing. The ED_{50} (dose reducing for the enzyme activity to 50% of pretest levels) was 0.385 mg/kg and the ED_{50} for plasma cholinesterase was 1.67 mg/kg. A dose of 2.5 mg parathion/kg reduced red blood cell cholinesterase activity by 64%, but did not induce clinical signs. However, single doses ≥6.3 mg parathion/kg induced tremors, ataxia, convulsions, and prostration. A time-course experiment showed that 36 days after dosing with 2.5 mg/kg, red blood cell cholinesterase activity was reduced by 11% and plasma cholinesterase had recovered to pre-dosing levels (NIOSH 1974). Similar studies in male Sprague-Dawley rats showed that a doses of 0.7 and 5.6 mg parathion/kg reduced red blood cell cholinesterase activity by 27.4 and 69.7%, respectively, at an unspecified time after dosing (NIOSH 1974). The ED_{50} values for red blood cell and plasma cholinesterase were 2.60 and 2.55 mg/kg, respectively. Tremors occurred in 10/10 rats given a single dose of 5 mg parathion/kg, but not in rats dosed with 4 mg parathion/kg. In a time-course experiment in rats administered a dose of 2.8 mg parathion/kg, red blood cell and plasma cholinesterase activities were 44 and 35% of pretest values, respectively, 4 hours after dosing and 67 and 89% of pretest values, respectively, 14 days after dosing. A study in female CD rats reported ED_{50} values of 1.7, 1.1, and 1.1 mg parathion/kg for red blood cell cholinesterase activity 2, 5, and 24 hours after dosing, respectively (Pasquet et al. 1976). The corresponding ED_{50} values for brain cholinesterase were >3.6, 3.6, and >3.6 mg parathion/kg. The ratio of red blood cell cholinesterase ED_{50}/LD_{50} was about 1/5.

In a neurobehavioral study in male Rhesus monkeys, a single dose of 1 mg parathion/kg abolished performance of a learned task 5 hours after dosing, an effect that lasted 3–7 days (Reiter et al. 1975). That dose inhibited blood cholinesterase activity by 40–45%. A dose of 0.5 mg parathion/kg, which reduced blood cholinesterase activity by about 20%, did not affect performance of the learned task. The highest dose tested in the study, 2 mg parathion/kg, produced mild signs of toxicity consisting of decreased postural tone and slight vomiting. Neurobehavioral screening of male Long-Evans rats with tests that assessed autonomic function, neuromuscular function, sensorimotor domain, activity levels, and excitability showed that a single gavage dose of 7 mg parathion/kg, which induced tremors and gait

alterations, affected all of the neurobehavioral parameters measured; the largest magnitude of effects was obtained on the day of dosing and the NOAEL was 4 mg/kg (Moser 1995). Cholinesterase activity was not measured in this study. In male Swiss-Webster mice, administration of a single gavage dose of 6 mg parathion/kg (only dose tested) blocked learning of a one-trial passive avoidance task, but did not significantly affect memory (Reiter et al. 1973). The maximum effect of parathion occurred when it was given within the first hour before the learning trial and correlated with maximum changes in brain and blood true cholinesterase and pseudocholinesterase activities (50–60% depression).

A study that examined the effects of parathion on the dark-adapted pupil dilation in cynomolgus monkeys reported that a single gavage dose of 2 mg parathion/kg (only dose tested) reduced red blood cell AChE activity by approximately 50% 3–12 hours after dosing and that the maximum depression of plasma cholinesterase (65–80% of pre-dosing) occurred approximately 3 hours after dosing (Elkner et al. 1991). The only clinical sign observed was loss of appetite in three of the four monkeys, which corresponded with the time of maximum enzyme inhibition. The study did not find a consistent pattern of change in pupil/iris diameter ratios following exposure to parathion due to high dispersion of the data, which led the investigators to conclude that measurements of pupil dilation after dark adaptation is not a sensitive indicator for systemic exposure to organophosphorus pesticides.

In intermediate-duration studies, exposure of male Sprague-Dawley rats to 0.1 mg parathion/kg/day by gavage 5 days/week for 6 weeks resulted in a 22% decrease in red blood cell cholinesterase activity; no significant inhibition occurred with doses of 0.05 mg/kg (NIOSH 1974). The highest dose of parathion tested, 0.25 mg/kg, reduced red blood cell cholinesterase activity by 26% on week 1 and to 43–57% of control on weeks 4–6 of exposure and on week 1 post-exposure. Plasma cholinesterase was inhibited about 48% on weeks 5–6 of exposure. No toxic signs were observed in the rats in this study. In another intermediate-duration study, dietary exposure of male Wistar rats to 0.4 mg parathion/kg/day significantly inhibited red blood cell AChE (>80%), 0.1 mg/kg inhibited the enzyme by 36–67%, and <20% inhibition occurred in males dosed with 0.024 mg/kg (Ivens et al. 1998). In females, doses of 0.036, 0.152, and 0.550 mg parathion/kg/day reduced red blood cell cholinesterase activity by 27, 67, and 92%, respectively; brain cholinesterase was reduced 10% in high-dose females. On week 15, plasma cholinesterase was significantly reduced in males dosed with 0.4 mg/kg (44%) and in females dosed with 0.55 mg/kg (52%); the red blood cell enzyme was reduced in mid-dose males and females (36–44%) and high-dose males and females (85%); brain cholinesterase was not affected. In a group of rats exposed for 13 weeks and tested on weeks 45–49, all cholinesterase levels had recovered. Ivens et al. (1998) also subjected the rats to four learning and memory tests during the study and reported that exposure to

parathion did not affect the results of the tests. In yet another study in male rats (strain not reported), 90 daily gavage doses of 2.6 mg parathion/kg (only dose tested) reduced brain cholinesterase activity by 50% and blood cholinesterase by 74%; no clinical signs were observed in the rats (Dikshith et al. 1978). In a chronic-duration study in Osborne-Mendel rats, the investigators reported that there were no significant clinical signs during the first 6 months of the study. However, during the second 6 months, 25/50 female rats dosed with approximately 3.5 mg parathion/kg/day, the highest dose tested, had generalized body tremors (NCI 1979). No information was provided regarding rats dosed with lower doses.

A 6-week study in male beagle dogs reported that doses of 0.05 mg parathion/kg/day in a capsule (the lowest doses tested) induced a maximal inhibition of red blood cell cholinesterase of 30% on week 1 post-treatment (NIOSH 1974); at that time, the highest dose tested, 0.5 mg/kg/day, reduced the enzyme's activity by 50%. No toxic signs were seen in the dogs. Similar results had been reported by Frawley and Fuyat (1957) in mixed breed dogs exposed to parathion in the diet for 24 weeks. A study that examined the ocular toxicity of parathion in male and female beagle dogs reported that the highest dose tested, 0.794 mg parathion/kg/day, induced a maximum decrease in red blood cell AChE of about 20% on week 6 of the 6-month study (Atkinson et al. 1994). At study termination, retinal cholinesterase was depressed by about 50% in males and females, ocular muscle cholinesterase was not significantly affected, and pons and cerebellum cholinesterase was reduced by 23–25%. Routine ophthalmoscopic and slit lamp examinations, refraction and intraocular pressure determinations, and electroretinograms performed at various intervals during the study were not significantly altered by exposure to parathion and microscopic examination of the retina, optic nerve, ocular muscles, and ciliary body did not show changes indicative of ocular toxicity.

A study examined the effects of parathion on auditory detection behavior in male squirrel monkeys during a 148-day period in which the monkeys were given a daily capsule with 0.1 mg parathion/kg (Reischl et al. 1975). The dose of parathion did not induce signs of toxicity. Hearing thresholds were determined at 500, 1000, 2000, 4000, 8000, and 16,000 Hz. Exposure to parathion did not significantly change the mean hearing thresholds at any auditory frequency. However, the group exposed to parathion showed a significantly increased standard deviation in hearing thresholds after 40 days of parathion exposure. The investigators suggested that parathion disrupted the monkey's tone reporting behavior during hearing threshold testing. The disruption became significant at tones presented near the animal's hearing threshold, but not for tones presented 20–25 dB above the threshold.

Chronic exposure of rats to up to 4.4 mg parathion/kg/day or of mice to up to 27.6 mg parathion/kg/day did not result in gross or microscopic alterations in the brain (Barnes and Denz 1951; NCI 1979). In the NCI (1979) study, the investigators noted that during the first half of the second year, clinical signs among dosed rats were noted at a low or moderate incidence, and during the second half of the year, they increased. However, no quantitative data were presented. In addition, the investigators mentioned that by week 60 of the study, all high-dose male mice (approximately 27.6 mg parathion/kg/day) were showing signs of hyperexcitability, but no data were provided.

3.2.2.5 Reproductive Effects

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

Limited information was located in the available studies regarding reproductive effects of parathion in animals. Thomas and Schein (1974) reported that daily gavage administration of up to 5.3 mg parathion/kg for 5 consecutive days to male Swiss-Webster mice did not significantly affect the weight of the testes or prostate. In an intermediate-duration study, daily gavage administration of 2.6 mg parathion/kg/day (only dose tested) to male rats (strain not reported) for 90 days caused tubular atrophy, necrosed spermatogenic cells, and enlargement of the interstitial space of the testes (Dikshith et al. 1978). There was also proliferation of new blood vessels in the interstitial space. Chronic exposure of rats to up to 4.4 mg parathion/kg/day or of mice to up to 27.6 mg parathion/kg/day did not result in gross or microscopic alterations in the reproductive organs (Barnes and Denz 1951; NCI 1979).

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to parathion.

Limited information is available regarding developmental effects of parathion in animals. Conventional developmental end points were examined in Wistar rats (Renhof 1984) and Himalayan rabbits (Renhof 1985). The rats were exposed to 0.1, 0.3, or 1 mg technical parathion/kg on gestation days 6 through 15 and cesarean sections were performed on gestation day 20. Treatment with parathion did not significantly affect the number of live fetuses/litter, number of resorptions/litter, mean fetal weight/litter, number of fetuses with slight bone alterations/litter, number of runts/litter, or number of fetuses with malformations/litter. Maternal toxicity, including significantly reduced weight gain during treatment and tremors, occurred in the group dosed with 1 mg/parathion/kg/day. Pregnant rabbits were administered 0.03, 0.1, or 0.3 mg parathion/kg/day on gestation days 6–18 and cesarean sections were performed on

gestation day 29. Evaluation of the same end points examined in rats showed no significant embryotoxic or teratogenic effects in rabbits under the conditions of the study. No significant maternal toxicity occurred in the rabbits.

In an earlier study, pregnant CD rats were administered 0, 0.01, 0.1, or 1.0 mg parathion /kg/day from day 2 of gestation through day 15 of lactation (Deskin et al. 1979). On postnatal day 25, five pups per sex were evaluated for pseudocholinesterase and red blood cell cholinesterase activities and plasma renin. An EKG was also performed in anesthetized pups. EKG values for males and females were combined. No data were presented regarding maternal effects. Perinatal exposure to parathion did not significantly affect red blood cell AChE activity, but reduced pseudocholinesterase activity in female pups by 17–27%. Heart rate was not significantly affected by parathion exposure, but there were alterations in the EKG including a 43% reduction in atrial depolarization (P-R interval) in low-dose pups. Plasma renin was also reduced in a dose-related manner (60% with the lowest dose).

3.2.2.7 Cancer

No studies were located regarding cancer effects in humans following oral exposure to parathion.

A bioassay for parathion was conducted in Osborne-Mendel rats and $B6C3F_1$ mice (NCI 1979). Rats were fed diets that provided approximately 0, 2.2, or 4.4 mg parathion/kg/day to males and 0, 1.8, or 3.5 mg parathion/kg/day to females for 80 weeks; the rats were then observed for 32–33 weeks. In males, analyses of neoplastic lesions showed significant increased incidence of cortical adenomas of the adrenal gland in high-dose group using pool controls (2/80 vs. 9/46, $p<0.002$). Analysis of combined cortical adenomas and carcinomas showed significantly increased incidences in both low- and high-dose groups (3/80 pooled control vs. 7/49 and 11/46, respectively). Also significantly elevated in high-dose males were the incidences of follicular cell adenoma of the thyroid (5/76 pooled control vs. 8/43, $p=0.046$) and carcinoma of the pancreatic islet-cell (0/79 pooled control vs. 3/46, $p=0.048$). In females, the incidences of adrenal cortical adenomas or adrenal cortical adenomas and carcinomas were significantly elevated when compared with pooled controls (adenomas 4/78 pooled control vs. 11/42 high-dose, $p=0.001$; adenomas plus carcinoma 4/78 pooled control vs. 13/42 high-dose, $p=0.001$). The investigators concluded that, under the conditions of the study, parathion was carcinogenic to Osborne-Mendel rats. The dose of 2.2 mg parathion/kg/day in male rats is listed as a CEL in Table 3-2 and is plotted in Figure 3-2.

Mice were fed a diet that provided approximately 0, 13.7, or 27.6 mg parathion/kg/day (NCI 1979). Low-dose males were treated for 71 weeks, high-dose males for 62 weeks, and low- and high-dose females for 80 weeks. All mice were killed at 89 or 90 weeks. Gross and microscopic examination of organs and tissues showed that neoplastic lesions were distributed equally between dosed and control groups. Therefore, under the conditions of the assay, parathion was not carcinogenic to $B6C3F_1$ mice.

Based on the results of the NCI (1979) bioassay, the EPA placed parathion on Group C, possible human carcinogen (IRIS 2003). Under updated guidelines, the data regarding carcinogenicity of parathion are "suggestive evidence of carcinogenic potential" (EPA 2005). A quantitative estimated of carcinogenic risk from oral exposure is not available.

3.2.3 Dermal Exposure

3.2.3.1 Death

Deaths have been reported in humans following occupational or accidental dermal exposure to parathion. In a study of 40 occupationally exposed subjects, Grob et al. (1950) reported that six of them died due to contact with the pesticide. Exposure occurred during the synthesis or handling of various parathion formulations; inhalation exposure was also likely to have occurred. All the men who died had been exposed on ≥1 days during the month preceding the day on which symptoms occurred. The average exposure length for the whole cohort was 8 hours/day for 12 days. Four of the patients who died walked into the hospital and two died before they could be brought to a hospital. Ataxia, tremor, drowsiness, difficulty in concentrating, mental confusion, occasionally disorientation, and changes in speech developed, followed by profound coma with absence of all reflexes. The coma began, on average, 4 hours after the onset of symptoms and lasted an average of 3.5 hours before death occurred. The immediate cause of death was not known but, according to Grob et al. (1950), contributing factors may have been depression of the respiratory and circulatory centers in the medulla, weakness of the muscles of respiration, and pulmonary edema.

Among 20 deaths reported in children due to exposure to parathion in the state of Florida from 1959 through 1964, four were due to dermal contact with the pesticide (Eitzman and Wolfson 1967). Limited information provided regarding two of these cases indicates that both developed cholinergic crisis and died within 5 hours of being seen by a physician. Autopsy was performed on one of them and revealed increased bronchial secretions.

Lores et al. (1978) described the case of a young man whose death was attributed to dermal contact with parathion residue <24 hours after application of the pesticide to a tobacco field where he had worked. He was found unconscious at home and was taken to the hospital where he was pronounced dead on arrival.

The dermal LD_{50} values for technical parathion in male and female Sherman rats were 21 and 6.8 mg/kg, respectively, suggesting sex-related differences in susceptibility (Gaines 1960). In males, the minimal survival time was 24 minutes and the maximum survival time was 3 days. In females, the minimal survival time was 1 hour and the maximum survival time was 4 days. Signs of poisoning included muscle fasciculation, excessive salivation and lacrimation, tremors, diarrhea, and involuntary urination. The doses tested were not specified. A dermal LD_{50} of 49.4 mg/kg was reported for technical parathion in male Sprague-Dawley rats; the LD_{50} in females was 19.5 mg/kg (EPA 1978). No information was provided regarding whether the application site was occluded or washed at some point. All rats exhibited typical signs of cholinesterase inhibition including salivation, lacrimation, exophthalmos, defecation, urination, and muscle fasciculations; the doses tested were not specified. This study also supports the view that female rats are more susceptible than male rats to the acute effects of parathion. A similar study reported a dermal LD_{50} of approximately 8 mg/kg for female CD rats (Pasquet et al. 1976). The rats were fitted with a collar for 24 hours and the application site was washed with soap and lukewarm water; the observation period was 10 days. No further information was provided.

The LD_{50} values mentioned above are recorded in Table 3-3.

3.2.3.2 Systemic Effects

No studies were located that provide information regarding endocrine, dermal, or body weight effects in humans following dermal exposure to parathion. The only effects in animals recorded in Table 3-3 are dermal effects in rats following dermal exposure to parathion.

Respiratory Effects. Using the AHS, Hoppin et al. (2006) examined the association of 40 individual pesticides (parathion among them) with wheeze. The AHS is a prospective cohort study of nearly 90,000 private pesticide applicators (mostly farmers), their spouses, and commercial pesticide applicators in Iowa and North Carolina. Exposure and medical history of farmers and pesticide applicators was assessed by means of self-administered questionnaires. Pesticides were evaluated using logistic regression models adjusted for age, sex, state, smoking status, and body mass index. The final analysis included 17,920 farmers and 2,255 commercial applicators. Nineteen percent of farmers and 22% of

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

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
ACUTE EXPOSURE							
Death							
Rat (Sprague-Dawley)	once				49.4 M mg/kg (LD50)	EPA 1978	
					19.5 F mg/kg (LD50)		
Rat (Sherman)	once				21 M mg/kg (LD50)	Gaines 1960	
					6.8 F mg/kg (LD50)		
Rat (CD)	once				8 F mg/kg (10-day LD50)	Pasquet et al. 1976	
Systemic							
Gn Pig NS	5 d 1 x/d	Dermal		0.004 F mg/kg/day (hyperkeratinization of epidermis; thickening of stratum corneum)		Dikshith and Datta 1972	
Neurological							
Human (NA)	5 d 2 hr/d		100 mg			Hayes et al. 1964	NOAEL is for RBC cholinesterase activity.

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

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE							
Systemic							
Gn Pig NS	15 d 1 x/d	Dermal		0.004 F mg/kg/day	(Hyperkeratinizationn of the dermis; proliferation of connective tissue)	Dikshith and Datta 1972	

d = day(s); F = Female; Gn pig = guinea pig; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NA = not applicable; NOAEL = no-observed-adverse-effect level; NS = not specified; RBC = red blood cell x = time(s)

commercial applicators reported wheezing at least once in the year before enrollment. For parathion, 7% of farmers reported past use and 1% reported current use (ever used in the year prior enrollment); the corresponding percentages for commercial applicators were 3 and 1%. The odds ratio (OR) was elevated for farmers, but did not achieve statistical significance (OR=1.37, 95% confidence interval [CI] 0.93–2.03). An OR was not calculated for parathion because there were fewer than five exposed cases. In a more recent report, the same group of investigators examined the association between pesticide exposure and allergic and non-allergic asthma among 19,704 male farmers in the AHS (Hoppin et al. 2009). Parathion was found to be significantly associated with allergic asthma (OR=2.05, 95% CI 1.21–3.46), although there was no exposure-response trend. Exposure to parathion was not associated with non-allergic asthma (OR=1.11, 95% CI 0.75–1.66). Exposure-response was evaluated using three measures of cumulative pesticide exposure: total years of use, lifetime days of use, and intensity-adjusted lifetime days of use.

Respiratory difficulty suggestive of bronchospasm, excessive bronchial secretions, and pulmonary edema with cyanosis were reported in workers acutely exposed to parathion during the synthesis or handling of various formulations of the pesticide (Grob et al. 1950). Pulmonary edema was reported in a child who later died following dermal exposure to parathion; shallow respiration was reported in a child who survived dermal exposure to the pesticide (Eitzman and Wolfson 1967).

Cardiovascular Effects. Elevated blood pressure was reported in most workers with moderate or severe symptoms described by Grob et al. (1950). The investigators noted that decreased blood pressure was not noticed, except shortly before death. EKGs performed in four patients who recovered did not show alterations. Eitzman and Wolfson (1967) reported hypotension in two children who eventually died following dermal contact with parathion; a third child who survived also had hypotension and bradycardia.

Gastrointestinal Effects. Anorexia, nausea, vomiting, abdominal cramps, and diarrhea were commonly reported in workers exposed during synthesis and handling various parathion formulations (Grob et al. 1950) and in agricultural workers exposed to parathion (Milby et al. 1964; Quinby and Lemmon 1958). Nausea and vomiting were also reported in two poisoning cases in children; one of them also complained of abdominal pain (Eitzman and Wolfson 1967).

Diarrhea and defecation were reported in rats given high dermal doses of parathion in LD_{50} studies (EPA 1978; Gaines 1960).

Hematological Effects. Hematological tests conducted in four workers who recovered from severe poisoning symptoms following exposure to parathion revealed no appreciable abnormality regarding red blood count, hematocrit, hemoglobin, and sedimentation rate (Grob et al. 1950). In 12 patients in whom the leucocyte count was determined, there was slight to moderate leukocytosis. The differential count showed a slight increase in the percent of mature polymorphonuclear leucocytes (Grob et al. 1950).

Musculoskeletal Effects. No direct effects on muscle or bone were reported in humans following dermal exposure to parathion. Clinical signs such as muscle fasciculation, twitching, and tremors are of neurological origin, as mentioned in Section 3.2.3.4.

Hepatic Effects. The only information located in the available literature regarding hepatic effects in humans following exposure to parathion is in the study of workers by Grob et al. (1950). Laboratory test performed in four subjects who recovered after severe symptoms showed cephalin flocculation, serum alkaline phosphatase activity, total serum protein, and albumin/globulin values within normal limits.

Renal Effects. Normal blood urea nitrogen (BUN) was reported in the four workers who recovered from severe parathion intoxication described by Grob et al. (1950). No further relevant information was located.

Dermal Effects. In a study in 30 female guinea pigs, the animals were applied 1 mL of a 1-ppm solution of parathion in 50% ethanol to a clipped latero-abdominal area daily for 5 or 10 days (approximately 4 μg/kg/day based on a body weight of 0. 250 kg) (Dikshith and Datta 1972). Ten guinea pigs were killed 24 hours after the 5th, 10th, and 15th application, and the skin was prepared for gross and microscopic examination. Treatment with parathion did not induce adverse clinical signs. Gross examination of the skin did not show dermatitis or any other noticeable changes. Microscopic examination showed hyperkeratinization of the epidermal layer and thickening of the stratum corneum after 5 days of treatment. Five applications also induced mild damage to the endothelial cells of the blood vessels. Ten days of treatment resulted in scattered infiltration of mononuclear cells in the dermis. The dermis also showed mild proliferation of connective tissue around hair follicles and sebaceous glands. Additional applications induced changes such as thickening of the wall of the blood vessels and swelling of the endothelial cells. A mild perivascular inflammatory infiltrate was also present.

Ocular Effects. Clinical signs such as miosis, unresponsive pupils, and blurred vision are caused by alterations in the neural control of the eye, but can be exacerbated by directly touching the eyes with contaminated objects or the hands.

3.2.3.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological and lymphoreticular effects in humans following dermal exposure to parathion, except for the report of an association (OR=2.05, 95% CI 1.21–3.46) between exposure to parathion and allergic asthma in participants in the AHS (Hoppin et al. 2009). Exposure to parathion was not associated with non-allergic asthma (OR=1.11, 95% CI 0.75–1.66).

3.2.3.4 Neurological Effects

Neurological effects have been studied in volunteers exposed to controlled amounts of parathion, in adults and children acutely exposed to high amounts of parathion, and in workers exposed chronically to lower levels of parathion. In addition, data are available regarding neurobehavioral effects in agricultural workers and on the possible role of parathion exposure and Parkinson's disease.

In an early study, Grob et al. (1950) described the effects of parathion in 38 men and 8 women involved in the synthesis or handling of various parathion formulations. About half of the subjects began to have symptoms while they were still exposed to parathion. The remaining subjects developed symptoms 0.5–8 hours after their last exposure to parathion. The severity of the acute cholinergic crisis seemed to depend on the severity of the intoxication. In cases of marked intoxication, ataxia, tremor, drowsiness, difficulty in concentrating, mental confusion, occasionally disorientation, and changes in speech developed. In the most severe cases, coma gradually developed. The average durations of the acute effects were 25 hours in four patients who had severe symptoms and 12 hours in 30 patients who had less severe effects. Patients who recovered from severe illness showed giddiness, uneasiness, headache, anxiety, insomnia, and weakness for 48–72 hours after their last exposure to parathion. In patients suspected of spraying or rubbing parathion into the eyes, it took several weeks for pinpoint pupils to return to normal size. Four patients who survived severe symptoms had red blood cell AChE activity reduced to11–22% of normal activity. In six subjects with less severe symptoms, red blood cell AChE activity ranged from 12 to 28% of normal. When 18 subjects whose enzyme had been depressed were removed from further exposure, red blood cell AChE activity increased at an average rate of approximately 10% of normal activity during the first 3 days and diminished to between 1 and 2% per day

by the fourth day. The rate of recovery subsequently remained fairly constant until a normal level of activity was reached.

Milder effects were described by Quinby and Lemmon (1958) among >70 subjects who had contact with parathion residues. The workers were engaged in picking, thinning, cultivating, and irrigating various crops. Dermal exposure appeared to have been favored by the removal of protective clothing and by the persistent wearing of contaminated clothing. Weakness, twitching of arm and leg muscles and of the eyelids, and some cases of miosis were reported. Effects such as headache, weakness, miosis, blurred vision, and dizziness were reported in a study of 186 peach orchard workers (Milby et al. 1964). Measurements of parathion residues in the fruit, on the subjects' skin, and in the air from two orchards that had produced the highest rates of clinical illness led to an estimate of total exposure by a picker of <4 mg; dermal exposure contributed the highest amount, approximately 3.2 mg. Ingestion and inhalation contributed only 0.5 and 0.3 mg, respectively.

Weakness, headache, muscle fasciculations, tremors, and severely depressed red blood cell AChE activity were reported in three children dermally exposed when a burlap sack heavily contaminated with parathion and filled with old clothing was used as a swing (Eitzman and Wolfson 1967).

Hayes et al. (1964) conducted a series of experiments with volunteers exposed to controlled amounts of parathion. Application of 5 g of 2% parathion dust at a constant temperature of 105°F onto the right hand and forearm for 2 hours on 5 consecutive days resulted in a maximum decrease of 14% in red blood cell cholinesterase activity 24 hours after exposure; no adverse clinical signs were noted. The daily amount applied was 100 mg parathion (5 g dust x 2 mg parathion/100 mg dust). This amount is listed as a NOAEL in Table 3-3. In additional experiments in which volunteers were exposed to other parathion formulations (4 L of 2% emulsion for 70 minutes at 81°F; unspecified amount of 47.5% emulsifiable concentrate for 120 minutes at 69°F or 90 minutes at 103°F), no significant depression of red blood cell cholinesterase was seen. Whole-body exposure of volunteers to 7 pounds of 2% parathion dust (~7 hours) or to parathion vapor (3 hours) did not significantly depress red blood cell AChE (<20%) activity, and no clinical signs were observed. Exposure of volunteers for 3 hours to filter paper pads containing 40–50 g of parathion did not result in significant depression of red blood cell AChE. In general, plasma cholinesterase was more affected than the red blood cell enzyme in all experiments.

The association between exposure to pesticides, parathion included, and self-reported hearing loss was examined among private pesticide applicators in the AHS (MacCrawford et al. 2008). Pesticide exposure

and medical history were assessed by questionnaires. The final sample available for analysis consisted of 14,229 applicators. Of these, 4,926 met the case inclusion criterion of self-reporting hearing troubles and 9,303 met the criterion to serve as controls. Logistic regression was performed with adjustment for state, age, and noise, solvents, and metals. Exposure to organophosphate pesticides was modestly associated with hearing loss, with a 17% increase in odds in the highest quartile of exposure (OR=1.17, 95% CI 1.03–1.31). Analysis of individual organophosphate pesticide using traditional logistic regression showed elevated odds for various pesticides, marginally significant for parathion (OR=1.21, 95% CI 1.04–1.40). Strengths of the study included a large population, an internal control group, detailed information on pesticide exposure, and information on additional potential causes of hearing loss.

The association between pesticide exposure and behavioral function has also been examined in the AHS (Starks et al. 2012). The cohort consisted of 701 males with a mean age of 61 years who were administered nine neurobehavioral tests to assess memory, motor speed and coordination, sustained attention, verbal learning, and visual scanning and processing. Associations between pesticide (parathion among them) use and neurobehavioral tests performance were estimated with liner regression controlling for age, height, education, state, smoking status, alcohol consumption, head injury, current antidepressant use, caffeine consumption, and exposure to other potentially neurotoxic substances. The results showed that parathion exposure was associated with better verbal learning and memory and better performance on a test of sustained attention. The investigators noted that given the large number of statistical tests performed, the possibility existed that the results were due to chance; however, a non-monotonic dose-effect function of parathion could not be ruled out.

Two studies were located that examined the relationship between exposure to parathion and Parkinson's disease. Neither one found a significant risk associated with exposure to parathion. In an ongoing population-based, case-control study of Parkinson's disease in western Washington State, Firestone et al. (2005) assessed occupational and home-base exposure using a structured interview. The final cohort consisted of 250 incident Parkinson's disease case patients and 388 healthy controls with a participation rate of 73% for cases and 66% for controls. ORs and 95% CIs were determined using logistic regression models controlling for age, sex, and smoking. Analysis of only the occupationally exposed subjects (156 cases and 241 controls) showed that parathion had the highest OR among organophosphate pesticides (OR=8.08, 95% CI 0.92–70.85). Analysis of the entire cohort showed an OR for the organophosphate class of 0.83 (95% CI 0.60–.16). Manthripragada et al. (2010) examined the association between Parkinson's disease and parathion (among other organophosphate pesticides) and the influence of a functional polymorphism at position 55 in the coding region of the PON1gene (PON1-55). Studies

have suggested that individuals with low PON1 activity might be at higher risk for organophosphate toxicity (reviewed in Costa et al. 2013). The cohort consisted of 351 incident cases and 363 controls from three rural California counties in a population-based, case-control study. Residential exposure was estimated for each study participant using their residential history and a geographic information system. The results showed no increased risk of Parkinson's disease for people exposed to parathion, and risk did not increase in carriers of the variant MM PON1-55 genotype. In a more recent study, the same group of investigators examined whether single nucleotide polymorphisms $PON1_{Q192R}$ and $PON1_{C-108T}$ impact the association between Parkinson's disease and residential exposure to parathion (Lee et al. 2013). $PON1_{Q192R}$ affects catalytic efficiency of PON1, whereas $PON1_{C-108T}$ has been associated with lower expression levels. The results of the analyses showed no significant increased risk associated with the variant genotypes studied (effect estimates included the null).

Acute toxicity studies aimed at determining dermal LD_{50} values in rats have reported cholinergic signs such as muscle fasciculations and tremors, but the dose levels at which these signs were observed were not provided (EPA 1978; Gaines 1960).

3.2.3.5 Reproductive Effects

A study of Chinese workers exposed to parathion and methamidophos reported that the workers (n=20) had a modestly lower sperm count, lower sperm concentration, and lower percentage of motile sperm than an unexposed control group (n=23) (Padungtod et al. 2000). However, the results should be interpreted with caution due to the small sample size. In addition, when the exposed subjects were assigned to a high- or low-exposure group based on job titles, measurements of exposure could not differentiate between them. Exposure was assessed by attaching a piece of gauze onto nine body areas, attaching a pump to the lapel of the subject's shirt to asses potential inhalation, and measuring urinary *p*-nitrophenol in five samples collected at the end of the shift. While the results were suggestive, the role of parathion, if any, remained unclear. It should also be noted that the mean number of pregnancies fathered by the exposed subjects was four, compared to two for the unexposed group, suggesting that fertility was not impaired.

3.2.3.6 Developmental Effects

Limited information is available regarding developmental effects in humans exposed to parathion. Eskenazi et al. (2004) studied the effects of organophosphate pesticide exposure during pregnancy on fetal growth and gestational length in a cohort of 488 low-income Latina women living in an agricultural

community in the Salinas Valley, California. Although exposure by multiple routes is likely to have occurred, touching produce sprayed with pesticides was likely the most significant exposure route. Exposure to parathion was assessed by measuring *p*-nitrophenol in the urine during pregnancy and by measuring cholinesterase in whole blood and butyl cholinesterase in plasma from the mothers during pregnancy and delivery and from umbilical cord. The investigators acknowledged that *p*-nitrophenol can also be derived from exposure to methyl parathion and other non-pesticide chemicals. Infant birth weight, crown-heel length, head circumference, and gestational length were obtained from medical records and hospital delivery logs. Linear regression models were used to test for associations between exposure measurements and length of gestation, birth weight, length, head circumference, and ponderal index. Logistic regression was used to test for associations between exposure measurements and low birth weight, preterm delivery, and small for gestational age births. The results of the analyses did not show an adverse association between fetal growth and any measure of in utero exposure to parathion, if there was true exposure to parathion. It is also possible that there was no exposure to parathion since, as mentioned above, *p*-nitrophenol may be derived from exposure to other chemicals.

3.2.3.7 Cancer

Dennis et al. (2010) examined the potential association between exposure to 50 agricultural pesticides, parathion among them, and the incidence of cutaneous melanoma in the AHS cohort of pesticide applicators along with ever-use of older pesticides that contain arsenic. Pesticide applicators completed an enrollment questionnaire that sought information on ever use of 50 pesticides and on a number of potential confounders. Pesticide applicators also completed an additional "take home" questionnaire that sought more extensive information on occupational activities. Logistic regression was used to examine ORs and 95% CIs associated with pesticide exposure adjusted for age, sex, and other potential confounders. A total of 150 cases of melanoma were identified among 24,704 subjects who completed the "take home" questionnaire. The investigators found no association between melanoma incidence and organophosphate insecticides as a class. However, there was a significant association between melanoma and parathion (≥56 days of exposure; OR, 2.4; 95% CI 1.3–4.4; p =0.003) based on 11 cases. The study also found a higher OR of 7.3 (95% CI 1.5–34.6) among those who had used arsenical pesticides. The investigators noted that strengths of the AHS include a prospective design, comprehensive pesticide exposure assessment, completeness of followup, and high participation rates. A limitation of the Dennis et al. (2010) study, noted by the investigators, was the small number of subjects who used parathion for at least 56 days and had melanoma (n=11). Overall, the study could not rule out the possibility that cutaneous melanoma was caused by exposure to arsenical pesticides. The investigators suggested that

more research is needed regarding chemicals and other environmental factors that may increase the risk of cutaneous melanoma.

3.2.4 Other Routes of Exposure

A series of publications from Slotkin and coworkers have provided evidence of neurological effects of parathion, as well as other organophosphate pesticides, dissociated from parathion-induced inhibition of AChE. The experiments were conducted in male and female Sprague-Dawley rats. To avoid the high first-pass removal by the liver, neonatal rats were injected with parathion subcutaneously on postnatal days 1–4 and neurochemical parameters were evaluated in various brain regions within days of dosing or during adulthood. Parathion was tested at doses of 0.02–0.1 mg/kg/day, which were below the threshold for overt toxicity as defined by mortality data. While parathion did not compromise the development of neuritic projections or emergence of the cholinergic phenotype in the forebrain and brainstem in 5-day-old pups (Slotkin et al. 2006a), it did decrease serotonin $5HT_{1A}$ receptors in the brainstem and forebrain but had no significant effect on $5HT_2$ receptors or serotonin transporter in 5-day-old pups (Slotkin et al. 2006b). In another study, examination of rats at older ages showed that parathion upregulated $5HT_{1A}$ receptors with a peak in the frontal/parietal cortex at about 60 days of age, followed by a decrease of the effect in most brain regions and eventually inducing deficits at 100 days of age (Slotkin et al. 2009a). The investigators also showed that parathion produced lasting alterations in acetylcholine markers in the frontal/parietal cortex, temporal/occipital cortex/ midbrain, hippocampus, and striatum in adolescence and adulthood; in general, effects were more pronounced in males than in females (Slotkin et al. 2008). In additional studies, parathion induced long-lasting selective behavioral alterations in adolescence and adulthood, some of which were sex-dependent (Levin et al. 2010; Timofeeva et al. 2008).

Subcutaneous administration of parathion to neonatal rats also caused a metabolic dysregulation in adult rats characterized in males by a net anabolic response at a low dose (0.1 mg parathion/kg) and a catabolic response at a higher dose (0.2 mg parathion/kg) and by a greater sensitivity to catabolic effects in females; the metabolic alterations were consistent with a pre-diabetic state (Lassiter et al. 2008). A likely mechanism for the pre-diabetic state involved a persistent parathion-induced disruption of adenylyl cyclase (the enzyme that synthesizes cyclic adenosine monophosphate [cAMP] from adenosine triphosphate [ATP]) signaling in peripheral tissues, particularly in the liver (Adigun et al. 2010). Studies also showed that a high-fat diet in adulthood reversed the parathion-induced alterations in acetylcholine systems and lessened some of the effects of parathion on serotonin synaptic function (Slotkin et al. 2009b, 2009c), presumably due to global changes in the composition of synaptic membrane lipids. Furthermore,

early exposure to parathion was found to disrupt major control points of lipid metabolism and induced an inflammatory response in adipose tissue. The changes in lipid metabolism were found to interact with deficits in synaptic function which, according to the investigators, may contribute to impaired behavioral performance (Lassiter et al. 2010).

Behavioral effects and effects on the brain morphology have been described following subcutaneous injections of parathion into neonatal rats. For example, treatment of 5-day-old rats with 1.3 or 1.9 mg/kg/day parathion until postnatal day 20 did not affect developmental landmarks such as eye opening or incisor eruption (Stamper et al. 1988). That treatment affected only one out of four tests of reflex development before weaning. However, evaluations conducted post-weaning showed small deficits in tests of spatial memory in both the T-maze and radial arm maze. These effects were associated with significant decreases in brain AChE activity (35–68%) and muscarinic receptor density, but not affinity, in the cerebral cortex. The investigators concluded that early exposure to parathion affected the performance of spatial memory tasks by interfering with the development of the cholinergic system. In a similar study, neonatal rats were administered 0.882 mg/kg/day parathion on gestation days 5–20 and morphological, histochemical, and biochemical tests were conducted in the hippocampus collected on gestation day 21 (Veronesis and Pope 1990). The results showed hippocampal damage consisting of cellular disruption and necrosis in the dentate gyrus, CA4, and CaA3c regions. On postnatal day 12, hippocampal AChE was depressed 73% while muscarinic receptor binding was depressed by 36%. Since the dosing period coincided with a time critical to hippocampal neurogenesis and synapse formation, the resulting changes may translate into permanent neurobehavioral alterations.

3.3 GENOTOXICITY

No information was located regarding genotoxic effects in humans exposed specifically to parathion. A study of 25 male workers in India occupationally exposed to organophosphate pesticides (parathion among them), organochlorine pesticides, and fertilizers reported that the frequency of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes were significantly elevated compared to unexposed control subjects; however, the role of parathion, if any, cannot be determined (Rupa et al. 1988). *In vivo* studies in animals have yielded negative results in tests for induction of micronuclei, chromosomal aberrations, and dominant lethality (Table 3-4). Intraperitoneal administration of a single dose of 10 mg parathion/kg to male mice did not significantly increase the frequency of chromosomal aberrations in bone marrow cells or spermatogonia assessed 12, 24, and 36 hours after dosing (Degraeve and Moutschen 1984). Gavage administration of a single dose of 2.2 mg parathion/kg

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

Species (test system)	End point	Results	Reference
Mammalian cells:			
Mouse spermatogonial cells	Chromosomal aberrations	–	Degraeve and Moutschen 1984
Mouse bone marrow cells	Chromosomal aberrations	–	Degraeve and Moutschen 1984
Mouse bone marrow cells	Micronuclei	–	Kevekordes et al. 1996
Eukaryotic organisms:			
Male mice	Dominant lethal	–	EPA 1977
Male mice	Dominant lethal	–	Degraeve and Moutschen 1984

– = negative results

to male mice or 1.5 mg/kg to female mice did not significantly increase the frequency of micronuclei in bone marrow cells assessed 48 hours after dosing (Kevekordes et al. 1996). Dietary administration of parathion to male mice for 7 weeks at levels of 62.5, 125, or 250 ppm followed by mating for 8 weeks did not provide evidence of mutagenicity by the dominant lethal procedure (EPA 1977). Females were sacrificed at midterm of pregnancy and were scored for early and late fetal deaths and for living fetuses. The lowest dose was intended to induce up to 20% weight loss, mild but transient clinical signs, no inhibition of breeding performance, and no mortality. In another study, male mice were given a single intraperitoneal injection of 10 mg parathion/kg and were then mated with untreated females for 7 consecutive weeks (Degraeve and Moutschen 1984). Pregnant females were sacrificed on day 14 of pregnancy and the numbers of corpora lutea, implants, live embryos, and dead fetuses were recorded. The results showed no significant effects of parathion on the end points monitored. However, administration of 0.3 mg paraoxon/kg resulted in a low number of live embryos per litter with females mated during the first and seventh week after dosing; the former case appeared to be associated with a higher number of pre-implantation loss and the latter case with a lower number of corpora lutea. The differences with control values were not statistically significant. Without specifying, Degraeve and Moutschen (1984) noted that the doses of parathion and paraoxon used, 10 and 0.3 mg/kg, respectively, induced obvious signs of intoxication, but little or no mortality. The data available in animal studies indicate that exposure to environmentally relevant levels of parathion is unlikely to represent a genotoxic hazard. No useful data in humans were found.

Studies of the genotoxic potential of parathion *in vitro* have yielded negative results, with one exception (Table 3-5). Parathion did not induce mutations in *Salmonella typhimurium*, *Escherichia coli*, or *Serratia marcescens* (Fahrig 1974; Mohn 1973; Simmon et al. 1976). Parathion also did not induce mitotic recombination, mitotic gene conversions, or forward mutations in yeast (Fahrig 1974; Gilot-Delhalle et al. 1983; Simmon et al. 1976). Only Gilot-Delhalle et al. (1983) conducted their test of forward mutation in *Schizosaccharomyces pombe* both with and without metabolic activation. In studies with mammalian cells *in vitro*, Nishio and Uyeki (1981) reported the only positive data for an increase frequency of sister chromatid exchanges in cultures of Chinese hamster ovary cells in the presence of parathion and in the absence of an activating system; no tests were conducted with metabolic activation. Tests conducted with equimolar concentrations of paraoxon also yielded positive results, and there was no significant difference in sister chromatid exchange frequencies induced by parathion and paraoxon (Nishio and Uyeki 1981). However, incubation of human lymphocytes with parathion for up to 48 hours did not result in an increase in the frequency of sister chromatid exchanges relative to controls (Kevekordes et al. 1996). The difference between the results of Nishio and Uyeki (1981) and Kevekordes et al. (1996) may be due, in

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

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation	–	No data	Simmon et al. 1976
Escherichia coli K-12	Forward mutation	No data	–	Fahrig 1974
E. coli K-12	Forward mutation	No data	–	Mohn 1973
Serratia marcescens	Reverse mutation	No data	–	Fahrig 1974
Eukaryotic organisms:				
Saccharomyces cerevisiae	Mitotic recombination	–	No data	Simmon et al. 1976
S. cerevisiae	Mitotic gene conversion	No data	–	Fahrig 1974
Schizosacchromyces pombe	Forward mutation	–	–	Gilot-Delhalle et al. 1983
Mammalian cells:				
Cultured human lymphocytes	Sister chromatid exchanges	–	–	Kevekordes et al. 1996
Chinese hamster ovary cells	Sister chromatid exchanges	No data	+	Nishio and Uyeki 1981

+ = positive results; – = negative results

part, to the different test systems used (Chinese hamster ovary cells vs. human lymphocytes) and the difference in the concentrations of parathion tested (mM range vs. μM range, respectively). The studies available suggest that parathion is not a mutagenic compound.

3.4 TOXICOKINETICS

Data on the absorption of parathion after inhalation and oral exposure are very limited, and do not allow for the estimation of absorption rates or fractional uptake by these exposure routes. However, volunteer studies and poisoning incidents confirm that parathion is absorbed through both the respiratory and gastrointestinal tracts. The dermal uptake of parathion has been well-studied in a variety of systems and has been shown to be highly variable, ranging from 9 up to 100%, depending on anatomical site, in one study of volunteers. Dermal uptake is also affected by parathion formulation, ambient temperature, relative humidity, and airflow across the exposed skin.

Few data on the distribution of parathion in body tissues are available; these data are limited to oral and intravenous or intraperitoneal exposure routes. Available *in vivo* data show high affinity of parathion for adipose tissue and the liver, with lower levels seen in the kidney, muscles, lung, and brain of animals exposed *in vivo*. Transplacental transfer of the parathion or its metabolite(s) has been demonstrated in sheep. In blood, as much as 94–99% of parathion is bound to proteins, particularly albumin.

The metabolism of parathion is important in assessing its toxicity, as bioactivation to the paraoxon metabolite is a key step in the toxicity associated with AChE inhibition. Metabolism of parathion reflects complex interactions among a number of cytochrome P450 isozymes capable of both bioactivation and detoxification, as well as detoxification by carboxylesterases and A-esterases, and elimination facilitated by glucuronidase, glutathione transferase, and other conjugating enzymes. The involvement of numerous bioactivating and detoxifying enzymes suggests that polymorphisms in the genes encoding these enzymes might lead to substantial interindividual variability; in addition, sex, age, and pregnancy status have been shown to change the metabolism of parathion in animals.

Parathion is eliminated primarily through metabolism and subsequent excretion of metabolites in urine; a small proportion of metabolites is eliminated through the feces. Excretion of metabolites in urine has been shown to continue for days after exposure has concluded.

3.4.1 Absorption

There are few data on the absorption of parathion after inhalation and oral exposure. Available information on inhalation exposure is limited to early volunteer studies in humans, in which the exposure levels were not measured; these studies indicate only that parathion can be absorbed via the respiratory tract. Likewise, an occupational study, volunteer studies, and case reports of poisonings in which AChE inhibition or parathion metabolites were detected confirm the oral absorption of parathion, but do not indicate the rate or degree of absorption. The oral bioavailability of parathion in dogs has been estimated to range from 1 to 29%. The dermal uptake of parathion has been extensively studied in humans, animals, and *in vitro*; the data indicate large variability in dermal absorption rates, which depend on ambient temperature, relative humidity, anatomical area of skin exposed, and skin condition (Gosselin et al. 2005). Depending on the anatomical region, between 9 and 100% of the applied dose was absorbed across the skin of volunteers in a study by Maibach et al. (1971).

3.4.1.1 Inhalation Exposure

The parathion metabolite, *p*-nitrophenol, was detected in a volunteer exposed to parathion via inhalation of vapors for 5 consecutive days (Hartwell et al. 1964). The exposure concentrations were not measured or estimated, but were generated by spreading fresh technical parathion over 36 square inches of area and heating to 105–150°F. The authors also measured decreases in cholinesterase activity in erythrocytes and plasma in volunteers exposed to parathion as vapor or dust, or from a chamber sprayed with an insecticide sprayer (exposure concentrations were neither measured nor estimated). These data indicate that parathion vapor and dust are absorbed across the respiratory tract, but do not provide enough information to estimate the fractions absorbed. An occupational study determined a maximum concentration of parathion in air of 0.8 mg/m^3 and an estimated average of about 0.2 or 0.3 mg/m^3 (Brown and Bush 1950). This level of exposure appeared to be associated with reduced levels of both plasma and erythrocyte cholinesterase activities.

3.4.1.2 Oral Exposure

Case reports of humans accidentally or intentionally poisoned by ingestion of parathion (i.e., Eyer et al. 2003 and others in Section 3.2.2) provide evidence of gastrointestinal absorption, but do not include measurements of parathion intake. For example, the concentration of parathion in plasma was 318 ng/mL in a 72-year old man hospitalized after ingesting an unknown amount of parathion in a suicide attempt (Hoffman and Papendorf 2006). Furthermore, absorption estimates made from poisoning incidents would

not be predictive of absorption in the absence of medical interventions that are intended to interfere with absorption (e.g., induced vomiting, gastric lavage, or activated charcoal). Morgan et al. (1977) measured metabolites of parathion in the urine of volunteers who ingested 1 or 2 mg/day of parathion in corn oil for 5 consecutive days, also providing evidence for oral absorption. Blood samples were not collected. Urine samples were not collected during the 5-day exposure period (collected only during the 2-day postdosing period); in addition, the average cumulative excretion of metabolites was not reported. Thus, these data do not provide a reliable estimate of oral absorption.

Braeckman et al. (1983) estimated the oral bioavailability of parathion to be between 1 and 29% in seven mongrel dogs given 10 mg/kg ^{14}C parathion via gavage. Bioavailability was estimated based on the ratios of the areas under the serum concentration-time curves after oral and intravenous administration. The peak serum concentrations in the seven treated dogs varied from 0.01 to 0.41 μg/mL, and time to peak ranged from 30 minutes to 5 hours, indicating substantial interindividual variability. Urinary excretion of radioactivity was similar after oral and intravenous administration of parathion to two dogs; the oral absorption estimates were 57 and 98% based on the ratios of the percentages of dose excreted after the two exposures.

