TOXICOLOGICAL PROFILE FOR GUTHION

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

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DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Guthion, Draft for Public Comment was released in September 2006. This edition supersedes any previously released draft or final profile.

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
Mailstop F-32
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FOREWORD

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

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

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

Each profile includes the following:

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

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

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

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

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

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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99 499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999(64 FR 56792); October 25, 2001 (66 FR 54014) and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

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

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

Other Sections of Interest:

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

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

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

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

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

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

Other Agencies and Organizations

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

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

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

Referrals

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

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 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 Applied 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 guthion. The panel consisted of the following members:

Draft for Public Comment:

1. Dr. Allan Flesot, Professor and Extention Specialist, Entomology and Environmental Toxicology, Food and Environmental Quality Lab, Washington State University-TriCities, Richland, Washington;

2. Dr. Maryce Jacobs, President, Health Science Institute, Inc., Las Cruces, New Mexico; and

3. Dr. Craig Wheelock, Junior Faculty, Microbiology and Tumorbiology Center, Karolinska Institute, Stockholm, Sweden.

These experts collectively have knowledge of guthion'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

This public health statement tells you about guthion and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Guthion has been found in at least 5 of the 1,699 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which guthion is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to guthion may be harmful.

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

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

1.1 WHAT IS GUTHION?

Description	Guthion is the common name of an organophosphorus insecticide. It is a formulation that includes the active ingredient of azinphos-methyl. Guthion does not occur naturally in the environment. Pure guthion is a colorless to white odorless crystalline solid. Technical-grade guthion is a cream to yellow-brown granular solid.
Uses **• Pestide uses**	Guthion is used to control pest insects on many crops, especially apples, pears, cherries, peaches, almonds, and pistachios. Many uses of guthion have been cancelled by the EPA and its few remaining uses are being phased out.

For more information on the physical and chemical properties of guthion, and its production, disposal and use, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO GUTHION WHEN IT ENTERS THE ENVIRONMENT?

Sources	Guthion is primarily released to air from its use as an insecticide. Guthion is sprayed on crops primarily using ground-based spray equipment, although it can also be sprayed on crops from light-weight planes and helicopters. Although a large part of the spray lands directly on the crop, some of the smaller droplets that make up the spray can be carried away from the crop by the wind to nearby water bodies and soils. Guthion residues may also reach nearby rivers, streams, lakes, or ponds by water runoff and erosion that occurs during rainfall. Manufacturing facilities that produce guthion can also release it to the environment during the production process.
How guthion breaks down	Guthion is not very persistent in the environment. Guthion is degraded to many other compounds by microorganisms found in soil and water. It is also degraded by sunlight and by reacting with water. Guthion does not evaporate very quickly from soil and water. It attaches strongly to soil surfaces and does not easily move into groundwater below the soil surface.

For more information on guthion in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO GUTHION?

Food—primary source of exposure	You are primarily exposed to guthion by ingesting foods treated with this pesticide. Apples, pears, peaches, and cherries are crops most likely to contain guthion residues, but fewer residues are being found as guthion use in agriculture has been diminishing.
Air	You may be exposed to guthion in air in areas close to fruit orchards or other crops where guthion is used.
Workplace	People who work in agricultural jobs such as pesticide applicators, fruit pickers, and other farm workers can be exposed to higher levels of guthion than the average individual, probably by skin contact with the insecticide and by inhalation. Families of workers can also be exposed because residues on workers' hands, clothes, vehicles, or other personal items can be brought into the home.
Children	Children playing on or near areas that have been treated with guthion may be exposed to guthion in soil by skin contact, when they accidentally or intentionally put soil into their mouths, and through hand-to-mouth activity. Children can also be exposed through food and drink. Since children have more fruit in their diets, their exposure to guthion may be higher than for adults on a body weight basis.

For more information on human exposure to guthion, see Chapter 6.

1.4 HOW CAN GUTHION ENTER AND LEAVE MY BODY?

Enter your body • **Inhalation**	If you breathe air containing guthion, you may absorb it into your body through the lungs.
• **Injection**	Most guthion in food or water can be absorbed from the digestive tract.
• **Dermal contact**	Guthion may enter your body across the skin.
Leave your body	Once in the body, guthion is rapidly broken down and eliminated from the body mainly in the exhaled air, urine, and feces.

For more information on how guthion enters and leaves the body, see Chapter 3.