Puga and Rodrigues (1996) estimated LD_{50} values in order to evaluate the effect of different solvents on the oral absorption of parathion in rats. Administration of 2% parathion (w/v) in arol vehicle yielded a slightly higher oral LD_{50} (130 mg/kg; 95% CI 98–152) than administration in xylene (LD_{50} of 102 mg/kg; 95% CI 78–121), suggesting greater oral absorption from xylene than from arol; however, the difference was small and the CIs overlapped.

3.4.1.3 Dermal Exposure

Evidence of dermal absorption of parathion is available from poisoning incidents in the general population (Eitzman and Wolfson 1967; Lores et al. 1978) and among agricultural workers (Grob et al. 1950; Milby et al. 1964; Quinby and Lemmon 1958). Lores et al. (1978) reported that the concentration of parathion in the whole blood was 0.034 ppm in a 13-year-old boy who died from organophosphate poisoning via dermal contact with treated tobacco; the only metabolite detected was diethyl phosphorothioate (0.26 ppm). In agricultural workers, Milby et al. (1964) estimated that a picker exhibiting cholinergic signs was exposed to a total of <4 mg/day and that dermal exposure contributed the highest amount, approximately 3.2 mg.

Available data indicate wide variability in the rates and fractional absorption of parathion across human skin. Dermal absorption rates vary depending on the form of parathion in contact with skin (e.g., vapor or dust), the temperature and relative humidity of the ambient air, the anatomical location of the exposed skin, and the condition of the exposed skin (Hayes et al. 1964; Maibach et al. 1971; Gosselin et al. 2005).

Measurement of urinary metabolites has suggested that dermal exposure may yield higher absorbed doses than respiratory exposure during parathion spraying activities. Durham et al. (1972) estimated the dermal and respiratory exposure of workers engaged in spraying parathion in orchards, and measured urinary excretion to estimate absorption. The average dermal exposure, extrapolated from measurements of parathion on pads worn by the workers on clothing near bare skin, was 137.9 mg. Based on total urinary excretion of *p*-nitrophenol (other metabolites were not measured), average dermal absorption was estimated to be 1.23% after subtracting the estimated respiratory exposure of 0.24 mg. The study authors also conducted controlled experiments to assess respiratory and dermal exposure separately with workers wearing either protective clothing or a respirator during exposure to an airblast spray machine. In these experiments, dermal exposure proved to be much greater (0.497–0.666 mg absorbed dose based on excretion of *p*-nitrophenol) than respiratory exposure (0.006–0.088 mg).

Higher ambient temperature is associated with higher dermal penetration of parathion in humans. Funckes et al. (1963) and Hayes et al. (1964) conducted a series of experiments investigating dermal absorption of parathion in various forms and at different ambient temperatures. Funckes et al. (1963) observed temperature-related increases in the urinary excretion of *p*-nitrophenol after dermal exposure to 2% parathion dust on one hand and forearm of each of four volunteers. Peak rates of *p*-nitrophenol excretion, occurring 5–6 hours after exposure, averaged 9.7, 25, 21.9, and 88.6 μg/hour at 58, 70, 82, and 105°F (respectively), indicating temperature-dependent increases in dermal penetration. Likewise, experiments by Hayes et al. (1964) showed markedly increased urinary excretion of *p*-nitrophenol at higher temperatures after 3 hours of exposure to filter paper pads containing 46–51 g of parathion. The total excretion of parathion over the 3 days after exposure was ~3- and 5-fold higher at 80 and 104°F, respectively, compared with similar exposure at 52°F.

Maibach et al. (1971) observed substantial variation in the absorption of parathion across skin from different anatomical regions of volunteers. In each experiment, six volunteers received a topical application of 4 μg/cm^2 ^{14}C-parathion, and urine was collected for 5 days after dosing. Based on total urinary excretion of radioactivity (and corrected for incomplete urinary recovery) the highest absorption estimates, ~100 and ~64% of the applied dose, were observed when the dose was applied to scrotal and

axillary skin, respectively; the lowest absorption estimates, ~9 and 12% of applied dose, were across the skin of the forearm and palm, respectively. Areas of the face and scalp exhibited relatively high absorption (about 30–40%); the study authors suggested that the presence of follicles in these areas enhanced penetration.

Experiments with animal skin tested *in vitro* also demonstrate the dependence of dermal uptake on ambient temperature and relative humidity. Chang and Riviere (1991) showed that increased humidity enhanced the penetration of parathion across porcine skin *in vitro*; the mean absorption efficiency increased more than 2-fold when relative humidity was increased from 60 to 90% in 8-hour experiments using doses from 4 to 400 μg/cm^2. Higher penetration was also observed when the air or perfusate temperature was increased from 37 to 42°C (Chang and Riviere 1991).

Knaak et al. (1984) evaluated dermal absorption of ^{14}C-parathion applied to the clipped backs of male and female rats. Male rats received 44 μg/cm^2 parathion over 13.7 cm^2 of skin, while females received 48 μg/cm^2 parathion over 12.5 cm^2 of skin. Recovery of radioactivity from excreta, plasma, liver, kidney, heart, and remaining carcass indicated that 59.2 and 57% of the applied dose was absorbed by males and females, respectively. The authors estimated permeability rates of 0.33 and 0.49 μg/hour/cm^2 for males and females, respectively, based on elimination from plasma; permeability constants (K_p) were estimated as 7.5x10^{-3} cm/hour for males and 1x10^{-2} cm/hour for females.

Based on quantification of radioactivity in plasma and excreta, Qiao and Riviere (1995) estimated the mean systemic bioavailability of parathion (40 μg/cm^2) applied to the back and abdomen of weanling pigs to be 14.7–19.7 and 8.9–9.2%, respectively.

Puga and Rodrigues (1996) estimated dermal LD_{50} values in order to evaluate the effects of different solvents on the percutaneous absorption of parathion in rats. Parathion (2% w/v) in arol or xylene vehicle was applied to the shaved back of rats over a 16 cm^2 area. As was seen with the oral study by these authors, administration in arol yielded a slightly higher LD_{50} (310 mg/kg; 95% CI 298–359) than administration in xylene (LD_{50} of 242 mg/kg; 95% CI 220–276), suggesting greater dermal absorption from xylene than from arol. However, plasma cholinesterase activity did not differ significantly in the rats treated with the different vehicles; thus, it is not clear that absorption differences were entirely responsible for the different lethality estimates.

Nabb et al. (1966) measured AChE inhibition to estimate dermal absorption of parathion by male albino rabbits. Technical parathion was applied to the animals' clipped sides while the rabbits were lightly anaesthetized; the parathion was left in place until symptoms of poisoning appeared between 5 and 8 hours later. Comparison of AChE inhibition rates after dermal exposure with rates observed with intravenous exposure yielded absorption rate estimates of 0.021–0.39 μg/minute/cm^2 (Nabb et al. 1966).

The flux of ^{14}C-parathion across freshly harvested skin flaps from weanling Yorkshire pigs peaked at about 4 hours after the end of dosing, reaching a peak rate of almost 0.01% of the dose/minute (Williams et al. 1990). The flux rate declined to about half the peak rate by 10 hours postexposure (Williams et al, 1990). A 5 cm^2 area of the skin flap was treated with 40 μg/cm^2 parathion for 8 hours. The authors estimated the fraction of dose that would be absorbed through 6 days postdosing to be 0.066, which compared favorably with the fraction of dose absorbed by whole animals exposed by topical application of 40 μg/cm^2 parathion on the abdomen (0.064, calculated from total excretion of radioactivity over 6 days).

In vitro estimates of parathion permeability across skin are shown in Table 3-6. Available *in vitro* data (Chang and Riviere 1993; Miller and Kasting 2010; Moody et al. 2007; Wester and Maibach 1985) suggest that the mass of parathion absorbed across the skin increases in proportion to applied dose up to doses as high as 3,200 μg/cm^2. Van der Merwe et al. (2006) measured the flux of parathion across porcine skin over the course of a 480-minute exposure at six different applied doses (6.3, 11.1, 22.5, 43.3, 106.9, and 209.1 μg/cm^2). The peak flux rate, as measured in percent of dose per hour, occurred at 180 minutes after the beginning of exposure; the rate remained the same for the remainder of the exposure time.

Qiao et al. (1996) studied how the interactions between two different solvents, dimethyl sulfoxide (DMSO) and acetone, the surfactant sodium lauryl sulfate (SLS), the rubefacient methyl nicotinate (MNA), and the reducing agent stannous chloride ($SnCl_2$) affected the absorption of radiolabeled parathion through isolated perfused porcine skin. The investigators used a full 2x4 factorial design to study treatment effects and potential interactions. The results showed that more radiolabeled was absorbed with DMSO than with acetone. SLS increased absorption of parathion in both DMSO and acetone vehicles, while MNA reduced absorption rates in DMSO and acetone without significantly changing total absorption. Stannous chloride blocked absorption of parathion and increased residue level on the skin surface and in the stratum corneum. Overall, the study showed interactive effects at multiple levels that need to be considered when studying dermal absorption of a chemical in a mixture.

Table 3-6. *In Vitro* Estimates of Parathion Dermal Permeability

Reference	Applied dose	Duration	Basis for absorption/ permeability estimate	Percent absorption of applied dose	Permeability coefficient (K_p; cm/hour)	Conditions
Wester et al. 2000	4 μg/cm^2	96 hours	Receptor liquid only	1.78±0.41	1.89x10^{-4}	Permeability of ^{14}C-parathion through human skin samples (1 cm^2 and 500 μm thick) measured in flow-through skin diffusion cells
				0.29±0.17	2.04x10^{-5}	As above with dry uniform material covering
				0.65±0.16	6.16x10^{-5}	As above with wet uniform material covering
Miller and Kasting 2010	0.4 μg/cm^2 4 μg/cm^2 41 μg/cm^2 117 μg/cm^2	76 hours	Receptor liquid + dermis	29.9±4.2 31.8±4.1 32.1±4.4 24.3±4.9	Not reported	Permeability of ^{14}C-parathion through human skin samples (400 μm thick) measured in modified Franz skin diffusion cells; unoccluded
	0.4 μg/cm^2 4 μg/cm^2 41 μg/cm^2 117 μg/cm^2			57.2±8.5 60.0±5.3 53.0±4.2 35.2±3.6	Not reported	As above, but occluded
Boudry et al. 2008	15 μg/cm^2	24 hours	Receptor liquid only receptor liquid + skin + stratum corneum	7.5±7.3 23.4±10.6	Not reported	Permeability of ^{14}C-parathion in ethanol through human abdominal skin samples (0.84 cm^2 and 420–550 μm thick) measured in dynamic glass diffusion cells; unoccluded
Shehata-Karam et al. 1988	38 μg/cm^2	48 hours		78.64	Not reported	Permeability of ^{14}C-parathion through fresh human newborn full thickness (882–1,093 μm) foreskin samples measured in modified static diffusion cell system

Table 3-6. *In Vitro* Estimates of Parathion Dermal Permeability

Reference	Applied dose	Duration	Basis for absorption/ permeability estimate	Percent absorption of applied dose	Permeability coefficient (K_p; cm/hour)	Conditions
Chang and Riviere 1991	4 μg/cm^2 40 μg/cm^2 400 μg/cm^2	8 hours	Receptor liquid only	7.69 1.91 0.46	Not reported	Permeability of ^{14}C-parathion through weanling pig skin (0.32 cm^2 and 500 μm thick) samples measured in Bronaugh flow-through Teflon diffusion cells at 60% relative humidity
	4 μg/cm^2 40 μg/cm^2 400 μg/cm^2			16.91 5.25 1.18	Not reported	As above, but 90% relative humidity

3.4.2 Distribution

Few data on the distribution of parathion in body tissues are available; only oral, intravenous, or intraperitoneal exposure routes were used in the available studies. Available *in vivo* data show high affinity of parathion for adipose tissue and the liver (Garcia-Repetto et al. 1995; Poore and Neal 1972) that is also seen in *in vitro* studies (Jepson et al. 1994; Sultatos 1990). Lower levels of parathion and/or paraoxon have been detected in the kidney, muscles, lung, and brain of animals exposed *in vivo* (Nielsen et al. 1991; Poore and Neal 1972). Radioactivity has been detected in ovine fetal blood and amniotic fluid after maternal intravenous exposure to ^{14}C-parathion, indicating transplacental transfer of the compound or its metabolite(s) (Villaneuve et al. 1971). In blood, parathion is largely bound to proteins, particularly albumin; a number of studies have suggested that 94–99% of parathion is protein-bound at equilibrium (Braeckman et al. 1983; Foxenberg et al. 2011; Nielsen et al. 1991).

3.4.2.1 Inhalation Exposure

No data on the distribution of parathion after inhalation exposure were located in the available literature.

3.4.2.2 Oral Exposure

Garcia-Repetto et al. (1995) measured the tissue concentrations of parathion at intervals between 4 hours and 20 days after dosing male Wistar rats via gavage with parathion in olive oil at 1/3 the oral LD_{50}. Parathion and paraoxon in various tissues were analyzed by gas chromatography. Parathion was detectable in adipose tissue and muscle 4 hours after dosing, and in these tissues as well as the liver and brain 4 days postdosing. Tissue:blood partitioning coefficients estimated for seven different time intervals showed increasing distribution to all four tissues; the highest partition coefficients (4.11–20.76) were in the liver at ≥12 days postdosing. Paraoxon appeared in the blood and adipose tissue within 4 hours of dosing and in the liver 8 days after dosing. When paraoxon was administered orally, only the liver showed tissue:blood partition coefficients >1 (ranging up to ~23 at 12–14 days postdosing).

Poore and Neal (1972) measured bound ^{35}S in the tissues of rats given an oral dose of 29 mg/kg ^{35}S parathion and sacrificed 35 minutes later; the results are shown in Table 3-7. The highest concentrations of ^{35}S were (in descending order) in the liver, intestine, kidney, muscles, lung, and brain.

Table 3-7. Concentration of Bound ^{35}S in Tissues of Male Sprague-Dawley Rats 35 Minutes After a Single Dose of 29 mg/kg ^{35}S Parathion Orally

Tissue	Tissue concentration (pmol ^{35}S bound/mg precipitate)
Liver	31.97±4.25
Intestine	13.75±6.41
Kidney	7.51±1.36
Intercostal muscle	5.44±0.26
Lung	3.99±1.02
Leg muscle	1.73±0.54
Brain	1.04±0.36
Heart	0.93±0.40
Diaphragm	0.70±0.09

Source: Poore and Neal 1972

3.4.2.3 Dermal Exposure

No data on the distribution of parathion after dermal exposure were located in the available literature.

3.4.2.4 Other Routes of Exposure

When piglets of different ages were administered 0.5 mg/kg ^{14}C-radiolabelled (ring-2,6) parathion intravenously, radioactivity was detected in the plasma as well as the kidney, liver, lung, brain, heart, and muscle tissues (Nielsen et al. 1991). Age-related differences in tissue distribution were observed; newborn piglets (1–2 days) exhibited much higher concentrations in all tissues than 1- or 8-week-old piglets. Mean tissue concentrations are shown in Table 3-8 for all three age groups, as are tissue:plasma concentration ratios; concentrations of parathion and its metabolites in plasma, liver, and kidney are shown in Table 3-9. Braeckman et al. (1983) estimated the hepatic extraction ratio as the percentage difference in parathion concentration (parent compound, measured by gas chromatography) in the femoral artery (as a surrogate for the portal vein concentration) compared with the hepatic vein. In anaesthetized dogs given intravenous administration of parathion in a foreleg vein, the hepatic extraction ratio was estimated to be 82–97%.

In vitro estimates of parathion partitioning to various tissues confirm the high partitioning to adipose tissue and liver (Jepson et al. 1994; Sultatos 1990); the available values are listed in Table 3-10.

Studies of pregnant animals demonstrate changes in toxicokinetics associated with physiological changes during gestation, and also show that parathion can cross the placenta. The distribution of parathion from blood to liver after intraperitoneal injection of 5 mg/kg was lower in pregnant mice (liver:blood ratio of 1.42) than in virgin mice (liver:blood ratio of 15.35) (Weitman et al. 1986). The authors postulated that the higher blood concentrations of parathion in pregnant mice would be available for extrahepatic activation and result in the higher toxicity of this compound in pregnant animals. Villeneuve et al. (1971) showed that ^{14}C-parathion administered intravenously at a dose of 1 mg/kg to pregnant sheep resulted in transfer of radioactivity to the fetal blood and amniotic fluid.

In the blood at equilibrium, 94–99% of parathion is bound to proteins, while only 60% of paraoxon is bound. Available information suggests that the degree of binding does not vary at parathion or paraoxon concentrations up to 50 μM. Nielsen et al. (1991) reported that 97% of parathion administered

Table 3-8. Tissue Distribution of ^{14}C in Piglets 3 Hours After a Single Dose of 0.5 mg/kg ^{14}C-Parathion Intravenously

	Tissue concentration (ng/g or mL)			Tissue:plasma ratio		
Tissue	Newborn	1 Week old	8 Weeks old	Newborn	1 Week old	8 Weeks old
Plasma	262±145	120±24	69±11	–	–	–
Kidney	1,360±546	746±129	509±83	5.2±0.6	6.5±2.3	7.4±0.8
Liver	1,254±638	156±10	46±8	5.4±2.1	1.3±0.3	0.67±0.04
Lung	421±92	78±9	47±5	1.6±0.3	0.66±0.10	0.71±0.18
Brain	215±76	38±10	16±4	0.8±0.3	0.33±0.15	0.25±0.10
Heart	302±85	53±3	22±2	1.1±0.3	0.50±0.19	0.32±0.07
Muscle	484±92	110±38	13±2	1.8±0.3	0.95±0.43	0.19±0.04

Source: Nielsen et al. 1991

Table 3-9. Concentrations of Parathion and its Metabolites in Piglets 3 Hours After a Single Dose of 0.5 mg/kg ^{14}C-Parathion Intravenously

	Tissue concentration (ng/g or mL)		
Tissue	Newborn	1 Week old	8 Weeks old
Total ^{14}C			
Plasma	262±145	120±24	69±11
Kidney	1,360±546	746±129	509±83
Liver	1,254±638	156±10	46±8
Parathion			
Plasma	83±47	11±5	3±1
Kidney	272±122	37±15	5±3
Liver	840±426	17±28	1±1
Paraoxon			
Plasma	2±0.8	0.06±0.11	0.14±0.06
Kidney	Not detected	Not detected	Not detected
Liver	6±5	0.2±0.5	Not detected
p-Nitrophenol			
Plasma	14±4	4±0.5	3±0.7
Kidney	762±136	433±127	81±15
Liver	100±50	12±9	1±1

Source: Nielsen et al. 1991

Table 3-10. Partition Coefficients for Parathion in Mice and Rats

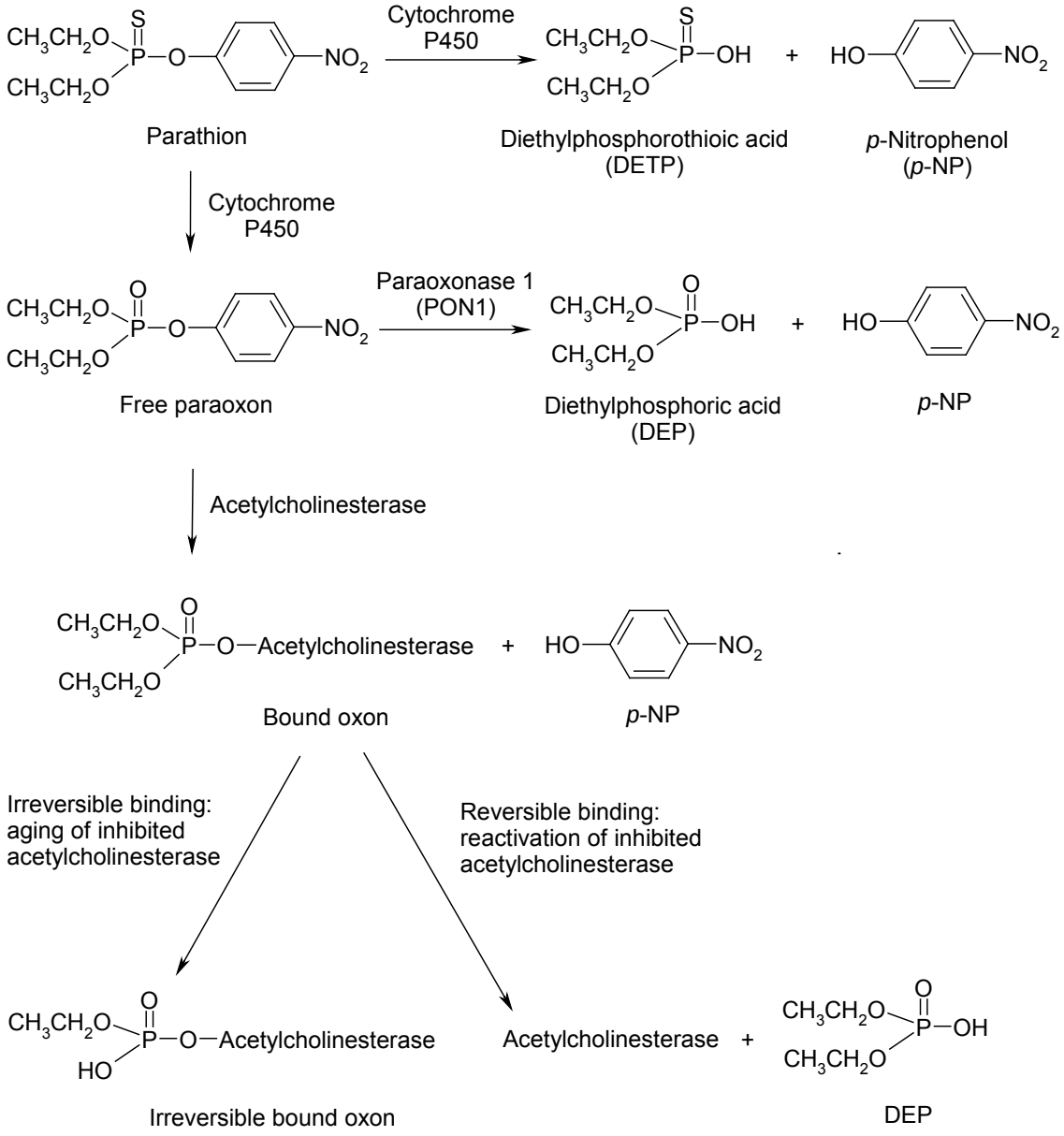
Tissue	Mouse	Rat	Method	Reference
Blood:saline		54.2	High pressure ultrafiltration	Jepson et al. 1994
Fat: saline		5,365	High pressure ultrafiltration	
Muscle:saline		136	High pressure ultrafiltration	
Liver:saline		270	High pressure ultrafiltration	
Skin: saline		160–180	High pressure ultrafiltration	
Liver: blood	6.56		Equilibrium dialysis	Sultatos 1990
Lung: blood	2.55		Equilibrium dialysis	
Brain: blood	3.51		Equilibrium dialysis	
Diaphragm: blood	1.37		Equilibrium dialysis	
Fat: blood	11.84		Equilibrium dialysis	
Rapidly perfused tissue:blood	6.56		Equilibrium dialysis	
Slowly perfused tissue:blood	4.51		Equilibrium dialysis	

intravenously to piglets was bound to plasma proteins. The fraction protein-bound did not differ by age (newborn and 1- and 8-week-old piglets were tested) or plasma concentration of parathion (ranging from 10 to 250 ng/mL). Foxenberg et al. (2011) evaluated parathion (25 or 50 μM) and paraoxon (10, 25, or 50 μM) binding to human serum albumin using the equilibrium dialysis method. Equilibrium was reached at about 60 minutes for both compounds; at this time, about 94% of parathion was bound to albumin and about 6% remained free at both concentrations, while about 60% of paraoxon was bound and 40% was free (at all concentrations). Sultatos et al. (1984) also used the equilibrium dialysis method to assess binding of parathion to fatty acid-free bovine serum albumin; the authors reported an apparent Kd value of 11.1 μM. Braeckman et al. (1983) obtained similar results (protein binding of 99%) in both human and dog serum treated with parathion *in vitro*; the fraction bound did not vary with parathion concentration in the range tested (0.2–30 μg/mL). When human albumin solution containing a typical albumin concentration was used instead of human serum, the measured protein binding fraction was also high (98%), indicating that parathion is largely bound to albumin in serum (Braeckman et al. 1983).

3.4.3 Metabolism

The metabolism of parathion is important in assessing its toxicity, as bioactivation to the paraoxon metabolite is a key step in the toxicity associated with AChE inhibition. Figure 3-3 outlines the metabolic pathways for parathion. Metabolism of parathion reflects complex interactions among a number of cytochrome P450 isozymes capable of both bioactivation and detoxification, as well as detoxification by carboxylesterases and A-esterases, and elimination facilitated by glucuronidase, glutathione transferase, and other conjugating enzymes. The complexity of these metabolic pathways is increased by the potential for both induction of P450 enzymes and inhibition of P450 enzymes by a sulfur radical produced when parathion is metabolized. The involvement of numerous bioactivating and detoxifying enzymes suggests that polymorphisms in the genes encoding these enzymes might lead to substantial interindividual variability; this variability has been seen in studies of paraoxon formation after incubation of human liver microsomes from a number of donors with parathion (Mutch and Williams 2006; Mutch et al. 2003). Sex, age, and pregnancy status have been shown to change the metabolism of parathion in animals. Pregnancy has been shown to alter the metabolism of parathion, possibly by increasing the systemic availability of parathion for extrahepatic metabolism (Weitman et al. 1983). In addition, an age-related decline in parathion toxicity was postulated to occur via enhancement of detoxification by A-esterases (Benke and Murphy 1974). Enhanced toxicity in female rats was associated with decreased detoxification of parathion (Benke and Murphy 1974).

Figure 3-3. Metabolism of Parathion



Sources: Buratti et al. 2003; Gosselin et al. 2004; El-Masri et al. 2004; Mutch et al. 2003

The bioactivation of parathion is generally well-understood, and is similar to other phosphorothionates. The initial step in bioactivation of parathion is desulfuration by cytochrome P450, yielding a theoretical unstable intermediate compound (phosphoxythiiran) that decomposes to paraoxon and a sulfur (S:) atom. Paraoxon may react with AChE to form the bound oxon and free *p*-nitrophenol, or it may be detoxified by A-esterase (also known as paraoxonase) to diethylphosphoric acid and *p*-nitrophenol. The bound oxon has two potential fates: irreversible binding to AChE, leading to "aging" of inhibited AChE (irreversible inhibition; see Section 3.5 for further details) or reversible binding with the release of free AChE and diethylphosphoric acid (Gosselin et al. 2005).

Cytochrome P450 isozymes are also responsible for detoxification of parathion via dearylation. This process, which may represent an alternative fate for the putative phosphoxythiiran intermediate (Tang et al. 2006), yields diethylphosphorothioic acid and *p*-nitrophenol. Diethylphosphorothioic acid may undergo desulfuration to diethylphosphoric acid. *p*-Nitrophenol may be eliminated as is or conjugated with glycine, glutathione, glucuronic acid, or sulfuric acid for excretion in urine. Paraoxon, diethylphosphorothioic acid, and diethylphosphoric acid were also shown to be formed non-enzymatically by a homogeneous preparation of rabbit liver cytochrome P450 (Kamataki et al. 1976). The three metabolites appeared to have been formed by breakdown by different pathways of a common enzymatically formed intermediate thought to be a sulfine derivative of parathion.

Neal (1967) first suggested that different cytochromes are involved in the formation of paraoxon and diethylphosphorothionate by showing that some enzyme inhibitors inhibited the formation of one parathion metabolite but not the other. For example, *p*-chloromercuribenzoate, Cu^{2+}, and 8-hydroxy-quinoline inhibited the formation of diethylphosphorothionate more than the formation of paraoxon. A number of investigators have attempted to identify the primary cytochrome isoforms involved in bioactivation and detoxification of parathion using recombinant human cytochromes (Buratti et al. 2003; Foxenberg et al. 2007; Mutch et al. 2002, 2003) and human liver microsomes (Mutch and Williams 2006; Mutch et al. 2003). Estimates of K_m, V_{max}, and in some cases, intrinsic clearance rate (V_{max}/K_m) for individual cytochrome enzymes have been calculated by Foxenberg et al. (2007), Mutch et al. (2006), and Buratti et al. (2002). Example estimates from Foxenberg et al. (2007) are shown in Table 3-11. Other studies have examined correlations between paraoxon formation and cytochrome-specific enzyme reactions, enzyme activities, or other cytochrome-specific markers (Buratti et al. 2002; Mutch et al. 1999) or by measuring the change in paraoxon formation that occurs when specific cytochromes are inhibited (Buratti et al. 2003; Butler and Murray 1997; Huhr et al. 2000). Taken together, the available data suggest that CYP1A2, CYP2B6, CYP2C19, and CYP2C8 may be important producers of paraoxon at low

Table 3-11. CYP-Specific Metabolism of Parathion by Recombinant Human P450s

Parameters	V_{max} (pmol/minute/nmol P450)	K_m (μM)	V_{max}/K_m (Clint)
Paraoxon formation			
CYP1A2	6,131±90.1	1.63±0.13	3.755
CYP2B6	4,827±134	0.61±0.08	7.875
CYP2C9	1,140±47.7	9.78±1.63	0.117
CYP2C19	4,879±73.7	0.56±0.04	8.705
CYP3A4	14,009±767	65.5±6.83	0.214
CYP3A5	2,020±540	43.2±27.1	0.047
CYP3A7	–	–	–
p-Nitrophenol formation			
CYP1A2	5,656±83.9	2.15±0.16	2.637
CYP2B6	1,804±46.4	0.74±0.10	2.447
CYP2C9	742±63.3	12.1±4.01	0.061
CYP2C19	2,338±65.4	0.60±0.09	3.872
CYP3A4	15,738±488	31.2±2.40	0.504
CYP3A5	1,175±1,039	68.2±121	0.017
CYP3A7	1,739±201	37.3±10.6	0.047

Source: Foxenberg et al. 2007

parathion exposures, and CYP2C9, CYP2D6, and CYP3A4/5 become more important at higher parathion exposures.

The initial step in bioactivation of parathion is desulfuration by cytochrome P450, yielding a theoretical unstable intermediate compound (phosphoxythiiran) that decomposes to paraoxon and a sulfur (S:) atom. While paraoxon is the active inhibitor of AChE, the free sulfur atom, S, is reactive, and can damage nearby proteins including the cytochromes (Tang et al. 2006).

The primary urinary metabolites identified in humans and animals exposed to parathion are *p*-nitrophenol, diethylphosphoric acid, and diethylphosphorothioic acid. Morgan et al. (1977) quantified levels of *p*-nitrophenol, diethylphosphoric acid, and diethylthiophosphate in the urine of four volunteers who ingested 1 or 2 mg/day parathion in corn oil for 5 consecutive days. Urinary excretion of diethylphosphoric acid represented between 3 and 13% of the daily dose of parathion during the first 24 hours postdosing and between 3 and 9% during the second 24 hours; *p*-nitrophenol and diethylthiophosphoric acid excretion represented 2–8 and 1–3% of the administered dose, respectively, during the first 24 hours and were not detected during day 2 (Morgan et al. 1977).

Urinary metabolites of parathion in male Sprague-Dawley rats given three consecutive daily gavage doses of 3.73 or 37.3 mg parathion/rat/day in peanut oil included diethylphosphoric acid, diethylphosphorothioic acid, and *p*-nitrophenol. The study authors estimated that diethylphosphoric acid and diethylphosphorothioic acid excretion represented 39.6 and 41.2% of the low and high administered doses, respectively, while *p*-nitrophenol excretion represented 37.3 and 11.8%, respectively, of the administered doses (Bradway et al. 1977).

Conjugates of *p*-nitrophenol have also been detected in the urine of humans exposed to parathion. Oneto et al. (1995) detected the sulfate and glucuronide conjugates of *p*-nitrophenol in the urine of a 20-year-old woman who died of parathion ingestion. *p*-Nitrophenol glururonide, *p*-nitrophenol sulfate, and free *p*-nitrophenol constituted approximately 7, 80, and 13%, respectively, of the total urinary *p*-nitrophenol.

Nielsen et al. (1991) measured urinary metabolites in newborn, 1-week-old, and 8-week-old piglets given a single dose of 0.5 mg/kg ^{14}C-parathion intravenously. The primary metabolites identified in urine were *p*-nitrophenyl-glucuronide (85% of the excreted radioactivity), *p*-nitrophenyl-sulfate (6%), and free *p*-nitrophenol (1%). The structural location of the radioactive label was not reported, but is presumed to be on the ring based on the detected urinary metabolites, which did not include diethylphosphoric acid or

diethylthiophosphoric acid. Hollingworth et al. (1973) identified the glutathione conjugate of *p*-nitrophenol when rat or mouse liver soluble fraction was incubated with paraoxon.

Parathion is bioactivated primarily in the liver, but also in extrahepatic tissues including the lung and brain. Norman and Neal (1976) observed metabolism of parathion to paraoxon and diethylphosphoric acid in rat lung microsomes incubated with ^{14}C-parathion ($5x10^{-5}$ M) in the presence of an NADPH-generating system *in vitro*, and this metabolism was inhibited by cytochrome inhibitors SKF-525A and piperonyl butoxide. The authors also detected paraoxon and diethylphosphoric acid when the 250,000 g centrifugal precipitate from rat brain was incubated with $15x10^{-5}$ M parathion. Poore and Neal (1972) detected radioactivity in the liver, lung, and brain of rats given an intraperitoneal dose of ^{35}S, ^{32}P-parathion (18 mg/kg). In addition, the authors measured ^{35}S in a number of tissues after oral administration of 29 mg/kg ^{35}S-parathion to adult male rats; radioactivity was detected in the liver, intestine, kidney, intercostal muscle, lung, leg muscle, brain, heart, and diaphragm. While it is possible that metabolites were formed in the liver and subsequently transported to other tissues, the authors postulated that this was unlikely given the reactivity of the sulfur formed by metabolism of parathion. Neal (1967) incubated microsomes with the 9000 g supernatant from four tissues with 0.35 μM parathion and measured the metabolites formed by each using thin-layer chromatography. The highest rate of metabolism was in the liver (98, 417, and 353 μmol/hour/g tissue formation of paraoxon, diethylphosphorothionate, and diethylphosphate, respectively) followed by kidney (32, 13, and 3 μmol/hour/g tissue), lung (13, 9, and 3 μmol/hour/g tissue), and brain (4, 9, and 2 μmol/hour/g tissue).

There is some evidence for dose-dependence of parathion metabolism to *p*-nitrophenol. Bradway et al. (1977) reported that the fractional urinary excretion of *p*-nitrophenol was lower (11.8% of administered dose) in male rats given 37.3 mg parathion/day for 3 days than in those given 3.73 mg/day for 3 days (37.3% of administered dose). The fractional excretion of diethylphosphoric acid and diethylphosphothioic acid (combined) was similar (~40%) at both doses (Bradway et al. 1977).

Physiological changes during pregnancy may alter the metabolism of parathion. Weitman et al. (1986) observed no differences between pregnant (gestation day 19) and nonpregnant mice in the levels of parathion, paraoxon, or *p*-nitrophenol measured in liver perfusate after 45 minutes of perfusion, suggesting that pregnancy does not alter the total hepatic metabolism of parathion. However, Weitman et a l. (1983) observed higher concentrations of both parathion and paraoxon in the blood and brain of pregnant (gestation day 19) mice given a single intraperitoneal dose of 5 mg parathion/kg compared with virgin mice given the same treatment; the higher levels of paraoxon correlated with significantly greater

inhibition of plasma and brain cholinesterase and with greater cholinergic toxicity in the pregnant mice. The authors suggested the possibility that extrahepatic metabolism of parathion might be a partial explanation for the enhanced toxicity in pregnant animals (Weitman et al. 1983).

Benke and Murphy (1975) observed an age-related decline in parathion toxicity (intraperitoneal LD_{50}) in rats tested at 1, 12–13, 23–24, and 35–40 days of age; no additional decline occurred in those 56–63 days of age. In addition, there was a sex difference in LD_{50} values; females were more sensitive. The authors attempted to correlate the changes in toxicity with changes in enzyme activities for bioactivation and detoxification. The age changes in toxicity were not explained by variation in cholinesterase inhibition or in oxidative bioactivation in the liver; however, the increasing LD_{50} values did correlate with increasing A-esterase activity in the rat liver and plasma, suggesting greater detoxification potential in older rats (Benke and Murphy 1975). The soluble liver fractions from adult male and female rats exhibited significant differences in GSH-dependent dearylation of parathion, with significantly ($p<0.005$) less dearylation in females; this correlated with increased toxicity in female rats.

3.4.4 Elimination and Excretion

Parathion is eliminated primarily through metabolism and subsequent excretion of metabolites in urine; a small proportion of metabolites is eliminated through the feces. Excretion of metabolites in urine has been shown to continue for days after exposure has concluded. Parathion elimination from the blood of a poisoned patient was estimated to exhibit a biphasic pattern, with a half-life of 3.1 hours for the early phase and 17.2 hours for the later phase. For the later phase; however, these elimination kinetics were likely substantially altered by the patient's treatment with gastric lavage and activated charcoal.

3.4.4.1 Inhalation Exposure

Urinary excretion of *p*-nitrophenol was measured in a volunteer exposed for 30 minutes each day for 4 days, followed by a 10-minute exposure on the fifth day (Hartwell et al. 1964). The exposure was reported as 1 mL of fresh technical parathion spread over 36 square inches of area and heated to 105–115°F (the first 4 days) or 5 mL spread over 80 square inches and heated to 150°F (day 5; exposure was terminated at 10 minutes due to illness of the volunteer). Daily urinary excretion of *p*-nitrophenol reached a peak of 3,517 μg/day on the fifth day of exposure and then declined to 300.5 μg/day 2 days later. When excretion of *p*-nitrophenol was highest, plasma and erythrocyte cholinesterase activities were 2 and 17% of pre-exposure values, respectively.

3.4.4.2 Oral Exposure

The concentration of parathion in plasma dropped rapidly (from 318 to <50 ng/mL) in the first 10 hours after a 72-year-old man was hospitalized after ingesting an unknown amount of parathion in a suicide attempt (Hoffman and Papendorf 2006). Blood levels declined more gradually thereafter. The study authors estimated a half-life of 3.1 hours for the early phase and 17.2 hours for the later phase. The elimination kinetics were likely altered by the patient's treatment with gastric lavage and activated charcoal, and do not represent elimination kinetics in the absence of treatment.

Morgan et al. (1977) measured metabolites of parathion in the urine of four volunteers (age and sex not specified) who ingested 1 or 2 mg/day of parathion in corn oil for 5 consecutive days. The same volunteers were exposed to both doses, separated by 4 undosed days; these volunteers had also been exposed to methyl parathion over two 5-day treatment periods prior to the experiments with parathion. Daily 24-hour urine samples were collected for analysis; mean levels of the three metabolites quantified in urine are provided in Table 3-12. Urinary excretion of diethyl phosphate peaked between 4 and 8 hours postdosing, and remained at detectable levels through the 2-day postdosing observation period. The study authors estimated that urinary excretion of diethyl phosphate represented between 3 and 13% of the daily dose of parathion during the first 24 hours postdosing and between 3 and 9% during the second 24 hours. *p*-Nitrophenol excretion was highest during the first 4 hours after dosing and declined rapidly thereafter to negligible levels by 24 hours postdosing. Diethylthiophosphate followed a similar pattern. The authors estimated that *p*-nitrophenol and diethylthiophosphate excretion represented 2–8 and 1–3% of the administered dose, respectively, during the first 24 hours; these metabolites were not detected during day 2.

3.4.4.3 Dermal Exposure

Hayes et al. (1964) assessed the time course of urinary excretion of *p*-nitrophenol over five consecutive daily 2-hour exposures to of 2% parathion dust (5 g) applied to the right hand and forearm of volunteers. The hourly rate of excretion of *p*-nitrophenol peaked (at ~60–80 μg/hour) 4–10 hours after each exposure and dropped rapidly thereafter.

The rate of urinary *p*-nitrophenol excretion in an individual with whole-body exposure (apart from the head) to parathion dust (2%) for 7 hours was 247.1 μg/hour in the first 24 hours after the start of exposure and dropped to 58.7 and 21.3 μg/hour in the subsequent 2 days (Hayes et al. 1986). No estimate of the total dermal dose was made.

Table 3-12. Urinary Excretion of Parathion Metabolites in Volunteers Exposed Via Ingestion

	Urine concentration (mg/L)		24-Hour excretion (mg)		Creatinine-adjusted excretion (mg/g)	
Metabolite	1 mg/day	2 mg/day	1 mg/day	2 mg/day	1 mg/day	2 mg/day
p-Nitrophenol	0.06	0.17	0.13	0.30	0.07	0.18
Diethyl phosphate	0.07	0.17	0.16	0.30	0.09	0.18
Diethylthiophosphate	0.03	0.07	0.06	0.12	0.03	0.07

Source: Morgan et al. 1977

3.4.4.4 Other Routes of Exposure

The total clearance of parathion from the body was age-dependent in piglets given 0.5 mg/kg ^{14}C-parathion intravenously; clearance rates of 7, 35, and 121 mL/minute/kg were estimated for newborn, 1-week-old, and 8-week-old piglets, respectively (Nielsen et al. 1991). The study authors estimated elimination rate constants (k_e) of 0.0038, 0.0265, and 0.0771 minute^{-1}, respectively, for elimination from the central compartment. Urinary excretion of radioactivity within the first 3 hours after dosing accounted for 18, 48, and 82% of the administered dose in the newborn, 1-week-old, and 8-week old piglets; all three groups excreted a small amount of radioactivity (0.1–0.2%) in the bile (Nielsen et al. 1991).

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 and Krishnan 1994; Andersen et al. 1987). 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 parameterization, (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) are 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.

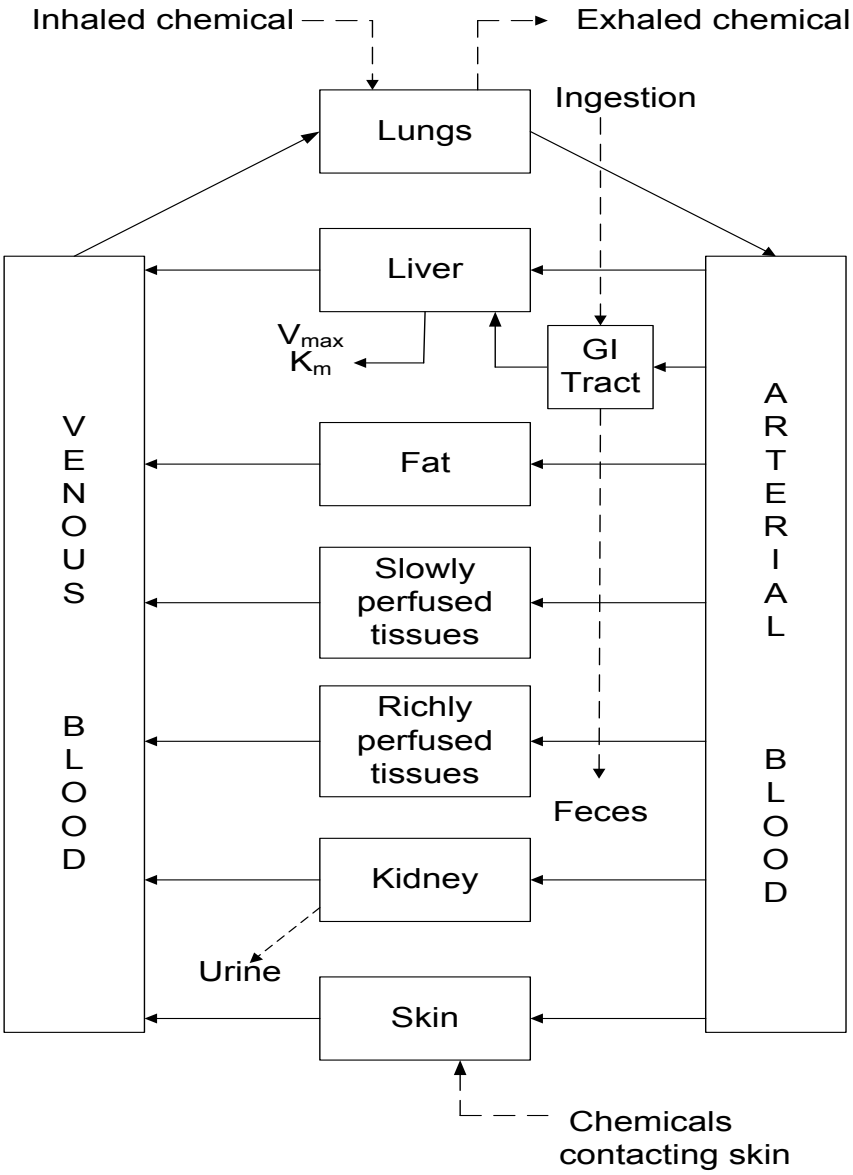
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in 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.

If PBPK models for parathion exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

PBPK models for parathion have been developed for a variety of purposes (El-Masri et al. 2004; Foxenberg et al. 2011; Gearhart et al. 1994; Gentry et al. 2002; Gosselin et al. 2005; Qiao et al. 1994; Sultatos 1990; van der Merwe et al. 2006). However, these models are inadequate for purposes of quantitative risk assessment.

Sultatos (1990) developed a PBPK model for parathion in the mouse based on parameters determined *in vitro*. The model included eight compartments (gastrointestinal tract, lungs, brain, diaphragm, fat, rapidly perfused tissue, slowly perfused tissues, and liver). Previous results from *in vitro* studies using mouse hepatic microsomes were used to estimate tissue/blood distribution coefficients (K_p) by equilibrium

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



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.

Source: adapted from Krishnan and Andersen 1994

dialysis and calculate Michaelis-Menten kinetic constants V_{max} and K_m used in the model (Sultatos 1986). Sources for physiological parameters used for the mouse were not specified in the study report. Application of the PBPK model to the calculation of a hepatic extraction ratio of parathion in the mouse yielded a value in agreement with that obtained from parathion-perfused mouse livers *in situ*. The development of the Sultatos (1990) PBPK model for parathion demonstrates the usefulness of *in vitro* data.

Gearhart et al. (1994) developed a PBPK model for the inhibition of AChE by organophosphate esters. The model was developed for diisopropylfluorophosphate pharmacokinetics and AChE inhibition in rats, mice, and humans, but included an adaptation for modeling parathion and its toxic metabolite, paraoxon. The model included eight compartments (lungs, brain, liver, kidney, rapidly perfused tissue, fat, slowly perfused tissue, and diaphragm). Major determinants of parathion and paraoxon disposition in the model were metabolism of parathion to paraoxon, hydrolysis of paraoxon by esterases, binding of paraoxon to esterases, and tissue solubility of parathion and paraoxon; parameters for these determinants were based on *in vivo* and *in vitro* results from rodent studies (Chemnitius et al. 1983; Maxwell et al. 1987; Pla and Johnson 1989; Wallace and Dargan 1987). Metabolism of parathion to paraoxon was described in the model to occur in the liver and kidney via Michaelis-Menten kinetics. Initial K_m and V_{max} were based on intrinsic metabolic clearance of parathion and paraoxon from livers of rodents (Wallace and Dargan 1987). Partitioning estimates in the rat brain were based on measured concentrations of parathion and paraoxon following intravenous injection of parathion (Eigenberg et al. 1983); partitioning to other tissues was estimated *in vitro* by equilibrium dialysis (Jepson et al. 1992). Simulations of parathion and paraoxon kinetics in brain, liver, and blood after intravenous injection generally reflected the measured concentrations of Eigenberg et al. (1983). The simulation of fat tissue required the addition of diffusion limitation to achieve agreement with experimental data. Sources for physiological parameters used for rats, mice, and humans were not specified.

Gentry et al. (2002) used the PBPK model for parathion and paraoxon developed by Gearhart et al. (1994) in combination with Monte Carlo analysis to incorporate information on polymorphisms in the PON1 gene into the analysis of variability in tissue dose of paraoxon. The results of the analyses suggested that polymorphisms in the PON1 gene make only a minor contribution to the overall variability in paraoxon tissue dose. Sensitivity analysis showed that the estimation of the area under the curve (AUC) was most sensitive to changes related to the polymorphism of paraoxonase. Other parameters with the greatest impact on the arterial AUC were the V_{max} and K_m for paraoxonase in the blood compartments. However, many other parameters also had a significant impact on the AUC, reducing the impact of the

polymorphism on the total variability. Overall, the results were consistent with *in vivo* studies in animals, which suggest that PON1 polymorphism has little impact on the differences in paraoxon toxicity (see Costa et al. 2013 for review).