1.5 HOW CAN GUTHION AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

Human exposure	Guthion affects the normal function of the nervous system by interfering with an important enzyme called acetylcholinesterase. Exposure to guthion can result in signs or symptoms of nervous system damage shortly after exposure. If you experience these symptoms, you should seek medical attention immediately. Emergency rooms have drugs that stop the harmful effects of guthion.
Laboratory animals	Symptoms observed in animals exposed to high levels of guthion include excess saliva, watery eyes, and mustle twitching. It is likely that humans exposed to high levels of guthion will have similar effects.
Cancer	Guthion has not been shown to cause cancer in people or animals. The Department of Health and Human Services (DHHS), the EPA, and the International Agency for Research on Cancer (IARC) have not classified the carcinogenic potential of guthion in humans.

Further information on the health effects of guthion in humans and animals can be found in Chapters 2 and 3.

1.6 HOW CAN GUTHION AFFECT CHILDREN?

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

Effects in children	We do not know whether children are more sensitive than adults to the health effects of guthion. The main target for guthion in adults is the nervous system, in particular acetylcholinesterase. It is expected that this will also be the main target in children.
Birth defects	We do not know if guthion can cause birth defects or other damage to developing children. Studies in animals have found decreases in fetal growth, nervous system damage, and reduced survival, but only at doses that also caused harmful health effects in the mothers.

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

Wash fruits and vegetables	To reduce the risk of exposure to guthion residue on fresh fruits or vegetables, wash the foods prior to eating them. If you go to an orchard and pick your own fruit, make sure you wash your hands when you are finished since guthion residues can be absorbed through the skin.
Those who live in agricultural areas	If you live near a farm where frequent ground or aerial spraying takes place, you may want to remain indoors with your children and pets while the crops are being sprayed to lessen your exposure. You should discourage your children from entering areas treated with guthion. Discourage your children from eating dirt and putting their hands in their mouth. Make certain your children wash their hands frequently, especially before eating. If children play in grass fields or orchards, any pesticides used in these areas could collect on clothing. Regular laundering of clothing can reduce the potential for this exposure.

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

Measuring effects	Guthion, like other organophosphorus pesticides, interferes in the human body with an enzyme called acetylcholinesterase. Most of the signs and symptoms resulting from guthion poisoning are due to this interference with acetylcholinesterase. A blood test that measures acetylcholinesterase in the red blood cells or a similar enzyme in plasma may be useful for detecting exposures to potentially harmful levels of guthion.
Detecting exposure	Because guthion changes to other compounds in the body quickly, it is difficult to directly analyze the amount of guthion in a person's body. Three chemicals formed when guthion breaks down can be measured in the urine. However, these three compounds are not specific to guthion only, but may also indicate exposure to other organophosphorus pesticides.

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

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic

substances. Recommendations provide valuable guidelines to protect public health, but cannot be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

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 that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

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 provides it.

Some regulations and recommendations for guthion include the following:

Food	The EPA has set tolerances for residues of guthion in various raw food products of 0.2–5 parts of guthion per million parts of food (ppm).
Workplace air	OSHA set a legal limit of 0.2 milligrams per cubic meter (mg/m^3) guthion in air averaged over an 8-hour work day. NIOSH designated a limit of 10 mg/m^3 as a concentration that is immediately dangerous to life and health.

For more information on standards and guidelines for guthion, see Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

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

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfilesTM CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

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

1. PUBLIC HEALTH STATEMENT

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2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO GUTHION IN THE UNITED STATES

Guthion, a trade name for azinphos-methyl, is a restricted use organophosphate insecticide that is primarily used as a foliar application against phytophagous insect pests on fruit, field, or vegetable crops and works as both a contact insecticide and a stomach poison. In 2002, the estimated annual agricultural use of guthion had declined to about 1.2 million pounds, nearly a 50% decline from 1997 usage data. The total amount of guthion reportedly used in 1997 was 2,091,014 pounds, which was an 18% decrease from the amount used (2,548,867 pounds) in 1992. In the Interim Registration Eligibility Decision (interim RED) document for guthion, EPA estimated that <2 million pounds are used annually. The greatest amounts of guthion have historically been applied to orchard fruits such as apples, pears, cherries, and peaches; however, guthion has also been used extensively on cotton, almonds, sugarcane, and several other crops. The uses of guthion have been severely restricted in recent years. In 2001, the EPA proposed the immediate cancellation of most uses of guthion. Currently, the only crops that guthion can still be applied to are: almonds; apples/crabapples; blueberries, lowbush and highbush; Brussels sprouts; cherries, sweet and tart; nursery stock (woody shrubs, vines, seeding trees, and nonbearing fruit trees); parsley; pears; pistachios; and walnuts. On June 9, 2006, EPA proposed the cancellation of guthion for apples, blueberries, cherries, parsley, and pears by 2010 and a phase out of guthion's other uses by the end of 2007. On August 8, 2007, the companies that produce guthion advised the EPA that they intended to amend their registrations to terminate certain uses (Brussels sprouts and nursery stock) of guthion by September 30, 2007. Uses on walnuts, almonds, and pistachios are scheduled to cease by October 30, 2009, and all other uses would be terminated by September 30, 2012.