El-Masri et al. (2004) developed PBPK rat models for parathion and paraoxon to estimate blood concentrations of paraoxon. These models were used in conjunction with PBPK models for chlorpyrifos and its desulfuration metabolite (chlorpyrifos-oxon) and linked to an AChE kinetics model to produce an overall PBPK model intended to describe interactions between parathion and chlorpyrifos in the rat. The parathion and paraoxon PBPK models each include eight compartments (lung, rapidly perfused tissue, slowly perfused tissue, fat-diffusion limited, diaphragm, brain, kidney, and liver). Physiological parameters and tissue/blood coefficients for parathion and paraoxon were obtained from the report of Gearhart et al. (1994). Metabolic and biochemical reaction parameters for parathion were based on parameters reported in earlier reports (Gearhart et al. 1994; Ma and Chambers 1994). Hydrolysis of parathion by esterases was assumed to occur in all compartments except for fat, slowly perfused tissue, and diaphragm. The overall model was designed to evaluate interactions between chlorpyrifos and parathion in AChE inhibition in rats.

Gosselin et al. (2005) developed a multi-compartment model to describe the kinetics of parathion and its urinary metabolites, *p*-nitrophenol and alkyl phosphates, in order to assess worker exposure and health risks. The model was designed to estimate the dose of parathion absorbed under dermal, oral, or inhalation exposure routes under various temporal exposure scenarios. Model compartments represent body burdens and excreta of parathion and its metabolites. Model parameter values were determined from statistical fits to published *in vivo* human kinetic data. The model was developed for the purpose of biological monitoring.

Foxenberg et al. (2011) converted an existing PBPK/PD model for chlorpyrifos that used metabolism parameters from rat liver into human cytochrome-based/age-specific models for chlorpyrifos using chemical-specific recombinant human cytochrome kinetic parameters (V_{max}, K_m), hepatic cytochrome content, and plasma binding measurements to estimate AChE and butyrylcholinesterase inhibition. These models were used to simulate single oral exposures of adults and infants to chlorpyrifos (0.1, 1.0, and 10 mg/kg) or parathion (0.005, 0.025, and 0.1 mg/kg).

Van der Merwe et al. (2006) developed a PBPK model to simulate the absorption of organophosphate pesticides, including parathion, through porcine skin with flow-through cells. Parameters related to the

structure of the stratum corneum and solvent evaporation rates were independently estimated. Solvent evaporation rate, diffusivity, and mass transfer factor parameters were optimized based on experimental dermal absorption data. Diffusion cell studies were conducted to validate the model under a range of parathion doses (6.3–106.9 μg/cm^2), a variety of solvents (ethanol, 2-propanol, acetone), different solvent volumes, occlusion versus nonoccluded administration, and corneocyte removal.

Qiao et al. (1994) developed a pharmacokinetic model to quantify disposition of parathion and its major metabolites following dermal or intravenous administration to weanling pigs. The model quantitates evaporative loss, dosing device binding, percutaneous absorption, first-pass metabolism, and distribution and excretion of parent compound and its metabolites.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

As discussed in detail in Section 3.4 (Toxicokinetics), parathion is absorbed following inhalation, oral, or dermal exposure. No studies were located in which mechanisms of parathion absorption were evaluated. It is expected that absorption occurs via passive diffusion. In blood, parathion binds reversibly to plasma proteins and can subsequently be distributed throughout the body (Foxenberg et al. 2011). Parathion is lipophilic, and thus has a higher affinity for adipose tissue compared with blood or saline solution (Jepson et al. 1994; Sultatos 1990). In addition, depending on exposure route, a large fraction of parathion may distribute to the liver (Braeckman et al. 1983), where it is bioactivated to paraoxon. The bioactivation of parathion to its active metabolite paraoxon may vary widely among individuals due to variations in P450 isozymes and their activities. When human liver microsomes from 27 individuals were incubated with 200 μM parathion, there was an 18-fold range (0.038–0.683 nmol/minute/mg protein) in formation of paraoxon and a 90-fold range in formation of *p*-nitrophenol (0.023–2.10 nmol/minute/mg protein; Mutch and Williams 2006; Mutch et al. 1999, 2003). No information was located regarding mechanisms of elimination and excretion of parent compound or metabolites of parathion.

3.5.2 Mechanisms of Toxicity

Effects Mediated by AChE Inhibition. The most salient systemic effects of exposure to parathion are related to its direct effect on the nervous system and the secondary effects that result from it. Parathion is known to exert direct systemic effects through inhibition of cholinesterase, specifically AChE in the central and peripheral nervous systems. Inhibition of AChE is common to all organophosphorus

pesticides (OPs), but there are mechanisms of toxicity of OPs that should be kept in mind when addressing toxic effects. AChE is also present in erythrocytes. Thus, inhibition of erythrocyte AChE is commonly used as a surrogate indicator of the extent of inhibition of neural AChE. In addition, cholinesterases can be found in plasma. In humans, plasma cholinesterase is almost exclusively composed of butyrylcholinesterase. Although butyrylcholinesterase is capable of hydrolyzing acetylcholine and butyrylcholine *in vitro*, the *in vivo* substrate of plasma cholinesterase is unknown. Parathion is bioactivated *in vivo* and *in vitro* to its oxygen analog form, paraoxon (e.g., Buratti et al. 2003; Forsyth et al. 1989; Lessire et al. 1996; Mutch et al. 1999; Sultatos and Minor 1986; Zhang et al. 1991). Paraoxon phosphorylates a hydroxyl group on serine at the active site of AChE. Under normal circumstances, AChE rapidly and efficiently degrades the neurotransmitter, acetylcholine, following its release at the nerve synapse or at a neuromuscular junction; however, the phosphorylated AChE enzyme cannot degrade acetylcholine and the neurotransmitter accumulates at the ending of cholinergic nerves, resulting in repetitive firing of postsynaptic fibers (Abou-Donia 1995; Bajgar 2004; Costa 2008).

Cholinergic terminals play an important role in the normal function of the neuromuscular, central nervous, endocrine, immunological, and respiratory systems (Carrier and Brunet 1999). Thus, the inhibition of the enzyme AChE by paraoxon may have profound and wide-ranging systemic effects. Acetylcholine can be found in the autonomic, somatic motor, and central nervous systems. In the autonomic nervous system, accumulation of acetylcholine leads to the overstimulation of the muscarinic receptors of the parasympathetic nervous system, which can lead to effects on the exocrine glands (increased salivation, perspiration, lacrimation), eyes (miosis, blurred vision), gastrointestinal tract (nausea, vomiting, diarrhea), respiratory system (excessive bronchial secretions, wheezing, tightness of chest), and cardiovascular system (bradychardia, decrease in blood pressure) (Abou-Donia 1995; Bajgar 2004; Costa 2008).

Stimulation of the nicotinic receptors in the parasympathetic or sympathetic nervous system may also cause adverse effects on the cardiovascular system such as tachycardia, pallor, and increased blood pressure. In the somatic nervous system, nerve fibers innervate the skeletal muscles motor end-plates. Accumulation of acetylcholine in the somatic nervous system may be manifested as muscle fasciculations, cramps, paralysis, and flaccid or rigid tone, among other signs and symptoms. Overstimulation of the nerves in the central nervous system, specifically the acetylcholine receptors of the brain, by the accumulation of acetylcholine may result in lethargy, drowsiness, and mental confusion among other effects. More severe effects on the central nervous system include a state of coma without reflexes, depression of the respiratory centers, and cyanosis (Abou-Donia 1995; Bajgar 2004; Costa

2008). It has been recognized that, after repeated exposures to organophosphate insecticides, humans and other animal species may develop a tolerance to the appearance of cholinergic signs (Costa et al. 1982). It has been proposed that this tolerance to the effect of excess acetylcholine develops by the down-regulation of postsynaptic cholinergic receptors. This reduces the apparent cholinergic symptoms even in the presence of marked reductions in erythrocyte AChE activity (Sultatos 1994).

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

Phosphorylated AChE may be reactivated or irreversibly inhibited through a process known as 'aging". The bond between AChE and the phosphorous atom is very stable, but may be hydrolyzed by water over the course of hours or days (Abou-Donia 1995; Bajgar 2004; Costa 2008). Some hydroxylamine derivatives known as oximes facilitate AChE dephosphorylation and are used to treat poisoning with organophosphates such as parathion. Phosphorylated AChE may not be reactivated if "aging" of the inhibited enzyme occurs; "aging" refers to the hydrolysis of one of the two alkyl groups of the organophosphate (Costa 2008), leading to irreversible inhibition of AChE.

Recent studies have demonstrated that plasma AChE levels in animals treated with organophosphate compounds may not only return to pretreatment levels, but may also increase to as much as 250% over pretreatment levels (Duysen and Lockridge 2011). Plasma AChE levels were 150% of pretreatment levels in male mice 3 days after a single subcutaneous dose of 12.5 mg parathion/kg (Duysen and Lockridge 2011). The study authors postulated that organophosphate treatment induces apoptosis, which then triggers induction of AChE leading to plasma levels that exceed pretreatment levels.

Effects Mediated by Mechanisms Other Than AChE Inhibition. As described in Section 3.2.4, a series of studies by Slotkin and coworkers have shown that exposure to parathion and other organophosphate pesticides can affect the nervous system via mechanisms not directly related to inhibition of AChE (Slotkin 2011; Slotkin et al. 2006a, 2006b, 2008, 2009a). In these studies, neonatal rats received subcutaneous injections of parathion and were evaluated at later times up to adulthood. Administration of parathion affected the development of neurotransmitter systems involved in critical functions such as learning and memory (cholinergic) and in the expression of emotion, appetite, and sleep patterns

(serotoninergic), and induced behavioral alterations (Levin et al. 2010; Timofeeva et al. 2008). These effects occurred with doses of parathion that did not induce significant inhibition of AChE. In addition, the fact that the effects of parathion differed from those of other organophosphate pesticides regarding brain areas targeted and sex selectivity supported the view that the mechanism(s) involved, although not elucidated, was not directly related to AChE inhibition. Additional studies showed that early-life exposure to parathion caused a metabolic dysregulation in adult rats that was consistent with a pre-diabetic state (Lassiter et al. 2008). The mechanism for the metabolic effects appeared to involve disruption of adenylyl cyclase signaling in peripheral tissues, particularly in the liver (Adigun et al. 2010). Adenylyl cyclase is the enzyme that synthesizes cAMP from ATP. Interestingly, some of the effects of early parathion exposure were ameliorated or reversed by a high-fat diet, including effects on lipid peroxidation associated with synaptic activity (Slotkin et al. 2009b, 2009c). This was presumably due to global changes in the composition of synaptic membrane lipids. The fact that effects on lipids interacted with deficits in synaptic function suggested that the former may contribute to impaired behavioral performance (Lassiter et al. 2010; Slotkin 2011).

3.5.3 Animal-to-Human Extrapolations

While there are clear parallels between the toxicokinetics (and toxicity) of parathion in animals and humans, little is known about how well the toxicokinetics of parathion in animals predicts its behavior in humans due to the lack of studies examining humans (or human tissues) and animals under the same conditions. Recent work suggests that the desulfuration of parathion to paraoxon in human liver is mediated by a large number of cytochromes (CYP1A2, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, and CYP3A4/5), which show different affinities for the substrate (see Section 3.4.3). Significant variations in the activities of these cytochromes among humans and laboratory animal species would be expected to result in differences in parathion metabolism.

In addition, there are four esterase enzymes in rodent blood (carboxylesterase, butyrylcholinesterase, AChE, and paraoxonase-1) that can detoxify organophosphate compounds, while human blood contains only three, lacking carboxylesterase (Duysen et al. 2012). Carboxylesterase has been shown to exert a protective effect against the toxicity of parathion in rats and mice. Karanth and Pope (2000) showed that the enhanced sensitivity of neonatal, juvenile, and aged rats (relative to adult) to the acute lethality of parathion was correlated with plasma carboxylesterase activity in these different age groups. Duysen et al. (2012) observed significantly enhanced inhibition of plasma AChE in carboxylesterase knockout mice

(73.1% inhibited), compared with their wild type counterparts (56% inhibited), after subcutaneous administration of 12.5 mg/kg parathion, but not after subcutaneous administration of 0.2 mg/kg paraoxon.

The efficiency of the parathion detoxification by serum paraoxonase (PON1) varies in laboratory animals. For example, PON1 knockout mice are no more sensitive to parathion toxicity (as measured by cholinesterase inhibition) than their wild type counterparts, while injection of rabbit PON1 into rats protects against paraoxon toxicity (Furlong et al. 2000). Furlong et al. (2000) suggested that these disparate findings suggest that rabbit PON1 has a higher catalytic efficiency for paraoxon hydrolysis than mouse PON1. Furlong et al. (2000) also performed *in vitro* measurements of paraoxon hydrolysis products after incubation of paraoxon with human serum from individuals with polymorphic PON1 genotypes ($PON1_{192QQ}$ and $PON1_{192RR}$). These experiments revealed variations in human PON1 K_m (0.36 and 0.42 mM for QQ and RR genotypes, respectively) and V_{max} (284 and 1,400 units/L, respectively), and showed that the QQ PON1 form is kinetically similar to the mouse PON1 (K_m of 0.34 mM and K_m of 300 units/L), while the RR form is more similar to the rabbit PON1 (K_m of 0.23 mM and K_m of 2,372 units/L).

There are indications that the response of the human nervous system to paraoxon exposure may differ from that in animals. Van den Beukel et al. (1998) observed greater sensitivity of the human nicotonic ACh receptor of SH-SY5Y neuroblastoma cells to blockage by paraoxon (as measured via membrane currents) than the nACh receptor of either mouse neuroblastoma cells or locust thoracic ganglion cells. Ecobichon and Comeau (1973) measured the *in vitro* inhibition of plasma cholinesterases by paraoxon in 11 different mammalian species; IC_{50} values (concentration necessary to achieve 50% enzyme inhibition) ranged from $0.2x10^{-7}$ M in hamster to $7.9x10^{-7}$ M in swine. IC_{50} values in humans, male rats, female rats, and mice were relatively similar, at $1.1x10^{-7}$, $1.4x10^{-7}$, $1.8x10^{-7}$, and $1.3x10^{-7}$ M, respectively (Ecobichon and Comeau, 1973).

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 Thomas and Colborn (1992), was also used in 1996 when Congress mandated the 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), and in 1998, the EDSTAC 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).

The effects of parathion on the uptake and metabolism of [^{3}H]-testosterone in the prostate from mice were studied (Thomas and Schein 1974). Gavage administration of up to 5.3 mg parathion/kg/day for 5 days did not significantly affect the uptake of labeled testosterone or the ability of the prostate to transform the androgen into its main metabolites. In addition, the *in vitro* metabolism of testosterone by hepatic microsomes from mice treated with parathion was not significantly affected, except for an increase in the polar metabolite, androstanediol. Furthermore, hepatic testosterone hydroxylase activity was not affected by treatment with parathion, as judged by unchanged amounts of 6-, 7-, and 16-hydroxytestosterone derivatives.

Several studies have examined potential interactions of parathion with the estrogen receptor (ER) and androgen receptor (AR) *in vitro*. The AR antagonistic activity of parathion was examined *in vi*tro in HepG2 human hepatoma cells transfected with human AR plus an androgen-responsive luciferase reported gene, MMTV-luc (Tamura et al. 2003). Dose-shift experiments were conducted by adding set

concentrations of parathion across a complete dose-response range of the natural ligand dihydrotestosterone (DHT). The results showed that parathion lacked sufficient AR antagonistic activity to determine potency in the dose-shift experiments. Parathion was reported to have weak anti-androgenic effects in a reporter gene assay in Chinese hamster ovary cells (CHO-K1) relative to DHT alone (Kojima et al. 2004). The concentration of parathion showing 20% inhibition on the androgenic activity induced by 10^{-10} M DHT was 2.2×10^{-6} M. In the same study, parathion did not exhibit androgenic transcriptional activity or agonism or antagonism to the two human estrogen receptor subtypes, hERα and hERβ. In yet another *in vitro* study, parathion exhibited anti-androgenic activity when tested using a human AR reporter gene assay in an African monkey kidney cell line CV-1 transiently transfected with the constructed reporter gene plasmid pMMTV-chloramphenicol acetyltransferase (CAT) and the human AR expression plasmid AR/pcDNA3.1 (Xu et al. 2008). The anti-androgenic activity was assessed by measuring the ability of parathion to inhibit the induction of the CAT product by DHT. At concentrations $\geq 10^{-7}$ M, parathion significantly inhibited DHT-induced CAT activity in a concentration-related manner. The concentration of parathion that induced 50% inhibition was approximately 2×10^{-7} M. In the same study, parathion did not exhibit androgenic activity, which is consistent with the results of Kojima et al. (2004).

Parathion was a potent activator of the constitutive androgen receptor (CAR) in HepG2 cells *in vitro* with an EC_{50} of 1.43 μM (Mota et al. 2010). CAR is a transcription factor that regulates several detoxification enzymes. Cells were cotransfected with a mCAR expression plasmid and a luciferase reporter plasmid containing the CYP2B6 PBREM and then were cotreated with the inverse agonist, dihydroandrosterone (DHA) plus parathion. In studies *in vivo* with wild type (WT) and CAR-null mice, administration of a dose of 5 mg parathion/kg did not activate CAR in hepatic microsomes of either strain (Mota et al. 2010). However, parathion was significantly more toxic to CAR-null mice than to WT mice, suggesting that CAR has a protective role against parathion toxicity. According to the investigators, the lack of CAR activation in hepatic microsomes by parathion may have been due to its short half-life possibly preventing reaching the required hepatic concentration to activate CAR (Mota et al. 2010).

The potential role of parathion in human breast cancer has been studied by Calaf and coworkers using human breast epithelial cells *in vitro*. The investigators reported that parathion alone and in combination with 17β-estradiol (E2) induced malignant transformation of an immortalized human breast cell line, MCF-10F (Calaf and Roy 2007a); E2 alone did not induce malignant transformation. Malignancy was confirmed by increased anchorage independent growth and invasive capabilities. It was also shown that parathion increased the expression of a few proteins associated with signaling pathways and mutant p53

proteins. Of particular interest was the increase in epidermal growth factor receptor (EGFR) since growth factors and their receptors are functionally related to cell proliferation. Studies of gene expression using an array-based approach to monitor genes involved in a wide range of functions including apoptosis, cell cycle, cell growth and differentiation, signal transduction pathway, and other cancer-related genes showed that a significant number of genes were altered by either parathion, E2, or the combination of both (Calaf and Roy 2007b, 2008a, 2008b; Calaf et al. 2009). These results suggested that E2 and parathion can induce changes in gene expression in breast epithelial cells influencing the process of carcinogenesis. In a related publication, Calaf and Roy (2007c) showed that the parathion-induced effects could be significantly diminished by the muscarinic acetylcholine antagonist atropine. However, how parathion could alter gene expression by a cholinergic mechanism was not discussed.

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 fetus/infant has an immature (developing) blood-brain barrier that past literature has often described as being leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-central nervous system interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the blood-brain barrier, there are differences between fetuses/infants and adults which are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; as it raises a very important toxicological question as to whether these mechanisms provide protection for the developing brain or do they render it more vulnerable to toxic injury. Each case of chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

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).

Acute parathion exposure affects children in the same manner as it affects adults. Regardless of the route of exposure, children exposed to high amounts of parathion exhibit the typical cholinergic signs and symptoms described in previous sections. Some examples are provided below.

Eitzman and Wolfson (1967) reported 30 deaths that occurred in children in the state of Florida from 1959 through 1964. The average age was 2.9 years and deaths occurred within hours of poisoning. Exposure occurred through ingestion of parathion from improper containers, through ingestion of parathion from the floor or windowsills where it was place to kill roaches, or due to inhalation or skin contact. There also have been numerous cases of children poisoned though ingestion of contaminated food. For example, Wishahi et al. (1958) reported that 200 people were accidentally poisoned in Cairo, Egypt, following ingestion of contaminated flour; 22 of them were children. There were eight fatalities and all were children. Signs and symptoms included abdominal pain, vomiting, and convulsions. All fatal cases fell into a deep coma accompanied by shock in six cases and hypertension in two cases. Death, which occurred 4–9 hours after the onset of symptoms, was due to respiratory failure. Postmortem examination of five cases selected at random showed cyanosis of the lips, conjunctiva, and face, and miosis of the pupils. The heart was enlarged and the lungs showed variable degrees of acute edema; some congestion and edema was reported in the brain. Diggory et al. (1977) reported that 79 cases of poisoning occurred in Jamaica due to ingestion of contaminated flour and involved an unspecified number of children. Illness began 10 minutes to 4 hours after a meal and the first symptoms were nausea, cramps and vomiting. Severe cases showed sialorrhea, diplopia, pinpoint pupils, “giddiness,” muscle fasciculation, dyspnea, bradycardia, coma, and convulsions. Deaths generally occurred within 6 hours as a result of respiratory arrest. Although the number of children involved was not specified, the investigators noted that case-fatality ratios (40%) were highest in children ≤4 years of age. Etzel et al. (1987) reported similar episodes in Sierra Leone that involved children eating bread baked with

parathion-contaminated flour. Signs and symptoms included loss of consciousness, shortness of breath, excess sweating, frothing of the mouth, wheezing, excess tearing, excess salivation, muscle twitching, convulsions, diarrhea, vomiting, increased urination, chest pains, and abdominal cramps. Children between the ages of 1 and 10 years had the highest rates of illness; however, this may have been due to higher consumption of bread than adults rather than increased susceptibility.

A study of women living in an agricultural community in California did not find a significant association between exposure to parathion and adverse developmental effects in the offspring including length of gestation, birth weight, length, head circumference, and ponderal index (Eskenazi et al. 2004). However, it should be noted that exposure to parathion was assessed by measuring urinary *p*-nitrophenol, which can also be produced as a result of exposure to substances other than parathion.

Gestational exposure of rats to up to 1 mg parathion/kg or of rabbits to up to 0.3 mg parathion/kg did not cause embryotoxicity or teratogenicity (Renhof 1984, 1985). However, another study in which rats were exposed to parathion during gestation and lactation reported that pups showed EKG alterations, even at the lowest dose of parathion tested, 0.01 mg/kg/day (Deskin et al. 1979).

Numerous studies in rats have demonstrated that younger animals are more sensitive to the effects of parathion than mature animals. This difference is likely due to age-related differences in toxicokinetics. It should be noted, however, that in all of these studies, the rats were administered parathion by either subcutaneous or intraperitoneal injection, both non-relevant routes of exposure. For example, Gagné and Brodeur (1972) showed that weanling rats given parathion intravenously are more susceptible to parathion than adult rats mainly because of deficient mechanisms of degradation of parathion and paraoxon. In addition, the brain from adult male rats appeared to be less sensitive to paraoxon than the brain from weanling rats. Another study in male rats of various ages (1–80 days old) given parathion intraperitoneally reported that the specific activities of AChE in cerebral cortex and of liver aliesterases increased with age, thus providing significantly more protection against parathion toxicity (Atterberry et al. 1997). The increase in specific activity of brain AChE occurred without developmental changes in sensitivity of the enzyme to paraoxon, but liver aliesterase sensitivity to inhibition by paraoxon decreased with age. Benke and Murphy (1975) examined how the rates of several alternate metabolic pathways affected the toxicity of parathion in rats of five ages. The pathways studied included oxidative activation and cleavage, hydrolysis by A-esterases, glutathione-S-alkyl-, and -S-aryl-transfer, and binding of paraoxon to tissue constituents. It was found that, in general, increasing LD_{50} values with age obtained after intraperitoneal injection of parathion correlated better with changes in rates of reactions that

represented detoxification pathways for paraoxon than for reactions that represented direct metabolism of parathion. The LD_{50} values were about 6 and 3 times higher in adult males and females than in the neonatal male and female rats, respectively. This suggests that the use of an uncertainty factor of 10 to protect susceptible populations, such as the young, is probably adequate, at least in rats. Benke and Murphy (1975) also found that age differences in susceptibility were not related to differences in sensitivity of cholinesterase to inhibition by paraoxon *in vitro*. Similar findings were reported by Pope et al. (1991) who found that neonatal rats were more sensitive than adults to the acute toxicity of parathion. However, the maximal brain AChE inhibition was similar in both age groups (>78%). In a subsequent paper, Pope and Chakraborti (1992) reported that ED_{50} estimates of brain AChE and plasma ChE (dose that inhibits 50% of enzyme activity) were highly correlated with maximal tolerated doses in neonates and adults. In their study of male rats of varying ages, Atterberry et al. (1997) also reported a progressive increase in activities of P 450-mediated activation (desulfuration, 6–14-fold) and detoxification (dearylation, 2–4-fold) as well as concentrations of P450 (7-fold) and protein (2-fold) between neonate and adult hepatic microsomes. It was also reported that microsomal pentoxyresorufin (PROD) activity increased 16-fold between neonates and adults, whereas ethoxyresorufin (EROD) activity increased 16-fold until 21 days of age and then decreased in adulthood to a 10-fold higher than neonates. Atterberry et al. (1997) noted that their results suggested that the lower levels of hepatic aliesterase-mediated protection and P450-mediated dearylation contribute significantly to the greater sensitivity of young rats to parathion toxicity. Karanth and Pope (2000) conducted a similar study but included an aged group of rats (24 months old). The maximum tolerated dose (i.e., the dose that caused 0% mortality 7 days after a subcutaneous injection of parathion) was 2.1, 4.8, 18, and 6 mg/kg in neonatal, juvenile, adult, and aged rats, respectively. The levels of carboxylesterases and A-esterases in liver, plasma, and lung from neonatal and juvenile rats were significantly lower than in adults. Aged rats had A-esterases levels in tissues and plasma similar to adults and carboxylesterase levels in liver and lung similar to adults, but had significantly lower carboxylesterase levels than adults in plasma. The authors concluded that carboxylesterase activity may play a more critical role in the differential sensitivity to parathion.

Harbison (1985) determined an intraperitoneal LD_{50} of 8.8 mg/kg for parathion in adult male rats vs. 1.8 mg/kg in newborn rats. Pretreatment of the newborns with the microsomal inducer phenobarbital increased the LD_{50} to 4.8 mg/kg. Since microsomal enzymes cannot only activate parathion to paraoxon, but can also detoxify parathion to *p*-nitrophenol and diethylphosphorothioic acid (DEPTA), the results suggested that inducing the metabolism of parathion in the newborn enhanced detoxification rather than bioactivation. A study in newborn pigs showed age-related distribution of parathion and metabolites in tissues (Nielsen et al. 1991). Three hours after an intravenous injection of 0.5 mg/kg ^{14}C-parathion to

newborn, 1-week-old, and 8-week-old piglets, tissues and plasma from newborns had significantly more ^{14}C than 1-week-old piglets, which in turn had more ^{14}C than 8-week-old animals. This could be explained by differences in body clearance (7, 35, and 121 mL/minute/kg with increasing age) and urinary excretion (18, 42, and 82% of the dose with increasing age) rather than by age-related differential affinity between parathion and the tissues.

As previously mentioned, a series of studies in which neonatal rats were administered subcutaneous doses of parathion that did not induce significant inhibition of AChE reported alterations in the development of neurotransmitter systems and metabolic dysregulation that were evident at later times up to adulthood (see Section 3.2.4, Other Routes of Exposure for references). Since the various organophosphorus pesticides tested seemed to induce effects of opposing direction, the investigators suggested that organophosphorus pesticides can affect the developing nervous system via mechanisms not directly related to AChE inhibition.

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).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of the U.S. population to environmental chemicals using biomonitoring. This report is available at http://www.cdc.gov/exposurereport/. The biomonitoring data for parathion from this report are discussed in Section 6.5. 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, 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 parathion are discussed in Section 3.8.1.

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

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

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Parathion

The most specific biomarkers for exposure to parathion are the parent compound itself and its metabolites in tissues and body fluids. Diethylphosphoric acid, diethylthiophosphoric acid, and *p*-nitrophenol are metabolic products of the *in vivo* degradation of parathion and have been detected in urine of humans under field and experimental conditions after oral, dermal, or otherwise unspecified exposure. For instance, Morgan et al. (1977) detected these metabolites in the urine of volunteers as early as 4 hours after they ingested 1 or 2 mg parathion/kg. Diethylphosphoric acid and diethylthiophosphoric acid can be detected after exposure to other organophosphate insecticides. Due to its rapid appearance in urine, *p*-nitrophenol was suggested early on as a biomarker for parathion (Arterberry et al. 1961; Denga et al. 1995; Wolfe et al. 1970) and remains in use for this purpose today (Arcury et al. 2007; Kissel et al. 2005). However, it should be noted that *p*-nitrophenol can also be derived from exposure to methyl parathion, O-ethyl O-4-nitrophenyl phenylphosphonothioate (EPN), and other non-pesticide chemicals. Davies et al. (1967) reported urinary *p*-nitrophenol concentrations in 14 fatal and 9 nonfatal cases of parathion poisonings in Dade County, Florida during the years 1962–1965; a number of these cases were children. The mean concentration of *p*-nitrophenol in the fatal cases was 40.3 ppm (range 2.4–122 ppm), while the

concentration in nonfatal cases averaged 10.79 ppm (range 0.7–22 ppm). In a recent study, Arcury et al. (2007) analyzed urine samples from 60 Latino children of farm workers for pesticide metabolites, including *p*-nitrophenol. *P*-nitrophenol was present in 90% of the urine samples at a mean creatinine-adjusted concentration of 1.25 μg/g. Kissel et al. (2005) measured organophosphate metabolites in urine samples from 13 children in Washington State who had been identified as having potentially elevated organophosphate exposure. Urine samples were collected before bed, during first morning void, after lunch, and before dinner in two seasons. A total of 96% of the samples contained *p*-nitrophenol, suggesting possible parathion exposure. The authors reported that the first morning void samples were the best predictors of the volume-weighted daily average (Kissel et al. 2005).

Noort et al. (2009) described a liquid chromatography-tandem mass spectrometry method for analyzing organophosphorothioate pesticides bound to albumin in blood. The method was able to detect covalent binding of parathion and other compounds to albumin at concentrations that did not inhibit butyryl-cholinesterase. The study authors suggested that measurement of protein adducts in blood might provide a better indication of chronic, low-level exposure than urinary metabolites because the adducts accumulate over time. Further evaluation and application of this method are needed to firmly establish its utility and reliability.

In humans, inhibition of cholinesterases in erythrocytes and plasma may be a useful marker of higher levels of exposure. However, Arterberry et al. (1961) detected significant quantities of urinary *p*-nitrophenol in individuals with occupational parathion exposure, in whom plasma and erythrocyte ChE levels were normal, indicating that urinary *p*-nitrophenol is a more sensitive indicator of exposure than plasma or erythrocyte AChE activity.

3.8.2 Biomarkers Used to Characterize Effects Caused by Parathion

Diagnosis of organophosphate poisoning, including parathion, can be made by the presence of characteristic clinical signs and measurements of serum (plasma) cholinesterase and red blood cell AChE 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 AChE is present in the central and peripheral nervous systems and in red blood cells. Plasma cholinesterase activity can be inhibited by 20–25% without significant physiological consequences (Abou-Donia 1995). Parathion is a stronger inhibitor of plasma cholinesterase than of red blood cell AChE (Maroni et al. 2000). Plasma cholinesterase regenerates at a more rapid rate than red blood cell AChE, 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 red blood cell AChE, plasma cholinesterase is less specific since the levels may also be suppressed due to genetic factors and a variety of conditions and diseases (Abou-Donia 1995; Tafuri and Roberts 1987). The rate of decrease of red blood cell AChE correlates better with appearance of symptoms than the absolute value reached after exposure (Maroni et al. 2000). Reduction of red blood cell AChE after severe exposure lasts up to 100 days, reflecting the time of production of new cells. Red blood cell AChE levels are representative of AChE 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 parathion (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 may occur at levels 10–20% of normal; and severe poisoning with respiratory distress and unconsciousness may occur with levels <10% of normal.

Several methods for measuring red blood cell AChE 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 red blood cell AChE 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

Numerous studies in animals have examined how co-exposure to parathion and other substances, particularly other pesticides, affect the toxicity of parathion. Of particular interest has been the study of substances that affect the metabolism of parathion, as this plays a crucial role in the toxicity of parathion. Some examples are summarized below. Overall, the data suggest that results from *in vivo* studies do not always parallel the results from *in vitro* studies, so that caution should be exercised when extrapolating

from *in vitro* to *in vivo* situations. Worth noting also is that the sequence of exposure can influence the toxic outcome of the interaction.

In mice, administration of three daily doses of DDT followed 24 hours later by a single dose of parathion reduced parathion's 24-hour LD_{50} from 10 to 7.2 mg/kg (Chapman and Leibman 1971). Four pre-doses of 3-methylcholanthrene (3-MC) increased the LD_{50} to 15 mg/kg, whereas pre-dosing with chlordane increased the LD_{50} to 35 mg/kg. Examination of the metabolism of parathion *in vitro* in mice pre-treated with DDT, 3-MC, or chlordane showed that DDT treatment preferentially enhanced the formation of DEPTA (parathion's detoxification pathway), 3-MC decreased DEPTA production, and chlordane enhanced both the activation and detoxification pathways. Since the *in vivo* results did not parallel the changes in the microsomal metabolism of parathion, the investigators suggested that factors other than metabolism, possibly tissues and plasma binding of parathion, contribute to the toxicity of parathion (Chapman and Leibman 1971). In a similar study, pretreatment of mice with DDT protected against parathion-induced lethality and inhibition of plasma, whole-blood, and brain cholinesterase; however, no protection was afforded against paraoxon toxicity (Bass et al. 1971). *In vitro* experiments showed that, contrary to what was expected from the *in vivo* results, pre-treatment with DDT increased the activation of parathion, as shown by a greater inhibition of cholinesterase, but did not significantly affect the detoxification of paraoxon (Bass et al. 1971). These seemingly inconsistent results could be explained by an increased rate of conversion of parathion to DEPTA by DDT pre-treatment, although this was not tested in the study.

Srivastava et al. (1976) studied the effect of di(2-ethylhexyl) phthalate (DEHP) on the toxicity of parathion. A single oral dose of parathion was given to rats 18 hours after receiving a single intraperitoneal dose of DEHP. Brain and whole-blood cholinesterase activities were assayed 30 minutes after parathion administration. The results showed that DEHP significantly decreased the parathion-induced inhibition of the two enzymes. Since the administration of DEHP followed by paraoxon did not affect the paraoxon-induced enzyme inhibition, the results suggested that DEHP increased the rate of conversion of parathion to paraoxon. Yasoshima and Masuda (1986) reported that carbon disulfide (CS_2) administered to mice 1 hour before a single parathion dose significantly potentiated the inhibitory effect of parathion on plasma cholinesterase activity, suggesting that CS_2 increased activation of parathion to paraoxon. This was consistent with the results of an experiment in which liver microsomes from mice treated with CS_2 incubated with parathion showed decreased *p*-nitrophenol production. However, in that experiment, cholinesterase inhibition was reduced, suggesting that although paraoxon formation may have been increased by pretreatment with CS_2, a greater stimulation of the detoxification pathway may

have also occurred *in vitro*. Studies by Kuntz et al. (1990) and Chaturvedi et al. (1991) showed that mixtures of toxaphene and parathion and 2,4-dichlorophenoxyacetic acid (2,4-D) reduced the parathion-induced decrease in serum cholinesterase activity in mice possibly by increasing the release of enzyme from the liver. In addition, the results suggested that toxaphene had the potential to reduce the toxicity of parathion and paraoxon by increasing the NADP-dependent metabolism of these substances to poor binders of acetylcholine esterase. Triolo and Coon (1966) showed that administration of aldrin to mice resulted in increased toxicity of parathion 1 hour after aldrin dosing, but it protected against parathion toxicity from 16 hours to 12 days after aldrin dosing. The investigators suggested that the initial effect of aldrin may have been due to inhibition of parathion detoxification, although this was not investigated. The second phase could be explained in part by a 38% increase in A-esterase activity in the liver and 24% increase in B-esterase in plasma, but it appeared that other factors, possibly involving the central nervous system, played a role in aldrin's protective effect against parathion poisoning.

In an intermediate-duration study, treatment of male rats with parathion plus lindane for 90 days resulted in more severe testicular toxicity than in a group treated with parathion alone, but no quantitative data were provided (Dikshith et al. 1978). Measurements of enzyme activities showed that parathion alone induced a 50% decrease in brain cholinesterase activity, whereas the parathion/lindane combination induced a 79.5% decrease; lindane did not significantly affect the parathion-induced inhibition of blood cholinesterase (about 80% in both cases) (Dikshith et al. 1978).

In a more recent study, Karanth et al. (2001) showed that the interactive toxicity of parathion and chlorpyrifos can be influenced by the sequence of exposure. Gavage administration of chlorpyrifos to rats followed by parathion 4 hours later resulted in significant more cholinergic toxicity than if the sequence was reversed. This suggested that in the former case, more inhibitor (the respective oxons) was allowed to reach the target tissues. Studies *in vitro* suggested a differential role of carboxylesterases and A-esterases in the detoxification of chlorpyrifos oxon and paraoxon. Carboxylesterases were found to detoxify both chlorpyrifos oxon and paraoxon, while A-esterases only detoxified chlorpyrifos oxon. In liver from rats pretreated with parathion, A-esterases still detoxified chlorpyrifos oxon, while the liver from rats pretreated with chlorpyrifos had little apparent effect on paraoxon. Similar findings were reported in a later study in neonatal rats (Kacham et al. 2006).

El-Masri et al. (2004) developed a PBPK model to estimate an interaction threshold for the joint toxicity between parathion and chlorpyrifos in the rat. The investigators first developed PBPK models for each chemical to estimate the blood concentration of their respective metabolites, paraoxon and chlorpyrifos

oxon. The estimated levels of metabolites were then linked to a model for AChE kinetics describing enzyme synthesis, degradation, binding to the metabolites of both chemicals, and aging after binding. The resulting overall PBPK model described interactions between parathion and chlorpyrifos at the levels of the P450 enzymatic activation site and at AChE binding sites. Calibration of the model was performed using interaction data from published studies. The results of the modeling showed that less-than-additive and additive interactions occurred at different dose ranges. The overall model simulations indicated that additivity is obtained at oral doses <0.8 mg/kg of each chemical, the interaction threshold.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Although no studies were found in humans regarding the role that diet plays in the toxicity of parathion, several studies in animals have examined this issue. The issue is relevant as it may impact people living in developing countries where both malnutrition and the use of certain pesticides, including parathion, are widespread. For example, in an early study, Boyd (1969) showed that reducing the amount of dietary casein from 26 to 3.5% during 28 days to male Wistar rats increased the acute oral toxicity of parathion by about 7 times. In a similar study, Casterline and Williams (1971) reported that exposure of protein-deprived Osborne-Mendel rats to parathion for 28 days resulted in much greater inhibition of serum and brain cholinesterase and serum and liver triacetinesterase than in rats exposed to parathion alone. The investigators speculated that reduced dietary protein resulted in reduced detoxifying enzymes. In another study in rats, food restriction simultaneous with daily parathion intake for 28 days increased the inhibition of plasma cholinesterase and plasma and liver carboxylesterase by parathion compared to rats fed a normal diet (Villenueve et al. 1978). Bulusu and Chakravarty (1986, 1987) studied the effects of a low-protein diet on the activities of liver β-glucuronidase and acid and alkaline phosphatases. Male rats were kept on normal or low-protein diets for 3 weeks and were given daily doses of parathion at the same time. Parathion increased β-glucuronidase and acid phosphatase activities and decreased alkaline phosphatase activity in rats on the normal protein diet. Maintaining the rats on a low-protein diet aggravated the effect of parathion on the enzyme's activities. The investigators speculated that the effects of parathion on

β-glucuronidase and acid phosphatase may be due to parathion-induced damage to lysosome membranes leading to enzyme leakage into the cytoplasm. The decrease in alkaline phosphatase was attributed to a possible action at the cell membrane level affecting transport mechanisms involving phosphate.

A more recent study provided evidence suggesting that people who consume excessive amounts of sugar may be at a higher risk from exposure to parathion based on the results of studies in rats (Olivier et al. 2001). The investigators provided rats with tap water or 15% glucose in tap water for up to 21 days. On day 7, the rats received a single subcutaneous injection of parathion or paraoxon, and signs of toxicity were recorded for the next 13 days. Exposure to high glucose resulted in a significant decrease in food intake (50%) and increase in total caloric consumption (20%). Rats exposed to glucose showed more severe and long-lasting signs of toxicity due to parathion than rats drinking tap water only. However, the excess glucose had no apparent effect on the toxicity induced by paraoxon. Glucose feeding also increased the magnitude and duration of the inhibition of brain and plasma cholinesterase by parathion, but not by paraoxon. Also, glucose feeding did not affect the biotransformation of parathion or paraoxon. Finally, while parathion exposure down-regulated total muscarinic receptor binding in the cortex of control and glucose-fed rats, a much greater reduction (43%) was noted in glucose-fed rats. The investigators suggested that the glucose-induced reduction in food intake, particularly of amino acids, may limit the *de novo* synthesis of AChE and consequent recovery of synaptic transmission. Liu et al. (2005) conducted a similar study in adult and juvenile rats provided with either tap water or 15% high fructose corn syrup (HFCS) in drinking water. The results showed that the cholinergic toxicity of parathion was significantly enhanced by feeding HFCS in both adults and juvenile rats. However, consumption of HFCS had no significant effect on parathion-induced AChE inhibition in the frontal cortex or the diaphragm. The latter suggested that differences in enzyme inhibition may not account for the greater parathion toxicity observed in sugar-fed rats than in water-only rats. Since feeding HFCS significantly reduced food intake in rats, the effects of parathion were examined in a pair-fed group of rats. The results showed that food restriction alone did not exacerbate parathion toxicity. In a later study, Liu et al. (2007) reported that the exacerbation of parathion toxicity by glucose feeding was associated with significant increases in nitric oxide and reductions in high-energy phosphates/metabolites in the brain. According to the investigators, these biochemical responses may be involved in the modulation of parathion toxicity by glucose feeding, but the precise contribution remains unclear. The investigators noted that their results may be particularly important in children because children often consume relatively higher proportions of sugar in their diets.

Paraoxonase (PON1), the A-esterase that hydrolyzes paraoxon, the active metabolite of parathion, is polymorphically distributed in humans, suggesting that there might be a genetically based differential susceptibility to the toxicity of parathion and similar organophosphorus pesticides. The information below has been extracted from a recent review of the topic by Costa et al. (2013). The reader is referred to references cited therein for more detailed information. Human PON1 displays two polymorphisms in the coding region, Q192R and L55M. A significant additional polymorphism found in the non-coding regions of the PON1 gene is that at position –108, with the 108C allele providing levels of PON1 about twice as high as those seen with the 108T allele. While the Q192R polymorphism significantly affects the catalytic efficiency of PON1 and is substrate-dependent, the L/M polymorphism at position 55 has been associated with plasma PON1 protein levels, with $PON1_{M55}$ being associated with low plasma PON1. The latter appears to be related to linkage with the low efficiency –108T allele of the –108 promoter region polymorphism. Both the Q192R and the –108 (C/T) polymorphisms contribute to determine an individual's PON1 "status". For adequately predicting risk of organophosphate toxicity, it is important to know the two variables of PON1 (192 genotype and level), as high catalytic efficiency and high concentrations of PON1 are the two determinants of PON1 protection. Plasma PON1 activity can vary up to 40-fold in a given population, and differences in PON1 protein levels up to 13-fold are also present within a single $PON1_{192}$ genotype in adults. Human studies have shown that PON1 activity is very low at birth and increases over time reaching a plateau between 6 months and a few years of age. There are also data indicating that PON1 activity may be even lower before birth as determined in premature babies compared to term babies. While this suggests that fetuses and young children may be at higher risk of organophosphate toxicity, it may not be the case regarding parathion based on data from studies with rat liver microsomes and human liver microsomes that have suggested that PON1 is not functionally important at the toxicologically relevant concentrations of paraoxon (Chambers et al. 1994; Mutch et al. 1999).

Studies in animals have shown that administration of rabbit PON1 (high PON1 activity) afforded significant protection against the cholinergic effects of oxons, including paraoxon. However, knockout ($PON1^{-/-}$) mice, which have no paraoxonase activity in plasma and liver, unexpectedly showed no increased sensitivity to paraoxon. Moreover, intravenous injection of purified human $PON1_{Q192}$ or $PON1_{R192}$ to $PON1^{-/-}$ mice did not afford protection against paraoxon toxicity. These results were explained by the fact that with paraoxon, the $PON1_{R192}$ alloform is much more efficient than the $PON1_{Q192}$ alloform, but its overall catalytic efficiency is too low to protect against paraoxon toxicity. This strongly suggested that PON1 may not degrade paraoxon efficiently *in vivo* and as such, it does not play an important role in modulating sensitivity to paraoxon toxicity. This is consistent with results of studies

that examined the association between Parkinson's disease and parathion and the influence of functional polymorphisms at position 55 in the coding region of the PON1 gene (PON1-55) (Manthripragada et al. 2010) and also the single nucleotide polymorphisms $PON1_{Q192R}$ and $PON1_{C-108T}$ impact (Lee et al. 2013) (see Section 3.2.3.4). The results showed no increased risk of Parkinson's disease for people exposed to parathion, and risk did not increase in carriers of the variant MM PON1-55 genotype or the variant genotypes $PON1_{Q192R}$ or $PON1_{C-108T}$.

The results of a series of studies in which neonatal rats were administered subcutaneous doses of parathion that did not induce significant inhibition of AChE suggested that young organisms may be especially sensitive to the effects of organophosphorus pesticides, parathion included (see Section 3.2.4 for references). These studies reported alterations in the development of neurotransmitter systems and metabolic dysregulation that were evident at later times up to adulthood. Since the various organophosphorus pesticides tested seemed to induce effects of opposing direction, the investigators suggested that organophosphorus pesticides can affect the developing nervous system via mechanisms not directly related to AChE inhibition.

A few studies suggest that female rats are more susceptible to the acute effects of parathion than males. For example, Gaines (1960) reported oral LD_{50} values of 13 and 3.6 mg/kg in male and female Sherman rats, respectively. To determine whether LD_{50} values underwent seasonal variations, Gaines and Linder (1986) conducted bimonthly determinations in male and female Sherman rats over a period of 1 year. The LD_{50} values ranged from 6.9 to 11.0 mg/kg in males and from 3.0 to 3.4 mg/kg in females. Pasquet et al. (1976) reported 10-day LD_{50} values of 16 and 6 mg/kg for technical parathion in male and female CD rats, respectively. Whether this reflects sex-related differences in toxicokinetics is unknown. Making inferences to possible sex-related differences in humans based on these limited data would be inappropriate.

Studies have shown that many cytochromes are involved in the hepatic metabolism of parathion and that glutathione S-transferases also participate in the elimination of parathion. Since the metabolism of parathion plays a key role in its toxicity, genetic polymorphisms may influence health outcomes and place certain individuals at a higher risk of parathion exposure. Studies have suggested that cytochrome CYP3A4 is the main human cytochrome involved in the metabolism of parathion (Butler and Murray 1997; Mutch et al. 1999). Although there is growing evidence for functional polymorphisms in CYP3A4, evidence is too preliminary to predict with certainty the extent to which polymorphism might impact parathion metabolism (Haber et al. 2002).

See also Section 3.7, Children's Susceptibility for related information regarding susceptibility of younger organisms to parathion toxicity.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

Goldfrank LR, Flomenbaum NE, Lewin NA, et al., eds. 2002. Goldfrank's toxicologic emergencies. 7th ed. Stamford, CT: Appleton and Lange.

Shannon MW, Borron SW, Burns MJ, eds. 2007. Haddad and Winchester's clinical management of poisoning and drug overdose. 4th 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 (2007), Clark (2002), and Osmundsen (1998).

The first priority following parathion intoxication should be airway management with frequent suctioning of secretions and respiratory support. Intubation may be required to facilitate control of secretions and for ventilator support if respiratory failure occurs. Patients with liquid contamination of skin and clothing may pose a skin contact risk, so health care personnel should wear neoprene or nitrile gloves. To prevent further dermal absorption, the patient should be disrobed as soon as possible and the skin should be washed thoroughly with alkali soap and water. The eyes should be irrigated copiously with water or saline. The removal of clothing should eliminate 85–90% of a contamination hazard. Although hypochlorite solutions deactivate organophosphate pesticides *in vitro*, their use on human tissues is not recommended because it may cause corneal burns and other toxicity. Agents such as soil, flour, or talcum powder may be applied to the skin followed by mechanical removal. Cutaneous absorption can also

occur as a result of contact with vomitus or diarrhea. Following oral poisoning, evacuation of the stomach contact is recommended if vomiting has not occurred. However, induced emesis should be avoided. If the patient is alert and asymptomatic, a single dose of activated charcoal is recommended (usually 1 g/kg) because ileus may develop during atropine therapy. Osmundsen (1998) points out that Ipecac should not be used for organophosphate poisoning. Cathartics may be unnecessary, as intestinal motility is greatly increased.