Guthion is not considered highly persistent in the environment and it degrades through a combination of biotic and abiotic mechanisms. Biodegradation occurs readily in soils and water under aerobic conditions with half-lives on the order of several days to a few weeks. Background environmental levels of guthion are typically below analytical detection limits, and it is rarely detected in areas where it is not being used. Elevated levels of guthion are often detected during its application. For example, during the application of insecticides to an apple orchard in Massachusetts approximately 1 acre in size by airblast ground sprayers, guthion applied at 0.75 kg/ha was detected downwind of the spray zone (75 feet away) at a maximum concentration of 3.87 $\mu g/m^3$. Within 2 hours, the atmospheric level had dropped to 0.031 $\mu g/m^3$. Guthion has moderate to low mobility in soils based on K_{oc} values in the range of 475–3,266. Its leaching potential is considered low and is therefore only occasionally detected in groundwater.

Guthion was only detected in 4 out of 2,451 groundwater samples collected from 1992 to 1996 in 20 major hydrological basins across the United States. Guthion is rarely detected in drinking water. In an analysis of finished drinking water in 12 states, guthion was detected in 5 out of 225 samples at a mean concentration of 0.059 μg/L and a maximum concentration of 0.114 μg/L. Spray drift following aerial application, as well as runoff and erosion of treated soils, often leads to contamination of rivers, lakes, ponds, and streams adjacent to fields or orchards where guthion has been used as an insecticide. Guthion was detected in 64 out of 98 surface water samples (maximum concentration 0.523 μg/L) obtained from various sites in a heavy apple growing region along the Yakima River Basin, Washington, during the period of May 1999 through January 2000. More recent monitoring data from April to October 2004 from two sites near the Yakima River had guthion levels ranging from 0.013 to 0.042 μg/L. The frequency of detection for guthion at these two sampling locations were approximately 9 and 13%.

The most important route of exposure to guthion for the general population is through the ingestion of foods, especially fruits and vegetables that have been sprayed with this insecticide. Ingestion of contaminated drinking water, inhalation exposure, and dermal exposure to guthion are expected to be low for the general population. The dietary average daily intake (AVDI) of guthion for eight different age and gender groups was estimated from market basket surveys conducted by the FDA from 1986 to 1991 (more recent surveys are not available). The dietary AVDI of guthion ranges from about 4 to 31 ng/kg/day (see Table 6-9). Agricultural workers, their family members including children, and persons residing near crops that are treated with guthion are expected to be exposed to higher levels than the general population. Since guthion is absorbed through the skin, dermal exposure to pesticide applicators or workers involved in picking, harvesting, and trimming of crops treated with guthion may be high. Although guthion is not considered highly volatile, dust samples in homes of agricultural workers, their vehicles, and personal items such as work clothing have been shown to contain detectable levels of guthion during the spraying season. This contaminated dust can be resuspended, resulting in dermal and inhalation exposures.

2.2 SUMMARY OF HEALTH EFFECTS

Available human and animal data suggest that reductions in acetylcholinesterase (AChE) activity are the most sensitive end points of guthion toxicity. In both humans and animals, erythrocyte AChE inhibition occurs at doses that are several times lower than doses eliciting clinical signs and symptoms. The neurotoxicity of guthion is dependent on its bioactivation via a cytochrome P450 mediated desulfuration to the oxon form gutoxon. Gutoxon inhibits the enzymatic action of nervous system AChE on the

neurotransmitter acetylcholine, leading to the accumulation of acetylcholine at the ending of cholinergic nerves and resultant continual stimulation of electrical activity. Cholinergic nerves play an important role in the normal function of the neuromuscular, central nervous, endocrine, immunological, and respiratory systems. In this manner, exposure to guthion may lead to adverse effects on the normal function of many important systems.