3.11.2 Reducing Body Burden

No information was located regarding reducing the body burden of parathion, or organophosphates, following exposure. As mentioned in Section 3.4, parathion 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

Seizure activity should be rapidly controlled with intravenous diazepam, midazolam, or lorazepam. Initial recommendations include the use of at least 10 mg intravenous diazepam or 5–10 mg intramuscular midozalam in adults (pediatric dose is 0.1–0.2 mg/kg intravenous diazepam or 0.1–0.3 mg/kg intramuscular midozalam). After stabilization of the patient and decontamination, the next priority should be to control excessive muscarinic activity with atropine. 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. Glycopyrrolate, a quaternary ammonium compound, has been suggested as an alternative to atropine. Unlike atropine, glycopyrrolate does not cross the blood-brain barrier and, therefore, has fewer central nervous system effects. Intravenous doses of atropine should begin at 1–5 mg in adolescents and adults and at 0.05 mg/kg in children up to adult doses, and should be repeated every 2–3 minutes until atropinization occurs. The latter is achieved when the patient exhibits dry skin and mucous membranes, decreased or absent bowel sounds, tachycardia, reduced secretions, no bronchospasm, and usually mydriasis. Patients with severe toxicity may require 75–100 mg atropine. Direct ocular exposure to parathion may respond only to topical ophthalmic atropine. Atropine does not antagonize nicotinic effects; therefore, pralidoxime (2-PAM) is needed for treatment of muscle weakness and respiratory depression. 2-PAM is a quaternary amine oxime that can reverse the phosphorylation of AChE and thereby restore activity. It may also prevent continued toxicity by detoxifying the organophosphate molecule and has an anticholinergic effect. 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 mg/L is suggested as the minimum therapeutic threshold. 2-PAM is considered a very safe drug with few side effects. In addition to 2-PAM, obidoxime has been used successfully to treat parathion poisoning (Eyer et al. 2003). Treatment consisted of an initial 250 mg intravenous bolus followed by continuous infusion at 750 mg/24 hours. This resulted in plasma obidoxime concentrations between 10 and 20 μmol/L.

Although the emergency medicine textbooks cited above do not specifically mention the use of substances to antagonize the nicotinic effects induced by organophosphotus pesticides, studies in animals provide some information. For example, Mehrani et al. (2008) reported that in rats treated intraperitoneally with paraoxon, simultaneous administration of atropine plus the nicotinic receptor antagonist, mecamylamine, resulted in less signs of toxicity (involuntary movements) than in rats treated with paraoxon and only atropine. Studies in animals also provide information regarding other types of treatments to interfere with parathion toxicity. Petrikovics et al. (1999) showed that intravenous injection of recombinant phosphotriesterase encapsulated in sterically stabilized liposomes into mice 1 hour prior to a subcutaneous injection of paraoxon significantly increased the 24-hour LD_{50} from 0.9 to 125 mg/kg. Combining the phosphodiesterase treatment with either atropine or 2-PAM further increased the LD_{50} to 540–550 mg/kg. An even higher LD_{50} of 920 mg/kg was obtained when the mice were pretreated with phosphotriesterase plus atropine and 2-PAM. Evron et al. (2007) reported that mice injected with the human AChE variant, AChE-R, exhibited reduced toxicity to a lethal dose of paraoxon than control mice. AChE-R was produced from plant-optimized cDNA in *Nicotiana benthamiana* plants and showed the same affinity for paraoxon as the mammalian cell culture-derived AChE. Yet another potentially useful mitigating agent was studied by Bird et al. (2008). These investigators reported that a single intravenous injection of a recombinant bacterial organophosphate hydrolase (OpdA), cloned from *Agrobacterium radiobacter*, to rats immediately or 10 minutes after an oral dose of parathion did not prevent lethality. However, repeated doses at 45 and 90 minutes after poisoning significantly improved survival to 62.5%. Administration of a single dose of OpdA in combination with 2-PAM therapy improved survival to 75%. Time-course experiments showed that OpdA maintained clinically relevant enzymatic activity *in vivo* for several hours.

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 parathion is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of parathion.

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

3.12.1 Existing Information on Health Effects of Parathion

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

Most of the literature reviewed concerning the health effects of parathion in humans described case reports and case series of occupational exposure and accidental or intentional ingestion of parathion. There are also a few studies of the general population and of controlled exposure in volunteers. The cases of occupational exposure to parathion concerned exposures of acute, intermediate, and chronic durations. The predominant route of exposure in the occupational case reports/series was believed to be dermal, but the possibility of some degree of inhalation exposure could not be ruled out. The information on current

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

	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
	Systemic									
Inhalation	●	●	●			●				
Oral	●	●	●			●				
Dermal	●	●	●	●		●	●	●		●

Human

	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
	Systemic									
Inhalation	●	●	●			●				
Oral	●	●	●	●	●	●	●	●	●	●
Dermal	●	●	●	●	●	●				

Animal

● Existing Studies

human exposure in the United States is limited because production and all uses of parathion in the United States were cancelled in 2003. The precise duration and level of exposure to parathion in the human studies available generally cannot be quantified from the information presented in the reports.

There is more information in the open literature regarding the health effects of parathion following acute and intermediate oral exposure in experimental animals than regarding chronic exposure. Also, as can be seen in Figure 3-5, considerably less information is available on the effects of inhalation and dermal exposure to parathion in animals. There is no evidence suggesting that the toxicity of parathion is route-specific. However, ingested parathion should reach the liver sooner.

People living near hazardous waste sites may be exposed to parathion primarily via dermal contact with, or through ingestion of, contaminated soils since parathion is found bound to soil particles. Another possible mechanism for oral exposure to parathion is the ingestion of pesticide-laden dust from a waste site. Ingestion of contaminated water is not expected to be a significant route of exposure since parathion is poorly soluble in water and is generally not found in groundwater. Likewise, inhalation exposure to parathion is not a major route of exposure due to its low volatility. Before the use of parathion was banned, the primary route of exposure to parathion for the general population was probably via ingestion of low-level residues on contaminated foods.

Recommendations made below regarding conducting additional studies where data gaps exist need to be balanced by the fact that the current risks of exposure have diminished significantly since all uses and production of parathion were cancelled several years ago.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Information is available regarding the effects of acute-duration exposure in humans following inhalation (Hartwell et al. 1964), oral (De Bleecker et al. 1992; De Jager et al. 1981; Diggory et al. 1977; Eitzman and Wolfson 1967; Etzel et al. 1987; Eyer et al. 2003; Hayes et al. 1964; He et al. 1998; Hoffman and Papendorf 2006; Morgan et al. 1977; Tsachalinas et al. 1971; Wishahi et al. 1958), and dermal exposure (Grob et al. 1950; Hayes et al. 1964; Milby et al. 1964; Quinby and Lemmon 1958). Parathion may be lethal to humans and animals by all routes of exposure studied, depending on the dose (Diggory et al. 1977; Eitzman and Wolfson 1967; EPA 1978; Etzel et al. 1977; Gaines 1960; Gaines and Linder 1986; Lores et al. 1978; NIOSH 1974; Pasquet et al. 1976; Wishahi et al. 1958). The main target of toxicity in humans and animals following acute, high-level exposure by any route is the

nervous system (Diggory et al. 1977; Eitzman and Wolfson 1967; EPA 1978; Etzel et al. 1977; Gaines 1960; Gaines and Linder 1986; Lores et al. 1978; NIOSH 1974; Pasquet et al. 1976; Wishahi et al. 1958). Adverse systemic effects (respiratory, cardiovascular, and gastrointestinal) reported in most cases of acute exposure to high amounts of parathion in humans and in animals are likely to be secondary to the serious neurological effects (i.e., tremors, seizures). Acute oral exposure to parathion also induced neurobehavioral alterations in animals at doses higher than those that inhibited cholinesterase activity (Moser 1995; Reiter et al. 1973, 1975). Acute-duration oral studies in mice also showed that parathion can affect immune function by inhibiting the production of antibodies and increase the sensitivity to allergens (Casale et al. 1983, 1984; Fukuyama et al. 2010, 2011, 2012; Kim et al. 2005; Wiltrout et al. 1978). In some studies, this was observed in mice treated with relatively low doses, comparable to doses that inhibited AChE activity (Fukuyama et al. 2011, 2012). It would be helpful to try to replicate these findings to add confidence to the results. An acute-duration study also reported that parathion altered the microscopic appearance of the skin of guinea pigs when applied directly onto the skin for 5 days (Dikshith and Datta 1972). As discussed in Section 2.3, studies of cholinesterase inhibition have shown that it takes approximately 21–28 days for inhibition of cholinesterase activity to reach a steady state and that values obtained in single-dose or short-duration studies carry great uncertainty. For this reason, and also based on data collected on enzyme inhibition for a great number of organophosphate pesticides (EPA 2006), acute-duration inhalation MRLs were not derived for parathion. However, as explained in Section 2.3, the intermediate-duration MRLs are protective of acute effects.

Intermediate-Duration Exposure. No intermediate-inhalation studies in humans were located. Only one intermediate-duration inhalation study in animals was located, and it provided information on neurological effects in rats and dogs during whole-body, intermittent exposure to parathion aerosol for 6 weeks (NIOSH 1974). An intermediate-duration inhalation MRL was derived for parathion from data regarding changes in red blood cell AChE in rats in the NIOSH (1974) study. Information is available regarding the effects of intermediate-duration exposure in humans in two studies that evaluated changes in blood cholinesterase levels in humans during controlled oral exposure to parathion (Edson 1964; Rider et al. 1969). Studies in animals provided information regarding death (Barnes and Denz 1951), systemic effects (hepatic, renal, and body weight) (Atkinson et al. 1994; Dikshith et al. 1978; NCI 1979; NIOSH 1974), neurological effects (Barnes and Denz 1951; Dikshith et al. 1978; Frawley and Fuyat 1957; Ivens et al. 1998; NCI 1979; NIOSH 1974; Reischchl et al. 1975), reproductive effects (Dikshith et al. 1978), and developmental effects (Deskin et al. 1979). The data from Rider et al. (1969) regarding changes in red blood cell AChE activity in volunteers exposed to parathion in a capsule for 30 days were used to derive an intermediate-duration oral MRL for parathion. It should be mentioned that in the

developmental study in rats by Deskin et al. (1979), the lowest dose tested, 0.01 mg parathion/kg/day, administered to pregnant rats during gestation and lactation induced alterations in EKGs in 25-day-old pups. Since this is not a developmental end point routinely tested in guideline developmental studies, it would be helpful to try to replicate these results. An acute-duration study also reported that parathion altered the microscopic appearance of the skin of guinea pigs when applied directly onto the skin for 15 days (Dikshith and Datta 1972). Additional intermediate-duration studies do not seem necessary at this time.

Chronic-Duration Exposure and Cancer. One study was located that provided information regarding changes in plasma cholinesterase and red blood cell AChE activity in workers at an industrial plant that manufactured the concentrated material and dusts containing various concentrations of parathion (Brown and Bush 1950). Uncertainties regarding exposure data and the extent of the changes in red blood cell AChE activity precluded the use of this study for derivation of a chronic-duration inhalation MRL for parathion. No chronic-duration inhalation studies in animals were found. Also, no chronic-duration oral data in humans were located. Two chronic-duration oral studies were located in the open literature (Barnes and Denz 1951; NCI 1979). Barnes and Denz (1951) reported that dietary exposure of rats to up to approximately 1.7 mg parathion/kg/day did not induce adverse clinical signs or gross or microscopic changes in organs or tissues. The NCI (1979) study reported that exposure of rats to up to 4.4 mg parathion/kg/day or mice to up to 27.6 mg parathion/kg/day did not cause gross or microscopic alterations in organs and tissues. However, the investigators noted that during the first half of the second year, clinical signs among dosed rats were noted at a low or moderate incidence, and during the second half of the year, they increased, but no quantitative data were presented. In addition, by week 60 of the study, all high-dose male mice were showing signs of hyperexcitability, but no data were provided. However, because these studies did not monitor red blood cell AChE activity and there is uncertainty in the NCI (1979) study regarding the incidence of clinical signs in rats and mice during the second year of exposure, they are inadequate for derivation of a chronic-duration oral MRL for parathion. A chronic-duration oral study with interim determinations of plasma, red blood cell, and brain cholinesterase activity would be valuable to confirm that enzyme activities reach a steady state and do not continue to decrease during long-term exposure to low-to-moderate doses of parathion. Data regarding chronic dermal exposure to parathion were provided in the AHS. The AHS provided information regarding respiratory effects (Hoppin et al. 2006, 2009), hearing loss (MacCrawford et al. 2008), behavioral function (Starks et al. 2010), and cancer (Dennis et al. 2010). A study of Chinese workers exposed to parathion provided information regarding reproductive effects (Padungtod et al. 2000).

Studies of the general population provided data regarding Parkinson's disease (Firestone et al. 2005; Manthripragada et al. 2010) and developmental effects (Eskenazi et al. 2004).

Very limited information is available regarding exposure to parathion and cancer. Dennis et al. (2010) examined the potential association between exposure to 50 agricultural pesticides, parathion among them, and the incidence of cutaneous melanoma in the AHS cohort of pesticide applicators along with ever-use of older pesticides that contain arsenic. The study found no association between melanoma incidence and organophosphate insecticides as a class. However, there was a significant association between melanoma and parathion (≥56 days of exposure; OR=2.4; 95% CI 1.3–4.4; p=0.003) based on 11 cases. The study also found a higher OR of 7.3 (95% CI 1.5–34.6) among those who had used arsenical pesticides. A limitation of the study was the small number of subjects who used parathion for at least 56 days and had melanoma (n=11). Since the AHS is a prospective study, continuous monitoring of the cohort will provide useful information. The carcinogenicity of parathion has been studied in a chronic oral bioassay using rats and mice (NCI 1979). That study concluded that parathion was carcinogenic to rats based on an increased incidence of combined adrenal cortical adenomas and carcinomas in males and females. Parathion was not carcinogenic in mice. No further information was located in the open literature. Additional studies do not seem necessary at this time.

Genotoxicity. No reliable data on humans exist to indicate whether parathion may act by a genotoxic mechanism. The results from available *in vivo* animal studies and *in vitro* studies showed that parathion is not a mutagenic or clastogenic agent (Degraeve and Moutschen 1984; EPA 1977; Fahrig 1974; Gilot-Delhalle et al. 1983; Kevekordes et al. 1996; Simmon et al. 1976). Additional studies do not seem necessary at this time.

Reproductive Toxicity. No studies were located regarding reproductive effects in humans after oral or inhalation exposure to parathion. A small study of Chinese workers exposed to parathion and methamidophos reported that the workers (n=20) had a modestly lower sperm count, lower sperm concentration, and lower percentage of motile sperm than an unexposed control group (n=23) (Padungtod et al. 2000). While the results were suggestive, the role of parathion, if any, remained unclear. Evaluation of participants in the AHS could provide valuable information regarding a possible association between exposure to parathion and reproductive effects. Since the AHS includes evaluation of pesticide applicators and their spouses, information could be collected regarding possible effects in males and females exposed to parathion in the past. No information was located regarding reproductive effects in animals following inhalation or dermal exposure to parathion and very limited data were available

regarding oral exposure. Parathion induced histological alterations in the testes of rats in an intermediate-duration oral study (Dikshith et al. 1978). However, chronic-duration oral studies in rats and mice did not find gross or microscopic alterations in the reproductive organs from male or female animals treated with higher doses of parathion than in the intermediate-duration study. It would be useful to try to replicate the findings of the intermediate-duration study of Dikshith et al. (1978). In addition, a 2-generation study in rats would provide valuable information.

Developmental Toxicity. No information was located regarding developmental effects in humans following inhalation or oral exposure to parathion. A study of Latina women living in an agricultural community in California did not find significant associations between several measures of *in utero* exposure to parathion and fetal growth (Eskenazi et al. 2004). However, as mentioned before, exposure to parathion was assessed by measuring urinary *p*-nitrophenol, which can also be produced as a result of exposure to substances other than parathion. It should be mentioned that studies of other pesticides with mechanisms of action similar to parathion (i.e., chlorpyrifos, diazinon) have reported neurodevelopmental alterations in children following maternal environmental exposure (for references, see Bouchard et al. 2011; Eskenazi et al. 2007; Rauh et al. 2011). Therefore evaluation of women participants in the AHS or other similarly exposed cohorts could provide important information regarding possible effects of exposure to parathion on various developmental end points. No studies were located regarding developmental effects in animal following inhalation or dermal exposure to parathion. In developmental studies in rats exposed orally to up to 1 mg parathion/kg on gestation days 6–5 and rabbits exposed to up to 0.3 mg parathion/kg on gestation days 6–18, there was no evidence of embryotoxicity or teratogenicity (Renhof 10984, 1985). In another study, 25-day-old pups from rats exposed to relatively low doses of 0.01 mg parathion/kg/day during gestation and lactation showed alterations in the EKGs (Deskin et al. 1979). Since this is not an end point routinely evaluated in standard developmental studies, it would be useful to conduct developmental studies to evaluate traditional end points in addition to examining the pups for possible cardiotoxicity.

Immunotoxicity. No information was located regarding immunological and lymphoreticular effects in humans following dermal exposure to parathion, except for the report of a significant association between exposure to parathion and allergic asthma in participants in the AHS (Hoppin et al. 2009). No information was located on immunotoxic effects in animals exposed to parathion by inhalation or dermally. Several studies in mice reported that acute oral exposure to parathion suppressed the antibody response to immunization with SRBC (Casale et al. 1984; Fukuyama et al. 2012; Kim et al. 2005; Wiltrout et al. 1978). The recent study by Fukuyama et al. (2012) reported that significant suppression

occurred with doses of 1.5 mg parathion/kg/day, but not 0.15 mg parathion/kg/day, for 5 days. In the Casale et al. (1984) study, significant suppression was observed with a single dose of 16 mg parathion/kg, but not 4 mg/kg, suggesting that repeated dosing may be necessary to induce immune suppression. Casale et al. (1984) also showed that cholinergic stimulation played a major role in the parathion-induced effect; further studies that examine the mechanism(s) involved would be valuable. It would also be useful to determine whether the parathion-induced immune suppression leads to increased susceptibility to infection by microorganisms. In addition, the possibility that immune suppression occurs also in longer-term studies may need to be examined.

Neurotoxicity. Information in both humans and animals indicates that the nervous system is the main target of parathion-induced toxicity following acute exposure by any route. This is particularly evident after exposure to high doses of parathion, as has occurred, for example, in cases of accidental or intentional ingestion of parathion formulations (Diggory et al. 1977; Eitzman and Wolfson 1967; Etzel et al. 1987; Eyer et al. 2003; He et al. 1998; Hoffman and Papendorf 2006; Tsachalinas et al. 1971; Wishahi et al. 1958) or in cases of high occupational exposure in workers involved in the manufacture or use of parathion (Diggory et al. 1977; Eitzman and Wolfson 1967; Etzel et al. 1987; Eyer et al. 2003; Grob et al. 1950; He et al. 1998; Hoffman and Papendorf 2006; Milby et al. 1964; Quinby and Lemmon 1958; Tsachalinas et al. 1971; Wishahi et al. 1958). As an organophosphate pesticide, parathion inhibits the activity of the enzyme, AChE, as well as that of plasma cholinesterase. The inhibition of AChE 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 (Abou-Donia 1995; Ecobichon 1994). Most of these signs and symptoms have been observed in the cases listed above. A few cases of intermediate syndrome and induced delayed neuropathy have also been reported following exposure to parathion (Besser et al. 1993; De Bleecker et al. 1992; De Jager et al. 1981; He et al. 1998; Nisse et al. 1998). Information is also available regarding behavioral function in humans exposed to parathion. Starks et al. (2012) evaluated 701 male participants in the AHS with a series of neurobehavioral tests and found that parathion exposure was associated with better verbal learning and memory and better performance on a test of sustained attention. A possible explanation was that given the large number of statistical tests performed, the results may have been due to chance. Followup evaluations of this cohort may provide valuable information. A study of controlled administration of parathion in capsules to volunteers identified NOAEL and LOAEL values for inhibition of red blood cell AChE of 0.06 and 0.11 mg/kg/day, respectively (Rider et al. 1969). This study confirmed the findings of an earlier study in volunteers (Edson 1964) and was used to derive an intermediate-duration oral MRL for parathion.

Information is lacking on long-term effects of acute high exposure to parathion. This information can only be obtained from evaluation of cohorts exposed only to parathion, 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 and monitoring clinical signs, a few oral studies have examined the effects of parathion on neurobehavioral parameters and showed that effects occurred at dose levels that induced significant depression of blood cholinesterase activity and/or induced clinical signs (Moser 1995; Reiter et al. 1973, 1975). Should additional chronic studies be conducted, it would be valuable to monitor long-term changes in red blood cell and brain AChE activities. 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 parathion. It should be noted that studies have been conducted that examined neurodevelopmental endpoints in rats treated as neonates with parathion by subcutaneous injection, see Section 3.2.4, Other Routes of Exposure for a summary of the findings.

Epidemiological and Human Dosimetry Studies. Most of the literature reviewed concerning the health effects of parathion in humans described case reports of occupational exposure, accidental or intentional ingestion of parathion, or accidental dermal exposure to the pesticide (Diggory et al. 1977; Eitzman and Wolfson 1967; Etzel et al. 1987; Eyer et al. 2003; He et al. 1998; Hoffman and Papendorf 2006; Tsachalinas et al. 1971; Wishahi et al. 1958), studies of workers involved in the manufacture of parathion (Brown and Bush 1950; Grob et al. 1950; Padungtod et al. 2000), studies of agricultural workers (MacCrawford et al. 2008; Dennis et al. 2010; Hoppin et al. 2006, 2009; Milby et al. 1964; Quinby and Lemmon 1958; Starks et al. 2012), members of the general population (Eskenazi et al. 2004; Firestone et al. 2005; Manthripragada et al. 2010), and a few controlled exposure studies with volunteers (Edson 1964; Hartwell et al. 1964; Hayes et al. 1964; Morgan et al. 1977; Rider et al. 1969). The predominant route of exposure in the occupational studies is believed to be dermal exposure (workers involved in pesticide manufacture, formulation, and application). Some studies of agricultural workers examined possible associations between exposure to parathion (and additional pesticides) and health outcomes such as respiratory effects (Hoppin et al. 2006, 2009), hearing loss (MacCrawford et al. 2008), behavioral function (Starks et al. 2012), and cutaneous melanoma (Dennis et al. 2010). The information from occupational studies is limited because of the possibility of concurrent exposure to other pesticides or other toxic substances, and the duration and level of exposure to parathion generally were not quantified. Likewise, exposure levels in cases of acute intentional or accidental exposure to high amounts

of parathion were generally not available. Because all production and uses of parathion were cancelled in the United States (EPA 2000a, 2007), it is difficult to identify a subpopulation currently at risk of significant exposure to parathion.

Biomarkers of Exposure and Effect.

Exposure. Available data indicate that urinary levels of *p*-nitrophenol may serve as biomarkers of ongoing exposure to parathion. Further research on biomarkers of low-level exposure to parathion is needed. Noort et al. (2009) described a method for measuring organophosphorothioate pesticides bound to albumin, and proposed that this method might be suited to evaluation of chronic, low-level exposure; however, further testing and application of this method is needed to establish its suitability to this purpose.

Effect. There are no biomarkers of effect specific for parathion. As an organophosphate pesticide, parathion, in sufficient amounts, produces typical signs and symptoms of cholinergic stimulation. Plasma and red blood cell 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 red blood cell cholinesterase are not usually available for non-occupationally exposed individuals, additional studies of normal values by age and sex are needed for assessing potential adverse effects, if useful for other pesticides.

Absorption, Distribution, Metabolism, and Excretion. Little is known about absorption after oral or inhalation exposure and the distribution of parathion and its metabolites throughout the body; these areas represent significant data gaps in the toxicokinetics of parathion. Data on the dermal absorption, metabolism, and excretion of parathion are generally adequate to describe these elements of the toxicokinetics of this compound in humans. Additional information on the role of specific cytochromes on bioactivation and detoxification of parathion in *in vivo* systems exposed to a range of parathion doses and exposure routes would be useful to better predict the interindividual variability in parathion toxicity and/or identify new strategies for therapeutic intervention. Available studies focusing on the role of specific cytochrome isozymes have given varying results (e.g., Buratti et al. 2003; Foxenberg et al. 2007; Mutch and Williams 2006; Mutch et al. 2002, 2003).

Comparative Toxicokinetics. No studies were located that directly evaluated the comparative toxicokinetics of parathion in animals and humans. Because human blood lacks the carboxylesterase

enzyme found in rodent blood, and this enzyme is capable of detoxifying parathion, further information on the importance of this enzyme in predicting parathion toxicity would serve to inform the relevance of rodent models to human toxicokinetics.

Recent work suggests that the desulfuration of parathion to paraoxon in human liver is mediated by a large number of cytochromes (CYP1A2, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CY 2D6, and CYP3A4/5), which show different affinities for the substrate (see Section 3.4.3). Significant variations in the activities of these cytochromes among humans and laboratory animal species would be expected to result in differences in parathion metabolism; additional information is needed to inform this question.

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 parathion, after acute exposures (Aaron 2007; Clark 2002; Osmundsen 1998). Case reports of acute poisoning with parathion involved the use of various drugs in different combinations and sequences as the specific situations required. The effectiveness of these drugs varied from case to case and probably depended on the time elapsed between poisoning and initiation of treatment and on the amount of parathion taken. Publishing treatments that have proven to be effective in randomized controlled trials in medical journals could help decrease the number of fatalities resulting from parathion poisoning, particularly in countries where it is still widely used. Research leading to the development of more efficient oximes should be encouraged. Studies in animals showed that treatment with phosphotriesterase encapsulated in liposomes, a bacterial organophosphorus hydrolase, or plant-derived AChE-R reduced the acute toxicity of parathion or paraoxon (Bird et al. 2008; Evron et al. 2007; Petrikovics et al. 1999). Further research on these and similar strategies would provide valuable information. No information is available on dealing with long-term, low-level exposures to parathion. 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. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Information on the effects of parathion in children is derived mainly from case reports of accidental ingestion or dermal contact with commercial formulations (i.e., Diggory et al. 1977; Eitzman and

Wolfson 1967; Etzel et al. 1987; Wishahi et al. 1958). In all of these cases, exposure to parathion 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. These case reports do not provide enough information to determine whether or not children are more susceptible to parathion exposure than adults. However, studies in animals have shown that young animals are more susceptible to the toxicity of high doses of parathion and that this is related to the metabolism and disposition of parathion and paraoxon rather than to differences in sensitivity to AChE inhibition (Atterberry et al. 1997; Benke and Murphy 1975; Gagné and Brodeur 1972; Harbison 1985; Karanth and Pope 2000; Nielsen et al. 1991).

Limited information is available regarding developmental effects of parathion in humans. A study of Latina women living in an agricultural community in California did not find an association between exposure to parathion and fetal growth and gestational length (Eskenazi et al. 2004). Evaluation of pregnancy outcomes in women participants in the AHS could provide valuable information regarding exposure to organophosphate pesticides and possible developmental effects. Conventional developmental studies in which female rats and rabbits were exposed during gestation showed that parathion was not embryotoxic or teratogenic (Renhof 1984, 1985). In a study in rats, 25-day-old pups from rats exposed to relatively low doses of 0.01 mg parathion/kg/day during gestation and lactation showed alterations in the EKGs (Deskin et al. 1979). Since this is not an end point routinely evaluated in standard developmental studies, it would be useful to try to replicate the results. Cross-foster studies in animals could provide information regarding differential transfer of parathion and/or metabolites through the placenta and the mother's milk.

There are no adequate data to evaluate whether pharmacokinetics of parathion in children are different from adults. However, to the extent that various cytochromes P450 that are involved in the metabolism of parathion in humans (Buratti et al. 2003; Foxenberg et al. 2007; Mutch and Williams 2006) are developmentally regulated (Tateishi et al. 1997), the metabolism of parathion in neonates and infants will likely differ from adults. Whether or not this would result in increased susceptibility of the young is not totally clear because cytochromes participate in both activation (desulfatation) and detoxification (dearylation) of parathion. No information was located regarding levels of parathion (or metabolites) in human milk. There is indirect evidence in animals that parathion (or its metabolites) can be transferred across the placenta and/or via breast milk to the offspring (Deskin et al. 1979; Villeneuve et al. 1972).

Further information on the dynamics of parathion 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 parathion. There are no data on the interaction of parathion 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 parathion (Boyd 1969; Bulusu and Chakravarty 1986, 1987; Casterline and Williams 1971; Villenueve et al. 1978). Further studies on children from malnourished populations should be conducted to explore this issue. The information available indicates that methods to reduce peak absorption of parathion 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 Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Information regarding ongoing research regarding parathion is presented in Table 3-13.

Table 3-13. Ongoing Studies on Parathion

Principal Investigator	Study topic	Institution	Sponsor
Baldwin, W	Role of CYP2B in the metabolism, fate, and toxicity of parathion using a CYP2B-knockdown mouse model; determine whether individuals with low CYP2B are sensitive to parathion	Clemson University, Clemson, South Carolina	National Institute of Environmental Health Sciences
Bird, SB	Determine the physiologic and electromyographic efficacy of the nicotinic receptor antagonist, rocurorium, in preserving function and architecture of the neuromuscular junction in parathion poisoning	University of Massachusetts, Worcester, Massachusetts	National Institute of Neurological Disorders and Stroke
Bird, SB	Test the safety and efficacy of a novel organophosphorus pesticide degrading enzyme, OpdA, in a nonhuman primate model	Harvard University, Boston, Massachusetts	National Center for Research Resources
Cerasoli, DM	Define, characterize, and develop a drug formulation that will afford post-exposure protection to victims of organophosphorus poisoning; the drug formulation will include a catalytic scavenger enzyme	U.S. Army Medical Research Institute for Chemical Defense, Aberdeen Proving Ground, Maryland	National Institute of Neurological Disorders and Stroke
Delorenzo, RJ	Develop a rat model to evaluate parathion toxicity and use this model to investigate mechanisms of toxicity that can be targeted to develop agent s to reverse these mechanisms and prevent morbidity and mortality	Virginia Commonwealth University, Richmond, Virginia	National Institute of Neurological Disorders and Stroke
Ford, BD	Evaluate the therapeutic benefit of the administration of neuroregulin-1, a neuroprotective anti-inflammatory compound alone or as a complement to standard therapy against parathion poisoning	Morehouse School of Medicine, Atlanta, Georgia	National Institute of Neurological Disorders and Stroke

Table 3-13. Ongoing Studies on Parathion

Principal Investigator	Study topic	Institution	Sponsor
Fryer, AD	Test the hypothesis that organophosphorus-induced airway hyper-reactivity in sensitized animals is mediated by the compounds affecting chemotactic factors and adhesion molecules that enhance eosinophil recruitment or nerves, and also compound-induced eosinophil activation	Oregon Health and Science University, Portland, Oregon	National Institute of Environmental Health Sciences
Garcia, GE	Evaluate novel sugar-linked reactivators of acetylcholinesterase with broader specificity, improved pharmacokinetics, and potential to cross the blood brain barrier; initial *in vitro* testing will be followed by testing in rodent species	U.S. Army Medical Research Institute for Chemical Defense, Aberdeen Proving Ground, Maryland	National Institute of Neurological Disorders and Stroke
Laskin, JD	Identify the precise site of action of a novel low-toxicity drug in the cytochrome P-450 system and test its efficacy in mitigating parathion toxicity in a rodent model	University of Medicine and Dentistry of New Jersey, Piscataway, New Jersey	National Institute of Neurological Disorders and Stroke
Lein, PJ	Elucidate the mechanism(s) by which organophosphorus compounds induce airway hyper-reactivity using physiological measurements *in vivo* and primary nerve cell cultures	University of California, Davis, California	National Institute of Environmental Health Sciences
Lein, PJ	Test the hypothesis that AMPA receptor antagonists and/or inhibitors of soluble epoxide hydrolases will significantly improve outcome following acute parathion poisoning	University of California, Davis, California	National Institute of Neurological Disorders and Stroke
Lein, PJ	Develop *in vivo* rodent models for assessing persistent neurological damage after seizures induced by parathion; identify effective therapeutic strategies for mitigating neurological damage	University of California, Davis, California	National Institute of Neurological Disorders and Stroke

Table 3-13. Ongoing Studies on Parathion

Principal Investigator	Study topic	Institution	Sponsor
Linney, EA	Examine how exposure of the developing nervous system to parathion can affect learning and/or behavior later in life; develop and use model vertebrate systems to examine possible mechanisms	Duke University, Durham, North Carolina	National Institute of Environmental Health Sciences
Pope, CH	Evaluate the role of endocannabinoid signaling in the expression of anticholinesterase toxicity of organophosphorus compounds and determine whether its differential modulation participates in selective toxicity	Oklahoma State University, Stillwater, Oklahoma	National Institute of Environmental Health Sciences
Wulff, H	Synthesize, characterize, test, and optimize the pharmacokinetic properties and central nervous system penetration of two distinct classes of therapeutic agents, sEH inhibitors and K-Ca channel activators	University of California, Davis, California	National Institute of Neurological Disorders and Stroke

Source: RePORTER 2013

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4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

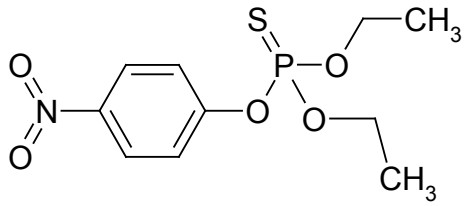
Information regarding the chemical identity of parathion is located in Table 4-1.

In the United States, parathion was sold in the form of emulsion concentrates, wettable powders, granules, dusts, aerosols, and oil sprays (Farm Chemicals Handbook 1987). In 1991, parathion became a restricted use pesticide and was formulated as Parathion EC and Ethyl Methyl Parathion 6-3, which were liquid, emulsifiable concentrates and applied using aerial equipment. Manufacture of parathion for manufacturing use products was discontinued as of September 2000, and manufacture of all end use products were discontinued effective December 31, 2002 (EPA 2000a). Internationally, parathion may be formulated as an aerosol, capsule suspension, dustable powder, emulsifiable concentrate, granule, and wettable powder. Formulations range from a 1% dust to an 83.5% concentrate. The technical-grade material is 98% pure (FAO 1997).

4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

Table 4-1. Chemical Identity of Parathion

Characteristic	Information	Reference
Chemical name	O,O-Diethyl O-(4-nitrophenyl) phosphorothioate	HSDB 2013
Synonyms(s)	O,O-Diethyl-O-4-nitrophenyl phosphorothioate; O,O-diethyl O-p-nitrophenyl thiophosphate; parathion, ethyl parathion; others	HSDB 2013
Registered trade name(s)	Alkron, Aileron, Aphamite, Bladen, Corothion, Etilon, Folidol, E-605, Fostox E, Geofos, Kriss, Niram, Orthophos, Panthion, Paramar, Paraphos, Parathene, Parawet, Penncap-E, Phoskil, Rhodiatox, SNP, Soprathion, Stathion, Thiophos, Vitrex, others	FAO 1997
	PESTANAL®	Sigma Aldrich 2014
Chemical formula	$C_{10}H_{14}NO_5PS$	HSDB 2013
Chemical structure		PhysProp 2013
Identification numbers:		
CAS registry	56-38-2	HSDB 2013
NIOSH RTECS	TF 4550000	NIOSH 2009
EPA hazardous waste	P089	HSDB 2013
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	UN 2783 Organophosphorous pesticides; IM06.1 Organophosphorous pesticides; solid	HSDB 2013
HSDB	197	HSDB 2013
NCI	C00226	NCI 1979

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

Table 4-2. Physical and Chemical Properties of Parathion

Property	Information	Reference
Molecular weight	291.26	HSDB 2013
Color	Pale yellow (pure); dark brown (technical grade liquid generally in an organic solvent); colorless to white (formulated solid)	FAO 1997; IPCS 2005
Physical state	Liquid (pure); solid (formulated)	HSDB 2013; IPCS 2005
Melting point	6.1°C	Tomlin 2010
Boiling point	375°C at 760 mm Hg	O'Neil et al. 2013
Density:		
at 25°C/4°C	1.26	HSDB 2013
Odor	Garlic-like Phenol-like	HSDB 2013
Odor threshold:		HSDB 2013
Water	4.00×10^{-2} mg/L	
Air	0.470 mg/m^3	
Taste threshold	No data	
Solubility:		
Water at 20°C	11 mg/L	Tomlin 2010
Organic solvent(s)	Miscible in alcohols, esters, ethers, ketones, aromatic hydrocarbons, and animal and vegetable oils; practically insoluble in petroleum ether, kerosene, and usual spray oils	HSDB 2013
Partition coefficients:		
Log K_{ow}	3.83	Tomlin 2010
Log K_{oc}	Eight soil types, 2.48–2.69; four soil types, 2.98–3.23; average for four soils, 4.019	Gerstl and Mingelgrin 1984; Sharom et al. 1980
Vapor pressure		
at 20°C	6.68×10^{-6} mm Hg	HSDB 2013
Henry's law constant	2.98×10^{-7} atm-m^3/mol	PhysProp 2013
Autoignition temperature	No data	HSDB 2013
Flashpoint	120–160°C until flammable impurities removed	HSDB 2013
Flammability limits	Not highly flammable	HSDB 2013
Explosive limits	Decomposes upon heating and residues can explode	HSDB 2013

FAO = Food and Agriculture Organization; HSDB = Hazardous Substances Data Bank; NIOSH = National Institute for Occupational Safety and Health

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

5.1 PRODUCTION

Parathion is an organophosphorus insecticide produced commercially by the reaction of diethyl phosphorothionchloridate with sodium *p*-nitrophenate (HSDB 2013). Parathion is a liquid or wettable powder that was often dissolved in a hydrocarbon solvent before use (Agency for Toxic Substances and Disease Registry 2011). In 1991, all of the technical parathion sold in the United States was produced by Cheminova Agro A/S, formulated at one location and sold under the Cheminova label. Two formulations were sold: parathion and ethyl methyl parathion emulsifiable concentrates (EPA 2000a). Prior to 1991, parathion was also sold in the form of emulsion concentrates, wettable powders, granules, dusts, aerosols, and oil sprays (Farm Chemicals Handbook 1987).

Recent production estimates for parathion are not available, as this substance is no longer produced in the United States. As of 1991, parathion was registered as a restricted use insecticide and had been limited to use on nine crops. Due to the toxicity of this chemical, the production of manufacturing use products was cancelled effective as of September 2000. The production of most end use products was terminated as of December 31, 2002, with the last legal use of most of this chemical and its products effective on October 31, 2003 (EPA 2000a). Even though the Drexel Chemical Company was no longer manufacturing or using parathion, it still had four products actively registered under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). On March 16, 2005, Drexel requested the cancellation of these four remaining products and this became effective on December 13, 2006 (EPA 2006b).

Beginning on January 1, 1995, parathion was listed as one of the newly added chemicals that manufacturing and processing facilities would be required to report under Title III of the Superfund Amendments and Reauthorization Act of 1986 (SARA) (EPA 2006). Table 5-1 lists the production year, number of facilities, the state where each facility is located, and the range (in pounds) for the sole domestic manufacturer that reported the presence of bulk parathion in 2011 (TRI11 2013). Although manufacturers are required to report Toxics Release Inventory (TRI) data to satisfy EPA requirements, parathion has not been manufactured in the United States since 2002. The TRI data should be used with caution since only certain types of facilities are required to report (EPA 2005); however, this is expected to be an exhaustive list regarding parathion.

Table 5-1. Facilities that Possessed Parathion in 2011

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	1,000	9,999	9, 12

[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. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacturing Aid
12. Ancillary/Other Uses
13. Manufacturing Impurity
14. Process Impurity

Source: TRI11 2013 (Data are from 2011)

5.2 IMPORT/EXPORT

The import of technical parathion in the United States was prohibited as of September 2000 (EPA 2000a). Internationally, parathion is subject to the Rotterdam Convention on Prior Informed Consent (PIC) procedure, which states that the export of this chemical can only take place with the prior informed consent of the importing party. This applies to all formulations of parathion, including aerosols, dustable powder, emulsifiable concentrate, granules, and wettable powders, with the only exception being capsule suspensions (WHO 2005).

Parathion has no import tolerances according to EPA and North American Free Trade Agreement (NAFTA) guidelines (EPA 2000a, 2000b). Import tolerances require information about pesticides use in exporting countries and resulting residues in imported commodities. As parathion has no import tolerances, commodities containing parathion residue may not be imported into the United States.

5.3 USE

Parathion was first registered as a pesticide in 1948 (EPA 2000a). It was used as a non-systemic insecticide to control sucking and chewing insects and mites in a wide variety of crops (Tomlin 2010). It was often repeatedly applied by fan or boom sprayers or by aircraft on a wide variety of orchard, row, and field crops (CDFA 1988). In 1991, due to emerging health and ecological concern posed by parathion, use sites were limited, and application and post-application practices were restricted in order to mitigate risk to workers exposed during and after application. Since 1991, parathion was a restricted use organophosphate insecticide and miticide limited to nine crops: alfalfa, barley, canola (rapeseed), corn, cotton, sorghum, soybeans, sunflowers, and wheat. In September 2000, some manufacturers began voluntarily cancelling parathion products registered under Section 3 of FIFRA. This started the termination of registration of most end use products effective December 31, 2002, with the last legal use of most of those products ending on October 31, 2003 (EPA 2000a). The Drexel Chemical Company was authorized to manufacture parathion through 2003 and had four products actively registered under FIFRA through 2006. On March 16, 2005, Drexel requested the cancellation of these four remaining products and this became effective on December 13, 2006 (EPA 2006b).

Consumption of parathion in 1978 was reported to be 7.2 million pounds. This number increased to 8.6 million pounds in 1982 (HSDB 2013). No recent use estimates are available for parathion, as this substance is no longer used in the United States.

5.4 DISPOSAL

Parathion is currently considered a toxic chemical under Section 313 of the Emergency Planning and Community Right-To-Know Act (EPA 2006). Since parathion is toxic and containers with parathion residue can explode upon heating, any containers or products containing parathion must be disposed of in accordance with State and Federal law (EPA 2000a).

Parathion is a potential candidate for rotary kiln incineration, using a temperature range of 820–1,600°C and a residence time of seconds. It is also a potential candidate for fluidized bed incineration, with a 450–980°C temperature range, and liquid injection incineration with a temperature range of 650–1,600°C. Reverse osmosis has been investigated as a waste water treatment technology for the removal of parathion (HSDB 2013).

An aqueous solution of parathion was found to completely decompose during a 5-hour exposure to granular zero valence iron (Fjordboge et al. 2013), indicating that this method might be suitable for *in situ* environmental remediation.

Dilute waste parathion solutions may be disposed of by chemical or biological treatment, incineration, or in soil pits. Because of the large volume of water involved, incineration is not a preferred method. Adsorption of parathion onto media such as activated charcoal, as well as chemical and biological treatment methods, are feasible, but they require frequent monitoring and maintenance. Soil pits have the advantage of less maintenance, less cost, and the ability to reduce the volume of waste by water evaporation (Sanders and Seiber 1984).

No information was found on the past and present volumes of parathion or parathion-contaminated wastes disposed of by each disposal method.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Parathion has been identified in at least 21 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). However, the number of sites evaluated for parathion is not known. The frequency of these sites can be seen in Figure 6-1. The locations of hazardous waste sites where parathion has been detected, as well as the media in which it was detected, are provided in Table 6-1.

6.2 RELEASES TO THE ENVIRONMENT

Parathion has not been manufactured, processed, or used in the U.S. mainly since 2000; so, it is likely that no significant releases to the environment have occurred in several years. The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

During its use as a broad spectrum insecticide in the United States, parathion directly entered the environment from point sources. These are associated with specific points of release, and from nonpoint sources, which are diffuse and widely dispersed, such as runoff to streams, seepage to groundwater, and deposition of pesticides from the atmosphere (USGS 2007). In order to reduce exposure to children and others, a 1991 agreement began that made parathion a restricted use organophosphate insecticide. In September 2000, most manufacturers agreed to cancel the registration of manufacturing use products. This was followed by the termination of registration of those end use products effective December 31, 2002. Most legal use of parathion products was cancelled as of October 31, 2003 (EPA 2000a).

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

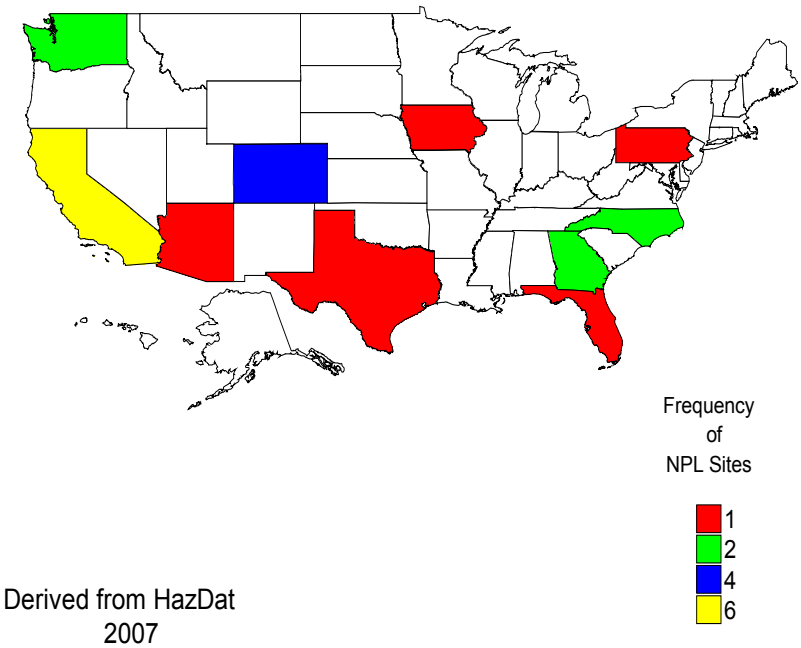


Table 6-1. NPL Sites with Parathion Contamination

Site name	City	State[a]	Number of detections	Contaminated media	Maximum concentration
Hassayampa Landfill	Hassayampa	AZ	1	MM	
FMC Corp.	Fresno	CA	1	ST	
FMC Corp.	Fresno	CA	1	SU	
FMC Corp.	Fresno	CA	1	WU	
T.H. Agriculture & Nutrition Co.	Fresno	CA	1	SS	22,262.0 ppm
T.H. Agriculture & Nutrition Co.	Fresno	CA	1	ST	
T.H. Agriculture & Nutrition Co.	Fresno	CA	2	WM	0.84 ppb
Lorentz Barrel & Drum Co.	San Jose	CA	2	SU	
Stoker Company	Imperial	CA	1	SE	57 μg/kg
Stoker Company	Imperial	CA	4	SU	4,700 μg/kg
Stoker Company	Imperial	CA	2	WS	0.4 μg/L
Frontier Fertilizer	Davis	CA	1	SS	7 ppm
Frontier Fertilizer	Davis	CA	1	SU	1 ppm
Waste Disposal, Inc.	Sante Fe Springs	CA	1	SH	
Waste Disposal, Inc.	Sante Fe Springs	CA	1	SU	
Rocky Mountain Arsenal (U.S. Army)	Adams County	CO	1	MA	
Rocky Mountain Arsenal (U.S. Army)	Adams County	CO	2	MM	
Rocky Mountain Arsenal (U.S. Army)	Adams County	CO	1	MO	
Rocky Mountain Arsenal (U.S. Army)	Adams County	CO	1	SL	110 ppb
Rocky Mountain Arsenal (U.S. Army)	Adams County	CO	1	SS	
Rocky Mountain Arsenal (U.S. Army)	Adams County	CO	1	ST	
Rocky Mountain Arsenal (U.S. Army)	Adams County	CO	1	WM	
Rocky Mountain Arsenal (U.S. Army)	Adams County	CO	1	WU	
Woodbury Chemical Co.	Commerce City	CO	1	ST	
Woodbury Chemical Co.	Commerce City	CO	1	SU	
Woodbury Chemical Co.	Commerce City	CO	1	WS	
Sand Creek Industrial	Commerce City	CO	1	SE	
Sand Creek Industrial	Commerce City	CO	1	SS	
Sand Creek Industrial	Commerce City	CO	1	ST	
Sand Creek Industrial	Commerce City	CO	2	WM	
Hollingsworth Solderless Terminal	Fort Lauderdale	FL	1	SE	

Table 6-1. NPL Sites with Parathion Contamination

Site name	City	State[a]	Number of detections	Contaminated media	Maximum concentration
Woolfolk Chemical Works, Inc.	Fort Valley	GA	1	MA	
Woolfolk Chemical Works, Inc.	Fort Valley	GA	1	SU	
T.H. Agriculture & Nutrition Co.	Albany	GA	1	SU	340 mg/kg
T.H. Agriculture & Nutrition Co.	Albany	GA	1	WU	20 ppb
Aidex Corp.	Mineola	IA	1	WM	
North Carolina State University (Lot 86)	Raleigh	NC	1	MM	
Aberdeen Pesticide Dumps	Aberdeen	NC	1	MM	
Aberdeen Pesticide Dumps	Aberdeen	NC	2	SU	
Ohio River Park	Neville Island	PA	1	SL	
Ohio River Park	Neville Island	PA	1	SU	240 ppb
Ohio River Park	Neville Island	PA	1	WL	
Ohio River Park	Neville Island	PA	1	WU	
Crystal City Airport	Crystal City	TX	1	SS	
Crystal City Airport	Crystal City	TX	1	ST	
FMC Corp. (Yakima Pit)	Yakima	WA	2	MM	13,000 ppm
FMC Corp. (Yakima Pit)	Yakima	WA	2	SS	30 ppm
FMC Corp. (Yakima Pit)	Yakima	WA	1	ST	
FMC Corp. (Yakima Pit)	Yakima	WA	3	SU	16,000 ppm
Mica Landfill	Mica	WA	1	MM	

[a]Post office state abbreviations are used.

MA = air, unspecified; MM = waste materials/containers; MO = other (50 characters); SE = sediment, unspecified; SH = hard surface/wipe samples; SL = sludge; SS = subsurface soil (>3-inch depth); ST = surface/top soil (≤3-inch depth); SU = soil depth not specified or not specifically ≤3 or >3 inches; WL = leachate; WM = groundwater, monitor; WS = surface water (lakes, streams, ponds, etc.); WU = groundwater, unspecified; WW = surface water, unspecified

Source: HazDat 2007

The Drexel Chemical Company was still authorized to continue manufacturing parathion through 2003 and still had four products actively registered under FIFRA. On March 16, 2005, Drexel requested the cancellation of these four remaining products and this became effective on December 13, 2006 (EPA 2006b). There are no known natural sources of parathion.

6.2.1 Air

Estimated releases of 3 pounds (~1.36×10^{-3} metric tons) of parathion to the atmosphere from one domestic manufacturing and processing facility in 2011, accounted for about 50% of the estimated total environmental releases from facilities required to report to the TRI (TRI11 2013). The remaining 50% was released to soil from the same facility. These releases are shown in Table 6-2.

Parathion was formerly released into the atmosphere solely by human activities associated with its production and use as an insecticide for agricultural purposes. One study assessed the rate at which parathion applied to soil or mixed with water (simulating wet agricultural soil and a retention pond, respectively) would volatilize to the surrounding air. The measured rates were low and similar to those predicted from the Henry's law constant, and were 0.8% d^{-1} for wet surface soil and 0.003 hr^{-1} of the surface water surface water concentration (Sanders and Seiber 1984). These values might overestimate what would occur in the environment where degradation and uptake by biota are in competition.

6.2.2 Water

No release of parathion to surface water or publically owned treatment works (POTWs) from one domestic manufacturing and processing facility in 2011 was reported from facilities required to report to the TRI (TRI11 2013). These releases are listed in Table 6-2.

Parathion was formerly released into water directly from point source discharges, from drift during pesticide applications, and from nonpoint-source runoff from agricultural areas.

6.2.3 Soil

Estimated releases of 3 pounds (~$1.36\text{x}10^{-3}$ metric tons) of parathion to soils from one domestic manufacturing and processing facility in 2011, accounted for about 50% of the estimated total environmental releases from facilities required to report to the TRI (TRI11 2013). The remaining 50% was released from the same facility to the atmosphere. No additional

Table 6-2. Releases to the Environment from Facilities that Possessed Parathion in 2011[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	1	3	0	0	3	0	3	3	6

[a]Normally, the TRI data should be used with caution since only certain types of facilities are required to report. However, this is an exhaustive list and no company was authorized to produce, process, or use parathion after 2006. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI11 2013 (Data are from 2011)

parathion was released via underground injection (TRI11 2013). These releases are summarized in Table 6-2.

Parathion was formerly released into soils primarily from its registered use on various agricultural crops. In agricultural areas, parathion may also have been transferred to aquatic sediments (Wan et al. 1994).

Since parathion undergoes various reduction and degradation reactions in the course of time ranging from hours to months, these loadings to soils and sediments were temporary phenomena.

6.3 ENVIRONMENTAL FATE

Parathion can move into various environmental compartments, but there does not appear to be a major reservoir or sink for this chemical in any specific environmental compartment primarily because of its relatively rapid degradation in each environmental medium.

6.3.1 Transport and Partitioning

Based on the vapor pressure of parathion (see Table 4-2) and the organic liquids with which it typically is mixed, parathion released to the atmosphere via agricultural spraying would be expected to exist in both the vapor and particulate phases (Eisenreich et al. 1981).

Parathion released to water from both point and nonpoint sources may be sorbed to soils and sediments, or accumulated in aquatic organism. While volatilization of parathion may not be expected to be significant based upon the Henry's law constant (see Table 4-2), it can be an important transport process from water surfaces. Sanders and Seiber (1984) measured a volatilization rate of 30×10^{-4}/hour from water for parathion, corresponding to a half-life of 9.6 days. A laboratory experiment determined that the volatilization half-life for parathion from water 4.5 cm deep was 14 and 9.3 days from unstirred and stirred solutions, respectively, at 24°C. This is equivalent to 311 and 206 days, respectively, from water 1 meter deep (Chiou et al. 1980). In another laboratory experiment designed to simulate an evaporation pond, 0.3% of parathion volatilized after 1 day (Sanders and Seiber 1983). Parathion released to water may also be adsorbed highly by soils and sediments based on its organic carbon partition coefficient (log K_{oc}) values measured to range from 2.50 to 4.20 for varying types of soil and sediment (Mingelgrin and Gerstl 1983).

The adsorption of parathion to soils and sediment attenuates the rate of volatilization and its mobility. Adsorption to suspended solids and sediment in the water column also affects its susceptibility to photolysis, its bioavailability for aquatic organisms, and its biodegradation (Schuurmann et al. 2006).

Parathion does not significantly bioaccumulate in aquatic organisms. A compilation of bioconcentration factors (BCFs) obtained for various freshwater fish and other species is presented in Table 6-3. The BCF values range from 63 to 462. Tadpoles, which are generally resistant to cholinesterase inhibitors such as parathion and are therefore suspected that they might accumulate the pesticide, had a reported BCF that averaged 64 (Hall and Kolbe 1980). This residue level in tadpoles is consistent with BCFs for vertebrate species.

Parathion may be metabolized in fish and other aquatic species after prolonged exposure. Some biotransformation pathways have been recognized. Sheepshead minnows (*Cyprinidon variegatus*) metabolized parathion to paraoxon, a toxic product, through catalysis by P450-dependent monooxygenation (James 1994). Parathion may be metabolized in fish and other aquatic species after prolonged exposure. Some biotransformation pathways have been recognized, such as metabolism of parathion to aminotparathion, with subsequent transformation to *p*-nitrophenol by fish microbes; see Figure 6-2 (EPA 1977). Sheepshead minnows (*Cyprinidon variegatus*) metabolized parathion to paraoxon, a toxic product, through catalysis by P450-dependent monooxygenation (James 1994). Hydrolysis of parathion has been demonstrated in several shrimp and crayfish species (James 1994).

Parathion released to soil partitions to the atmosphere through volatilization, to surface water via runoff, and to groundwater as a result of leaching. Volatilization of parathion from moist and dry soils is not expected to be a significant transport process based upon the Henry's law constant and vapor pressure (see Table 4-2). The vapor loss rate of technical-grade parathion from a non-absorbing glass surface is 0.210 $\mu g/cm^2$/hour (Spencer et al. 1979). Vapor losses from parathion-incorporated soil are expected to be much lower due to binding by the soil. Simulations of parathion losses from dry soil resulted in only 0.1–0.3% losses in 30 days when incorporated into 10 cm of soil (Jury et al. 1984). Volatilization in a laboratory environmental chamber designed to simulate a soil pit resulted in 0.8% volatilization in 1 day from wet soil and approximately an order of magnitude less from dry soil (Sanders and Seiber 1984).

The mobility of parathion in soils and sediments is expected to be low based on measured K_{oc} values. Parathion was reported to have average K_{oc} values of 674 and 1538 in Israeli soils (0.11–5.82% organic matter) and sediments (3.08–7.85 organic matter), respectively (Gerstl and Mingelgrin 1984). In four

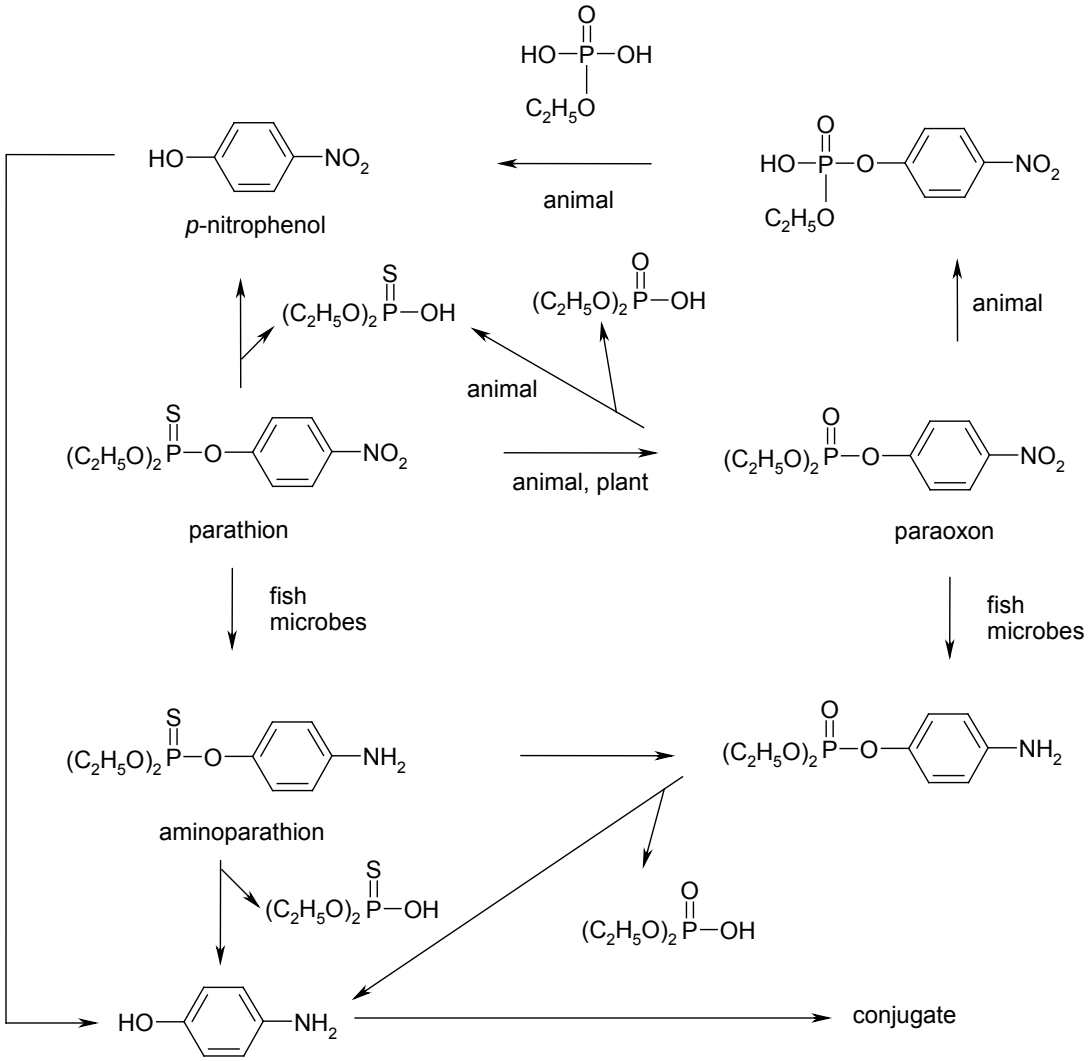
Table 6-3. Bioconcentration Data for Parathion

Species common name/ scientific name	Exposure type	Exposure concentration (μg/L)	Duration (days)	BCF	Reference
Freshwater fish					
Bluegill/*Lepomis macrochirus*	F	510	0.5	63	HSDB 2013
Bluegill/*L. macrochirus*	F	640	3	462	HSDB 2013
Brook trout/*Salvelinus fontinalis*	F	3,180	0.33	68	HSDB 2013
Brook trout/*S. fontinalis*	F	270	5.83	344	HSDB 2013
Killifish/*Oryzias latipes*	F	–	1–3	98[a]	Tsuda et al. 1995
Tadpoles	I	64			Hall and Kolbe 1980

[a]Average BCF value reported in the cited reference.

BCF = bioconcentration factor; F = flow-through exposure system; I = immersion

Figure 6-2. Degradation Pathways for Parathion



Adapted from EPA (1977)

soils with an organic carbon range of 0.087–0.65%, parathion had an average K_{oc} of 10,454 ppm (Hamaker and Thompson 1972). Mingelgrin and Gerstl (1983) reported a K_{oc} range of 314–15,860 for parathion for an unspecified number of soils with an organic content ranging from 0.2 to 6.1%. In four soil types with organic carbon content ranging from 0.41 to 43.7%, parathion had K_{oc} values ranging from 965 to 1,700 (Sharom et al. 1980). In five sterilized Iowa soils (organic matter content 0.88–31.65%), parathion had K_{oc} values ranging from 602 to 805 (Felsot and Dahm 1979). Chu and Chan (2000) reported a K_{oc} value of 10,700 mL/g for parathion. A log K_{oc} of 3.20 (K_{oc} of 1,585) was reported by Sabljic et al. (1995). Adsorption patterns indicated that parathion has an initial fast adsorption reaction occurring within 4 hours. Adsorption was almost complete 1 hour after application (~86% of added parathion) and equilibrium (88% of added parathion) was reached within 4 hours (Saffih-Hdadi et al. 2003).

Because this insecticide is highly adsorbed by soils, leaching into groundwater is expected to be minimal. Additional parameters influencing the leaching potential of this chemical include the soil type (e.g., clay versus sand), amount of rainfall, depth of the groundwater, and the extent of degradation (Kenaga 1980). Sorption of parathion is positively correlated with organic matter content of the soil (Felsot and Dahm 1979). Parathion had a mobility of 0.01 compared to that of water in a French soil (Moreale and Van Bladel 1983) and ranked 36 and 40 in a ranking of 41 pesticides by attenuation factor and retardation factor, respectively, in two sandy soils (Rao et al. 1985). The fraction of parathion leached from soil by 10 successive 200-mL applications of water to a soil column was 1.24 and 4.36% for an organic soil and sand, respectively (Sharom et al. 1980). Only a small fraction (10%) of parathion adsorbed to a sterile sandy loam was found to undergo diffusion (the diffusion constant in soil with highest moisture content was 0.03 cm^2/day) (Gerstl et al. 1979). In soil columns of Nacodoches clay subsoil, parathion leached to 60 inches when 230 inches of rainfall was simulated, while in Houston black clay, 1,725 inches of rain were required to produce leaching to 60 inches (EPA 1977). Parathion applied at 0.1 lbs/acre, followed by flooding and a subsequent application of 0.2 lbs/acre, was degraded before reaching drainage tiles 6 feet below the soil surface (EPA 1977). In field studies, little leaching occurred in a sandy loam soil in 16 years after four annual applications of parathion despite 42 inches of precipitation per year (Stewart et al. 1971). Little parathion was found below 9 inches, 6 years after 30,000–95,000 ppm was applied to the soil (Wolfe et al. 1973). In a 15-year study of residues in a light sand soil, no parathion was found to have leached below 8 inches (EPA 1977). In an 8-month persistence test under experimental conditions with 20 cm of simulated rain, no parathion was found below 1 inch. In cases where small amounts of parathion penetrated into the soil, it was believed to be the result of the movement of particulate or microparticulate matter containing sorbed parathion rather than by leaching (EPA 1977). In a field study

involving the application of parathion to a peach orchard providing watershed for a 2.7-acre pond, no residue was found below 6 inches and there appeared to be little desorption of the insecticide from the bottom sediment of the pond (Faust and Suffet 1966).

6.3.2 Transformation and Degradation

Parathion is subject to a variety of abiotic and biotic degradation processes in all environmental compartments. The adsorption of parathion to suspended solids and sediments in the water column may affect its rate of volatilization, photolysis, biodegradation, and its bioavailability to aquatic organisms (Schuurmann et al. 2006). It follows two major fate pathways: degradation to less toxic compounds or oxidative conversion to the toxic bioactive product, paraoxon (CDFA 1988). The extent of conversion to paraoxon is dependent upon the amount of sunlight, atmospheric oxidants present, and type of formulation applied (CDFA 1988).

6.3.2.1 Air

Parathion in the atmosphere may be subject to direct photolysis since it absorbs light in the spectra above 290 nm. Under atmospheric conditions, oxidation especially influences the transformation rates of parathion to its degradation product, paraoxon (Mansour et al. 1983). Parathion conversion to paraoxon occurs rapidly in air, is promoted by sunlight, and takes place largely in the vapor phase (Seiber and Woodrow 1984). The presence of ozone catalyzes the conversion of parathion to paraoxon. While at normal ozone levels (30 ppb), paraoxon production was quite low (approximately 2.1–4.1% in 8 hours), at ozone levels found under smog conditions (300 ppb), 10–65% conversion was found in 8 hours (HSDB 2013). The photolysis half-life of parathion as determined in a laboratory photoreactor was 41 minutes. This half-life was reduced to 23 minutes in the presence of >1 ppm ozone (Woodrow et al. 1978, 1983). Field experiments performed by releasing parathion as an emulsifiable concentrate and sampling downwind resulted in a half-life of 5 minutes at 4 PM (early June), and 131 minutes after sunset (Woodrow et al. 1978, 1983). The half-life (first-order kinetics) for the vapor-phase reaction of parathion with hydroxyl radicals in the atmosphere is estimated to be 4.2 hours, assuming an atmosphere containing $5x10^5$ hydroxyl radicals/m^3 at 25°C (Meylan and Howard 1993).

6.3.2.2 Water

Parathion released to water may be subject to both abiotic degradation (i.e., hydrolysis and photolysis) and biotic degradation by microorganisms. Microbial metabolism is the major means of parathion detoxification in soil and aquatic environments (Sethunathan et al. 1977).

Parathion slowly undergoes hydrolysis to form toxic products, paraoxon and *p*-nitrophenol, which are much more soluble than the parent compound. At pH 7 and 20°C, the hydrolysis half-life of parathion was reported as 130 days (EPA 2002). A hydrolysis half-life of 62 days was reported for parathion in dilute solutions at pH 6.3 and 20°C. It was also reported to hydrolyze at 1% in river water at pH 7.2, with a half-life of 60 days (Mansour et al. 1999). In a natural aqueous medium, approximately 70% of parathion was hydrolyzed in 4 weeks and 72% was hydrolyzed in 6 weeks (EPA 1977).

The fate of parathion in water is dependent upon physical factors such as temperature, pH, and microbial composition. Parathion is relatively stable in neutral or acidic pH range, but is hydrolyzed rapidly in alkaline conditions (Sethunathan et al. 1977). Chapman and Cole (1982) reported the half-lives of parathion in sterile aqueous buffer solutions to be 39, 43, 33, 24, and 15 weeks at pH levels of 4.5, 5, 6, 7, and 8, respectively. Fisher and Lohner (1987) studied factors affecting the stability of parathion in the aquatic environment, with emphasis on pH. In water of aquatic microcosms adjusted to pH 4, 6, and 8, pH was found to be insignificant in controlling levels of parathion. After 7 days, parathion accounted for 29.7, 28.7, and 36.6% of total radioactivity in the water of microcosms held at pH 4, 6, and 8, respectively. In abiotic water, however, no parathion breakdown was observed in 40 days at any of the pH levels, demonstrating the importance of biotic factors, particularly microorganisms, in degrading parathion (Fisher and Lohner 1987). A half-life of 8.77 days was reported for parathion in an experiment using samples of non-filtered Limon River water that was exposed to sunlight and in contact with the atmosphere (Medina et al. 1999).

Temperature has been shown to be an important factor in the degradation of parathion through elevation of the rate of hydrolysis. An increase in temperature from 20 to 37.5°C (pH 7.4) resulted in a decrease in the half-life of parathion from 130 to 27 days in an aqueous system (Freed et al. 1979).

The presence of metal ions can have a catalytic effect on hydrolysis as was shown by the decrease in half-life of formulation parathion sprays in the presence of copper ions and in other experiments done in the presence of copper and calcium ions (Plastourgou and Hoffmann 1984). However, it was not clear how

much of an effect the presence of metal ions will have in natural waters. The half-life for chemical hydrolysis in sterile seawater was reported to be approximately 1 year at 4°C and pH between 7.8 and 8.8, showing that the pH was not a demonstrable factor in degradation (Wade 1979). It was reported, however, that divalent cations may have catalyzed the hydrolysis.

The rate of aqueous photolysis is dependent upon the intensity and wavelength distribution of sunlight, which varies by the time of day and season of the year. The presence of natural photosensitizers, such as humic and fulvic acid also affects the potential rate of photolysis of parathion in natural waters. Measured photodegradation half-lives for parathion in lake water, river water, marine water, groundwater, and distilled water were 17.8, 23.7, 18.9, 21.6, and 19.6 days, respectively. Paraoxon was found to be the primary degradation product by this process, while small amounts of *p*-nitrophenol, aminoparathion, and triethyl phosphothioate were also observed (Sakellarides et al. 2003). Half-lives of 120 and 86 days were observed when parathion was incubated in pH 7.3 river water in darkness at 6 and 22°C, respectively; the half-life decreased to 8 days when parathion was incubated in sunlight in pH 7.3 river water (Lartiges and Garrigues 1995). Half-lives of 542 and 44 days were observed when parathion was incubated in pH 8.1 seawater in darkness at 6 and 22°C, respectively; a half-life of 18 days was observed when parathion was incubated in seawater in sunlight (Lartiges and Garrigues 1995). Irradiation for 10 hours in aerated distilled water resulted in 88% degradation attributed to photolysis (Mansour et al. 1983).

Photosensitizers that are present in eutropic natural waters accelerate photolysis. In river water, parathion had a photolysis half-life of 1.2 days, and this half-life was reduced to 0.69 days in the presence of the photosensitizer, riboflavin (Zhao and Hwang 2009). While 20% of parathion in distilled water was lost by photolysis in 18 hours, the same loss occurred in only 2 hours in Okeefenokee Swamp water (Zepp and Baughman 1978). The presence of hydrogen peroxide at concentrations that occur naturally in agricultural irrigation water and other surface water has been shown to increase the rate of photodegradation. The addition of hydrogen peroxide to distilled water reduced parathion remaining in solution from 65 to 28% when exposed to October sunlight for 245 hours (Draper and Crosby 1984).

Parathion has been shown to biodegrade in acclimated natural waters within several weeks. Parathion (5 ppm) completely degraded within 2 weeks in acclimated water from Holland Marsh, a vegetable growing area in Ontario, being almost quantitatively converted to aminoparathion, while only 10% degradation occurred in 16 weeks when the water was sterilized (Sharom et al. 1980). In the waters of the Little Miami River, Ohio, a small stream that receives domestic and industrial waste as well as farm

runoff, 50% of parathion (10 ppb) degraded in 1 week and none could be detected after 4 weeks (Eichelberger and Lichtenberg 1971).

In non-acclimated seawater, marine plankton were responsible for both chemical and biological degradation of parathion. Surface water of varying salinity (0–28 ppt) collected from the Mississippi Sound estuary system degraded parathion with a 45-day half-life at 30°C and was shown to be independent of salinity (HSDB 2013). The half-life of parathion in sterile seawater was reported as approximately 1 year, but was reduced to 56 days under nonsterile conditions (Wade 1979). After 30 days of incubation in non-sterile coastal river water (24 ppt salinity), only 21, 14, and 6% of parathion remained at pH values of 6, 7, and 8.16, respectively, while in sterile coastal river water, 64, 57, and 49% of the initial parathion remained at pH 6, 7, and 8.16, respectively (Wang and Hoffman 1991). In an experimental study performed by Carvalho et al. (1998), the persistence half-life of parathion dissolved in marine water at 32°C was 9–46 days, depending on the salinity of the water.

Parathion has been shown to degrade in activated sludge treatment plants. With adequate aeration, high levels of parathion wastes were destroyed within 7–10 days in a treatment plant (Sethunathan et al. 1977).

6.3.2.3 Sediment and Soil

Once released to soils and sediments, parathion can be degraded by hydrolysis, photolysis, and biodegradation by several genera of microorganisms. In an experiment studying the relative decomposition rates of ^{14}C-labeled parathion in sterilized and non-sterilized soil, degradation was principally of biological origin based on measurements of cumulative $^{14}CO_2$ released. At 7 days after application, <3% of abiotic degradation was observed for parathion in sterilized soil compared with 18% in non-sterilized soil. After 56 days of incubation, the respective values were relatively much closer (34% and 55%), indicating that there was less parathion available for biological activity and that the biodegradation pathway may be cometabolic. Parathion may be transformed by reduction to aminoparathion, which is then hydrolyzed to 4-aminophenol, or by oxidative desulfurization to paraoxon, which is hydrolyzed to *p*-nitrophenol, depending on the type of soil and, therefore, the type of microbial biomass (Saffih-Hdadi et al. 2003).

Moisture content of soil and initial concentration of parathion can have an effect on the rate of degradation and evaporation, both of which contribute to removing parathion. The elimination of parathion in soil with three different moisture contents increased with initial concentration (1.4–28 ppm)

and moisture content (Gerstl et al. 1979). The percentage of parathion eliminated after 11 days of incubation ranged from 96% at high initial concentrations and moisture content to 20% at low concentrations and moisture levels.

Based on several degradation studies using sterile and nonsterile samples and isolated cultures of microorganisms, it has been shown that microbial metabolism is the major means of parathion detoxification in soil and aquatic environments (Sethunathan et al. 1977). After 8 weeks of incubation in an organic and a mineral soil, <2 and 6% of the 1 ppm parathion applied remained, respectively, while 80 and 95% remained in sterilized controls, respectively (Chapman et al. 1981). Miles et al. (1979) reported the half-lives of parathion (10 ppm) in a sandy loam and organic soil to be <1 and 1.5 weeks, respectively, with only 5% remaining after 3 and 10 weeks, respectively. During three composting trials in 1979, 1982, and 1983 consisting of 56–75-day composting periods, composting of organic wastes was characterized by very high biological activity (Vogtmann et al. 1983).

Parathion has also been shown to degrade under anaerobic conditions with reduction of parathion to aminoparathion as the main degradation pathway. When parathion (500 ppm) was incubated in flooded anaerobic alluvial soil, 43 and 0.09% remained after 6 and 12 days, respectively, with degradation occurring by reduction to aminoparathion (Adhya et al. 1981a). In a parallel experiments in which parathion was incubated for 30 minutes in soil suspensions of five 30-day flooded (anaerobic) soils and aerobic soils that had been previously reduced, no degradation occurred in the aerobic soils, while 35–68% degradation occurred in the anaerobic soils (Adhya et al. 1981b). The most reduced soils produced the most rapid degradation. The effect of sulfur content of the soils was also investigated in the study. In anoxic sulfur-containing environments such as flooded acid sulfate soils, hydrogen sulfide evolved as the end product of anaerobic metabolism of sulfate, readily reacted with the aminoparathion degradation product to form desethyl aminoparathion (Adhya et al. 1981b). After repeated application of parathion to flooded soils, the degradation pathway shifted from reduction to hydrolysis (Adhya et al. 1981c).

Two microorganisms isolated from flood soils also were found to hydrolyze parathion (Adhya et al. 1981c). Parathion was rapidly hydrolyzed within 24 hours by both *Flavobacterium* sp. and *Pseudomonas* sp. A hydrolysis product of parathion, *p*-nitrophenol, was not metabolized further by the *Flavobacterium* sp., while the *Pseudomonas* sp. readily metabolized *p*-nitrophenol to yield nitrate (Adhya et al. 1981c).

Studies with sterile soils and clay minerals have shown that parathion may undergo slow chemical hydrolysis in soil systems. During 130 days of incubation in gamma irradiated soils (30 kGy) of differing

organic matter and clay mineralogy at room temperature, 3–23% of parathion was hydrolyzed in air-dried soil and <10% was hydrolyzed in moist soils. Among the soil constituents, clay and organic matter (kaolinite > montmorillonite > organic matter) were the most important in catalyzing the chemical hydrolysis of parathion in sterile soils. However, adsorption follows the reverse order, indicating that catalysis occurs at active absorption sites at the soil surface (Sethunathan et al. 1977). In 14 soil studies, 3–33% of the initial parathion was degraded after 130 days of incubation in dry soil (Yaron 1975). For most of the soils, the presence of water hindered degradation, presumably by blocking active sites on the soil (Yaron 1975). Parathion degradation decreased as moisture content of various kaolinite clays increased until a moisture content equivalent to the upper limit of bound water was reached (Saltzman and Mingelgrin 1984). As moisture content was increased beyond this point (e.g., in flooded conditions) the hydrolysis rate of the parathion sharply increased (Saltzman and Mingelgrin 1984).

Although the treatment of crops with pesticides such as parathion often resulted in significant contamination of the adjacent soils, photolysis is only an important environmental fate process for contaminated surface soils since sunlight is rapidly attenuated and does not penetrate much beyond the soil surface. Measured photodegradation half-lives for parathion in sandy clay loam (0.90% organic matter), clay loam (1.94% organic matter), and sandy loam (3.52% organic matter) were 21.3, 15.6, and 20.8 days, respectively (Sakellarides et al. 2003). No correlation was observed between the percentage of organic matter present in the soil and the rate of photodegradation.

6.3.2.4 Other Media

Thin films of parathion that may be formed on leaves and other surfaces after spraying have a photodegradation half-life of 88 hours (Chen et al. 1984). Conversion products on leaf surfaces and dry dust particles in field tests are paraoxon and *p*-nitrophenol (Crosby 1979). In a photodegradation study, parathion applied to epicuticular leaf and fruit wax of a tomato degraded 16.3 and 20.7% after 8 hours of exposure, respectively. The presence of the wax interacts with parathion at the nitro group that participated in the photoreduction, leading to the formation of the azo derivative 4,4’-bis(di-ethoxy-phosphinothioyloxy)azobenzene (Fukushima and Katagi 2006).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to parathion, which has not been used in the United States for several years, depends in part on the limits of detection of supporting analytical data and appropriate sampling of environmental media and biological specimens. Concentrations of parathion in

unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on parathion levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring parathion in a variety of environmental media are detailed in Chapter 7.

Care should be taken when assessing analytical results for which a limit of detection (LOD) or similar sensitivity value is not provided for the substance of interest, and the study reports not having detected that substance; failing to detect a substance does not mean that it is not present.

Most information on parathion concentrations in various environmental media derived from large-scale monitoring networks dates from before the mid-1990s and no longer reflects current conditions. There is a noticeable lack of national monitoring studies that would allow meaningful estimation of current parathion concentrations associated with various environmental media. Reliable evaluation of the potential for human exposure to parathion depends, in part, on the LOD of supporting analytical data and appropriate sampling of environmental media and biological specimens.

6.4.1 Air

When parathion was still being used as a registered pesticide in the United States, a range of ambient air concentrations of 0.017–0.089 μg/m^3 was reported (CDFA 1988). Ambient air concentrations of parathion and its oxidation product, paraoxon, converted to parathion were measured by the Air Resources Board in the San Joaquin Valley, California from January 6 to February 14, 1986 and in the Imperial Valley, California from September 23 to October 22, 1986. In this study, the highest individual 24-hour values measured in the northern San Joaquin Valley for parathion and for combined parathion plus converted paraoxon were 0.834 and 1.423 μg/m^3, respectively, with means of 0.141 and 0.170 μg/m^{3}for all samples collected from the six sites sampled over the 23-day study period. In the southern San Joaquin Valley and in the Imperial Valley, respectively, the peak amounts of parathion (excluding converted paraoxon) in the air were considerably lower; the highest measured individual 24-hour values were 0.089 and 0.150 μg/m^3 with means of 0.023 and 0.025 μg/m^3 for each area. The low values in the southern San Joaquin Valley were potentially the result of the wet, foggy weather prevailing during the winter months. In the Imperial Valley, the low ambient levels of parathion could have been the result of increased volatility during the very warm weather of the fall months (CDFA 1988). Ambient parathion concentrations were measured under foggy atmospheric conditions in and around the Central

Valley of California (Parlier, California), which is a prime agricultural area dominated by fruit, nut, and citrus orchards (Glotfelty et al. 1990; Seiber et al. 1993; Zabik and Seiber 1993). Parathion was detected in air samples collected from Parlier, California on January 12, 1986 under foggy atmospheric conditions at a total concentration of 9.4 ng/m^3, with 78.5% existing in the vapor phase (Glotfelty et al. 1990). Zabik and Seiber (1993) studied the atmospheric transport of parathion from California's Central Valley to the Sierra Nevada Mountains. Air samples collected from January through February 1991 represented the simultaneous collection of both vapor and particulate phases. Concentrations of parathion and paraoxon were 26–13,000 pg/m^3 (0.026–13 ng/m^3) and 8–3,800 pg/m^3 (0.008–3.8 ng/m^3), respectively, for samples collected at the 114 m elevation and below the LOD and 71 pg/m^3 (<LOD–0.071 ng/m^3) and <LOD–220 pg/m^3 (<LOD–0.22 ng/m^3), respectively, at the 533-m elevation. The pesticide concentrations in air samples decreased with distance and elevation moving east from the Central Valley into the higher elevations of the Sierra Nevada Mountains. At times, air concentrations of parathion at the 114-m elevation were 1,000 times greater than concentrations detected at the 533-m elevation. Concentrations at the 1,920-m elevation were typically below the limit of quantification for parathion, but paraoxon was detected at concentrations of up to 10 pg/m^3. The higher paraoxon than parathion concentrations at higher elevations indicate that the oxygenation process occurs during atmospheric transport resulting in increasing conversion of parathion to paraoxon as residence time in the atmosphere increases. Wet deposition samples (rain and snow) collected at the 114-m elevation contained up to 7,600 pg/mL parathion and 8,300 pg/mL paraoxon. Seiber et al. (1993) reported an average parathion concentration of 63.5 ng/m^3 in 24-hour ambient air samples collected near dormant orchards in the northern San Joaquin Valley, California during 17 days in January 1989, the most intensive period of dormant orchard spraying. The average day- and night-time concentrations were 52.0 and 119.6 ng/m^3, respectively. Those values are significantly lower that reported by the California Department of Food and Agriculture (CDFA) for the same location and time frame (CDFA 1988).

In a study of rain and air samples collected from agricultural and urban sites in Mississippi during April to September 1995, parathion was not detected (method reporting level of 24 pg/m^3) in urban air or rain and agricultural air. It was detected once in agricultural rain samples (Coupe et al. 2000; Foreman et al. 2000).

Parathion was included in the National Air Pesticide Monitoring Program from 1970 to 1972 at selected sites in 14–16 states. In 1970, 3.2% of 787 samples tested positive at a mean concentration of 64.2 ng/m^3 and a maximum concentration of 834 ng/m^3. In 1971, 2.3% of 667 samples tested positive at a mean concentration of 9.3 ng/m^3 and a maximum concentration 109 ng/m^3. In 1972, parathion was not detected

in 1,025 samples (Kutz et al. 1976); however, the LOD was not provided. Stanley et al. (1971) reported the results of a pilot study of atmospheric contamination of pesticides, in which air was sampled at nine localities in the United States, representing both urban and agricultural areas. Parathion was detected in only one location (Orlando, Florida) at a maximum concentration of 465 ng/m^3 (37% samples positive). In a study of pesticide levels in ambient suburban air, parathion was detected in Miami, Florida (60% positive, 2.8 ng/m^3 mean, 12.1 ng/m^3 maximum), but not in Jackson, Michigan or Fort Collins, Colorado (Kutz et al. 1976); the LOD appears to be <0.4 mg/m^3 since that value, for Pennsylvania, was the lowest positive result reported in the study.

In addition to its presence in the ambient atmosphere, parathion has also been monitored in both outdoor and indoor air associated with its use in occupational exposure situations. The highest levels of parathion measured when it was still in use in the United States were reported in the wash down area for crop-dusting aircraft (320 μg/m^3) and in the cockpits of those aircraft during application (179 μg/m^3). These levels were followed by air levels of 48 and 43 μg/m^3 measured in the truck cab and tractor towing spray-rigs, respectively (CDFA 1988). Lewis and Lee (1976) reported concentrations of parathion in a formulating plant and storage shed in South Florida to be 557 and 48.9 ng/m^3, respectively. Mean air concentrations in open and closed tractors with an oscillating boom during spray application of parathion on citrus trees ranged from 4 to 93 μg/m^3 (Carman et al. 1982).

Reported levels of parathion in the air at a site of application ranged from 2 to 18 μg/m^3 within a day of application and decreased to a range of not detected (LOD not stated) to 0.005 μg/m^3 21 days after application. Reported off-site downwind levels ranged from 34 μg/m^3, 40 yards from the sprayed field during application, to 0.002 μg/m^3 100 yards from the field 6 days after application (CDFA 1988). The highest parathion concentration found by one study within an orchard during spraying and dusting operations was 0.74 mg/m^3. Other studies found parathion concentrations as high as 15 mg/m^3 during spraying and dusting (Wolfe 1976). Concentrations of parathion in the air of a plum orchard were 3,500 ng/m^3 immediately after spraying and 4,100, 394, 149, 21, and 16 ng/m^3 1, 2, 5, 14, and 21 days after spraying, respectively (Seiber and Woodrow 1984). Downwind 100 m from the plum orchard, parathion concentrations of 35, 9, 1.6, and 0.9 ng/m^3 were detected 2, 3, 6, and 21 days after spraying, respectively.

The Colorado Community Pesticide Sampling Programs detected parathion in monthly air samples taken inside and outside the homes of 12 men who were occupationally exposed to parathion either as

formulators or farmers. The higher levels were found for formulators, with indoor exceeding outdoor levels for both groups (Tessari and Spencer 1971).

In the Canadian Atmospheric Network for Currently Used Pesticides, a nationwide air surveillance study of pesticides in agricultural regions in Canada, the highest concentrations of parathion were found at Vineland where the peak concentrations were 784 pg/m^3 in 2004 and 81.5 pg/m^3 in 2005 (Yao et al. 2008). Parathion may be found in environmental media in agricultural regions of other countries that still use parathion, indicating that it could be brought into the United States (e.g., on produce).

6.4.2 Water

Spray drift, runoff, and erosion flux may result in the contamination of streams and adjacent water bodies in locations where pesticides are applied. Leaching from the soil surface may also contaminate groundwater; however, streams and other surface waters appear to be more vulnerable to contamination than groundwater in most hydrologic settings (USGS 2007). During Iowa's Ambient Surface Water Monitoring program that included about 80 sampling sites between 1999 and 2001, only one detection of parathion occurred and the concentration was low (in the 0.05 ppb range) (EPA 2002). In a USGS program for monitoring pesticides in the streams of the western United States for the period of October 1968 to September 1971 in which parathion was tested for quarterly at 20 stations, it was detected at 40 ppt in two samples from the Gila River, Arizona and at 40 and 160 ppt in two samples from the Sacramento River, Verna, California (Schulze et al. 1973). Parathion was not detected in any water samples collected from July to September 1984 from Little Miami River, Ohio above or below a municipal waste water outfall, although the LOD was not reported (HSDB 2013). No parathion was detected in water or particulate matter samples collected from Lake Superior or Lake Huron at quantification limits of 5 ppt and 100 pg, respectively (Glooschenko et al. 1976). In the Erie River Basin, parathion was not detected (LOD not reported) in the over 100 samples collected before 1974 (Waldron 1974). Parathion (LOD not reported) was detected in 1 of 174 sampling stations across the nation's rivers collected prior to 1985 during a USGS water supply study (HSDB 2013). In a monitoring program by the California Department of Water Resources, the highest concentration of parathion detected in Sacramento-San Joaquin Delta Water was 0.035 μg/L (Lam et al. 1994). Parathion (LOD not reported) was not detected in any surface water samples collected during 1999–2000 as part of the USGS National Water-Quality Assessment (NAWQA) Program in which samples were collected from 34 sites located throughout the Yakima River Basin, Washington (Ebbert and Embrey 2001). Parathion was detected in

1 of 215 surface water samples (Cherry Creek, Denver, Colorado) at a concentration of 0.014 μg/L during a study monitoring eight urban streams in the United States from 1993 to 1994 (Hoffman et al. 2000).

Parathion was detected in ditch water draining cranberry bogs that had been treated with parathion in the Lower Fraser Valley of British Colombia, Canada, at concentrations ranging from not detected to 21 μg/L (Wan et al. 1995). In farm ditch water collected from seven locations in the Lower Fraser Valley, British Columbia in 1991, parathion was detected at mean concentrations of 0.13 and 0.20 μg/L at Westham Island and Colverdale, respectively (Wan et al. 1994).

Water samples collected from 15 lakes and 2 creeks on the Sparta, Illinois National Guard Armory, which is surrounded primarily by agricultural land, in the winter of 2003 contained a mean parathion concentration of 17 ng/L (4 of 39 samples). Parathion (LOD not reported) was not detected in 42, 41, and 33 samples collected in the spring, summer, and fall 2003, respectively (Ownby et al. 2004).

Parathion has been included in several state monitoring programs. In a groundwater quality study conducted in a rural region of Baltimore County by the Maryland Geological Survey, parathion was detected above the minimum reporting limit (0.004 μg/L) in 1 out of 112 samples, at a concentration of 0.022 μg/L (EPA 2002). Parathion (LOC not reported) was not detected in ground water from five shallow monitoring wells, where the insecticide was used within 300 feet of the wells, sampled in North Carolina between 1991 and 1995 (EPA 2002). In a groundwater monitoring program run by the North Dakota Department of Health that collected approximately 2,700 samples from 1,465 wells between 1992 and 2001, parathion was detected in 3 samples from 2 wells at concentrations of 0.274, 0.322, and 1.833 μg/L (EPA 2002).

No parathion was detected (LOD 0.5 ppb) in 36 drinking water wells sampled in Hawaii in March, 2001 (EPA 2002). In Iowa's Statewide Rural Well-Water Study (LOD not reported) that included 686 private wells sampled once during 1988–1989, with 10% of the wells repeat-sampled during 1990 and 1991, no parathion was detected (EPA 2002). No parathion was detected in drinking water (LOD not reported) in the FDA Total Diet Study for infants and toddlers conducted between 1980 and 1982 and the FDA Total Diet Study for adult groups conducted from 1980 to 1982 (Gartrell et al. 1986a,1986b). No parathion was detected in 54 monitored wells (primarily municipal) (LOD not reported) in selected California communities in the early 1980s (Maddy et al. 1982). A parathion concentration of 4.6 ppb was measured in a California drinking water well sample in 1979 (Burmaster 1982). Parathion was not detected in Ottawa tap water (LOD <1 ppt) in the late 1970s (Lebel et al. 1979).

Parathion concentrations were measured under foggy atmospheric conditions in and around the Central Valley of California, which is a prime agricultural area dominated by fruit, nut, and citrus orchards Parathion was detected in atmospheric fog water collected from agricultural areas Parlier, Corcoran, and Lodi, California in 1985 at concentrations of 9,000, 950, and 184,000 ng/L, respectively (Glotfelty et al. 1987). It was also detected in fog samples collected near Parlier, California in January 1986 at concentrations of 3.6, 31, 30, 2.7, 39, and 23 μg/L (Glotfelty et al. 1990). Seiber et al. (1993) reported parathion concentrations ranging from 4.3 to 19.0 ppb in fog water samples collected from the San Joaquin Valley, California in January 1989 during the spraying of near dormant orchards.

6.4.3 Sediment and Soil

Parathion has not been the focus of many national soil or sediment monitoring programs in the United State, but has been monitored in regional studies associated with agricultural applications in both the United States and Canada. In the 1972 National Soils Monitoring Program, which included 1,246 samples of cropland soil in 37 states, parathion was detected in 0.6% of the samples at mean and maximum concentrations of <0.01 and 19 ppm, respectively (Carey et al. 1979a). Parathion (LOD not reported) was not detected in the 1971 Urban Soils Monitoring Program that sampled soils from five U.S. cities (Carey et al. 1979b). In a 1972 survey of rice growing soils (99 samples) in five states, parathion was detected in Arkansas (4.2% of samples) and California (10% of samples) at mean concentrations of 0.01 and <0.01 ppm (dry weight), respectively, and maximum concentrations of 12 and 0.01 ppm, respectively (Carey et al. 1980).

Parathion was detected in the organic soil of 12 of 28 farms in six vegetable growing regions of southwestern Ontario in 1976 at concentrations ranging from 6 to 2,500 ppb (Miles and Harris 1978). In Southern Ontario orchard soil, parathion was detected in 5% of the apple orchards sampled at a mean concentration of 5 ppb (Carey et al. 1980). Frank et al. (1976) reported that trace amounts of parathion residues (<0.001 ppm mean concentration, 0.021 ppm maximum concentration) were found in the upper 15 cm of soils from 31 apple and 16 sweet cherry orchards in Southern Ontario collected between 1972 and 1975. No parathion was detected in subsurface (15–30 cm) soils (LOD not reported). In soil samples collected from an evaporation pit in California between May and September 1985, parathion was detected at concentrations of 1,064–1,972 ppm at 0–7.5 cm surface soils, 51–60 ppm at 7.5–15 cm below the soil surface, 37 ppm at 22.5–30 cm below the surface, and 18 ppm at 60–67.5 cm below the soil surface (Winterlin et al. 1989). Parathion was detected in crop soils collected from the Lower Fraser Valley,

British Columbia, Canada, between July and December 1991 at mean concentrations of 10, 19, 15, and 1,419 μg/kg in Westham Island, Ladner, Burnaby, and Cloverdale, respectively (Wan et al. 1994). Krapac et al. (1995) reported that parathion was detected in 4 of 822 soil samples collected from 49 agrichemical facilities located throughout Illinois at concentrations ranging from 69 to 5,540 μg/kg and a median value of 805 μg/kg.

Parathion was under the LOD of 0.1 ppb at industrial and agricultural locations in 11 sediment samples taken from the Delaware River estuary during a 1980–1981 USGS study (Hochreiter 1982). It was also not detected in any sediment samples collected from Lake Superior or Lake Huron during the summer of 1974 with a quantitation limit of 20 ppb (Glooschenko et al. 1976). Parathion was detected in bed sediments and suspended sediments collected from three locations in the Windrush River catchment, Oxforshire, United Kingdom in 1992 at concentrations of 0.3, 0.6, and 1.0 μg/kg and 13, 3.3, and 8.8 μg/kg, respectively (House et al. 1992).

Parathion (LOD not reported) was not detected in sediment in irrigation water collected lagoons sampled from corn and sorghum fields in Kansas in 1974 (Kadoum and Mock 1978). Parathion was detected in sediments in a ditch draining cranberry bogs that had been treated with parathion in the Lower Fraser Valley of British Colombia, Canada, at concentrations ranging from not detected to 515 μg/kg (Wan et al. 1995). In farm ditch sediments collected from seven locations in the Lower Fraser Valley, British Columbia in 1991, parathion was detected at a concentration of 8 μg/kg (Wan et al. 1994).

6.4.4 Other Environmental Media

Parathion (LOD not reported) was not detected in fish fillets collected from 15 lakes and 2 creeks on the Sparta, Illinois National Guard Armory, which is surrounded primarily by agricultural land, in 2003 (Ownby et al. 2004). IARC (1983) reported that fish collected from 144 estuaries throughout the United States contained mean parathion levels of 10–75 ppb. Fish and shellfish specimens collected in May 1973 in the United States contained 10–40 ppb (IARC 1983). Clam, rainbow trout, and oyster samples collected from Massachusetts contained parathion concentrations of 20–30, 15–17, and 38–41 ppb, respectively (IARC 1983). In a nationwide estuarine fish monitoring program conducted from 1972 to 1976, 1,524 samples from 144 primary and secondary estuaries in 19 coastal states, parathion was detected in 1 of 39 samples from Connecticut, 1 of 251 samples from North Carolina, and 3 of 51 samples from Texas at mean concentrations of 10, 12, and 75 ppb, respectively (Butler and Schutzmann 1978). Parathion was detected at a concentration of 10 ng/g in oysters from Waikane Stream in Kaneohe Bay,

Hawaii (Hunter et al. 1995). Parathion was detected in 2 of 20 samples of rodent muscle (40–110 ppb), 3 of 19 whole lizards (10–100 ppb), and 6 of 19 samples of bird muscle (10–210 ppb) obtained from an unspecified location within the state of Texas (HSDB 2013).

In the EPA's Revised Organophosphate Pesticides Cumulative Risk Assessment, a summary of residue monitoring data on organophosphate pesticides in food for the years 1994–2000 was reported (EPA 2002). The detection of parathion in these various foods and its concentration are presented in Table 6-4. The report also included a summary of FDA Total Diet Study analyses on organophosphate pesticides on meats for the years 1991–1999. No parathion residue (LOD not reported) was found in any of the tested meats (EPA 2002). Parathion was detected in 53 of 234 ready-to-eat foods tested repetitively for 10 years, 1982–1991, through the U.S. FDA's Revised Market Basket Survey at an average concentration of 0.0043 μg/g (HSDB 2013). In a survey of U.S. produce conducted from 1989 to 1991, parathion was detected in 13 of 6,970 produce samples, including apples (1 of 335), grapefruit (1 of 106), lemons (2 of 139), limes (1 of 78), oranges (6 of 220), peaches (1 of 84), and strawberries (1 of 76) (Schattenberg and Hsu 1992). It was also detected in 39 (2%) Total Diet Study foods between 1984 and 1986 (Gunderson 1995).