There is a paucity of data regarding the inhalation, oral, and dermal toxicity of guthion in humans. Limited data are available in studies of the effect of guthion on human erythrocyte AChE and plasma cholinesterase (ChE) activities. These studies reported no significant changes in plasma ChE or erythrocyte AChE activity in a small group of subjects ingesting 0.057–0.086 mg/kg/day for 4 weeks. Nevertheless, there is evidence suggesting that dermal, and perhaps inhalation, exposures of workers to guthion may lead to adverse health effects. An increased association was observed between the occurrence of systemic illness (defined as an acute illness following pesticide exposure, with symptoms and signs not restricted to the eyes or skin) in workers and agricultural use of guthion; however, interpretation of this study is complicated by the absence of worker exposure data and the potential exposure to other pesticides and formulation components. Although studies of agricultural workers have used the detection of urinary metabolites of guthion and ChE activity monitoring to demonstrate exposure to guthion, no symptoms or signs of organophosphate poisoning were observed in the exposed workers even with documented reductions of 10–20% in erythrocyte AChE activity or whole blood ChE activity. These findings are in agreement with animal studies, which indicate that erythrocyte AChE activity is very sensitive to guthion and that clinical signs in laboratory animals exposed to guthion are generally observed at concentrations that are several times higher than the lowest concentrations eliciting reductions in erythrocyte AChE activity. For instance, clinical signs, including hypercholinergy and nicotinic effects, salivation, lacrimation, exophthalmus, defecation, urination, and muscle fasciculations, have been observed in rats or mice administered single (16–26 mg/kg) or repeated (8 mg/kg/day) lethal oral doses of guthion and in rats and mice administered doses ≥3.2 mg/kg/day. However, doses in the range of 0.55–3 mg/kg/day in rats and dogs are sufficient to elicit 20–80% reductions in erythrocyte AChE activity with reductions >80% being observed at higher doses. Studies with rats and dogs suggest that reductions in erythrocyte AChE activity are not related to exposure duration. For instance, 75–92% reductions in erythrocyte AChE activity were observed in rats or dogs administered 2–4.3 mg/kg/day guthion on gestation days 6–15 or for 13 or 52 weeks and doses of 0.55–1.1 mg/kg/day elicited reductions in the 20–47% range in animals dosed for 13 weeks to 2 years.

Erythrocyte AChE activity appears to be more sensitive than plasma ChE or brain AChE activity to the toxic effects of guthion. Biologically significant (≥20%) reductions in erythrocyte AChE activity were observed in male and female rats exposed to 4.72 mg/m^3 guthion during 6 hours/day, 5 days/week for up to 12 weeks, but brain AChE activity was not affected and plasma ChE activity was reduced by ≥20% only in females at one sampling time. Reductions in erythrocyte AChE activity have been observed in rats or dogs administered ≥0.55 mg/kg/day, whereas reductions in brain AChE and plasma ChE activity in rats and dogs were generally observed at ≥0.96 mg/kg/day.

Plasma ChE inhibition is used as an indicator of exposure, but does not serve as a reliable indicator of a neurotoxic effect. However, inhibition of erythrocyte and brain AChE represents a relevant neurological effect. Erythrocyte and/or brain AChE inhibition of 20–59% is considered to represent a less serious adverse neurological effect in the absence of more serious indicators of neurotoxicity. In this Toxicological Profile, "less serious" effects are those that are not expected to cause significant dysfunction or death, or those in which the significance to the organism is not entirely clear. The animal studies identified exposure levels at which guthion caused erythrocyte AChE inhibition in the absence of more serious indicators of neurotoxicity, which indicates that erythrocyte AChE inhibition at such exposure levels may represent the most sensitive effect for guthion toxicity.

No association was detected between occupational exposure to guthion and the occurrence of congenital malformations in a study of male agricultural workers in Spain during 1993 and 1994. Single oral doses ≥16 mg/kg administered to mice during gestation, elicited reductions in fetal body weight and skeletal anomalies. Adverse developmental outcomes such as skeletal abnormalities, decreased pup weight and survival, reduced brain weight and ChE activity, and neuromuscular effects were observed in the offspring of pregnant rats or mice treated with ≥3.7 mg/kg/day guthion during gestation and gestation and lactation. Developmental effects were not evident in rats or mice at oral doses ≤2.5 mg/kg/day. Reductions in litter and pup viability were observed in the fetuses of pregnant mice after a single oral dose of 20 mg/kg and in the offspring of rats after exposure to 1.3 mg/kg/day during gestation and lactation.

No studies were located regarding the carcinogenic potential of guthion in humans. A 2-year carcinogenicity study in rats showed an increased combined incidence of islet cell carcinoma or carcinomas of the pancreas in males receiving guthion in the diet for 80 weeks at a concentration resulting in an average dose of 10.9 mg/kg/day, followed by a 35-week observation period. However, this lesion occurs at a high spontaneous incidence in the animals used in this study and the increased incidence in the

treated males could not be positively associated with guthion exposure. Similarly, increases in the incidence of benign thyroid tumors, malignant thyroid tumors, or combined follicular cell tumors observed in male rats exposed to 5.5 or 10.9 mg/kg/day could not be ascribed to treatment with guthion due to the high spontaneous incidence of these neoplasms in male rats in this laboratory. There was no evidence of the occurrence of treatment-related tumors in female rats in this study or in another study of male and female Wistar rats exposed to 0.25–3.11 mg/kg/day for 2 years. Benign and malignant neoplasms were observed among dosed and control B6C3F1 mice, but these lesions occur spontaneously in mice in this laboratory and the effect could not be positively associated with guthion exposure. The incidence of hepatocellular adenomas in male mice administered 5.4–10.7 mg/kg/day groups provide equivocal evidence of an association between these lesions and guthion exposure. There were no statistically significant associations between tumor incidence and guthion exposure in female mice. The results of these studies led the NCI to conclude that, under the conditions of this bioassay, guthion was not carcinogenic in male or female B6C3F1 mice or female Osborne-Mendel rats. The incidences of neoplasms of the pancreatic islets and of the follicular cells of the thyroid in male rats provide suggestive but insufficient evidence of the carcinogenic potential of guthion in male rats. The Department of Health and Human Services and the International Agency for Research on Cancer (IARC) have not classified guthion as to its carcinogenicity. In 1993, EPA concluded that there was a lack of evidence of carcinogenicity of guthion in male and female mice and rats. Currently, the EPA has no carcinogenicity classification for guthion.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for guthion. 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 MRL of 0.02 mg/m^3 has been derived for acute-duration inhalation exposure (14 days or less) to guthion.

Only two studies examining the acute-duration toxicity of inhaled guthion were located. Kimmerle (1976) examined a number of end points in rats, but biologically significant alterations were limited to a 25% reduction in erythrocyte AChE activity in male rats exposed to 4.72 mg/m^3, 6 hours/day, 5 days/week, for 2 weeks. The reduction in erythrocyte AChE activity in female rats was 18%. No adverse effects were observed in male or female rats at exposure concentrations ≤1.24 mg/m^3. EPA (1978a) reported a 41% (range 27–59%) reduction in blood ChE activity in rats exposed to guthion aerosols (39 mg/m^3) for 1 hour. The results of these studies are strongly supported by several acute- (Astroff and Young 1998; Pasquet et al. 1976), intermediate- (Allen et al. 1990; Holzum 1990; Sheets et al. 1997), and chronic-duration (Allen et al. 1990; Schmidt and Chevalier 1984) studies in rats and dogs, which identified reductions in erythrocyte AChE activity as the most sensitive end point following oral exposure to guthion. It is unclear if EPA (1978a) measured reductions in activity of whole blood or plasma ChE or erythrocyte AChE. Thus, the erythrocyte AChE inhibition observed in the Kimmerle (1976) study was selected as the basis of the acute-duration inhalation MRL.

In the study by Kimmerle (1976), SPF Wistar rats (10/sex/group) were exposed to aerosolized guthion at 0.195, 1.24, or 4.72 mg/m^3, 6 hours/day, 5 days/week, for up to 12 weeks. Erythrocyte AChE activity measurements were made every 2 weeks after dosing began. Guthion aerosols were generated by first dissolving technical-grade guthion in a 1:1 solution of ethanol/polypropylene glycol. Ninety-seven percent of the droplets had a diameter of 1±0.5 μm (Kimmerle 1976). The animals were inspected daily and weighed weekly. Erythrocyte AChE and plasma ChE activities were determined after 2, 4, 6, 8, 10, and 12 weeks. There were no significant changes in appearance or behavior of male or female rats. After 2 weeks of exposure at 4.72 mg/m^3, erythrocyte AChE activity was reduced by 25 and 18% in males and females, respectively. This study identified a no-observed-adverse-effect level (NOAEL) of 1.24 mg/m^3 and a lowest-observed-adverse-effect level (LOAEL) of 4.72 mg/m^3 for reductions in erythrocyte AChE activity in male rats.