In the U.S. FDA pesticide residue monitoring study conducted from October 1993 to September 1994, which analyzed 11,348 domestic and import food samples from commodity groups, parathion was detected in unspecified foods (FDA 1995). In 1993–1994, the U.S. FDA conducted a study of pesticide residues in domestic and imported fresh apples and processed rice (LODs not reported). For apples, 769 domestic and 1,062 imported samples were collected and for rice, 598 domestic and 612 imported samples were collected. Parathion was detected in one domestic apple sample at a concentration of 0.02 ppm and was not detected in any imported apple samples. Parathion was not detected in any rice samples (Roy et al. 1997). In an FDA survey of domestic and imported pears and tomatoes conducted between 1992 and 1993, parathion was detected in 1 out of 710 domestic and 2 out of 949 imported pears at maximum concentrations of 0.02 and 0.04 ppm, respectively, and in 2 out of 1,219 domestic tomatoes at a maximum concentration of 0.01 ppm, while it was not detected in 144 imported tomato samples (Roy et al. 1995). During a 5-year period from 1982 to 1986 in which the FDA Los Angeles District analyzed 19,851 samples of domestic and imported food and feed commodities, parathion was detected on 119 various agricultural commodities at concentrations ranging from 0.05 to 2 ppm (Luke et al. 1988).

Table 6-4. Parathion Residues in Various Foods from 1994 to 2000

Food item	Number analyzed	Number of detections	Average concentration (ppm)[a]	Maximum concentration (ppm)
Apple juice	1,344	0	0	0
Apples	2,263	5	8.1×10^{-5}	0.14
Apples (single serving)	377	0	0	0
Bananas	1,036	0	0	0
Broccoli	635	0	0	0
Cantaloupe	1,100	1	5.0×10^{-6}	0.005
Carrots	1,823	30	1.59×10^{-4}	0.044
Celery	143	0	0	0
Cherries	275	0	0	0
Corn syrup	430	0	0	0
Cucumbers	1,288	0	0	0
Grape juice	1,114	2	1.1×10^{-5}	0.007
Grapes	2,487	16	7.4×10^{-5}	0.043
Green beans (canned)	730	0	0	0
Green beans (fresh)	1,758	1	2.0×10^{-6}	0.003
Green beans (frozen)	639	0	0	0
Lettuce	1,580	1	1.2×10^{-5}	0.019
Milk	1,364	0	0	0
Nectarines	345	0	0	0
Oats (bran)	45	0	0	0
Oats (rolled)	287	0	0	0
Orange juice	1,212	0	0	0
Oranges	2,460	1	1.0×10^{-6}	0.003
Peaches (canned)	654	0	0	0
Peaches (fresh)	1,512	2	1.7×10^{-5}	0.022
Peaches (single serving)	534	1	2.1×10^{-5}	0.011
Peanut butter	716	0	0	0
Pears (canned)	647	0	0	0
Pears (fresh)	1,505	4	2.47×10^{-4}	0.31
Pears (single serving)	570	0	0	0
Pineapples	364	0	0	0
Potatoes	1,746	0	0	0
Poultry (adipose tissue)	476	0	0	0
Poultry (liver)	479	0	0	0
Poultry (muscle)	145	0	0	0
Rice	178	0	0	0

Table 6-4. Parathion Residues in Various Foods from 1994 to 2000

Food item	Number analyzed	Number of detections	Average concentration (ppm)[a]	Maximum concentration (ppm)
Soybean grain	748	0	0	0
Spinach (canned)	749	12	3.035×10^{-3}	1.6
Spinach (fresh)	1,385	0	0	0
Spinach (frozen)	715	1	2.4×10^{-5}	0.017
Strawberries (fresh)	1,768	0	0	0
Strawberries (frozen)	155	0	0	0
Sweet bell peppers	1,468	0	0	0
Sweet corn (canned)	652	0	0	0
Sweet corn (fresh)	19	0	0	0
Sweet corn (frozen)	635	0	0	0
Sweet peas (canned)	746	0	0	0
Sweet peas (fresh)	9	0	0	0
Sweet peas (frozen)	703	1	4.0×10^{-6}	0.003
Sweet potatoes	1,487	0	0	0
Tomatoes (canned)	737	0	0	0
Tomatoes (fresh)	1,766	5	2.9×10^{-5}	0.012
Wheat	1,563	1	1.4×10^{-5}	0.022
Winter squash (fresh)	1,078	5	3.2×10^{-5}	0.007
Winter squash (frozen)	343	2	4.1×10^{-5}	0.007

[a]Nondetects were counted as zero in calculating the average.

Source: EPA 2002

In whole pasteurized milk collected monthly during 1990–1991 from 63 sampling stations located in large metropolitan areas throughout the United States, parathion was detected in 1 out of 2,739 samples at a concentration of 0.06 ppm (Yess et al. 1993).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Quantitative information from the TRI program for 2011 reports that up to 3 pounds of parathion was released to air and the same amount to soil from a single hazardous waste treatment and disposal facility in the United States (TRI11 2013). Inhalation exposure to parathion as a liquid or a dust at a hazardous waste treatment or disposal facility is unlikely due to its low vapor pressure, its degradation in the environment, and its high adsorption to soils. In order to mitigate the exposure and risk to the general population, especially children, the EPA terminated the production of most end use products as of December 31, 2002 (EPA 2000a), and terminated the last registration for parathion products effective on December 31, 2006 (EPA 2006b). Because of these actions and environmental degradation processes, it is likely that neither the general population nor workers are exposed to parathion in the United States.

Parathion and its degradation products may be transported in the atmosphere and deposited to surface soils. Run off and erosion of soils containing parathion or other pesticides may contaminate nearby surface water bodies or leach into groundwater. Human exposure may result from contaminated surface or groundwater that is used in private wells or for a public water supply. Since parathion has not been used in the United States for several years, the likelihood of parathion concentrations exceeding a human health benchmark in a public supply well or domestic well is considered non-existent (EPA 2006b; USGS 2007).

The general public may have been exposed to parathion by dermal and inhalation exposure from spray drift onto adjacent area or by ingesting food containing parathion residues (HSDB 2013) during the time when parathion was used as a registered insecticide.

Given its cancellation of registered uses, the potential for human exposure to parathion through the diet and or drinking water is low (CDC 2009). During its use, intakes from diet and drinking water were reported to be below recommended limits. In 1982-84, a national U.S. FDA Total Diet Study was performed that showed the average daily intakes of parathion in the United States were 1.5, 1.4, and 2.0 ng/kg body weight/day, respectively, for females 14–16, 25–30, and 60–65 years of age and 1.2, 1.1, and 1.8 ng/kg body weight/day, respectively, for males 14–16, 25–30, and 60–65 years of age (Gunderson

1988). In the FDA Total Diet Study performed between July 1986 and April 1991, the average daily intakes of parathion in the United States were 0.0008, 0.0009, and 0.0016 μg/kg body weight/day, respectively, for males 14–16, 25–30, and 60–65 years of age and 0.0011, 0.0011, and 0.0018 μg/kg body weight/day, respectively, for females 14–16, 25–30, and 60–65 years of age (Gunderson 1995).

When it was in use, pesticide workers may have had much higher levels of parathion exposure following pesticide application compared to the general population. Exposure was often estimated by measuring the urinary metabolite *p*-nitrophenol; however, this substance is not unique to parathion as it is also a metabolite of methyl parathion and nitrobenzene. In a study of workers who handled parathion, end-of-shift urinary metabolite *p*-nitrophenol levels ranged from 190 to 410 μg/g of creatinine, a range of values several hundred times higher than levels found in the U.S. general population (CDC 2009). Urinary levels of the metabolite *p*-nitrophenol ranged from <1 to 63 ppb (median <1 ppb; 41% detection in 974 samples) during the NHANES III study assessing exposure to a subset of general population adults from 1988 to 1994 (Needham et al. 2000). For survey years 1999–2000 and 2001–2002, no geometric mean urinary concentration of the *p*-nitrophenol could be calculated because the proportion of results below the detection limit was too high to provide a valid result (CDC 2009). The 95th percentile concentrations of *p*-nitrophenol in urine were 5.00 and 3.71 ppb in survey years 1999–2000 (sample size 1,989) and 2001–2002 (sample size 2,477), respectively.

Workers historically were exposed to parathion primarily during field application and formulation of the insecticide before its use was banned. The dermal route is considered to be the most important route of entry during field applications, in formulation plants, and in other work situations where airborne pesticide drift is evolved, because of the disproportionately high levels of parathion which may drift onto exposed skin areas compared to the amount taken in during respiratory exposure. Dermal contact with treated surfaces such as leaves of sprayed crops is also an important route of exposure. Inhalation is the second most common route, especially when fine mists are formed as from concentrated spray (Wolfe 1976).

Workers of cotton fields were exposed to parathion at inhalation levels from 0.09 to 1.06 μg/30 minutes at 0–72 hours after application (Ware et al. 1973). Cab operators were exposed to average air concentrations of parathion ranging from 4 to 93 μg/cm^3 during the spraying of citrus crops (Carman et al. 1982). Mean dermal and respiratory exposure levels to parathion of various categories of workers were (category, dermal mg/hour, respiratory mg/hour): air blast operator, 18, 0.03; tractor driver hauling portable tower hand gun power sprayer during application, 12, 0.03; high pressure power hand gun

spraying from tower position, 11, 0.03; high pressure power hand gun spraying from ground position, 47, 0.09; pilot dusting orchard, 13, 0.02; flagging for airplane spraying, 84, 0.02; operating tractor drawn boom ground duster, 8, 0.16; and operating tractor drawn boom ground sprayer, 4.7, <0.01 (Wolfe et al. 1967).

Hands were probably the greatest source of absorbed parathion for dermal exposure to workers until its use was banned. It is estimated that a worker can absorb 6.0 mg of parathion from cotton 24 hours post-treatment with parathion and 3.0 mg 48 hours post-treatment during an actual 5-hour work day field exposure (Ware et al. 1973). Mean parathion residues extracted from the hands, shirts, and pants of four workers following a 5-hour field exposure in cotton fields 24 hours after application were 0.25, 6.1, and 9.8 mg, respectively, while estimated respiratory exposure during that time was 19.2 μg (mean air concentration of 3.2 ng/L) (Ware et al. 1974). Carman et al. (1982) reported mean levels of parathion ranging from <0.01 to 7.5 $\mu g/cm^2$/hour were deposited on test patches on the bodies of workers while using airblast spray equipment and different formulations of parathion to spray citrus trees.

Before the use of parathion was banned, it was found to be transported into homes by translocation of vapors and by track-in from outdoors on shoes and clothing from workers. There have been studies showing that the air inside and outside the homes of workers that used parathion contained measurable amounts of parathion, with inside air containing higher concentrations (IARC 1983), which would be a source of exposure to family members. The Colorado Community Pesticide Sampling Programs detected parathion in monthly air samples taken inside and outside the homes of men occupationally exposed to parathion, with 64 of 94 and 44 of 87 samples testing positive, respectively (Tessari and Spencer 1971).

NIOSH recommends that the occupational exposure level not exceed 0.05 mg/m^3 for a 10-hour TWA workday (NIOSH 2013). In addition, the American Conference of Governmental Industrial Hygienists has recommended a time-weighted average threshold limit value (TWA-TLV) of 0.05 mg/m^3 with an inhalable, vapor, skin notation for occupational exposure to parathion (NIOSH 2013).

The National Occupational Hazard Survey (NOHS) conducted by NIOSH in 1974 estimated that 302 workers employed at 43 facilities were potentially exposed to parathion in the United States (NIOSH 2013). The NOHS survey did not contain information on the frequency, concentration, or duration of exposure; the survey provided only estimates of workers potentially exposed to chemicals in the workplace. Since parathion is no longer used, there is no updated information in regards to worker exposure.

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 Section 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 can be exposed to pesticides from multiple sources and pathways. In addition to the standard pathways of diet and drinking water, children in agricultural communities may be exposed through farm proximity and parental take-home from agricultural use (Fenske et al. 2000).

Children are not likely to be exposed to parathion and its residues in the foods that they eat since parathion has not been made or used in the U.S. for several years. A good indicator of general public exposure to a substance is the National Report on Human Exposure to Environmental Chemicals. Concentrations of the parathion metabolite, *p*-nitrophenol, were low in the urine of children and all other segments of the population during the initial 1999–2000 and final 2001–2002 sampling periods; however, these detections may not be attributed solely to parathion since *p*-nitrophenol is also a metabolite to several other organophosphorus pesticides, including methyl parathion (CDC 2005). Since then, it is likely that the levels of parathion metabolites in children have been reduced.

In the FDA Total Diet Study for infants and toddlers conducted between 1980 and 1982, the average concentration and the calculated average daily intake of parathion in different food groups were determined (Gartrell et al. 1986a). In the infant diet, parathion was only detected in fruit and fruit juices at an average concentration (mg/kg) and average daily intake (μg/day) of 0.0002 and 0.0211, respectively, while none was detected in the other food groups. In the toddler diet, the average concentrations (mg/kg) and average daily intakes (μg/day) of parathion by food group were 0.0001 and 0.0080 in vegetables and

0.0002 and 0.0147 in fruit and fruit juices, respectively. No parathion was detected in drinking water for either study groups, although the LOD was not reported. Data on the weight-adjusted intake of parathion 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. 1986a). The reported weight-adjusted intakes of parathion ranged from 0.002 to 0.005 μg/kg body weight/day for infants and from not detected to 0.003 μg/kg body weight/day for toddlers for the study years.

In 1982–1984, a national U.S. FDA Total Diet Study was performed that showed the average daily intakes of parathion in the United States for children 6–11 months of age and 2 years of age were 11.2 and 5.0 ng/kg body weight/day, respectively (Gunderson 1988). In the FDA Total Diet Study performed between July 1986 and April 1991, the average daily intakes of parathion in the U.S. for children 6–11 months of age and 2 years of age were 0.008 and 0.004 μg/kg body weight/day, respectively (Gunderson 1995).

Children of agricultural families are likely exposed to agricultural chemicals, even if they are not involved in farm activities. Simcox et al. (1995) designed a study to determine whether such children were exposed to higher levels of pesticides, including parathion, than children whose parents were not involved in agriculture and whose homes were not close to farms. Household dust and soil samples were collected from children's play areas from 59 residences in eastern Washington State (26 farming, 22 farmworkers, and 11 non-farming families) during the 1992 spray season. The study reported that parathion was detected in yard soil samples collected from farm families, a majority living within 200 feet of an operating apple or pear orchard, at concentrations ranging from not detected to 932 ng/g, with a mean concentration of 46 ng/g, while none was detected in non-farm reference family's yard soil. In household dust samples, parathion was detected at concentrations ranging from below the limit of quantitation (LOQ) to 2,786 ng/g (mean of 365 ng/g) in agricultural families homes and <LOQ to 425 ng/g (mean of 76 ng/g) in non-farm family homes. Household dust concentrations were significantly lower in reference homes when compared to farmer/farmworker homes, demonstrating that children of agricultural families have a higher potential for exposure to parathion than children of non-farm families.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Since parathion is no longer used in the United States and parathion residues in the environment from historical spraying would be degraded at present, there are no populations with potentially high exposures

to this substance. In the past, pesticide formulators and applicators employed in facilities that manufactured parathion, and farmers were exposed to levels greater than the general population.

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 parathion is available. Where adequate information is not available, ATSDR, in conjunction with 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 parathion.

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

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical-chemical properties of parathion are provided in Chapter 4. Important properties such as melting point, boiling point, vapor pressure, solubility, log K_{ow} and Henry's Law constant are available. No data needs are identified.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2011, became available in November of 2012. This database is updated yearly and should provide a list of industrial production facilities and emissions. Since parathion is not registered for use any longer in the United States, it is unlikely to be produced in any significant quantities.

Environmental Fate. The environmental fate and transport of parathion is understood and no data needs are identified. The mobility of parathion in soils is expected to be low based on measured K_{oc} values. Volatilization is generally considered low. Hydrolysis, photolysis, and biodegradation account for the removal of parathion from the environment. Sorption of parathion to organic matter in natural

waters and soils affects its susceptibility for aquatic photolysis, its bioavailability for aquatic organisms, and its biodegradation (Schuurmann et al. 2006). It follows two major fate pathways: degradation to less toxic compounds or oxidative conversion to the toxic bioactive product, paraoxon (CDFA 1988).

Bioavailability from Environmental Media. Parathion has been detected in aquatic and terrestrial organisms (HSDB 2013) and is, therefore, bioavailable to some extent from environmental media. Adsorption to organic matter in soil and sediment reduces its bioavailability (Schuurmann et al. 2006). No data needs are identified.

Food Chain Bioaccumulation. Measured BCFs of parathion in fish suggest that bioaccumulation in aquatic organisms is not high. A better understanding of the biochemical and physiological basis of the processes of parathion uptake, biotransformation, and excretion is needed in order to fully understand species differences in parathion metabolism in fish and shellfish. The use of molecular biology in obtaining further knowledge about the enzymes and transport proteins important in pesticide metabolism should provide further advances in this field. This will be useful for predicting the likelihood that parathion residue will remain in edible parts of food-producing fish and shellfish (James 1994) if the future use of parathion is authorized.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of parathion in contaminated media at hazardous waste sites are needed so that the information obtained on levels of parathion in the environment can be used in combination with any known body burden of parathion to assess the potential risk of adverse health effects in populations living in the vicinity of those hazardous waste sites.

Exposure Levels in Humans. When parathion was used, humans were exposed to it by inhalation of air and intake from food and drinking water. Since parathion is no longer used in the United States, exposure to humans is expected to be low. Future research to assess the potential for parathion exposure due to contaminated hazardous waste sites would be useful.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Parathion's former use may have led to low levels of exposure to children; however, since the last uses of parathion were cancelled more than a decade ago, current exposure is considered low. No data needs are identified.

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

Exposure Registries. No exposure registries for parathion were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries 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 this substance.

6.8.2 Ongoing Studies

Since parathion is no longer produced or used in the United States (EPA 2000a), no ongoing studies regarding its environmental fate or physical properties are being investigated.

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7. ANALYTICAL METHODS

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

7.1 BIOLOGICAL MATERIALS

Parathion was widely used for agricultural purposes, which may have resulted in human exposure during its application, and residues on or in foods can result in exposure to humans by ingestion. All use of parathion has been cancelled to mitigate the risk of human exposure (EPA 2000a). Methods for the determination of parathion in biological samples can be used to verify that exposure and absorption has occurred. Table 7-1 lists the applicable analytical methods for determining parathion in biological fluids and tissues.

The principal method used for the detection of parathion or its metabolites in biological samples is gas chromatography (GC) using a flame photometric detector (FPD), a mass spectroscopy (MS) detector, or an electron capture detector (ECD). The preparation of samples usually involves variations of solid-phase extraction (SPE), and/or liquid/liquid extraction with organic solvents.

Garcia-Repetto et al. (2001) reported a method for parathion identification and quantification in human blood using SPE, GC-nitrogen phosphorus detection (NPD) analysis followed by GC-MS confirmation. The average recovery of parathion in blood is 96.1%, which is in the acceptable range established by the EPA. The LOD and LOQ reported in the study are 1.21 and 4.03 μg/L, respectively. This method has improved a previous method that involved liquid-liquid extraction with *n*-hexane and benzene resulting in more complex chromatograms. Not only is the method more precise, it also eliminates hazardous waste emissions and exposure of technicians to toxic solvents.

Table 7-1. Analytical Methods for Determining Parathion and Transformation Products in Biological Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human blood	Addition of 1 mg/L azobenzene, 0.2 g ammonium sulfate and 2 mL 0.1 M sulfuric acid to a 0.5 mL sample of blood. Mixture is sealed and heated in a vial. Samples are collected by HS-SPME.	GC/MS	0.02 μg/g	Absolute recovery compared to a methanolic solution: 4.7%	Musshoff et al. 2002
Human blood	Extraction with methanol and triphenylphosphate followed by dilution. Silica gel SPE with C_{18} cartridges.	GC/NPD; GC/MS	1.21 μg/L	96.1% (1.29% RSD)	Garcia-Repetto et al. 2001
Human urine (*p*-nitrophenol)	Hydrolysis with β-glucuronidase, solid phase extraction, liquid/liquid extraction, and evaporation.	RP-HPLC-MS/MS	0.1 ng/mL urine	106% (1.4% RSD) low dose; 94% (2.2% RSD) high dose	Olsson et al. 2003
Rat urine (*p*-nitrophenol)	Acid hydrolysis followed by extraction with diethyl ether and redissolve in methanol.	HPLC/UV	12 ng/mL	89% (<11% CV)	Chang et al. 1997
Bovine liver, rumen content (partially digested grain and vegetation mixture)	Extraction of homogenized sample with methanol-dichloromethane (10–90, v/v) followed by gel permeation chromatography and silica gel solid phase extraction clean-up.	GC/FPD	0.01–0.05 μg/g using 5 g sample	Rumen content: 99% (2% RSD) at 0.1 μg/g; liver: 103 (6% RSD) at 0.05 μg/g	Holstege et al. 1991
Animal fat	Sweep codistillation, Florisil clean-up elution with methylene chloride-light petroleum-acetonitrite (50:48.5:1.5).	GC/FPD	No data	No data	Brown et al. 1987

[a]Parathion is the target analytes unless otherwise specified.

CV = coefficient of variation; FPD = flame photometric detector; GC = gas chromatography; HPLC = high-performance liquid chromatography, HS = head space, MS = mass spectrometry; MS/MS = tandem mass spectrometry, NPD = nitrogen phosphorus detector; RP-HPLC = reverse phase high-performance liquid chromatography, RSD = relative standard deviation; SPE = solid-phase extraction; SPME = solid-phase microextraction; UV = ultraviolet

A method for the rapid quantification of parathion metabolite, *p*-nitrophenol, in human urine using liquid chromatography/electrospray ionization-tandem mass spectrometry has been published (Olsson et al. 2003).

Parathion was determined in bovine liver and rumen content by GC/FPD by Holstege et al. (1991) using a method with an LOD reported to be 0.01–0.05 μg/g using a 5-g sample. Recoveries were reported to be 99% from rumen content and 103% from liver. Brown et al. (1987) used GC/FPD and sweep codistillation to determine parathion in animal fat. No recovery or LOD information was given.

7.2 ENVIRONMENTAL SAMPLES

Table 7-2 lists the methods used for determining parathion and its degradation products in environmental samples. The principal separation and detection methods of parathion and degradation products in environmental samples include GC or high performance liquid-chromatography (HPLC), in conjunction with MS, NPD, or FPD. Sample preparation methods vary depending on the sample matrix (Driss et al. 1993; OSHA 1986; USGS 2002). The method of Leoni et al. (1992) is applicable to both parathion and paraoxon. The NIOSH (1994) method has been fully validated for use in occupational settings where regulatory exposure limits are of concern.

Many methods were reported for the determination of parathion in water. Sample preparation methods include either some form of liquid/liquid extraction or the use of SPE, usually C_{18}-silica, for isolation of parathion residues. Mattern et al. (1991) reported an LOD for parathion in surface water of 0.005 ppb using GC in conjunction with chemical ionization ion trap MS. An LOD of 0.025 μg/L was reported for degradation product paraoxon in water with a recovery of 87% (2% relative standard deviation [RSD]) by Seiber et al. (1990). SPE provides an easy method to isolate residues and can greatly reduce the amounts of solvent used in sample preparation. Driss et al. (1993) preconcentrated parathion from drinking water onto C_{18}-silica or polystyrene-divinylbenzene co-polymer with a subsequent backflush onto an HPLC column (ultraviolet [UV] detection). LODs as low as 0.03 μg/L were reported. Kwakman et al. (1992) preconcentrated parathion from drinking water onto C_{18}-SPE disks and eluted the adsorbed compounds directly into a GC pre-column. Detection was by NPD and excellent LODs (20 pg/L) and recoveries (>95% with <4% RSD at 200 pg/L) were reported. Lebel et al. (1979) developed a method using macroreticular XAD-2 resin to isolate and concentrate parathion from drinking water at the ng/L level.

Table 7-2. Analytical Methods for Determining Parathion and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Preconcentration of pesticide onto OVS-2 tube (13-mm) quartz filter, XAD-2, 270 mg/140 mg. Elution with 90% toluene/10% acetone.	GC/FPD (NIOSH Method 5600)	0.0004 mg/m^3 (400 ng/m^3) for 240 L sample	92% (2.1% RSD at 1.2 μg) (0.005 μg/m^3, 240 L sample)	NIOSH 1994
Air	Air is drawn through a glass tube with a glass fiber filter and XAD-2 adsorbent. The samples are desorbed with toluene.	GC/FPD	3.1 μg/m^3	96.7% (2.9% CV)	OSHA 1986
Drinking water	Extraction with Amberlite XAD-2 resin from 100 L water. Elution with 15% acetone/85% hexane.	GC/NPD; GC/MS (SIM)	1 ng/L (ppt)	95% (±2% RSD at 100 ng/L); 102% (±1% RSD at 10 ng/L)	Lebel et al. 1979
Drinking water	Preconcentration onto 5 μm C_{18}-silica or 7 μm polystyrene-divinyl benzene co-polymer with subsequent backflush onto analytical HPLC column.	Reverse-phase-HPLC/UV (254 nm)	0.03–0.06 μg/L (ppb)	91% (±10% RSD) at sample volumes up to 300 mL	Driss et al. 1993
Drinking water	Preconcentration of 2.5 mL water onto C_{18} extraction disks, rinsing with additional 1 mL and purging disk with gas to remove residual water. Elution with ethyl acetate directly onto GC pre-column with solvent venting.	GC/NPD	20 pg/mL	>95% (<4% RSD at 200 ppt)	Kwakman et al. 1992
Surface water	Adsorption of pesticides from 2 L of water onto XAD-2 and XAD-7 resins. Elution with methylene chloride, water removal, and use of K-D to reduce volume.	GC/chemical ionization ion trap MS	0.005 μg/L	109.3% (3.4% CV) at 1 ppb level	Mattern et al. 1991
Water	Filtration using glass-fiber filters followed by SPE. Elution of dry SPE columns with ethyl acetate then evaporation.	GC/FPD (Method O-1402-01)	0.012 μg/L	81% (14% RSD at 0.02 ppb)	USGS 2002a

Table 7-2. Analytical Methods for Determining Parathion and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Extraction with methylene chloride for 6 hours. Evaporation of solvent followed by solvent exchange to ethyl acetate.	cap. GC/FPD (Method O-3402-03)	0.015 μg/L	77% (15% RSD at 0.02 ppb)	USGS 2002b
Water (paraoxon)	Filtration of 1 L of water followed by extraction 3 times with 100 mL methylene chloride after addition of 20 g sodium sulfate. Concentration using K-D and solvent exchange to benzene. Concentrations done under nitrogen. Fractionation by HPLC.	GC/ECD (HECD-N mode)	0.025 μg/L	87% (2% RSD)	Seiber et al. 1990
Water	SPME of filtered water sample; thermal desorption of diazinon from SPME fiber.	GC/AED	1 μg/L with carbon line (193 nm); 3 μg/L with S line (181 nm)	No data (precision 8–12 RSD)	Eisert et al. 1994
Water	Extraction of analytes from water using SPE; elution with ethyl acetate (108 μL) directly onto retention gap with solvent venting.	GC/AED	1 ng/L (100 mL sample) with P channel	92% (7% RSD) at 5 μg/L	Hankemeier et al. 1995
Water	UV activation of 1 mL water containing 5 μg of antiparathion polyclonal antibody (APA). UV-assisted absorption of APA onto QCM. Mix parathion solution with BSA solution to form a complex that will interact with the antibody.	QCM	4 ppb	No data	Funari et al. 2013
Industrial and municipal waste water	Extraction of 1 L of sample with 60 mL methylene chloride 3 times. Water removal from extract and solvent exchange to hexane during K-D concentration.	GC/FPD or thermionic detection (P-mode); GC/MS for qualitative identifications recom-mended. (Method 1657)	10 ng/L	61–121% (10% RSD)	EPA 1993a

Table 7-2. Analytical Methods for Determining Parathion and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Waste water	Extraction of 1 L of water with 15% methylene chloride in hexane using a separatory funnel. Concentration using K-D. Cleanup (if needed) by Florisil fractionation or acetonitrile partition.	GC/FPD (P-mode) or GC/ thermionic detection. GC/MS for qualitative compound identification recom-mended. (Method 614)	0.012 μg/L	102% (4.1% RSD)	EPA 1993b
Bed sediment (lake and stream), aqueous suspended sediment and soil	Extraction with Soxhlet apparatus of minimum 25-g equivalent dry-weight samples using 350 mL dichloromethane and 25 mL methanol (93:7). Concentration and filtration of extract. Elution with dichloro-methane through chromato-graphic column. Concentration and resolution in ethyl acetate.	GC/FPD	0.951 ppb	76% (5% RSD)	USGS 2002c
Cucumber, lettuce, grapes	Chopping of produce and extraction with acetone/ methylene chloride/petroleum ether (1:1:1). Evaporation to dryness and redissolution in acetone and concentration.	SFC/NPD	No data	No data	Zegers et al. 1994
Green beans, lettuce, carrot, bell pepper (parathion; paraoxon)	Homogenization of produce with acetonitrile. Addition of NaCl to affect phase separation, removal of acetonitrile, water removal volume reduction, addition of deuterated internal standards.	GC/MS	0.05 μg/g (parathion); 0.15 μg/g (paraoxon)	93% (21% RSD) (parathion); 91% (17% RSD) (paraoxon)	Liao et al. 1991
Kale, endive, carrots, lettuce, apples, potatoes, strawberries	Extraction of crops with ethyl acetate and granular sodium sulfate, filtration, concentration with K-D. Sweep co-distillation cleanup for GC.	GC thermionic detector	No data for GC	No data	AOAC 1990a

Table 7-2. Analytical Methods for Determining Parathion and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Numerous non-fatty crops	Extraction with acetonitrile and partition into petroleum ether. Concentration using K-D and purification using Florisil column chromatography.	GC/KCl thermionic detector; identifications by combin-ations of gas, thin layer, and paper chroma-tography; polarographic confirmatory method	Polarographic method: 0.2 ppm based on 1 g crop in 1 mL cell	>80%	AOAC 1990a, 1990b, 1990c
Soybeans and rice	Grinding of 25-g samples and extraction with 150 mL of 2:1 acetone: methanol; filtration and reduction of volume to 100 mL. Addition of water, NaCl followed by extraction with methylene chloride (2 times); solvent evaporation and redissolution in methylene chloride:cyclohexane (1:1) and fractionation on Bio-Bead S-X3. Evaporation under N_2 stream and redissolution in 2 mL hexane.	GC/NPD or GC/MS (SIM)	Rice: 0.007 ppm soybeans: 0.04 ppm	Rice: 86.8% (1.2% RSD) at 1 ppm soybeans: 91.3% (1.2% RSD) at 1 ppm	Hong et al. 1993
Strawberries and cherries	Spike samples were sliced and homogenized.	HS-SPME	8.9 ppb in strawberries; 12.3 ppb in cherries	Strawberries: 81–86% (9–12% RSD); cherries: 77–79% (9–10% RSD)	Lambropoulou and Albanis 2003
Various fruits and vegetables	Homogenization of sample (adding water if needed) and adsorption on activated Florisil to produce a free-flowing powder. Elution with ethyl acetate or methylene chloride.	GC/NPD or FPD	5 ppb	96–103% at 0.05 mg/kg	Kadenczki et al. 1992
Various produce	Homogenization of sample and extraction with acetonitrile, filtration, addition of salt and solvent evaporation. Redissolution of residue in acetone for analysis.	GC/FPD or alkali FID	0.1 ppm	No data	Hsu et al. 1991

Table 7-2. Analytical Methods for Determining Parathion and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Various prepared foods	Blending of sample with acetone, filtration and transfer to Hydromatrix column. Elution with methylene chloride and concentration.	GC/FPD	No data	94% at 300 ppb	Hopper 1988
Apples, whole milk, olive oil, eggs	Blending of samples with acetone and extraction with dichloromethane and acetone, water removal and volume reduction. Cleanup using carbon-celite (apples), Extrelut-3 minicolumns with hexane (whole milk; olive oil), or C_{18} SPE (eggs).	GC/FPD	0.26 ng	Apples: 71%; whole milk: 85%; olive oil: 98%; eggs: 80%	Leoni et al. 1992
Apples, whole milk, olive oil (paraoxon)	Blending of samples with acetone and extraction with dichloromethane and acetone, water removal and volume reduction. Cleanup using carbon-celite (apples), or Extrelut-3 minicolumns with hexane (whole milk; olive oil).	GC/FPD	0.15 ng	Apples: 97%; whole milk: 89%; olive oil: 90%	Leoni et al. 1992
Cow's milk	Extraction of milk 3 times with 70% acetonitrile in water, filtration, removal of fat by zinc acetate addition, and partitioning with methylene chloride. Reduction of volume after drying.	GC/FPD (P-mode)	10 ppb	92.9% (2.9% RSD) at 100 ppb	Toyoda et al. 1990

Table 7-2. Analytical Methods for Determining Parathion and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Cow's milk	Homogenization of milk, acetonitrile and ethanol followed by equilibration with a mixture of light petroleum-acetonitrile-ethanol and separation of the upper phase and elution through a solid matrix cartridge. Concentration and drying of the eluates to a residue that is dissolved.	GC/FPD	No data (0.016 MDL)	92.7% (5% RSD) at 0.8 μg/mL	Di Muccio et al. 1996

[a]Unless otherwise stated, parathion was determined.

AED = atomic emission detection; AOAC = Association of Official Analytical Chemists; BSA = bovine serum albumin; CV= coefficient of variation; ECD = Ni electron capture detector; EPA = U.S. Environmental Protection Agency; FID = flame ionization detector; FPD = flame photometric detector; GC = gas chromatography; HECD = Hall Electrolytic Conductivity Detector; HPLC = high-performance liquid chromatography; HS = head space, KCl = potassium chloride; K-D = Kuderna-Danish; MDL = method detection limit; MS = mass spectrometry; NaCl = sodium chloride; NIOSH = National Institute for Occupational Safety and Health; NPD = nitrogen phosphorus detector; OSHA = Occupational Safety and Health Administration; QCM = quartz crystal microbalance; RSD = relative standard deviation; SFC = supercritical fluid chromatography; SIM = selected ion monitoring; SPE = solid phase extraction; SPME = solid-phase microextraction; USGS = U.S. Geological Survey; UV = ultraviolet absorbance detection

An LOD of 1 ng/L was reported using GC with a nitrogen-phosphorus selective detector and by GC/MS using selected ion monitoring (SIM). Funari et al. (2013) describe the use of a photonic immobilization technique (PIT) to produce UV-activated antibodies that interact with quartz crystal microbalance (QCM) electrodes to develop an immunosensor for the detection of parathion in water, with a LOD of <4 ppb. Anti-parathion polyclonal antibodies are adsorbed to a gold electrode and activated with UV light using a custom-built femtosecond laser having a highly tunable pulse rate. The ultrashort UV (258 nm) pulses disrupt disulfide bridges of the antibody solution allowing free thiol groups to adsorb to the gold surface, causing the antibody to orient in a manner that increases antigen-antibody specific binding, thus increasing sensitivity of the immunosensor (Funari et al. 2013).

Supercritical fluid extraction (SFE) is also used in sample preparation methods. A supercritical fluid chromatography (SFC)-based method for cucumber, lettuce, and grapes (Zegers et al. 1994) was published, but did not specify the LOD or recovery.

Three standardized methods were found in the *Official Methods of Analysis of the Association of Official Analytical Chemists* (AOAC 1990a, 1990b, 1990c). The first of these methods is based on the extraction of crops (kale, endive, carrots, lettuce, apples, potatoes, and strawberries) with ethyl acetate and isolation of the residue followed by a sweep codistillation cleanup prior to GC/thermionic detection (Method 968.24). In the second method (Method 970.52), the sample is extracted with acetonitrile and the residue is partitioned into petroleum ether followed by Florisil clean-up and GC/potassium chloride (KCl) thermionic detection. Chemical identifications are based on combinations of gas, thin-layer, and paper chromatography. The recovery for parathion in this method is stated to be >80%; no data on LODs were given. The third method utilizes the same extraction and clean-up techniques as the second and then GC/FPD for detection (Method 970.53).

Some methods employ the homogenization of the plant material with aqueous acetonitrile (Hsu et al. 1991) or other polar organic solvents such as acetone/methanol mixtures (Hong et al. 1993). Phase separation is brought about with the addition of a salt. The acetonitrile approach is preferred by the California Department of Food and Agriculture because of the possible higher recoveries (see Table 7-2) (Lee et al. 1991). The advantage of acetonitrile is found in its ability to more readily solvate residues and in the ease with which the phase separation can be accomplished through the addition of salt (Lee et al. 1991). Reported LODs for parathion were typically 10–50 ppb. One of the methods eliminated any clean-up steps after the initial extraction (Hsu et al. 1991) to provide a method with a faster turnaround time with some loss in sensitivity (LOD approximately 0.1 ppm) relative to the purified samples.

Methods found for the determination of parathion in animal products also used homogenization with a polar organic solvent as the first step in residue recovery. Toyoda et al. (1990) isolated parathion from cow's milk via partition into methylene chloride after extraction of the milk with 70% acetonitrile in water. Based on GC/FPD, an LOD of 10 ppb and a recovery of 92.9% (2.9% RSD) at 100 ppb were reported. Parathion residues in eggs were studied (Leoni et al. 1992) after blending the eggs with acetone and partitioning into dichloromethane and acetone followed by C_{18}-silica SPE. Based on GC/FPD analysis, an LOD of 0.26 ng and a recovery of 80% at 13 ppb were reported.

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 parathion is available. Where adequate information is not available, ATSDR, in conjunction with 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 parathion.

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

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Section 3.8.1 provided information on biomarkers used to identify or quantify exposure to parathion. Some methods for the detection of the parent compound in biological samples were described above. The parent chemical is quickly metabolized so the determination of metabolites can also serve as biomarkers of exposure. The use of GC coupled with MS has recently been reported for the elucidation and confirmation of parathion in biological samples (Musshoff et al. 2002). The most specific biomarkers will be those metabolites related to *p*-nitrophenol. Methods for the detection of this compound in human urine have been reported (Olsson et al. 2003). A method for *p*-nitrophenol in rat urine has been described

by Chang et al. (1997) with reported sensitivities in the sub-ppm range. Further studies designed to refine the identification of metabolites specific to parathion and provide dosimetric data will be useful in the search for a more dependable biomarker of parathion exposure.

Effect. Biomarkers of effect include plasma cholinesterase and erythrocyte (red blood cell) and brain AChE, enzymes inhibited by insecticidal organophosphorus compounds (see Chapter 3). Rapid, simple, and specific methods should be sought to make assays readily available to the clinician. Currently, no effect specific to parathion exposure has been identified by any study. Future studies designed to provide such information would be useful in identifying exposure to parathion.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Human exposure to parathion may have occurred via inhalation of ambient air; ingestion of contaminated food and water; and dermal uptake through occupational and non-occupational contact with contaminated soils, surface water, and commercial preparations. Methods have been reported for the measurement of parathion in various foods, soils, sediment, waste water, drinking water, and air. The method of OSHA (1986) (LOD 3.1 $\mu g/m^3$) and NIOSH (1994) (LOD 400 ng/m^3) are adequate for the determination of parathion in air. If a 70-kg individual is assumed, method LODs of 0.007 mg/L (7 ppb) and 0.007 mg/kg (7 ppb) in water and foods, respectively, are required for the method to be adequate at the oral intermediate MRL. All of the methods for detection of parathion in water shown in Table 7-2 are adequate. With regard to foods, the methods of Kadenczki et al. (1992) and Leoni et al. (1992) for detection of parathion are adequate. Methods for other non-fatty crops would need to be validated or developed if routine use were desired. Di Muccio et al. (1996) describe a quick and simple method for the determination of parathion in cow's milk; however, no data were provided given on LODs. Additional methods for detection of parathion in fatty foods are needed to permit the evaluation of the residues in those fatty media.

There are also methods for the analysis of parathion degradation products in water and food. Seiber et al. (1990) reported a method for parathion and its oxon in water. Several methods were reported for the determination of parathion and paraoxon in various food products, including produce, whole milk, olive oil, and eggs (Leoni et al. 1993; Liao et al. 1991). Additional methods are needed for the quantitative analysis of parathion transformation products in environmental matrices. It will also be important to establish MRLs for the transformation products to put the analytical requirements into perspective.

7.3.2 Ongoing Studies

Since parathion is no longer produced or used in the United States (EPA 2000a), no ongoing studies regarding its detection by analytical methods are being investigated.

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8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

ATSDR has derived an intermediate-duration inhalation MRL of 20 ng/m^3 for parathion based on a NOAEL of 0.01 mg/m^3 for neurological effects in rats (NIOSH 1974). The MRL was derived by dividing the duration-adjusted NOAEL by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived an intermediate-duration oral MRL of 0.009 mg/kg/day for parathion based on a NOAEL of 0.09 mg/kg/day for neurological effects in humans (Rider et al. 1969). The MRL was derived by dividing the NOAEL by an uncertainty factor of 10 (for human variability).

IARC has classified parathion as a Group 3 carcinogen (*not classifiable as to its carcinogenicity to humans*) (IARC 2013). The World Health Organization (WHO) has not established any air quality guidelines for parathion (WHO 2010). A water quality guideline value was not established for parathion because it occurs in drinking water at concentrations well below those of health concern (WHO 2011).

OSHA has established an enforceable permissible exposure limit (PEL) of 0.1 mg/m^3 for parathion (OSHA 2013b). OSHA has required employers of workers who are occupationally exposed to parathion to institute engineering controls and work practices to reduce and maintain employee exposure at or below the PEL. NIOSH has established a recommended exposure limit (REL) of 0.05 mg/m^3 and an immediately dangerous to life or health (IDLH) value of 10 mg/m^3 (NIOSH 2013). The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended a threshold limit value (TLV) of 0.05 mg/m^3 for an 8-hour workday (ACGIH 2012).

The Department of Energy (DOE) has established protective action criteria (PAC-1, -2, and -3) values of 0.14, 1.5, and 2.0 mg/m^3, respectively, for airborne parathion when responding to potential releases for use in community emergency planning (DOE 2012). These values represent increasing severity of effects (mild, irreversible, and life-threatening) for a 1-hour exposure.

EPA has classified parathion as Group C carcinogen (*possible human carcinogen*) (IRIS 2003) and ACGIH (2012) has classified parathion as an A4 carcinogen (*not classified as to human carcinogenicity*). The National Toxicology Program (NTP) has not classified parathion as a human carcinogen (NTP 2011). EPA has not derived an oral reference dose (RfD) or a chronic inhalation reference concentration (RfC) for parathion (IRIS 2003).

EPA has designated parathion as a hazardous air pollutant (HAP) under the Clean Air Act (CAA) (EPA 2013b). Parathion is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" and has been assigned a reportable quantity (RQ) limit of 10 pounds (EPA 2012f). Parathion is also considered to be an extremely hazardous substance (EPA 2012g). The RQ represents the amount of a designated hazardous substance which, when released to the environment, must be reported to the appropriate authority.

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

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Parathion

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	3[a]	IARC 2013
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines	No data[b]	WHO 2011
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)[c,d]	0.05 mg/m^3	ACGIH 2012
AIHA	ERPG-1, -2, -3	No data	AIHA 2011
DOE	PAC-1[e]	0.14 mg/m^3	DOE 2012
	PAC-2	1.5 mg/m^3	
	PAC-3	2.0 mg/m^3	
EPA	AEGL-1[f]	Not recommended due to insufficient data	EPA 2013a
	AEGL-2		
	10-minutes	2.8 mg/m^3	
	30-minutes	1.9 mg/m^3	
	60-minutes	1.5 mg/m^3	
	4-hours	0.96 mg/m^3	
	8-hours	0.48 mg/m^3	
	AEGL-3		
	10-minutes	3.6 mg/m^3	
	30-minutes	2.5 mg/m^3	
	60-minutes	2.0 mg/m^3	
	4-hours	1.3 mg/m^3	
	8-hours	0.63 mg/m^3	
	Hazardous air pollutant	Yes	EPA 2013b 42 USC 7412
	NAAQS	No data	EPA 2013e
NIOSH	REL (10-hour TWA)[g]	0.05 mg/m^3	NIOSH 2011
	IDLH	10 mg/m^3	
OSHA	PEL (8-hour TWA) for general industry[h]	0.1 mg/m^3	OSHA 2013b 29 CFR 1910.1000, Table Z-1
	Highly hazardous chemicals	No data	OSHA 2013a 29 CFR 1910.119, Appendix A

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Parathion

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2012a 40 CFR 116.4
EPA	Drinking water contaminant candidate list	No data	EPA 2009a 74 FR 51850
	Drinking water standards and health advisories	No data	EPA 2012b
	National primary drinking water standards	No data	EPA 2009b
	National recommended water quality criteria for freshwater		EPA 2009c
	Criteria maximum concentration (acute)	0.065 μg/L	
	Criterion continuous concentration (chronic)	0.013 μg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	10 pounds	EPA 2012d 40 CFR 117.3
c. Food			
FDA	EAFUS[i]	No	FDA 2013
d. Other			
ACGIH	Carcinogenicity classification	A4[j]	ACGIH 2012
	BEI		
	Total p-nitrophenol in urine (end of shift end)	0.5 mg/g creatinine	
	Cholinesterase activity in red blood cells (discretionary)	70% of individual's baseline	
EPA	Carcinogenicity classification	Group C[k]	IRIS 2003
	RfC	No data	
	RfD	No data	
	Identification and listing of hazardous waste	P089	EPA 2012c 40 CFR 261, Appendix VIII
	Inert pesticide ingredients in pesticide products approved for nonfood use only	No data	EPA 2013c
	Master Testing List	No data	EPA 2013d
	RCRA waste minimization PBT priority chemical list	No data	EPA 1998 63 FR 60332
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list	Yes	EPA 2012e 40 CFR 264, Appendix IX

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Parathion

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity pursuant to Section 311(b)(2) of the Clean Water Act, Section 112 of the Clean Air Act, and Section 3001 of RCRA	10 pounds	EPA 2012f 40 CFR 302.4
	Effective date of toxic chemical release reporting	01/01/1987	EPA 2012h 40 CFR 372.65
	Extremely hazardous substances and its threshold planning quantity		EPA 2012g 40 CFR 355, Appendix A
	Reportable quantity	10 pounds	
	Threshold planning quantity	100 pounds	
	TSCA chemical lists and reporting periods	No data	EPA 2012i 40 CFR 712.30
	TSCA health and safety data reporting	No data	EPA 2012j 40 CFR 716.120
NTP	Carcinogenicity classification	No data	NTP 2011

[a]Group 3: not classifiable as to its carcinogenicity to humans.
[b]A guideline value was not established for parathion because it occurs in drinking-water at concentrations well below those of health concern (WHO 2011).
[c]Inhalable fraction and vapor; material exerts sufficient vapor pressure such that it may be present in both particles and vapor phases, with each contributing a significant portion of the dose at the TLV-TWA concentration (ACGIH 2012).
[d]Skin designation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, by contact with vapors, liquids, and solids (ACGIH 2012).
[e]PAC-1: mild, transient health effects; PAC-2: irreversible or other serious health effects that could impair the ability to take protective action; PAC-3: life-threatening health effects (DOE 2012).
[f]AEGL-1: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects; however, these effects are not disabling and are transient and reversible upon cessation of exposure; AEGL-2: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting, adverse health effects or an impaired ability to escape; AEGL-3: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death (EPA 2013a).
[g]Skin designation indicates the potential for dermal absorption; skin exposure should be prevented as necessary through the use of good work practices, gloves, coveralls, goggles, and other appropriate equipment (NIOSH 2011).
[h]Skin designation.
[i]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[j]A4: not classified as to human carcinogenicity.
[k]Group C: possible human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; BEI = biological exposure indices; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency;

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Parathion

Agency	Description	Information	Reference

ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = generally recognized as safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NAAQS = National Ambient Air Quality Standards; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PBT = persistent, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

9. REFERENCES

*Aaron CK. 2007. Organophosphates and carbamates. In: Shannon MW, Borron SW, Burns MJ, eds. Haddad and Winchester's clinical management of poisoning and drug overdose. Philadelphia, PA: Saunders Elsevier, 1171-1184.

*Abadin HG, Chou CSJ, Llados FT. 2007. Health effects classification and its role in the derivation of minimal risk levels: Immunological effects. Regul Toxicol Pharmacol 47:249-256.

*Abou-Donia MB. 1995. Organophosphorus pesticides. In: Chang LW, Dyer RS, Eds. Handbook of neurotoxicology. New York, NY: Marcel Dekker, 419-473.

*Abou-Donia MB, Lapadula DM. 1990. Mechanisms of organophosphorus ester-induced delayed neurotoxicity: Type I and Type II. Ann Rev Pharmacol Toxicol 30:405-440.

*ACGIH. 2012. Parathion. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 46, 109.

*Adhya TK, Barik S, Sethunathan N. 1981c. Hydrolysis of selected organophosphorus insecticides by two bacteria isolated from flooded soil. J Appl Bacteriol 50:167-172.

*Adhya TK, Subhakar B, Sethunathan N. 1981b. Fate of fenitrothion, methyl parathion, and parathion in anoxic sulfur-containing soil systems. Pestic Biochem Physiol 16(1):14-20.

*Adhya TK, Sudhakar B, Sethunathan N. 1981a. Stability of commercial formulation of fenitrothion, methyl parathion and parathion in anaerobic soils. J Agric Food Chem 29(1):90-93.

*Adigun AA, Wrench N, Seidler FJ, et al. 2010. Neonatal organophosphorus pesticide exposure alters the developmental trajectory of cell-signaling cascades controlling metabolism: Differential effects of diazinon and parathion. Environ Health Perspect 118(2):210-215.

*Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. Dev Med Child Neurol 27(4):532-537.

*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect Suppl 103(7):103-112.

*Agency for Toxic Substances and Disease Registry. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Fed Regist 54(174):37618-37634.

*Agency for Toxic Substances and Disease Registry. 2011. Medical Management Guidelines for parathion.

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* Cited in text
+ Cited in supplemental document

*AIHA. 2011. Emergency response planning guidelines (ERPG). Fairfax, VA: American Industrial Hygiene Association. http://www.aiha.org/INSIDEAIHA/GUIDELINEDEVELOPMENT/ERPG/Pages/default.aspx. April 24, 2013.

*Alavanja MCR, Sandler DP, McMaster SB, et al. 1996. The Agricultural Health Study. Environ Health Perspect 104(4):362-369.

*Altman PL, Dittmer DS. 1974. Biological handbooks: Biology data book. Vol. III. 2nd ed. Bethesda, MD: Fed Am Soc Exp Biol.

*Andersen ME, Krishnan K. 1994. Relating *in vitro* to *in vivo* exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, and replacement. New York, NY: Marcel Dekker, Inc., 9-25.

*Andersen ME, Clewell HJ, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87(2):185-205.

*AOAC. 1990a. Organophosphorus pesticide residues. Sweep codistillation method. In: Helrich K, ed. AOAC official methods of analysis. 15th ed. Arlington, VA: Association of Official Analytical Chemists, 287-289.

*AOAC. 1990b. Pesticide and industrial chemical residues. In: Helrich K, ed. Official methods of analysis of the Association of Official Analytical Chemists. 15th ed. Arlington, VA: Association of Official Analytical Chemists, Inc., 274-282.

*AOAC. 1990c. Organophosphorus pesticide residues. Single sweep oscillographic polarographic confirmatory method. In: Helrich K, ed. Official methods of analysis of the Association of Official Analytical Chemists. 15th ed. Arlington, VA: Association of Analytical Chemists, Inc., 289-290.

*Arcury TA, Grzywacz JG, Barr DB, et al. 2007. Pesticide urinary metabolite levels of children in eastern North Carolina farmworker households. Environ Health Perspect 115(8):1254-1260.

*Arterberry JD, Durham WF, Elliott JW, et al. 1961. Exposure to parathion. Measurement by blood cholinesterase level and urinary p-nitrophenol excretion. Arch Environ Health 3:476-485.

+*Atkinson JE, Bolte HF, Rubin LF, et al. 1994. Assessment of ocular toxicity in dogs during 6 months' exposure to a potent organophosphate. J Appl Toxicol 14(2):145-152.

*Atterberry TT, Burnett WT, Chambers JE. 1997. Age-related differences in parathion and chlorpyrifos toxicity in male rats: Target and nontarget esterase sensitivity and cytochrome P450-mediated metabolism. Toxicol Appl Pharmacol 147(2):411-418.

*Bajgar J. 2004. Organophosphates/nerve agent poisoning: Mechanism of action, diagnosis, prophylaxis, and treatment. Adv Clin Chem 38:151-216.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8(4):471-486.

+*Barnes JM, Denz FA. 1951. The chronic toxicity of p-nitrophenyl diethyl thiophosphate (E. 605); a long-term feeding experiment with rats. J Hyg 49(4):430-441.

*Bass SW, Triolo AJ, Coon JM. 1972. Effect of DDT on the toxicity and metabolism of parathion in mice. Toxicol Appl Pharmacol 22(4):684-693.

*Benke GM, Murphy SD. 1974. Anticholinesterase action of methyl parathion, parathion and azinphosmethyl in mice and fish: Onset and recovery of inhibition. Bull Environ Contam Toxicol 12(1):117-122.

*Benke GM, Murphy SD. 1975. The influence of age on the toxicity and metabolism of methyl parathion and parathion in male and female rats. Toxicol Appl Pharmacol 31(2):254-269.

*Berger GS, ed. 1994. Epidemiology of endometriosis. In: Endometriosis: Modern surgical management of endometriosis. New York, NY: Springer-Verlag, 3-7.

*Besser R, Gutmann L, Weilemann LS. 1993. Polyneuropathy following parathion poisoning. J Neurol Neurosurg Psychiatry 56(10):1135-1136.

*Bird SB, Sutherland TD, Gresham C, et al. 2008. OpdA, a bacterial organophosphorus hydrolase, prevents lethality in rats after poisoning with highly toxic organophosphorus pesticides. Toxicology 247(2-3):88-92.

*Bouchard MF, Chevrier J, Harley KG, et al. 2011. Prenatal exposure to organophosphate pesticides and IQ in 7-year old children. Environ Health Perspect 119(8):1189-1195.

*Boudry I, Blanck O, Cruz C, et al. 2008. Percutaneous penetration and absorption of parathion using human and pig skin models *in vitro* and human skin grafted onto nude mouse skin model *in vivo*. J Appl Toxicol 28(5):645-657.

*Boyd EM. 1969. Dietary protein and pesticide toxicity in male weanling rats. Bull World Health Organ 40(5):801-805.

*Bradway DE, Shafik TM, Lores EM. 1977. Comparison of cholinesterase activity, residue levels, and urinary metabolite excretion of rats exposed to organophosphorus pesticides. J Agric Food Chem 25(6):1353-1358.

*Braeckman RA, Audenaert F, Willems JL, et al. 1983. Toxicokinetics of methyl parathion and parathion in the dog after intravenous and oral administration. Arch Toxicol 54(1):71-82.

*Brown HV, Bush BA. 1950. Parathion inhibition of cholinesterase. Arch Ind Hyg Occup Med 1:633-636.

*Brown RL, Farmer CN, Millar RG. 1987. Optimization of sweep codistillation apparatus for determination of coumaphos and other organophosphorus pesticide residues in animal fat. J AOAC 70(3):442-445.

*Bulusu S, Chakravarty I. 1986. Subacute administration of organophosphorus pesticides and hepatic drug metabolizing enzyme activity in normal and malnourished rats. Bull Environ Contam Toxicol 36(1):73-80.

*Bulusu S, Chakravarty I. 1987. Effect of subacute administration of three organophosphorus pesticides on the hepatic phosphatases under various nutritional conditions. Environ Res 44(1):126-135.

*Buratti FM, Volpe MT, Fabrizi L, et al. 2002. Kinetic parameters of OPT pesticide desulfuration by c-DNA expressed human CYPs. Environ Toxicol Pharmacol 11(3-4):181-190.

*Buratti FM, Volpe MT, Meneguz A, et al. 2003. CYP-specific bioactivation of four organophosphorothioate pesticides by human liver microsomes. Toxicol Appl Pharmacol 186(3):143-154.

*Burmaster DE. 1982. The new pollution. Groundwater contamination. Environment 24(2):6-36.

*Butler AM, Murray M. 1997. Biotransformation of parathion in human liver: Participation of CYP3A4 and its inactivation during microsomal parathion oxidation. J Pharmacol Exp Ther 280(2):966-973.

*Butler PA, Schutzmann RL. 1978. Fish, wildlife, and estuaries. Residues of pesticides and PCBs in estuarine fish, 1972-1976, National Pesticide Monitoring Programs. Pestic Monit J 12(2):51-59.

*Calaf GM, Roy D. 2007a. Gene and protein expressions induced by 17β-estradiol and parathion in cultured breast epithelial cells. Mol Med 13(5-6):255-265.

*Calaf GM, Roy D. 2007c. Gene expression signature of parathion-transformed human breast epithelial cells. Int J Mol Med 19(5):741-750.

*Calaf GM, Roy D. 2007b. Human drug metabolism genes in parathion-and estrogen-treated breast cells. Int J Mol Med 20(6):875-881.

*Calaf GM, Echiburu-Chau C, Roy D. 2009. Organophosphorous pesticides and estrogen induce transformation of breast cells affecting *p53* and *c-Ha-ras* genes. Int J Oncol 35(5):1061-1068.

*Carey AE, Douglas P, Tai H, et al. 1979b. Pesticide residue concentrations in soils of five United States cities, 1971- Urban soils monitoring program. Pestic Monit J 13(1):17-22.

*Carey AE, Gowen JA, Tai H, et al. 1979a. Pesticide residue levels in soils and crops from 37 states, 1972. National Soils Monitoring Program (IV). Pestic Monit J 12(4):209-229.

*Carey AE, Yang HSC, Wiersma GB, et al. 1980. Soils. Residual concentration of propanil, TCAB, and other pesticides in rice-growing soils in the United States, 1972. Pestic Monit J 14(1):23-25.

*Carman GE, Iwata Y, Pappas JL, et al. 1982. Pesticide applicator exposure to insecticides during treatment of citrus trees with oscillating boom and airblast units. Arch Environ Contam Toxicol 11:651-659.

*Carrier G, Brunet RC. 1999. A toxicokinetic model to assess the risk of azinphosmethyl exposure in humans through measures of urinary elimination of alkylphosphates. Toxicol Sci 47:23-32.

*Carvalho FP, Fowler SW, Readman JW. 1998. The fate and effects of agrochemical residues in tropical coastal lagoons investigated with ^{14}C-labelled compounds and radiotracer techniques. Verch Internat Verein Limnol 26:1430-1432.

+*Casale GP, Cohen SD, DiCapua RA. 1983. The effects of organophosphate-induced cholinergic stimulation on the antibody response to sheep erythrocytes in inbred mice. Toxicol Appl Pharmacol 68(2):198-205.

+*Casale GP, Cohen SD, DiCapua RA. 1984. Parathion-induced suppression of humoral immunity in inbred mice. Toxicol Lett 23(2):239-247.

*Casterline JL, Jr., Williams CH. 1971. The effect of 28-day pesticide feeding on serum and tissue enzyme activities of rats fed diets of varying casein content. Toxicol Appl Pharmacol 18(3):607-618.

*CDC. 2005. Third national report on human exposure to environmental chemicals. Atlanta, GA: Centers for Disease Control and Prevention, Department of Health and Human Services.

*CDC. 2009. Fourth national report on human exposure to environmental chemicals. Centers for Disease Control and Prevention, Department of Health and Human Services.

*CDFA. 1988. Evaluation of ethyl parathion as a toxic air contaminant. California Department of Food and Agriculture.

*Chambers JE, Ma T, Boone JS, et al. 1994. Role of detoxication pathways in acute toxicity levels of phosphorothionate insecticides in the rat. Life Sci 54(18):1357-1364.

*Chang MJW, Chen YC, Yang HJ. 1997. Comparative evaluation on the biological monitoring of exposure to parathion and its methyl analog. Arch Environ Contam Toxicol 32:422-425.

*Chang SK, Riviere JE. 1991. Percutaneous absorption of parathion *in vitro* in porcine skin: Effects of dose, temperature, humidity, and perfusate composition on absorptive flux. Fundam Appl Toxicol 17(3):494-504.

*Chapman RA, Cole CM. 1982. Observations on the influence of water and soil pH on the persistence of pesticides. J Environ Sci Health B17(5):487-504.

*Chapman RA, Tu CM, Harris CR, et al. 1981. Persistence of five pyrethroid insecticides in sterile and natural, mineral and organic soil. Bull Environ Contam Toxicol 26:513-519.

*Chapman SK, Leibman KC. 1971. The effects of chlordane, DDT, and 3-methylcholanthrene upon the metabolism and toxicity of diethyl-4-nitrophenyl phosphorothionate (parathion). Toxicol Appl Pharmacol 18(4):977-987.

*Chaturvedi AK, Kuntz DJ, Rao NG. 1991. Metabolic aspects of the toxicology of mixtures of parathion, toxaphene and/or 2,4-D in mice. J Appl Toxicol 11(4):245-251.

*Chemnitius JM, Losch H, Losch K, et al. 1983. Organophosphate detoxicating hydrolases in different vertebrate species. Comp Biochem Physiol 76C:85-93.

*Chen ZM, Zabik MJ, Leavitt RA. 1984. Comparative study of thin film photodegradative rates for 36 pesticides. Ind Eng Chem Prod Res Dev 23:5-11.

*Chiou CT, Freed VH, Peters LJ, et al. 1980. Evaporation of solutes from water. Environ Int 3:231-236.

*Chu W, Chan KH. 2000. The prediction of partitioning coefficients for chemicals causing environmental concern. Sci Total Environ 248(1):1-10.

*Clark RF. 2002. Insecticides: Organic phosphorus compounds and carbamates. In: Goldfrank LR, ed. Goldfrank's toxicologic emergencies. 7th ed. New York, NY: McGraw-Hill, Medical Publishing Division, 1346-1360.

*Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

*Costa LG. 2008. Toxic effects of pesticides. In: Klaassen CD, ed. Casarett and Doull's toxicology. The basic science of poisons. 7th ed. New York, NY: McGraw-Hill Medical, 883-930.

*Costa LG, Aschner M, Vitalone A, et al. 2004. Developmental neuropathology of environmental agents. Annu Rev Pharmacol Toxicol 44:87-110.

*Costa LG, Giordano G, Cole TB, et al. 2013. Paraoxonase 1 (PON1) as a genetic determinant of susceptibility to organophosphate toxicity. Toxicology 307:115-122.

*Costa LG, Schwab BW, Murphy SD. 1982. Tolerance to anticholinesterase compounds in mammals. Toxicology 25:79-97.

*Coupe RH, Manning MA, Foreman WT, et al. 2000. Occurrence of pesticides in rain and air in urban and agricultural areas of Mississippi, April-September 1995. Sci Total Environ 248:227-240.

*Coye MJ, Barnett PG, Midtling JE, et al. 1987. Clinical confirmation of organophosphate poisoning by serial cholinesterase analyses. Arch Intern Med 147:338-342.

*Crosby DG. 1979. The significance of light induced pesticide transformations. In: Geissbuhler H, ed. Advances in pesticide science. Oxford: Pergamon Press, 568-576.

*Davies JE, Davis JH, Frazier DW, et al. 1967. Disturbances of metabolism in organophosphate poisoning. Ind Med Surg 36(1):58-62.

*De Bleecker J, Vogelaers D, Ceuterick C, et al. 1992. Intermediate syndrome due to prolonged parathion poisoning. Acta Neurol Scand 86(4):421-424.

*Degraeve N, Moutschen J. 1984. Absence of genetic and cytogenetic effects in mice treated by the organophosphorus insecticide parathion, its methyl analogue, and paraoxon. Toxicology 32(2):177-183.

*De Jager AE, van Weerden TW, Houthoff HJ, et al. 1981. Polyneuropathy after massive exposure to parathion. Neurology 31(5):603-605.

*Denga N, Moldeus P, Kasilo OM, et al. 1995. Use of urinary p-nitrophenol as an index of exposure to parathion. Bull Environ Contam Toxicol 55(2):296-302.

*Dennis LK, Lynch CF, Sandler DP, et al. 2010. Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural heath study. Environ Health Perspect 118(6):812-817.

+*Deskin R, Rosenstein L, Rogers N, et al. 1979. Parathion toxicity in perinatal rats exposed *in utero*. Toxicol Lett 3(1):11-14.

*Diggory HJ, Landrigan PJ, Latimer KP, et al. 1977. Fatal parathion poisoning caused by contamination of flour in international commerce. Am J Epidemiol 106(2):145-153.

+*Dikshith TS, Datta KK. 1972. Effect of parathion on the skin of guinea-pigs. Experientia 28(2):169-171.

+*Dikshith TS, Tandon SK, Datta KK, et al. 1978. Comparative response of male rats to parathion and lindane: Histopathological and biochemical studies. Environ Res 17(1):1-9.

*Di Muccio A, Pelosi P, Camoni I, et al. 1996. Selective, solid-matrix dispersion extraction of organophosphate pesticide residues from milk. J Chromatogr A 754:497-506.

*DOE. 2012. Protective action criteria (PAC). Oak Ridge, TN: U.S. Department of Energy and Subcommittee on Consequence Assessment and Protective Actions (SCAPA). http://orise.orau.gov/emi/scapa/chem-pacs-teels/default.htm. April 24, 2013.

*Draper WM, Crosby DG. 1984. Solar photooxidation of pesticides in dilute hydrogen peroxide. J Agric Food Chem 32:231-237.

*Driss MR, Hennion MC, Bouguerra ML. 1993. Determination of carbaryl and some organophophorus pesticides in drinking water using on-line liquid chromatographic preconcentration techniques. J Chromatogr 639:352-358.

*Durham WF, Wolfe HR, Elliott JW. 1972. Absorption and excretion of parathion by spraymen. Arch Environ Health 24(6):381-387.

*Duysen EG, Lockridge O. 2011. Induction of plasma acetylcholinesterase activity in mice challenged with organophosphorus poisons. Toxicol Appl Pharmacol 255(2):214-220.

*Duysen EG, Cashman JR, Schopfer LM, et al. 2012. Differential sensitivity of plasma carboxylesterase-null mice to parathion, chlorpyrifos and chlorpyrifos oxon, but not to diazinon, dichlorvos, diisopropylfluorophosphate, cresyl saligenin phosphate, cyclosarin thiocholine, tabun thiocholine, and carbofuran. Chem Biol Interact 195(3):189-198.

*Ebbert JC, Embrey SS. 2001. Pesticides in surface water of the Yakima River Basin, Washington, 1999-2000: Their occurrence and an assessment of factors affecting concentrations and loads. Portland, OR: U.S. Department of the Interior, U.S. Geological Survey.

*Ecobicon DJ. 1994. Organophosphorus ester insecticides. In: Pesticides and neurological diseases. 2nd ed. Boca Raton, FL: CRC Press, Inc., 171-249.

*Ecobichon DJ, Comeau AM. 1973. Pseudocholinesterases of mammalian plasma: Physicochemical properties and organophosphate inhibition in eleven species. Toxicol Appl Pharmacol 24:92-100.

+*Edson EF. 1964. Summaries of toxicological data. No-effect levels of three organophosphates in the rat, pig and man. Food Cosmet Toxicol 2:311-316.

*Eichelberger JW, Lichtenberg JJ. 1971. Persistence of pesticides in river water. Environ Sci Technol 5(6):541-544.

*Eigenberg DA, Pazdernik TL, Doull J. 1983. Hemoperfusion and pharmacokinetic studies with parathion and paraoxon in the rat and dog. Drug Metab Dispos 11(4):366-370.

*Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15(1):30-38.

*Eisert R, Levsen K, Wunsch G. 1994. Element-selective detection of pesticides by gas chromatography-atomic emission detection and solid-phase microextraction. J Chromatogr A 683:175-183.

*Eitzman DV, Wolfson SL. 1967. Acute parathion poisoning in children. Am J Dis Child 114(4):397-400.

*Ek CJ, Dziegielewska KM, Habgood MD, et al. 2012. Barriers in the developing brain and neurotoxicology. Neurotoxicology 33(3):586-604.

+*Elkner KP, Fenske RA, Gallo M. 1991. Effect of systemic exposure to parathion on the dark adapted pupil dilation of cynomolgus monkeys. J Toxicol Environ Health 32(1):75-88.

*El-Masri HA, Mumtaz MM, Yushak ML. 2004. Application of physiologically-based pharmacokinetic modeling to investigate the toxicological interaction between chlorpyrifos and parathion in the rat. Environ Toxicol Pharmacol 16(1-2):57-71.

*EPA. 1977. The degradation of selected pesticides in soil: A review of the published literature. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development.

+*EPA. 1978. Teratology and acute toxicology of selected chemical pesticides administered by inhalation. Environmental health effects research series. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA600178003. PB277077.

*EPA. 1990. Interim methods for development of inhalation reference concentrations. Washington, DC: U.S. Environmental Protection Agency. EPA600890066A. PB90238890.

*EPA. 1993a. Methods for the determination of nonconventional pesticides in municipal and industrial wastewater. Method 1657. The determination of organo-phosphorus pesticides in municipal and industrial wastewater. Washington, DC: U.S. Environmental Protection Agency, Office of Water. EPA821R93010A.

*EPA. 1993b. Methods for the determination of nonconventional pesticides in municipal and industrial wastewater. Method 614. The determination of organophosphorus pesticides in municipal and industrial wastewater. Washington, DC: U.S. Environmental Protection Agency, Office of Water. EPA821R93010A.

*EPA. 1997. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency. EPA630R96012.

*EPA. 1998. RCRA waste minimization PBT priority chemical list. U.S. Environmental Protection Agency. Fed Regist 63 FR 60332. http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2000a. Ethyl parathion. R.E.D. Facts. U.S. Environmental Protection Agency. www.epa.gov/oppsrrd1/REDs/factsheets/0155fct.pdf. June 3, 2013.

*EPA. 2000b. Pesticides: Guidance on pesticide import tolerances and residue data for imported food: Request for comment. Fed Regist 65(106):35069-35090.

*EPA. 2001. Preliminary cumulative risk assessment of the organophosphorus pesticides. U.S. Environmental Protection Agency. http://www.epa.gov/opp00001/cumulative/rra-op/. June 7, 2013.

*EPA. 2002. Organophosphate pesticides: Revised cumulative risk assessment. U.S. Environmental Protection Agency. http://www.epa.gov/pesticides/cumulative/rra-op/. May 15, 2013.

*EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency, Office of Environmental Information. EPA260B05001.

*EPA. 2006a. Organophosphorus cumulative risk assessment-2006. Update. U.S. Environmental Protection Agency. http://www.epa.gov/oppsrrd1/cumulative/2006-op/index.htm. June 3, 2013.

*EPA. 2006b. Ethyl parathion; product cancellation order. Fed Regist 71(239):74904-74905. http://www.epa.gov/fedrgstr/EPA-PEST/2006/December/Day-13/p20988.htm. July 16, 2013.

*EPA. 2009a. Drinking water contaminant candidate list. U.S. Environmental Protection Agency. Fed Regist 74 FR 51850:51850-51862. http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2009b. National primary drinking water regulations. Washington, DC: Office of Ground Water and Drinking Water, U.S. Environmental Protection Agency. http://water.epa.gov/drink/contaminants/upload/mcl-2.pdf. April 24, 2013.

*EPA. 2009c. National recommended water quality criteria. Washington, DC: U.S. Environmental Protection Agency, Office of Water, Office of Science and Technology. http://water.epa.gov/scitech/swguidance/standards/criteria/current/index.cfm. April 24, 2013.

*EPA. 2012a. Designated as hazardous substances in accordance with section 311(b)(2)(a) of the Clean Water Act. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 116.4. http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012b. Drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water. EPA822S12001. http://water.epa.gov/drink/standards/hascience.cfm. April 24, 2013.

*EPA. 2012c. Identification and listing of hazardous waste. Hazardous constituents. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 261, Appendix VIII. http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012d. Reportable quantities of hazardous substances designated pursuant to section 311 of the Clean Water Act. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 117.3. http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012e. Standards for owners and operators of hazardous waste TSD facilities. Groundwater monitoring list. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 264, Appendix IX. http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012f. Superfund, emergency planning, and community right-to-know programs. Designation, reportable quantities, and notifications. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 302.4. http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012g. Superfund, emergency planning, and community right-to-know programs. Extremely hazardous substances and their threshold planning quantities. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 355, Appendix A. http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012h. Superfund, emergency planning, and community right-to-know programs. Toxic chemical release reporting. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 372.65. http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012i. Toxic Substances Control Act. Chemical lists and reporting periods. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 712.30. http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2012j. Toxic Substances Control Act. Health and safety data reporting. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 716.120. http://www.gpo.gov/fdsys. April 24, 2013.

*EPA. 2013a. Acute exposure guideline levels (AEGLs). Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. http://www.epa.gov/oppt/aegl/. April 24, 2013.

*EPA. 2013b. Hazardous air pollutants. Clean Air Act. U.S. Environmental Protection Agency. United States Code 42 USC 7412. http://www.epa.gov/ttn/atw/orig189.html. April 24, 2013.

*EPA. 2013c. Inert ingredients permitted for use in nonfood pesticide products. Washington, DC: U.S. Environmental Protection Agency. http://iaspub.epa.gov/apex/pesticides/f?p=124:1. April 24, 2013.

*EPA. 2013d. Master testing list. Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. http://www.epa.gov/opptintr/chemtest/pubs/mtl.html. April 24, 2013.

*EPA. 2013e. National ambient air quality standards (NAAQS). Washington, DC: U.S. Environmental Protection Agency, Office of Air and Radiation. http://www.epa.gov/air/criteria.html. April 24, 2013.

*Eskenazi B, Harley K, Bradman A, et al. 2004. Association of *in utero* organophosphate pesticide exposure and fetal growth and length of gestation in an agricultural population. Environ Health Perspect 112(10):1116-1124.

*Eskenazi B, Marks AR, Bradman A, et al. 2007. Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. Environ Health Perspect 115(5):792-798.

*Etzel RA, Forthal DN, Hill RH, Jr., et al. 1987. Fatal parathion poisoning in Sierra Leone. Bull World Health Organ 65(5):645-649.

*Evron T, Geyer BC, Cherni I, et al. 2007. Plant-derived human acetylcholinesterase-R provides protection from lethal organophosphate poisoning and its chronic aftermath. FASEB J 21(11):2961-2969.

*Eyer F, Meischner V, Kiderlen D, et al. 2003. Human parathion poisoning. A toxicokinetic analysis. Toxicol Rev 22(3):143-163.

*Fahrig R. 1974. Comparative mutagenicity studies with pesticides. IARC Sci Publ 10:161-181.

*FAO. 1997. Parathion. Food and Agricultural Organization of the United Nations. http://www.fao.org/docrep/W5715E/w571e05.htm#parathion.

*Farm Chemicals Handbook. 1987. Parathion. In: Farm chemicals handbook '87. Meister Publishing Company, C192-C193.

*Faust SD, Suffet IH. 1966. Recovery, separation, and identification of organic pesticides from natural and potable waters. In: Gunther FA, ed. Residue reviews. Residues of pesticides and other foreign chemicals in foods and feeds. New York, NY: Springer-Verlag, 44-116.

*FDA. 1995. Residue monitoring. Food and Drug Administration Pesticide Program.

*FDA. 2013. Everything added to food in the United States (EAFUS). Washington, DC: U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting. April 24, 2013.

*Felsot A, Dahm PA. 1979. Sorption of organophosphorus and carbamate insecticides by soil. J Agric Food Chem 27(3):557-563.

*Fenske RA, Lu C, Simcox NJ, et al. 2009. Strategies for assessing children's organophosphorus pesticide exposures in agricultural communities. J Expo Anal Environ Epidemiol 10:662-671.

*Finkelstein Y, Wolff M, Biegon A. 1988. Brain acetylcholinesterase after acute parathion poisoning: A comparative quantitative histochemical analysis post mortem. Ann Neurol 24(2):252-257.

*Firestone JA, Smith-Weller T, Franklin G, et al. 2005. Pesticides and risk of Parkinson disease: A population-based case-control study. Arch Neurol 62(1):91-95.

*Fisher SW, Lohner TW. 1987. Changes in the aqueous behavior of parathion under varying conditions of pH. Arch Environ Contam Toxicol 16:79-84.

*Fjordboge AS, Baun A, Vastrup T, et al. 2013. Zero valent iron reduces toxicity and concentrations of organophosphate pesticides in contaminated groundwater. Chemosphere 90:627-633.

*Fomon SJ. 1966. Body composition of the infant: Part 1: The male reference infant. In: Faulkner F, ed. Human development. Philadelphia, PA: WB Saunders, 239-246.

*Fomon SJ, Haschke F, Ziegler EE, et al. 1982. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 35(Suppl 5):1169-1175.

*Forsyth CS, Chambers JE. 1989. Activation and degradation of the phosphorothionate insecticides parathion and EPN by rat brain. Biochem Pharmacol 38(10):1597-1603.

*Foxenberg RJ, Ellison CA, Knaak JB, et al. 2011. Cytochrome P450-specific human PBPK/PD models for the organophosphorus pesticides: Chlorpyrifos and parathion. Toxicology 285:57-66.

*Foxenberg RJ, McGarrigle BP, Knaak JB, et al. 2007. Human hepatic cytochrome p450-specific metabolism of parathion and chlorpyrifos. Drug Metab Dispos 35(2):189-193.

*Frank R, Braun HE, Ishida K, et al. 1976. Persistent organic and inorganic pesticide residues in orchard soils and vineyards of southern Ontario. Can J Soil Sci 56:463-484.

+*Frawley JP, Fuyat HN. 1957. Effect of low dietary levels of parathion and systox on blood cholinesterase of dogs. J Agric Food Chem 5(5):346-348.

*Freed VH, Chiou CT, Schmedding DW. 1979. Degradation of selected organophosphate pesticides in water and soil. J Agric Food Chem 27(4):706-708.

*Fukushima M, Katagi T. 2006. Photodegradation of fenitrothion and parathion in tomato epicuticular waxes. J Agric Food Chem 54(2):474-479.

+*Fukuyama T, Kosaka T, Hayashi K, et al. 2012. Immunotoxicity in mice induced by short-term exposure to methoxychlor, parathion, or piperonyl butoxide. J Immunotoxicol 10(2):150-159.

+*Fukuyama T, Kosaka T, Tajima Y, et al. 2010. Prior exposure to organophosphorus and organochlorine pesticides increases the allergic potential of environmental chemical allergens in a local lymph node assay. Toxicol Lett 199(3):347-356.

+*Fukuyama T, Tajima Y, Ueda H, et al. 2011. Prior exposure to immunosuppressive organophosphorus or organochlorine compounds aggravates the T(H)1- and T(H)2-type allergy caused by topical sensitization to 2,4-dinitrochlorobenzene and trimellitic anhydride. J Immunotoxicol 8(2):170-182.

*Funckes AJ, Hayes GR, Jr., Hartwell WV. 1963. Urinary excretion of paranitrophenol by volunteers following dermal exposure to parathion at different ambient temperatures. J Agric Food Chem 11(6):455-457.

*Furlong CE, Li WF, Brophy VH, et al. 2000. The PON1 gene and detoxication. Neurotoxicology 21(4):581-587.

*Funari R, B. DV, Schiavo L, et al. 2013. Detection of parathion pesticide by quartz crystal microbalance functionalized with UV-activated antibodies. Anal Chem 85(13):6392-6397.

*Gagne J, Brodeur J. 1972. Metabolic studies on the mechanisms of increased susceptibility of weanling rats to parathion. Can J Physiol Pharmacol 50(9):902-915.

+*Gaines TB. 1960. The acute toxicity of pesticides to rats. Toxicol Appl Pharmacol 2:88-99.

+*Gaines TB, Linder RE. 1986. Acute toxicity of pesticides in adult and weanling rats. Fundam Appl Toxicol 7(2):299-308.

*Gallo MA, Lawryk NJ. 1991. Organic phosphorus pesticides. In: Hayes WJ, Laws ER, eds. Handbook of pesticide toxicology, classes of pesticides. New York: Academic Press Inc., 1040-1049, 1091-1123.

*Garcia-Repetto R, Gimenez MP, Repetto M. 2001. New method for determination of ten pesticides in human blood. J AOAC Int 84(2):342-349.

*Garcia-Repetto R, Martinez D, Repetto M. 1995. Coefficient of distribution of some organophosphorous pesticides in rat tissue. Vet Hum Toxicol 37(3):226-229.

*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1986a. Pesticides, selected elements, and other chemicals in infant and toddler total diet samples, October 1980-March 1982. J Assoc Off Anal Chem 69(1):123-145.

*Gartrell MJ, Craun JC, Podrebarac DS, et al. 1986b. Pesticides, selected elements, and other chemicals in adult total diet samples, October 1980-March 1982. J Assoc Off Anal Chem 69(1):146-161.

*Gearhart JM, Jepson GW, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic model for the inhibition of acetylcholinesterase by organophosphate esters. Environ Health Perspect 102(11):51-60.

*Gentry PR, Hack CE, Haber L, et al. 2002. An approach for the quantitative consideration of genetic polymorphism data in chemical risk assessment: Examples with warfarin and parathion. Toxicol Sci 70(1):120-139.

*Gerstl Z, Mingelgrin U. 1984. Sorption of organic substances by soils and sediments. J Environ Sci Health B19(3):297-312.

*Gerstl Z, Yaron B, Nye PH. 1979. Diffusion of a biodegradable pesticide. I. In a biologically inactive soil. Soil Sci Soc Am J 43:839-842.

*Gilot-Delhalle J, Colizzi A, Moutschen J, et al. 1983. Mutagenicity of some organophosphorus compounds at the *ade6* locus of *Schizosaccharomyces pombe*. Mutat Res 117:139-148.

*Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect 101(Supp 2):65-71.

*Glooschenko WA, Strachan WMJ, Sampson RCL. 1976. Residues in water. Distribution of pesticides and polychlorinated biphenyls in water, sediments, and seston of the Upper Great Lakes, 1974. Pestic Monit J 10(2):61-67.

*Glotfelty DE, Majewski MS, Seiber JN. 1990. Distribution of several organophosphorus insecticides and their oxygen analogues in a foggy atmosphere. Environ Sci Technol 24(3):353-357.

*Gosselin NH, Bouchard M, Brunet RC, et al. 2005. Toxicokinetic modeling of parathion and its metabolites in humans for the determination of biological reference values. Toxicol Mech Methods 15(1):33-52.

*Gramatica P, Corradi M, Consonni V. 2000. Modelling and prediction of soil sorption coefficients of non-ionic organic pesticides by molecular descriptors. Chemosphere 41:763-777.

*Grob D, Garlick WL, Harvey AM. 1950. The toxic effects in man of the anticholinesterase insecticide parathion (p-nitrophenol diethyl thionophosphate). Johns Hopkins Med J 87:106-129.

*Gunderson EL. 1988. FDA Total Diet Study, April 1982-April 1984, dietary intakes of pesticides, selected elements, and other chemicals. J Assoc Off Anal Chem 71(6):1200-1209.

*Gunderson EL. 1995. FDA total diet study, July 1986-April 1991, dietary intakes of pesticides, selected elements, and other chemicals. J Assoc Off Anal Chem Int 78(6):1353-1362.

*Guzelian PS, Henry CJ, Olin SS. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences and Press Institute Press.

*Haber LT, Maier A, Gentry PR, et al. 2002. Genetic polymorphisms in assessing interindividual variability in delivered dose. Regul Toxicol Pharmacol 35(2 Pt 1):177-197.

*Hall RJ, Kolbe E. 1980. Bioconcentration of organophosphorus pesticides to hazardous levels by amphibians. J Toxicol Environ Health 6(4):853-860.

*Hankemeier T, Louter AJH, Rinkema FD, et al. 1995. On-line coupling of solid-phase extraction and gas chromatography with atomic emission detection for analysis of trace pollutants in aqueous samples. Chromatographia 40(3/4):119-124.

*Harbison RD. 1975. Comparative toxicity of some selected pesticides in neonatal and adult rats. Toxicol Appl Pharmacol 32(2):443-446.

*Hartwell WV, Hayes GR, Jr., Funckes AJ. 1964. Respiratory exposure to volunteers to parathion. Arch Environ Health 8:820-825.

+*Hayes G, Funckes AJ, Hartwell WV. 1964. Dermal exposure of human volunteers to parathion. Arch Environ Health 8:829-833.

*HazDat. 2007. Parathion. HazDat Database: ATSDR's Hazardous Substance Release and Health Effects Database. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

*He F, Xu H, Qin F, et al. 1998. Intermediate myasthenia syndrome following acute organophosphates poisoning--an analysis of 21 cases. Hum Exp Toxicol 17(1):40-45.

*HHS. 2009. Public welfare. Protection of human subjects. U.S. Department of Health & Human Services. Code of Federal Regulations 45 CFR 46, Subpart C. http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc. May 14, 2014.

*Hochreiter JJ. 1982. Chemical-quality reconnaissance of the water and surficial bed material in the Delaware River estuary and adjacent New Jersey tributaries, 1980-1981. Trenton, NJ: U.S. Geological Survey, Water Resources Division.

*Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J Natl Cancer Inst 84(5):313-320.

*Hoffman RS, Capel PD, Larson SJ. 2000. Comparison of pesticides in eight U.S. urban streams. Environ Toxicol Chem 19(9):2249-2258.

*Hoffmann U, Papendorf T. 2006. Organophosphate poisonings with parathion and dimethoate. Intensive Care Med 32(3):464-468.

*Hollingworth RM, Alstott RL, Litzenberg RD. 1973. Glutathione S-aryl transferase in the metabolism of parathion and its analogs. Life Sci 13(3):191-199.

*Holstege DM, Scharberg DL, Richardson ER, et al. 1991. Multiresidue screen for organophosphorus insecticides using gel permeation chromatography- silica gel cleanup. J Assoc Off Anal Chem 74(2):394-399.

*Hong J, Eo Y, Rhee J, et al. 1993. Simultaneous analysis of 25 pesticides in crops using gas chromatography and their identification by gas chromatography-mass spectrometry. J Chromatogr 639:261-271.

*Hopper ML. 1988. Improved method for partition of organophosphate pesticide residues on a solid phase partition column. J Assoc Off Anal Chem 71(4):731-734.

*Hoppin JA, Umbach DM, London SJ, et al. 2006. Pesticides and adult respiratory outcomes in the Agricultural Health Study. Ann N Y Acad Sci 1076:343-354.

*Hoppin JA, Umbach DM, London SJ, et al. 2009. Pesticide use and adult-onset asthma among male farmers in the Agricultural Health Study. Eur Respir J 34(6):1296-1303.

*House WA, Rae JE, Kimblin RT. 1992. Source-sediment controls on the riverine transport of pesticides. Brighton Crop Protection Conference- Pests and Diseases-1992, 865-870.

*HSDB. 2013. Parathion. Hazardous Substances Data Bank, National Library of Medicine. http://toxnet.nlm.nih.gov. June 03, 2013.

*Hsu JP, Schattenberg HJ, III, Garza MM. 1991. Fast turnaround multiresidue screen for pesticides in produce. J Assoc Off Anal Chem 74(5):886-892.

*Hunter CL, Stephenson MD, Tjeerdema RS, et al. 1995. Contaminants in oysters in Kaneohe Bay, Hawaii. Mar Pollut Bull 30(10):646-654.

*Hurh E, Lee E, Lee A, et al. 2000. Effects of enzyme inducers or inhibitors on the pharmacokinetics of intravenous parathion in rats. Biopharm Drug Dispos 21(5):193-204.

*IARC. 1983. Parathion in animals. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Lyon, France: International Agency for Research on Cancer, 162-163.

*IARC. 2013. Agents classified by the IARC monographs. Volumes 1–107. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Classification/index.php. April 24, 2013.

*IPCS. 2005. Methyl parathion. ICSC: 0626. International Chemical Safety Cards (ICSCs). International Programme on Chemical Safety. http://www.inchem.org/documents/icsc/icsc/eics0626.htm. August 25, 2014.

*IRIS. 2003. Parathion. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/iris/. April 24, 2013.

+*Ivens IA, Schmuck G, Machemer L. 1998. Learning and memory of rats after long-term administration of low doses of parathion. Toxicol Sci 46(1):101-111.

*James MO. 1994. Pesticide metabolism in aquatic organisms. In: Chemistry of plant protection. Vol. 9. Berlin Heidelberg: Springer-Verlag, 153-189.

*Jepson GW, Hoover DK, Black RK, et al. 1994. A partition coefficient determination method for nonvolatile chemicals in biological tissues. Fundam Appl Toxicol 22(4):519-524.

*Johnson MK. 1975. Organophosphorus esters causing delayed neurotoxic effects. Mechanism of action and structure/activity studies. Arch Toxicol 34:259-288.

*Jury WA, Spencer WF, Farmer WJ. 1984. Behavior assessment model for trace organics in soil: III. Application of screening model. J Environ Qual 13(4):573-579.

*Kacham R, Karanth S, Baireddy P, et al. 2006. Interactive toxicity of chlorpyrifos and parathion in neonatal rats: Role of esterases in exposure sequence-dependent toxicity. Toxicol Appl Pharmacol 210(1-2):142-149.

*Kadenczki L, Arpad Z, Gardi I. 1992. Column extraction of residues of several pesticides from fruits and vegetables: A simple multiresidue analysis method. J Assoc Off Anal Chem Int 751(1):53-61.

*Kadoum AM, Mock DE. 1978. Herbicide and insecticide residues in trailwater pits: Water and pit bottom soil from irrigated corn and sorghum fields. J Agric Food Chem 26(1):45-50.

*Kamataki T, Lee Lin MCM, Belcher DH, et al. 1976. Studies of the metabolism of parathion with an apparently homogeneous preparation of rabbit liver cytochrome P-450. Drug Metab Dispos 4(2):180-189.

*Karanth S, Pope C. 2000. Carboxylesterase and *A*-esterase activities during maturation and aging: Relationship to the toxicity of chlorpyrifos and parathion in rats. Toxicol Sci 58(2):282-289.

*Karanth S, Olivier K, Jr., Liu J, et al. 2001. *In vivo* interaction between chlorpyrifos and parathion in adult rats: Sequence of administration can markedly influence toxic outcome. Toxicol Appl Pharmacol 177(3):247-255.

*Kearns GL, Abdel-Rahman SM, Alander SW, et al. 2003. Developmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med 349(12):1157-1167.

*Kenaga EE. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol Environ Saf 4:26-38.

*Kevekordes S, Gebel T, Pav K, et al. 1996. Genotoxicity of selected pesticides in the mouse bone-marrow micronucleus test and in the sister-chromatid exchange test with human lymphocytes *in vitro*. Toxicol Lett 89(1):35-42.

+*Kim DO, Lee SK, Jeon TW, et al. 2005. Role of metabolism in parathion-induced hepatotoxicity and immunotoxicity. J Toxicol Environ Health A 68(23-24):2187-2205.

*Kissel JC, Curl CL, Kedan G, et al. 2005. Comparison of organophosphorus pesticide metabolite levels in single and multiple daily urine samples collected from preschool children in Washington State. J Expo Anal Environ Epidemiol 15(2):164-171.

*Knaak JB, Yee K, Ackerman CR, et al. 1984. Percutaneous absorption and dermal dose-cholinesterase response studies with parathion and carbaryl in the rat. Toxicol Appl Pharmacol 76(2):252-263.

*Kojima H, Katsura E, Takeuchi S, et al. 2004. Screening for estrogen and androgen receptor activities in 200 pesticides by *in vitro* reporter gene assays using Chinese hamster ovary cells. Environ Health Perspect 112(5):524-531.

*Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. Biochemistry 29(18):4430-4433.

*Krapac IG, Roy WR, Smyth CA, et al. 1995. Occurrence and distribution of pesticides in soil at agrichemical facilities in Illinois. J Soil Contam 4(3):209-226.

*Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.

*Krishnan K, Anderson ME, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures. Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

*Kuntz DJ, Rao NG, Berg IE, et al. 1990. Toxicity of mixtures of parathion, toxaphene and/or 2,4-D in mice. J Appl Toxicol 10(4):257-266.

*Kutz FW, Yobs AR, Yang HSC. 1976. National pesticide monitoring programs. In: Air pollution from pesticides and agricultural processes. Cleveland, OH: CRC Press, 95-136.

*Kwakman PJM, Vreuls JJ, Brinkman UA, et al. 1992. Determination of organophosphorus pesticides in aqueous samples by on-line membrane disk extraction and capillary gas chromatography. Chromatographia 34(1/2):41-47.

*Lam RHF, Brown JP, Fan AM. 1994. Chemicals in California drinking water: Source of contamination, risk assessment, and drinking water standards. In: Wang RGM, ed. Water contamination and health. New York, NY: Marcel Dekker, Inc., 15-44.

*Lambropoulou DA, Albanis TA. 2003. Headspace solid-phase microextraction in combination with gas chromatography-mass spectrometry for the rapid screening of organophosphorus insecticide residues in strawberries and cherries. J Chromatogr A 993:197-203.

*Lankisch PG, Muller CH, Niederstadt H, et al. 1990. Painless acute pancreatitis subsequent to anticholinesterase insecticide (parathion) intoxication. Am J Gastroenterol 85(7):872-875.

*Lartiges SB, Garrigues PP. 1995. Degradation kinetics of organophosphorus and organonitrogen pesticides in different waters under various environmental conditions. Environ Sci Technol 29(5):1246-1254.

*Lassiter TL, Ryde IT, Levin ED, et al. 2010. Neonatal exposure to parathion alters lipid metabolism in adulthood: Interactions with dietary fat intake and implications for neurodevelopmental deficits. Brain Res Bull 81(1):85-91.

*Lassiter TL, Ryde IT, MacKillop EA, et al. 2008. Exposure of neonatal rats to parathion elicits sex-selective reprogramming of metabolism and alters the response to a high-fat diet in adulthood. Environ Health Perspect 116:1456-1462.

*LeBel GL, Williams DT, Griffith G, et al. 1979. Isolation and concentration of organophosphorus pesticides from drinking water at the ng/L level, using macroreticular resin. J Assoc Off Anal Chem 62(2):241-249.

*Lee P, Rhodes SL, Sinsheimer JS, et al. 2013. Functional paraoxonase 1 variants modify the risk of Parkinson's disease due to organophosphate exposure. Environ Int 56:42-47.

*Lee SM, Papathakis ML, Feng HC, et al. 1991. Multipesticide residue method for fruits and vegetables: California Department of Food and Agriculture. Fresenius J Anal Chem 339:376-383.

*Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44(1):55-77.

*Leoni V. 1992. Multiresidue method for quantitation of organophosphorus pesticides in vegetable and animal foods. J Assoc Off Anal Chem Int 75(3):511-518.

*Lessire F, Gustin P, Delaunois A, et al. 1996. Relationship between parathion and paraoxon toxicokinetics, lung metabolic activity, and cholinesterase inhibition in guinea pig and rabbit lungs. Toxicol Appl Pharmacol 138(2):201-210.

*Leung H. 1993. Physiologically-based pharmacokinetic modelling. In: Ballantyne B, Marrs T, Turner P, eds. General and applied toxicology. Vol. 1. New York, NY: Stockton Press, 153-164.

*Levin ED, Timofeeva OA, Yang L, et al. 2010. Early postnatal parathion exposure in rats causes sex-selective cognitive impairment and neurotransmitter defects which emerge in aging. Behav Brain Res 208(2):319-327.

*Lewis RG, Lee RE, Jr. 1976. Air pollution from pesticides. In: Air pollution from pesticides and agricultural processes. Cleveland, OH: CRC Press, 5-51.

*Liao W, Joe T, Cusick WG. 1991. Multiresidue screening method for fresh fruits and vegetables with gas chromatographic/mass spectrometric detection. J Assoc Off Anal Chem 74(3):554-565.

*Liu J, Gupta RC, Goad JT, et al. 2007. Modulation of parathion toxicity by glucose feeding: Is nitric oxide involved? Toxicol Appl Pharmacol 219(2-3):106-113.

*Liu J, Karanth S, Pope C. 2005. Dietary modulation of parathion-induced neurotoxicity in adult and juvenile rats. Toxicology 210(2-3):135-145.

*Livingston AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4(2-3):301-324.

*Lores EM, Bradway DE, Moseman RF. 1978. Organophosphorus pesticide poisonings in humans: Determination of residues and metabolites in tissues and urine. Arch Environ Health 33(5):270-276.

*Luke MA, Masumoto HT, Cairns T, et al. 1988. Levels and incidences of pesticide residues in various foods and animal feeds analyzed by the Luke Multiresidue Methodology for fiscal years 1982-1986. J Assoc Off Anal Chem 71(2):415-420.

*Ma T, Chambers JE. 1994. Kinetic parameters of desulfuration and dearylation of parathion and chlorpyrifos by rat liver microsomes. Food Chem Toxicol 32(8):763-767.

*MacCrawford J, Hoppin JA, Alavanja MCR, et al. 2008. Hearing loss among licensed pesticide applicators in the Agricultural Health Study. J Occup Environ Med 50(7):817-826.

*Maddy KT, Fong HR, Lowe JA, et al. 1982. A study of well water in selected California communities for residues of 1,3-dichloropropene, chloroallyl alcohol and 49 organophosphate or chlorinated hydrocarbon pesticides. Bull Environ Contam Toxicol 29(3):354-359.

*Maibach HI, Feldman RJ, Milby TH, et al. 1971. Regional variation in percutaneous penetration in man. Pesticides. Arch Environ Health 23(3):208-211.

*Mansour M, Thaller S, Korte F. 1983. Action of sunlight on parathion. Bull Environ Contam Toxicol 30(3):358-364.

*Manthripragada AD, Costello S, Cockburn MG, et al. 2010. Paraoxonase 1, agricultural organophosphate exposure, and Parkinson disease. Epidemiology 21(1):87-94.

*Maroni et al. 2000. Organophosphorous pesticides. Toxicology 143:9-37.

*Mattern GC, Louis JB, Rosen JD. 1991. Multipesticide determination in surface water by gas chromatography/chemical ionization/mass spectrometry/ion trap detection. J Assoc Off Anal Chem 74(6):982-986.

*Maxwell DM, Lenz DE, Groff WA, et al. 1987. The effects of blood flow and detoxification on *in vivo* cholinesterase inhibition by soman in rats. Toxicol Appl Pharmacol 88:66-76.