A NOAEL/LOAEL approach was used to derive a point of departure to estimate an acute-duration inhalation MRL for guthion. The lack of individual animal data or standard errors or standard deviations for the mean erythrocyte AChE activity precludes using a benchmark dose analysis approach. The NOAEL of 1.24 mg/m^3 was adjusted for intermittent exposure ($NOAEL_{[ADJ]}$) and a human equivalent concentration ($NOAEL_{[HEC]}$) was calculated using the following equations:

$NOAEL_{[ADJ]}$ = 1.24 mg/m^3 x 6 hours/24 hours = 0.31 mg/m^3

$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RDDR_{ER}$ = 0.31 mg/m^3 x 1.626 = 0.50 mg/m^3

The Regional Deposited Dose Ratio (RDDR) for the extrarespiratory (ER) effects was used to extrapolate deposited doses from rats to humans. The RDDR was calculated using EPA software (version 2.3) (EPA 1994b) with the following parameters: a particle size (mass median aerodynamic diameter, MMAD) of 0.88 µm with a default geometric standard deviation (sigma g) of 1.0, a default human body weight of 70 kg and minute volume of 13.8 L, and a rat body weight of 182 g (estimated from the data from Kimmerle 1976) and minute volume of 139 mL.

Based on the information provided by Kimmerle (1976) it was assumed that the sizes of the aerosol particles were log-normally distributed in a manner such that 1.5% of these were <0.5 µm and 1.5% were >1.5 µm. Based on these assumptions a geometric mean and geometric standard deviation of 0.9 and 0.23 µm, respectively, were calculated. These values were used to calculate a MMAD of 0.88 µm using the recommended equation in Table H-2 of the guidance document Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b).

The $NOAEL_{[HEC]}$ of 0.50 mg/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability), resulting in an acute-duration inhalation MRL of 0.02 mg/m^3.

- An MRL of 0.01 mg/m^3 was derived for intermediate-duration inhalation exposure (15–364 days) to guthion.

Only one study examining the intermediate-duration toxicity of inhaled guthion was located. Kimmerle (1976) examined a number of end points in rats, but biologically significant alterations were limited to a 26–48% reduction in erythrocyte AChE activity in male and female rats exposed to 4.72 mg/m^3,

6 hours/day, 5 days/week, for up to 12 weeks and a 20% reduction in body weight gain in male rats exposed to 4.72 mg/m^3 for 12 weeks; no adverse effects were observed in rats at exposure concentrations ≤1.24 mg/m^3. Support to the findings of Kimmerle (1976) is provided by several intermediate- (Allen et al. 1990; Holzum 1990; Sheets et al. 1997) and chronic-duration (Allen et al. 1990; Schmidt and Chevalier 1984) studies in rats and dogs, which identified a reduction in erythrocyte AChE activity as the most sensitive end point following oral exposure to guthion. Thus, the erythrocyte AChE inhibition observed in the Kimmerle (1976) study was selected as the basis of the intermediate-duration inhalation MRL.

In the study by Kimmerle (1976), SPF Wistar rats (10/sex/group) were exposed to aerosolized guthion at 0.195, 1.24, or 4.72 mg/m^3, 6 hours/day, 5 days/week, for up to 12 weeks. Erythrocyte AChE activity measurements were made every 2 weeks after exposures began. Guthion aerosols were generated by first dissolving technical-grade guthion in a 1:1 solution of ethanol/polypropylene glycol. Ninety-seven percent of the droplets had a diameter of 1±0.5 μm (Kimmerle 1976). The animals were inspected daily and weighed weekly. Erythrocyte AChE and plasma ChE activities were determined after 2, 4, 6, 8, 10, and 12 weeks and determinations of hematology, serum glutamic-oxalacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), alkaline phosphatase (AP), urea, creatinine, and bilirubin were conducted after 12 weeks of exposure. At study termination, animals were sacrificed for gross examination. The thyroid, thymus, heart, lungs, liver, spleen, kidneys, adrenals, and gonads were weighed and examined histologically. Brain AChE activity was also determined. There were no significant changes in appearance or behavior of male or female rats. Male rats in the 4.72 mg/m^3 group showed a 20% reduction in body weight gain after 12 weeks of exposure. No effects were detected in examinations of hemoglobin, erythrocyte counts, thrombocytes, packed cell volume, or leucocyte differential counts in male or female rats (Kimmerle 1976). There were also no effects on SGOT, SGPT, AP, urea, creatinine, or bilirubin. There were no observed differences in absolute or relative organ weights. There were no evident morphological changes or variations in organs or tissues in any of the rats. After 4–12 weeks of exposure at 4.72 mg/m^3, erythrocyte AChE activity was reduced by 29–48 and 26–39% in males and females, respectively. The magnitude of the alterations in erythrocyte AChE activity established during the intermediate-duration time points did not appear to be exposure duration-related. No biologically significant alterations in erythrocyte AChE activity were observed at lower concentrations. The investigators noted that brain AChE activity was not reduced at any of the concentrations tested, but the brain AChE activity data were not provided. This study identified a NOAEL of 1.24 mg/m^3 and a LOAEL of 4.72 mg/m^3 for reductions in erythrocyte AChE activity in male rats.