*Mayr U, Butsch A, Schneider S. 1992. Validation of two *in vitro* test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74(2-3):135-149.

*Medina D, Prieto A, Ettiene G, et al. 1999. Persistence of organophosphorus pesticide residues in Limon River waters. Bull Environ Contam Toxicol 63:39-44.

*Mehrani H, Asadi B, Golmanesh L. 2008. Protective effects of mecamylamine and atropine against $\alpha_4\beta_2$ nicotinic receptor expression and functional toxicity in paraoxon-treated rats. Environ Toxicol Pharmacol 26: 247-254.

*Meylan WM, Howard PH. 1993. Computer estimation of the atmospheric gas-phase reaction rate of organic compounds with hydroxyl radicals and ozone. Chemosphere 26(12):2293-2299.

*Milby TH, Ottoboni F, Mitchell HW. 1964. Parathion residue poisoning among orchard workers. J Am Med Assoc 189(5):351-356.

*Miles JRW, Harris CR. 1978. Insecticide residues in organic soils of six vegetable growing areas in southwestern Ontario, 1976. J Environ Sci Health B13(3):199-209.

*Miles JRW, Tu CM, Harris CR. 1979. Persistence of eight organophosphorus insecticides in sterile and non-sterile mineral and organic soils. Bull Environ Contam Toxicol 22:312-318.

*Miller MA, Kasting GB. 2010. Toward a better understanding of pesticide dermal absorption: Diffusion model analysis of parathion absorption *in vitro* and *in vivo*. J Toxicol Environ Health A 73(4):284-300.

*Mingelgrin U, Gerstl Z. 1983. Reevaluation of partitioning as a mechanism of nonionic chemicals adsorption in soils. J Environ Qual 12(1):1-11.

*Mohn G. 1973. 5-Methyltryptophan resistance mutations in *Escherichia coli* K-12. Mutagenic activity of monofunctional alkylating agents including organophosphorus insecticides. Mutat Res 20(1):7-15.

*Moody RP, Akram M, Dickson E, et al. 2007. *In vitro* dermal absorption of methyl salicylate, ethyl parathion, and malathion: First responder safety. J Toxicol Environ Health A 70(12):985-999.

*Moreale A, Van Bladel R. 1983. [Transport vertical de solutes vers les eaux souterraines. Une approche sur colonne de sol non perturbe]. Rev Agric 6:1669-1676. (French)

+*Morgan DP, Hetzler HL, Slach EF, et al. 1977. Urinary excretion of paranitrophenol and alkyl phosphates following ingestion of methyl or ethyl parathion by human subjects. Arch Environ Contam Toxicol 6(2-3):159-173.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokinet 5(6):485-527.

+*Moser VC. 1995. Comparisons of the acute effects of cholinesterase inhibitors using a neurobehavioral screening battery in rats. Neurotoxicol Teratol 17(6):617-625.

*Mota LC, Hernandez JP, Baldwin WS. 2010. Constitutive androgen receptor-null mice are sensitive to the toxic effects of parathion: Association with reduced cytochrome p450-mediated parathion metabolism. Drug Metab Dispos 38(9):1582-1588.

*Musshoff F, Junker H, Madea B. 2002. Simple determination of 22 organophosphorous pesticides in human blood using headspace solid-phase microextraction and gas chromatography with mass spectrometric detection. J Chromatogr Sci 40:29-34.

*Mutch E, Williams FM. 2006. Diazinon, chlorpyrifos and parathion are metabolised by multiple cytochromes P450 in human liver. Toxicology 224(1-2):22-32.

*Mutch E, Blain PG, Williams FM. 1999. The role of metabolism in determining susceptibility to parathion toxicity in man. Toxicol Lett 107(1-3):177-187.

*Mutch E, Daly AK, Leathart JB, et al. 2003. Do multiple cytochrome P450 isoforms contribute to parathion metabolism in man? Arch Toxicol 77(6):313-320.

*Nabb DP, Stein WJ, Hayes WJ, Jr. 1966. Rate of skin absorption of parathion and paraoxon. Arch Environ Health 12(4):501-505.

*Namba T, Nolte CT, Jackrel J, et al. 1971. Poisoning due to organophosphate insecticides. Acute and chronic manifestations. Am J Med 50(4):475-492.

*NAS/NRC. 1989. Report of the oversight committee. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

+*NCI. 1979. Bioassay of parathion for possible carcinogenicity. National Cancer Institute. Tech Rep Ser 70:1-123.

*Neal RA. 1967. Studies on the metabolism of diethyl 4-nitrophenyl phosphorothionate (parathion) *in vitro*. Biochem J 103(1):183-191.

*Needham LL, Blount B, Rogers HS, et al. 2000. Levels of selected nonpersistent endocrine disrupters in humans. ACS Symp Ser 747(Analysis of Environmental Endocrine Disruptors):147-157.

*Nielsen P, Friis C, Gyrd-Hansen N, et al. 1991. Disposition of parathion in neonatal and young pigs. Pharmacol Toxicol 69(4):233-237.

*NIH. 2014. The Agricultural Health Study. National Institute of Health and National Institute of Environmental Health Sciences in collaboration with the U.S. Environmental Protection Agency and National Institute for Occupational Safety and Health. http://aghealth.nih.gov/. August 25, 2014.

+*NIOSH. 1974. Inhalation and oral studies of ethyl parathion administered acutely and sub-acutely to the rat and dog. National Institute of Occupational Safety and Health.

*NIOSH. 1994. NIOSH manual of analytical methods. Method 5600 organophosphorus pesticides. National Institute of Occupational Safety and Health.

*NIOSH. 2009. Phosphorothioic acid, O,O-diethyl O-(p-nitrophenyl) ester. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh-rtecs/tf456d70.html. July 26, 2013.

*NIOSH. 2011. Parathion. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. http://www.cdc.gov/niosh/npg/. April 24, 2013.

*NIOSH. 2013. Phosphorothioic acid, 0,0-diethyl 0-(p-nitrophenyl) ester. National Institute for Occupational Safety and Health. http://ww.cdc.gov/niosh-rtecs/tf456d70.html. May 14, 2013.

*Nishio A, Uyeki EM. 1981. Induction of sister chromatid exchanges in Chinese hamster ovary cells by organophosphate insecticides and their oxygen analogs. J Toxicol Environ Health 8(5-6):939-946.

*Nisse P, Forceville X, Cezard C, et al. 1998. Intermediate syndrome with delayed distal polyneuropathy from ethyl parathion poisoning. Vet Hum Toxicol 40(6):349-352.

*Noort D, Hulst AG, van Zuylen A, et al. 2009. Covalent binding of organophosphorothioates to albumin: A new perspective for OP-pesticide biomonitoring? Arch Toxicol 83(11):1031-1036.

*Norman BJ, Neal RA. 1976. Examination of the metabolism *in vitro* of parathion (diethyl p-nitrophenyl phosphorothionate) by rat lung and brain. Biochem Pharmacol 25(1):37-45.

*NRC. 1993. Pesticides in the diets of infants and children. Washington, DC: National Research Council.

*NRC. 2004. Executive summary and recommendations. In: Intentional human dosing studies for EPA regulatory purposes: Scientific and ethical issues. National Research Council. National Academy of Sciences, 1-20. http://www.nap.edu/catalog.php?record_id=10927. May 14, 2014.

*NTP. 2011. Report on carcinogens. 12th edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. http://ntp-server.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf. April 24, 2013.

*Olivier K, Liu J, Karanth S, et al. 2001. Glucose feeding exacerbates parathion-induced neurotoxicity. J Toxicol Environ Health A 63:253-271.

*Olsson AO, Nguyen JV, Sadowski MA, et al. 2003. A liquid chromatography/electrospray ionization-tandem mass spectrometry method for quantification of specific organophosphorus pesticide biomarkers in human urine. Anal Bioanal Chem 376(6):808-815.

*O'Neil MJ, Heckelman PE, Dobbelaar PH, et al. 2013. Parathion. In: O'Neil MJ, Heckelman PE, Dobbelaar PH, et al., eds. The Merck index. An encyclopedia of chemicals, drugs, and biologicals. 15th ed. Whitehouse Station, NJ: RSC Publishing, 1306.

*Oneto ML, Basack SB, Kesten EM. 1995. Total and conjugated urinary paranitrophenol after an acute parathion ingestion. Sci Justice 35(3):207-211.

*OSHA. 1986. Chlorpyrifos (dursban), DDVP (dichlorvos), diazinon, malathion, and parathion. Occupational Safety and Health Administration, U.S. Department of Labor. http://www.osha.gov/dts/sltc/methods/organic/org062/org062.html. March 02, 2006.

*OSHA. 2013a. List of highly hazardous chemicals, toxics, and reactives. Occupational safety and health standards. Occupational Safety and Health Administration. Code of Federal Regulations 29 CFR 1910.119, Appendix A. http://www.osha.gov/law-regs.html. April 24, 2013.

*OSHA. 2013b. Toxic and hazardous substances. Occupational safety and health standards. Occupational Safety and Health Administration. Code of Federal Regulations 29 CFR 1910.1000, Table Z-1. http://www.osha.gov/law-regs.html. April 24, 2013.

*Osmundson M. 1998. Insecticides and pesticides. In: Viccelllio P, ed. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers, 401-413.

*Owen GM, Brozek J. 1966. Influence of age, sex and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 222-238.

*Ownby DR, Trimble TA, Cole KA, et al. 2004. Pesticide residues in water, sediment, and fish at the Sparta, IL, USA, National Guard Armory. Bull Environ Contam Toxicol 73:802-809.

*Padungtod C, Savitz DA, Overstreet JW, et al. 2000. Occupational pesticide exposure and semen quality among Chinese workers. J Occup Environ Med 42(10):982-992.

+*Pasquet J, Mazuret A, Fournel J, et al. 1976. Acute oral and percutaneous toxicity of phosalone in the rat, in comparison with azinphosmethyl and parathion. Toxicol Appl Pharmacol 37(1):85-92.

+*Pauluhn J, Machemer L, Kimmerle G. 1987. Effects of inhaled cholinesterase inhibitors on bronchial tonus and on plasma and erythrocyte acetylcholine esterase activity in rats. Toxicology 46(2):177-190.

*Petrikovics I, Hong K, Omburo G, et al. 1999. Antagonism of paraoxon intoxication by recombinant phosphotriesterase encapsulated within sterically stabilized liposomes. Toxicol Appl Pharmacol 156(1):56-63.

*PhysProp. 2013. Parathion. http://www.syrres.com/what-we-do/databaseforms.aspx?id=386. June 05, 2013.

*Pla A, Johnson MK. 1989. Degradation by rat tissues *in vitro* of organophosphorus esters which inhibit cholinesterase. Biochem Pharmacol 38(9):1527-1533.

*Plastourgou M, Hoffmann MR. 1984. Transformation and fate of organic esters in layered-flow systems: The role of trace metal catalysis. Environ Sci Technol 18(10):756-764.

*Poore RE, Neal RA. 1972. Evidence for extrahepatic metabolism of parathion. Toxicol Appl Pharmacol 23:759-768.

*Pope CN, Chakraborti TK. 1992. Dose-related inhibition of brain and plasma cholinesterase in neonatal and adult rats following sublethal organophosphate exposures. Toxicology 73(1):35-43.

*Pope CN, Chakraborti TK, Chapman ML, et al. 1991. Comparison of *in vivo* cholinesterase inhibition in neonatal and adult rats by three organophosphorothioate insecticides. Toxicology 68(1):51-61.

*Puga FR, Rodrigues MA. 1996. Evaluation of the role of formulation on parathion toxicity. Ecotoxicol Environ Saf 35(1):38-40.

*Qiao GL, Riviere JE. 1995. Significant effects of application site and occlusion on the pharmacokinetics of cutaneous penetration and biotransformation of parathion in vivo in swine. J Pharm Sci 84(4):425-432.

*Qiao GL, Brooks JD, Baynes RE, et al. 1996. The use of mechanistically defined chemical mixtures (MDCM) to assess component effects on the percutaneous absorption and cutaneous disposition of topically exposed chemicals. I. Studies with parathion mixtures in isolated perfused porcine skin. Toxicol Appl Pharmacol 141(2):473-486.

*Qiao GL, Williams PL, Riviere JE. 1994. Percutaneous absorption, biotransformation, and systemic disposition of parathion *in vivo* in swine. I. Comprehensive pharmacokinetic model. Drug Metab Dispos 22(3):459-471.

*Quinby GE, Lemmon AB. 1958. Parathion residues as a cause of poisoning in crop workers. J Am Med Assoc 166(7):740-746.

*Rao PSC, Hornsby AG, Jessup RE. 1985. Indices for ranking the potential for pesticide contamination of groundwater. Proceedings of the Soil and Crop Science Society of Florida 44:1-8.

*Rauh V, Arunajadai S, Horton M, et al. 2011. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. Environ Health Perspect 119(8):1196-1201.

+*Reischl P, Van Gelder GA, Karas GG. 1975. Auditory detection behavior in parathion-treated squirrel monkeys (*Saimiri sciureus*). Toxicol Appl Pharmacol 34(1):88-101.

+*Reiter L, Talens G, Woolley D. 1973. Acute and subacute parathion treatment: Effects on cholinesterase activities and learning in mice. Toxicol Appl Pharmacol 25(4):582-588.

+*Reiter LW, Talens GM, Woolley DE. 1975. Parathion administration in the monkey: Time course of inhibition and recovery of blood cholinesterases and visual discrimination performance. Toxicol Appl Pharmacol 33(1):1-13.

+*Renhof M. 1984. Parathion. Study for embryotoxic effects on rats after oral administration. Report no. 12909. Wuppertal-Elberfeld: Bayer Institute of Toxicology.

+*Renhof M. 1985. Parathion. Study for embryotoxic effects on rabbits after oral administration. Report no. 13288. Wuppertal-Elberfeld: Bayer Institute of Toxicology.

*RePORTER. 2013. Parathion. National Institutes of Health, Research Portfolio Online Reporting Tools. http://projectreporter.nih.gov/reporter.cfm. August 28, 2013.

+*Rider JA, Moeller HC, Puletti EJ, et al. 1969. Toxicity of parathion, systox, octamethyl pyrophosphoramide, and methyl parathion in man. Toxicol Appl Pharmacol 14(3):603-611.

*Roy RR, Wilson PD, Laski RR, et al. 1997. Monitoring of domestic and imported apples and rice by the U.S. Food and Drug Administration Pesticide Program. J Assoc Off Anal Chem Int 80(4):883-894.

*Rupa DS, Rita P, Reddy PP, et al. 1988. Screening of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes of vegetable garden workers. Hum Toxicol 7(4):333-336.

*Sabljić A, Güsten H, Verhaar H, et al. 1995. QSAR modelling of soil sorption. Improvements and systematics of log KOC vs. log KOW correlations. Chemosphere 31(11–12):4489-4514.

*Saffih-Hdadi K, Bruckler L, Barriuso E. 2003. Modeling of sorption and biodegradation of parathion and its metabolite paraoxon in soil. J Environ Qual 32:2207-2211.

*Sakellarides TM, Siskos MG, Albanis TA. 2003. Photodegradation of selected organophosphorus insecticides under sunlight in different natural waters and soils. Int J Environ Anal Chem 83(1):33-50.

*Saltzman S, Mingelgrin U. 1984. Nonbiological degradation of pesticides in the unsaturated zone. Ecol Stud 47:153-161.

*Sanders PF, Seiber JN. 1983. A chamber for measuring volatilization of pesticides from model soil and water disposal systems. Chemosphere 12(7/8):999-1012.

*Sanders PF, Seiber JN. 1984. Organophosphorus pesticide volatilization. Model soil pits and evaporation ponds. ACS Symposium Series. Treatment and disposal of pesticide wastes 259:279-295.

*Saunders NR, Ek CJ, Habgood MD, et al. 2008. Barriers in the brain: A renaissance? Trends Neurosci 31(6):279-286.

*Saunders NR, Liddelow SA, Dziegielewska KM. 2012. Barrier mechanisms in the developing brain. Front Pharmacol 3(10.3389/fphar.2012.00046):Article 46.

*Schattenberg HJ, III, Hsu JP. 1992. Pesticide residue survey of produce from 1989 to 1991. J AOAC Int 75(5):925-933.

*Scheuplein R, Charnley G, Dourson M. 2002. Differential sensitivity of children and adults to chemical toxicity. I. Biological basis. Regul Toxicol Pharmacol 35(3):429-447.

*Schulze JA, Manigold DB, Andrews FL. 1973. Pesticides in water. Pesticides in selected western streams, 1968-1971. Pestic Monit J 7(1):73-84.

*Schuurmann G, Ebert R, Kuhne R. 2006. Prediction of the sorption of organic compounds into soil organic matter from molecular structure. Environ Sci Technol 40(22):7005-7011.

*Seiber JN, Woodrow JE. 1984. Airborne residues and human exposure. Stud Environ Sci 24:133-146.

*Seiber JN, Glotfelty DE, Lucas AD, et al. 1990. A multiresidue method by high performance liquid chromatography-based fractionation and gas chromatographic determination of trace levels of pesticides in air and water. Arch Environ Contam Toxicol 19:583-592.

*Seiber JN, Wilson BW, McChesney MM. 1993. Air and fog deposition of four organophosphate insecticides used on dormant orchards in the San Joaquin Valley, California. Environ Sci Technol 27(10):2236-2243.

*Senanayake N, Karalliedde L. 1987. Neurotoxic effects of organophosphorus insecticides. N Engl J Med 316:761-763.

*Setchell BP, Waites GMH. 1975. The blood testis barrier. In: Creep RO, Astwood EB, Geiger SR, eds. Handbook of physiology: Endocrinology V. Washington, DC: American Physiological Society, 143-172.

*Sethunathan N, Siddaramappa R, Rajaram KP, et al. 1977. Parathion: Residues in soil and water. Residue Rev 68:91-122.

*Sharom MS, Miles JRW, Harris CR, et al. 1980. Behavior of 12 insecticides in soil and aqueous suspensions of soil and sediment. Water Res 14:1095-1100.

*Shehata-Karam H, Monteiro-Riviere NA, Guthrie FE. 1988. *In vitro* penetration of pesticides through human newborn foreskin. Toxicol Lett 40(3):233-239.

*Sigma-Aldrich. 2014. Parathion. 45607 Fluka. Sigma-Aldrich Co., LLC. http://www.sigmaaldrich.com/catalog/product/fluka/45607?lang=en&region=US. August 25, 2014.

*Simcox NJ, Fenske RA, Wolz SA, et al. 1995. Pesticides in household dust and soil: Exposure pathways for children of agricultural families. Environ Health Perspect 103(12):1126-1134.

*Simmon VF, Poole DC, Newell GW. 1976. *In vitro* mutagenic studies of twenty pesticides. Toxicol Appl Pharmacol 37:109.

*Slotkin TA. 2011. Does early-life exposure to organophosphate insecticides lead to prediabetes and obesity? Reprod Toxicol 31(3):297-301.

*Slotkin TA, Bodwell BE, Ryde IT, et al. 2008. Exposure of neonatal rats to parathion elicits sex-selective impairment of acetylcholine systems in brain regions during adolescence and adulthood. Environ Health Perspect 116(10):1308-1314.

*Slotkin TA, Lassiter TL, Ryde IT, et al. 2009c. Consumption of a high-fat diet in adulthood ameliorates the effects of neonatal parathion exposure on acetylcholine systems in rat brain regions. Environ Health Perspect 117(6):916-922.

*Slotkin TA, Levin ED, Seidler FJ. 2006a. Comparative developmental neurotoxicity of organophosphate insecticides: Effects on brain development are separable from systemic toxicity. Environ Health Perspect 114(5):746-751.

*Slotkin TA, Levin ED, Seidler FJ. 2009a. Developmental neurotoxicity of parathion: Progressive effects on serotonergic systems in adolescence and adulthood. Neurotoxicol Teratol 31(1):11-17.

*Slotkin TA, Tate CA, Ryde IT, et al. 2006b. Organophosphate insecticides target the serotonergic system in developing rat brain regions: Disparate effects of diazinon and parathion at doses spanning the threshold for cholinesterase inhibition. Environ Health Perspect 114(10):1542-1546.

*Slotkin TA, Wrench N, Ryde IT, et al. 2009b. Neonatal parathion exposure disrupts serotonin and dopamine synaptic function in rat brain regions: Modulation by a high-fat diet in adulthood. Neurotoxicol Teratol 31(6):390-399.

*Spencer WF, Shoup TD, Clisth MM, et al. 1979. Vapor pressures and relative volatility of ethyl and methyl parathion. J Agric Food Chem 27(2):273-278.

*Srivastava SP, Agarwal DK, Mushtaq M, et al. 1976. Interaction of di-2-ethylhexyl phthalate (DEHP) with parathion in rats. Chemosphere 5(3):177-181.

*Stamper CR, Balduini W, Murphy SD, et al. 1988. Behavioral and biochemical effects of postnatal parathion exposure in the rat. Neurotoxicol Teratol 10(3):261-266.

*Stanley CW, Barney JE, Helton MR, et al. 1971. Measurement of atmospheric levels of pesticides. Environ Sci Technol 5(5):430-435.

*Starks SE, Gerr F, Kamel F, et al. 2012. Neurobehavioral function and organophosphate insecticide use among pesticide applicators in the Agricultural Health Study. Neurotoxicol Teratol 34(1):168-176.

*Stewart DKR, Chisholm, Regab MTH. 1971. Long term persistence of parathion in soil. Nature 229(5279):7.

*Sultatos LG. 1986. The effects of phenobarbital pretreatment on the metabolism and acute toxicity of the pesticide parathion in the mouse. Toxicol Appl Pharmacol 86(1):105-111.

*Sultatos LG. 1990. A physiologically based pharmacokinetic model of parathion based on chemical-specific parameters determined *in vitro*. J Am Coll Toxicol 9(6):611-619.

*Sultatos LG. 1994. Mammalian toxicology of organophosphorus pesticides. J Toxicol Environ Health 43:271-289.

*Sultatos LG, Minor LD. 1986. Factors affecting the biotransformation of the pesticide parathion by the isolated perfused mouse liver. Drug Metab Dispos 14(2):214-220.

*Tafuri J, Roberts J. 1987. Organophosphate poisoning. Ann Emerg Med 16:193-202.

*Tamura H, Yoshikawa H, Gaido KW, et al. 2003. Interaction of organophosphate pesticides and related compounds with the androgen receptor. Environ Health Perspect 111(4):545-552.

*Tang J, Rose RL, Chambers JE. 2006. Metabolism of organophosphorus and carbamate pesticides. In: Gupta RC, ed. Toxicology of organophosphate and carbamate compounds. Burlington, MA: Elsevier Academic Press, 127-143.

*Tateishi T, Nakura H, Asoh M, et al. 1997. A comparison of hepatic cytochrome P450 protein expression between infancy and postinfancy. Life Sci 61(26):2567-2574.

*Tessari JD, Spencer DL. 1971. Air sampling for pesticides in the human environment. J Assoc Off Anal Chem 54(6):1376-1382.

+*Thomas JA, Schein LG. 1974. Effect of parathion on the uptake and metabolism of androgens in rodent sex accessory organs. Toxicol Appl Pharmacol 29:53-58.

*Thomas K, Colborn T. 1992. Organochlorine endocrine disruptors in human tissue. In: Colborn T, Clement C, eds. Chemically induced alterations in sexual and functional development: The wildlife/human connection. Princeton, NJ: Princeton Scientific Publishing, 365-394.

*Timofeeva OA, Sanders D, Seemann K, et al. 2008. Persistent behavioral alterations in rats neonatally exposed to low doses of the organophosphate pesticide, parathion. Brain Res Bull 77(6):404-411.

*Tomlin CDS. 2010. Parathion. In: The e-pesticide manual. 15th ed. British Crop Production Council.

*Toyoda M, Adachi K, Ida T, et al. 1990. Simple analytical method for organophosphorus pesticide residues in milk. J Assoc Off Anal Chem 73(5):770-772.

*TRI11. 2013. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Office of Environmental Information. U.S. Environmental Protection Agency. Toxics Release Inventory. http://www.epa.gov/triexplorer/. January 15, 2013.

*Triolo AJ, Coon JM. 1966. The protective effect of aldrin against the toxicity of organophosphate anticholinesterases. J Pharmacol Exp Ther 154(3):613-623.

*Tsachalinas D, Logaras, Paradelis A. 1971. Observations on two hundred forty six cases of acute poisoning with parathion in Greece. Eur J Toxicol 4:46-49.

*Tsuda T, Aoki S, Inoue T, et al. 1995. Accumulation of IBP, parathion and EPN by killifish: Comparison of individual and mixed pesticides. Comp Biochem Physiol C 111(1):19-22.

*USGS. 2002a. Methods of analysis by the U.S. Geological Survey National Water Quality Laboratory. Determination of organophosphate pesticides in filtered water by gas chromatography with flame photometric detection. Water-resource investigation report 02-4071. U.S. Geological Survey, U.S. Department of the Interior.

*USGS. 2002b. Methods of analysis by the U.S. Geological Survey National Water Quality Laboratory. Determination of organophosphate pesticides in whole water by continuous liquid-liquid extraction and capillary-column gas chromatography with flame photometric detection. U.S. Geological Survey Method 0-3402-03. U.S. Geological Survey, U.S. Department of the Interior.

*USGS. 2002c. Methods of analysis by the U.S. Geological Survey National Water Quality Laboratory. Determination of organophosphate pesticides in bottom sediment by gas chromatography with flame

photometric detection. Water-resources investigation report 02-4222. U.S. Geological Survey, U.S. Department of the Interior.

*USGS. 2007. Pesticides in the nation's streams and ground water, 1992-2001. U.S. Geological Survey, National Water-Quality Assessment Program.

*van den Beukel I, van Kleef RG, Oortgiesen M. 1998. Differential effects of physostigmine and organophosphates on nicotinic receptors in neuronal cells of different species. Neurotoxicology 19(6):777-787.

*van der Merwe D, Brooks JD, Gehring R, et al. 2006. A physiologically based pharmacokinetic model of organophosphate dermal absorption. Toxicol Sci 89(1):188-204.

*Veronesi B, Pope C. 1990. The neurotoxicity of parathion-induced acetylcholinesterase inhibition in neonatal rats. Neurotoxicology 11(4):609-626.

*Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238(2):476-483.

*Villeneuve DC, Grant DL, Phillips WE, et al. 1971. Effects of PCB administration on microsomal enzyme activity in pregnant rabbits. Bull Environ Contam Toxicol 6(2):120-128.

*Villeneuve DC, vanLogten MJ, denTonkelaar EM, et al. 1978. The combined effect of food restriction and parathion exposure in rats. Arch Environ Contam Toxicol 7(1):37-45.

*Vogtmann H, Fragstein PV, Draeger P. 1983. The degradation of agrochemicals during composting. Second International Symposium Bet Degan, Israel, 357-377.

*Wade MJ. 1979. Organophosphorus pesticides in the marine environment: Their transport and fate. Diss Abst Int 40:4704-4705.

*Waldron AC. 1974. Pesticide movement from cropland into Lake Erie. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development.

*Wallace KB, Dargan JE. 1987. Intrinsic metabolic clearance of parathion and paraoxon by livers from fish and rodents. Toxicol Appl Pharmacol 90:235-242.

*Wan MT, Szeto S, Price P. 1994. Organophosphorus insecticide residues in farm ditches of the Lower Fraser Valley of British Columbia. J Environ Sci Health B29(5):917-949.

*Wan MT, Szeto SY, Price P. 1995. Distribution and persistence of azinphos-methyl and parathion in chemigated cranberry bogs. J Environ Qual 24:589-596.

*Ware GW, Morgan DP, Estesen BJ, et al. 1973. Establishment of reentry intervals for organophosphate-treated cotton fields based on human data. I. Ethyl- and methyl parathion. Arch Environ Contam Toxicol 1(1):48-59.

*Ware GW, Morgan DP, Estesen BJ, et al. 1974. Establishment of reentry intervals for organophosphate-treated cotton fields based on human data. II. Azodrin, ethyl and methylparathion. Arch Environ Contam Toxicol 2(2):117-129.

*Weitman SD, Vodicnik MJ, Lech JJ. 1983. Influence of pregnancy on parathion toxicity and disposition. Toxicol Appl Pharmacol 71(2):215-224.

*Weitman SD, Vodicnik MJ, Lech JJ. 1986. Mechanism of enhanced parathion-paraoxon toxicity during pregnancy in the mouse. Fundam Appl Toxicol 6(1):155-161.

*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatr 32:10-18.

*Wester RC, Maibach HI. 1985. *In vivo* percutaneous absorption and decontamination of pesticides in humans. J Toxicol Environ Health 16:25-37.

*Wester RM, Tanojo H, Maibach HI, et al. 2000. Predicted chemical warfare agent VX toxicity to uniformed soldier using parathion *in vitro* human skin exposure and absorption. Toxicol Appl Pharmacol 168(2):149-152.

*WHO. 2005. The WHO recommended classification of pesticides by hazard and guidelines to classification 2004. Geneva, Switzerland: World Health Organization.

*WHO. 2010. Guidelines for indoor air quality: Selected pollutants. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. April 24, 2013.

*WHO. 2011. Guidelines for drinking-water quality. 4th Edition. Geneva, Switzerland: World Health Organization. http://www.who.int/water_sanitation_health/publications/2011/dwq_guidelines/en/index.html. April 24, 2013.

*Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advance treatise. Volume II: The elements Part A. New York, NY: Academic Press, 1-247.

*Williams PL, Carver MP, Riviere JE. 1990. A physiologically relevant pharmacokinetic model of xenobiotic percutaneous absorption utilizing the isolated perfused porcine skin flap. J Pharm Sci 79(4):305-311.

+*Wiltrout RW, Ercegovich CD, Ceglowski WS. 1978. Humoral immunity in mice following oral administration of selected pesticides. Bull Environ Contam Toxicol 20(3):423-431.

*Winterlin W, Seiber JN, Craigmill A, et al. 1989. Degradation of pesticide waste taken from a highly contaminated soil evaporation pit in California. Arch Environ Contam Toxicol 18:734-747.

*Wishahi A, Aboul-Dahab YW, Sherif Y, et al. 1958. Parathion poisoning phosphorus compound: A report on 22 children in an outbreak. Arch Pediatr 75(9):387-396.

*Wolfe HR. 1976. Field exposure to airborne pesticides. In: Air pollution pesticides and agricultural processes. Cleveland, OH: CRC Press, 137-163.

*Wolfe HR, Durham WF, Armstrong JF. 1967. Exposure of workers to pesticides. Arch Environ Health 14:622-633.

*Wolfe HR, Durham WF, Armstrong JF. 1970. Urinary excretion of insecticide metabolites. Excretion of para-nitrophenol and DDA as indicators of exposure to parathion. Arch Environ Health 21(6):711-716.

*Wolfe HR, Staiff DC, Armstrong JF, et al. 1973. Persistence of parathion in soil. Bull Environ Contam Toxicol 10(1):1-9.

*Woodrow JE, Crosby DG, Mast T, et al. 1978. Rates of transformation of trifluralin and parathion vapors in air. J Agric Food Chem 26(6):1312-1316.

*Woodrow JE, Crosby DG, Seiber JN. 1983. Vapor-phase photochemistry of pesticides. Residue Rev 85:111-125.

*Xu LC, Liu L, Ren XM, et al. 2008. Evaluation of androgen receptor transcriptional activities of some pesticides *in vitro*. Toxicology 243(1-2):59-65.

*Yao Y, Harner T, Blanchard P, et al. 2008. Pesticides in the atmosphere across Canadian agricultural regions. Environ Sci Technol 42(16):5931-5937.

*Yaron B. 1975. Chemical conversion of parathion on soil surfaces. Soil Sci Soc Am Proc 39:639-643.

*Yasoshima M, Masuda Y. 1986. Effect of carbon disulfide on the anticholinesterase action of several organophosphorus insecticides in mice. Toxicol Lett 32(3):179-184.

*Yess NJ, Gunderson EL, Roy RR. 1993. U.S. Food and Drug Administration monitoring of pesticide residues in infant foods and adult foods eaten by infants/children. J Assoc Off Anal Chem Int 76(3):492-507.

*Zabik JM, Seiber JN. 1993. Atmospheric transport of organophosphate pesticides from California's Central Valley to the Sierra Nevada Mountains. J Environ Qual 22:80-90.

*Zegers BN, Hogenboom AC, Dekkers SEG, et al. 1994. Packed capillary supercritical fluid chromatography of organophosphorus pesticides: Selective detection and applications. J Microcol Sep 6(1):55-62.

*Zepp RG, Baughman GL. 1978. Prediction of photochemical transformation of pollutants in the aquatic environment. In: Hutzinger O, Van Lelyveld IH, Zoeteman BCJ, eds. Aquatic pollutants. Transformation and biological effects. Oxford: Pergamon Press, 237-263.

*Zhang HX, Sultatos LG. 1991. Biotransformation of the organophosphorus insecticides parathion and methyl parathion in male and female rat livers perfused *in situ*. Drug Metab Dispos 19(2):473-477.

*Zhao X, Hwang HM. 2009. A study of the degradation of organophosphorus pesticides in river waters and the identification of their degradation products by chromatography coupled with mass spectrometry. Arch Environ Contam Toxicol 56(4):646-653.

*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12(1):29-34.

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 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 that 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 of people that 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.

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.

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.

***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 that 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 that 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) that 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 OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

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 dynamic behavior of a material in the body, used to predict 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, whereas 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 that 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) concentration 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 group.

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 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 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 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 100-fold 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 and Human Health Sciences, 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 and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Parathion
CAS Numbers: 56-38-2
Date: August 2014
Profile Status: Draft for Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 9
Species: Rat

Minimal Risk Level: 20 [ ] mg/kg/day [X] ng/m^3

Reference: NIOSH. 1974. Inhalation and oral toxicity 13 studies of ethyl parathion administered acutely and subacutely to the rat and dog. National Institute of Occupational Safety and Health Report No. 00134578. Aberdeen Proving Ground, MD: Edgewood Arsenal, Toxicology Division.

Experimental design: Groups of male rats (20/group) were exposed whole-body to 0, 0.01, 0.1, or 0.74 mg parathion aerosol/m^3 7 hours/day, 5 days/week for 6 weeks. It should be noted that since the rats were not prevented from grooming themselves, ingestion of some amount of parathion may have occurred. Blood samples obtained from 71 rats were assayed for red blood cell and plasma cholinesterase and served as baseline controls. Ten rats per exposure group and control group were sacrificed at various times during the exposure period and during a 6-week post-exposure period to collect blood samples. The rats were observed for clinical signs and were weighed before blood sampling and sacrifice.

Effect noted in study and corresponding doses: No clinical signs were seen in rats exposed to 0.01 or 0.1 mg parathion/m^3. Some rats in the high-concentration group showed signs of parathion toxicity, including tremors and ataxia. Blood collected from the high-dose group after the last exposure showed no significant alteration in hematocrit. Body weight was not significantly altered by exposure to parathion. In the low-exposure group, red blood cell AChE activity was maximally decreased by approximately 30% on exposure weeks 4 and 5; no data were ava ilable for week 3. On exposure week 6, red blood cell AChE activity in the low-exposure group had recovered to 97.3% of control levels. In the mid-exposure group, the maximum decrease in red blood cell AChE was 43% and occurred on week 1. During the rest of the exposure period, red blood cell cholinesterase activity was 60–70% of pretest levels, suggesting that a steady state had been achieved. Red blood cell AChE activity during the first and second week of the post-exposure period was 82 and 84.4% of controls, indicating that recovery was in progress. In the high-exposure group, red blood cell AChE activity achieved its maximal depression on week 5 of exposure, reaching 15% of controls. In general, enzyme activities recovered during the 6-week post-dosing period. Changes in plasma cholinesterase activity paralleled red blood cell changes, recovered faster and exceeded control levels by week 1 or 2 post-exposure. Since the exposure level of 0.1 mg parathion/m^3 induced a level of depression of red blood cell AChE activity that appeared to achieve steady state at approximately 60–70% of controls during exposure, and no clinical signs were observed at this exposure level, 0.1 mg/m^3 constitutes a less serious LOAEL for neurological effects in rats; the exposure concentration of 0.01 mg parathion/m^3 is a NOAEL.

Since only means without deviation parameters were reported for red blood cell AChE values, dose-responses using benchmark dose approaches cannot be constructed to estimate points of departure from the rat data. Therefore, a NOAEL/LOAEL approach will be used and the NOAEL of 0.01 mg parathion/m^3 for red blood cell AChE in rats is the point of departure for MRL derivation.

Exposure concentration and end point used for MRL derivation: 0.01 mg/m^3; NOAEL for neurological effects (red blood cell AChE inhibition).

[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? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: A human equivalent dose could not be determined because the study did not provide information regarding information about particle size.

Was a conversion used from intermittent to continuous exposure? Yes (7 hours/24 hours) x (5 days/7 days).

Other additional studies or pertinent information that lend support to this MRL: A 6-week inhalation study in dogs also established a NOAEL of 0.01 mg/m^3 for red blood cell AChE activity (NIOSH 1974). In that study, male beagle dogs (6/group) were exposed to parathion aerosol at concentrations of 0, 0.001, 0.01, or 0.2 mg/m^3 7 hours/day, 5 days/week for 6 weeks and were held for an additional 6-week post-exposure period. Blood samples obtained from the dogs at various times during the exposure and post-exposure periods were assayed for red blood cell AChE and plasma cholinesterase. Blood samples were taken pre-exposure so that each dog served as its own control. No clinical signs were observed in the dogs. Exposure to parathion did not affect body weight gain in the dogs. No significant effects on levels of red blood cell AChE activity were observed at the low-exposure level. Exposure to 0.01 mg parathion/m^3 reduced red blood cell AChE activity by 21% by the end of the second week of exposure, but levels recovered to 14% of pre-exposure values by the third week of exposure and to 100% of pretest levels during the remaining of the exposure period. In the high-exposure group, red blood cell AChE activity was reduced between 26 and 46% during the first 5 weeks of exposure and inhibition reached a maximum of 41% of pre-exposure levels on week 6 of exposure. Slow recovery was evident during the post-exposure period. Plasma cholinesterase activity was inhibited to a greater extent during the exposure period, but seemed to recover faster during the post-exposure period. Based on the fact that red blood cell AChE activity was depressed over 20% (21%) only on week 2 of exposure in the 0.01 mg/m^3 group, this exposure level is considered a NOAEL for neurological effects in dogs in an intermediate-duration study; the LOAEL is 0.2 mg/parathion/m^3.

Agency Contacts (Chemical Managers): Jewell Wilson

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Parathion
CAS Numbers: 56-38-2
Date: August 2014
Profile Status: Draft for Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 50
Species: Human

Minimal Risk Level: 0.009 [X] mg/kg/day [ ] mg/m^3

Reference: Rider JA, Moeller HC, Puletti EJ, et al. 1969. Toxicity of parathion, systox, octamethyl pyrophosphoramide, and methyl parathion in man. Toxicol Appl Pharmacol 14(3):603-611.

Experimental design: Five male volunteers* were administered 3, 4.5, 6, or 7.5 mg parathion/day in a capsule (0.04, 0.06, 0.09, and 0.11 mg/kg/day, assuming 70 kg body weight) for approximately 30 days; two additional subjects served as controls. In a pretest period of 30 days, blood was collected to establish baseline levels of plasma cholinesterase and red blood cell AChE. The subjects were also monitored during a post-test period of about 30 days. At the beginning of the pretest period, routine blood counts, urinalysis, and prothrombin time were performed, and these were repeated at the end of each test period.

Effect noted in study and corresponding doses: Doses of 0.04 or 0.06 mg parathion/kg/day did not affect the levels of either enzyme. Administration of 0.09 mg parathion/kg/day caused a slight depression of plasma cholinesterase (data not provided). Doses of 0.11 mg parathion/kg/day induced a 27% decrease in the plasma enzyme in one subject on day 4. On day 9, two subjects showed 36 and 32% inhibition of the plasma enzyme. On day 16, the levels of plasma cholinesterase in these two subjects were 50 and 52% of pretest levels and parathion dosing was discontinued. In the other three subjects, plasma cholinesterase levels were 97, 82, and 69% of pretest levels. On day 16, the mean levels of plasma cholinesterase in the five exposed subjects was reduced by 28% from the control value. On day 23, plasma cholinesterase activity in a third exposed subject was 54% of his pretest level and dosing was also discontinued. Therefore, of the five dosed subjects, three had the treatment discontinued by day 23 (two on day 16 and one on day 23). In the two subjects who received parathion during 35 days, the lowest plasma cholinesterase levels were 86 and 78% of their pretest values.

Red blood cell AChE activity in the three subjects who discontinued parathion dosing achieved maximal inhibition levels of 63, 78, and 86% of pretest levels. In the two subjects who completed the test period, there was no significant effect on red blood cell AChE activity. By the end of the post-test period, both enzymes had returned to pretest levels. No information was provided regarding blood counts, urinalysis, or prothrombin test results. Based on a >20% inhibition of red blood cell AChE activity in two out of five subjects for 16 days, the dose of 0.11 mg parathion/kg/day is a LOAEL for neurological effects; the next lower dose, 0.09 mg parathion/kg/day, is a NOAEL.

Benchmark dose analysis cannot be performed because the data were not presented as means plus or minus a measure of dispersion. The intermediate-duration oral MRL for parathion is derived by dividing the NOAEL of 0.09 mg parathion/kg/day by an uncertainty factor of 10 (to account for human variability); this yields an MRL of 0.009 mg parathion/kg/day (9 µg/kg/day).

Dose and end point used for MRL derivation: 0.09 mg/kg/day; NOAEL for neurological effects (inhibition of red blood cell AChE activity).

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

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

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

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Edson (1964) identified a NOAEL of 0.1 mg parathion/kg/day (the highest dose tested) for red blood cell AChE activity in female volunteers administered the pesticide orally for 6 weeks. The available intermediate-duration oral studies in animals suggest that significant inhibition (>20%) of red blood cell AChE occurs with repeated doses ≥0.1 mg parathion/kg/day. In a study in dogs, red blood cell AChE activity was depressed approximately 25% with doses of 0.047 mg parathion/kg/day for 12 weeks, but appeared to increase to near 90% of pretest values on week 16 of exposure (Frawley and Fuyat 1957). Another study in dogs showed that a constant inhibition of the enzyme of >20% could be achieved only with repeated doses of 0.5 mg parathion/kg/day (NIOSH 1974). Two studies in rats dosed for several weeks identified LOAELs of 0.1 mg parathion/kg/day for red blood cell AChE; the NOAELs were 0.024 and 0.05 mg parathion/kg/day (Ivens et al. 1998; NIOSH 1974).

*Note: ATSDR endorses the highest ethical standards in conducting human dosing studies. Thus, it should be noted that the Rider et al. (1969) study raises ethical concerns about human subjects' protection and would not be approved today based on the current human subject protection regulations (HHS 2009). The participants in the study were prisoners in San Quentin State prison and the California Medical Facility in Vacaville, raising questions about their ability to make a truly voluntary and uncoerced decision whether or not to participate in the study. The study report provides no detailed information regarding consent procedures other than to state that the participants were volunteers. ATSDR believes that the use of the study is consistent with the recommendations by the NRC (2004).

> Recommendation 7-2 states that: "*The cholinesterase inhibition studies that already have been submitted to EPA, if determined to be scientifically valid and justified for EPA's regulatory purposes, may be considered for use in risk assessment and standard setting if they were not unethically conducted (see Recommendation 5-7.)*"
>
> Recommendation 5-7 states that: "*EPA should accept scientifically valid studies conducted before its new rules are implemented unless there is clear and convincing evidence that the conduct of those studies was fundamentally unethical (e.g., the studies were intended to seriously harm participants or failed to obtain informed consent.)*"

Although there is limited information about the consent procedures used in this study, the information that is provided about the participants being volunteers suggests that there is no clear and convincing evidence that the conduct of this study was fundamentally unethical.

> Recommendation 4-1 further states that: *"EPA should consider a human dosing study intended to reduce the interspecies uncertainty factor (for example, a study of a biomarker such as cholinesterase inhibition) as conferring a societal benefit only if it was designed and conducted in a manner that would improve the scientific accuracy of EPA's extrapolation from animal to human data."*

As discussed above, the available intermediate-duration oral studies suggest that in humans, rats, and dogs, significant inhibition (>20%) of red blood cell AChE activity occurs with repeated doses ≥0.1 mg parathion/kg/day. The human study by Rider et al. provides a basis for an MRL that improves the accuracy of the value based on the animal data alone, and eliminates the interspecies uncertainty factor. Any human dosing study must have a useful purpose and convey a benefit to participants and/or society (NRC 2004). ATSDR believes that the Rider et al. (1969) study provides a benefit to society in that the data provide the basis for a health guidance value (i.e., MRL) that can be used to protect exposed populations to parathion.

Agency Contacts (Chemical Managers): Jewell Wilson

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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 that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and 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.

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, ATSDR has derived 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.

MRLs 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 that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

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 no-observed-adverse-effect level (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 levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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, 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 NOAELs, 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 Sample LSE Table 3-1 (page B-6)

(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. Typically when sufficient data exist, 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 Tables 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 two "18r" data points in sample 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 regimens 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 “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 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, one systemic effect (respiratory) was investigated.

(8) NOAEL. A 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 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 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 that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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 acute and intermediate 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 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL 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

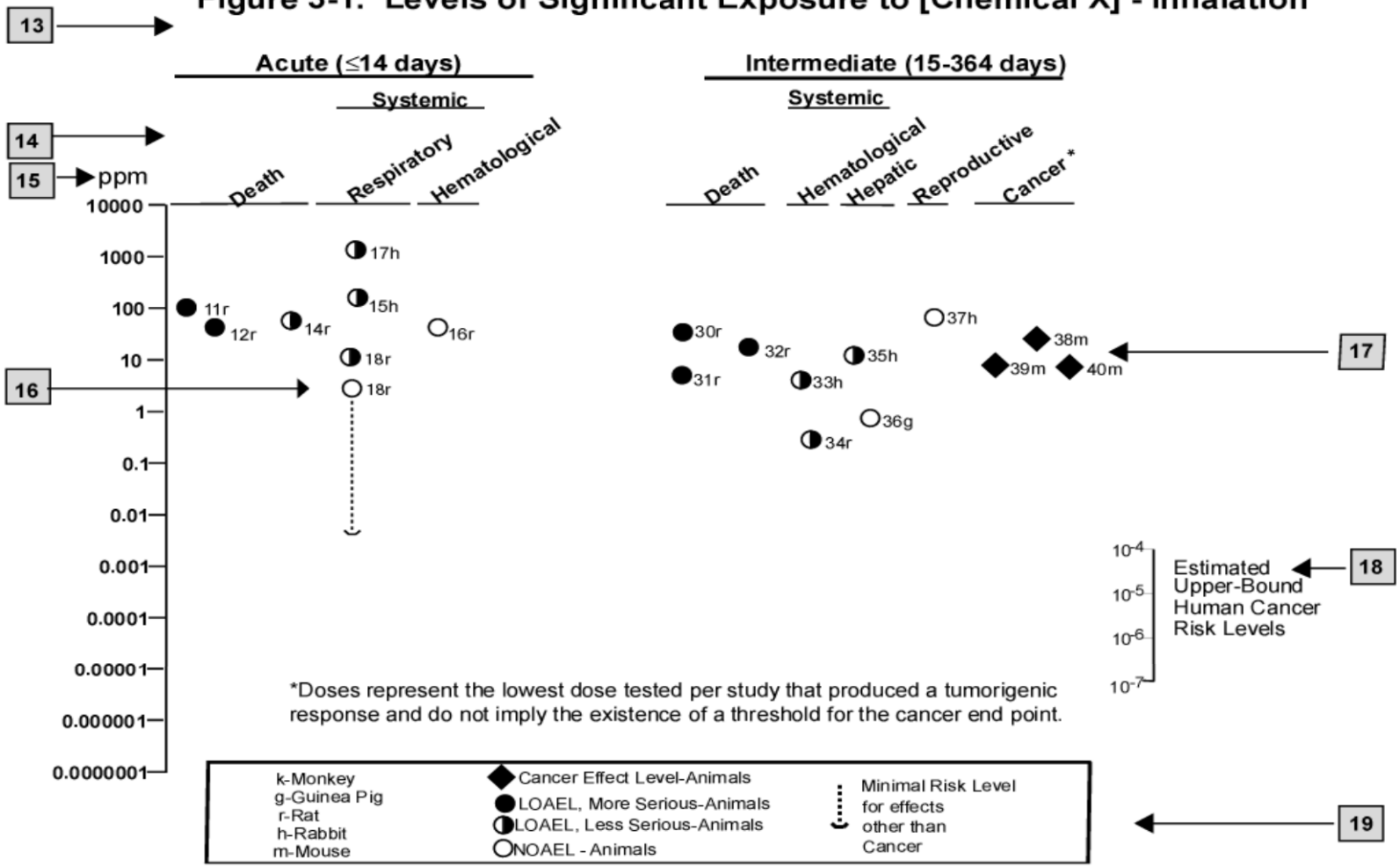
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
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
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
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
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
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/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental 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
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
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
NHANES	National Health and Nutrition Examination Survey
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
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
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
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
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
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

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APPENDIX D. INDEX

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