A NOAEL/LOAEL approach was used to derive a point of departure to estimate an intermediate-duration inhalation MRL for guthion. The lack of individual animal data or standard errors or standard deviations for the mean erythrocyte AChE activity precludes using a benchmark dose analysis approach. The NOAEL of 1.24 mg/m^3 was adjusted for intermittent exposure ($NOAEL_{[ADJ]}$) and a human equivalent concentration ($NOAEL_{[HEC]}$) was calculated using the following equations:

NOAEL[ADJ] = 1.24 mg/m^3 x 6 hours/24 hours x 5 days/7 days = 0.22 mg/m^3

$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RDDR_{ER}$ = 0.22 mg/m^3 x 1.695 = 0.37 mg/m^3

The RDDR for the extrarespiratory (ER) effects was used to extrapolate deposited doses from rats to humans. The RDDR was calculated using EPA software (version 2.3) (EPA 1994b) with the following parameters: a particle size MMAD of 0.88 µm with a default geometric standard deviation (sigma g) of 1.0, a default human body weight of 70 kg and minute volume of 13.8 L, and a rat body weight of 253 g (from Kimmerle 1976) and minute volume of 182 mL.

Based on the information provided by Kimmerle (1976), it was assumed that the sizes of the aerosol particles were log-normally distributed in a manner such that 1.5% of these were <0.5 µm and 1.5% were >1.5 µm. Based on these assumptions, a geometric mean and geometric standard deviation of 0.9 and 0.23 µm, respectively, were calculated. These values were used to calculate a MMAD of 0.88 µm using the recommended equation in Table H-2 of the guidance document Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b).

The $NOAEL_{[HEC]}$ of 0.37 mg/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability), resulting in an intermediate-duration inhalation MRL of 0.01 mg/m^3.

- An MRL of 0.01 mg/m^3 was derived for chronic-duration inhalation exposure (365 days or more) to guthion.

No studies were located that allowed the derivation of a chronic-duration inhalation MRL. However, the available acute- and intermediate-duration inhalation studies and the acute-, intermediate-, and chronic-duration oral exposure studies support adopting the intermediate-duration MRL for chronic-duration exposures.

Erythrocyte AChE activity was reduced by 29–48% in male rats and 26–39% in female rats exposed to guthion aerosols at 4.72 mg/m^3 for 4–12 weeks without evident biologically significant changes in activity within the observation period (Kimmerle 1976). Similarly, intermediate- and chronic-duration oral exposures to 0.69–0.78 mg/kg/day in dogs (Allen et al. 1990) and 0.75–0.96 mg/kg/day in rats (Schmidt and Chevalier 1984) demonstrated biologically significant reductions in erythrocyte AChE activity that did not increase in severity with increasing exposure duration for up to 2 years (Allen et al. 1990; Schmidt and Chevalier 1984). Thus, a chronic-duration inhalation MRL of 0.01 mg/m^3 is adopted from the intermediate-duration inhalation MRL and supported by the intermediate- and chronic-duration oral exposure studies in dogs and rats, which suggest that there are no duration-dependent increases in the severity of the inhibition of erythrocyte AChE activity.

Oral MRLs

- An MRL of 0.01 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to guthion.

Dose-related reductions of 23–82% in erythrocyte AChE activity were observed in rats after single oral doses of 2–18 mg/kg guthion (Pasquet et al. 1976) and in female rats following daily oral doses of 2 mg/kg/day on gestation days 6–15 (Astroff and Young 1998). Dose-related reductions of 21–75% of brain AChE activity were observed in rats after single oral doses of 2–18 mg/kg/day (Pasquet et al. 1976). Although reductions >20% were observed at the lowest dose 2 hours after exposure, brain AChE activity levels had returned to 94–95% of control values after 5 and 24 hours (Pasquet et al. 1976). Brain AChE activity was reduced by 27–40% in rats after repeated oral doses of 2 mg/kg/day on gestation days 6–15 (Astroff and Young 1998) and by 78% in female rats administered 5.7 mg/kg/day guthion in the feed for 1 week (Su et al. 1971). Su et al. (1971) estimated that 4.0 mg/kg/day of guthion were required to reduce brain AChE activity by 50%. Clinical signs of neurotoxicity such as lacrimation, salivation, defecation, and muscle fasciculatíons were observed in rats and mice receiving lethal oral doses ≥8 mg/kg/day (EPA 1978a; Short et al. 1980). Developmental effects such as increased incidence of supernumerary ribs and malaligned sternebrae, and reduced fetal weight and viability of litters were observed in mice or rats at doses ≥5 mg/kg (Kavlock et al. 1985; Pasquet et al. 1976; Short et al. 1980). The available data suggest that reduction in erythrocyte AChE activity is the most sensitive end point following acute-duration oral exposures to guthion. Although the studies by Astroff and Young (1998) and Pasquet et al. (1976) identified a LOAEL of 2 mg/kg/day for significant reductions in erythrocyte

AChE activity, only the study by Astroff and Young (1998) identified a NOAEL (1 mg/kg/day) and thus, it was selected for derivation of the acute-duration oral MRL.

Pregnant Sprague-Dawley rats were administered guthion (87.7% active ingredient [a.i.]) at 0.5, 1.0, or 2.0 mg/kg/day by gavage on gestation days 6–15. Erythrocyte AChE was determined on gestation days 16 and 20 and brain AChE activity was determined on day 20 (Astroff and Young 1998). Inseminated females were examined daily for clinical signs. Dam body weight was determined on gestation days 0, 6, 8, 10, 12, 15, and 20. Food consumption was also determined periodically. Two groups of dams were used to establish maternal plasma ChE and erythrocyte and brain AChE activity on gestation days 16 and 20. Gross pathological examination of dams was conducted. Several reproductive and developmental end points, including early or late resorptions, implantation losses, and fetal survival, growth, and malformations, were evaluated. The reduction in AChE activity was the most sensitive end point in this study.

A >80% reduction in erythrocyte AChE activity was observed 24 hours after the last 2 mg/kg/day dose. A 40% reduction in brain AChE activity was also observed in dams in the 2 mg/kg/day group. Maternal plasma ChE activity in the 2.0 mg/kg/day group was approximately 30% lower than in controls on gestation day 16, but the effect was not statistically significant. On gestation day 20, maternal brain AChE activity remained 27% lower than control values but erythrocyte AChE and plasma ChE activities were not significantly different from those in control animals (Astroff and Young 1998). In spite of the magnitude of the AChE and ChE activity reductions, no adverse clinical signs were observed in the treated dams. There were no reductions in brain or erythrocyte AChE or plasma ChE activities in rats administered 0.5 or 1 mg/kg/day (Astroff and Young 1998).

In order to derive a point of departure to calculate an acute-duration oral MRL, a benchmark dose (BMD) approach was applied to the changes in erythrocyte AChE activity observed in female rats exposed to guthion by gavage during gestation (Astroff and Young 1998). BMDs and the lower bound of the 95% confidence limits of the benchmark doses (BMDLs) were calculated using the EPA Benchmark Dose Software (BMDS version 1.3.2; available from EPA). The BMDs and BMDLs are estimates of the doses associated with a 20% change in erythrocyte AChE activity. Reductions in erythrocyte AChE activity of magnitude <20% are not considered to be biologically significant. The BMD modeling is described in greater detail in Appendix A. The BMD and BMDL predicted from the power model are 1.33 and 1.04 mg/kg/day, respectively.

An acute-duration oral MRL of 0.01 mg/kg/day was calculated by dividing the BMDL of 1.04 mg/kg/day by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

- An MRL of 0.003 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to guthion.

Dose-related reductions of 37–84% in erythrocyte AChE activity were observed in rats receiving 0.91–3.2 mg/kg/day guthion from the feed for 13 weeks (Sheets et al. 1997) and in male and female rats given guthion in the feed at 1.3 and 0.55 mg/kg/day, respectively, for 14 weeks and during mating, gestation, and parturition (Holzum 1990). Erythrocyte AChE activity was inhibited by 22–40 and 66–88% in male dogs receiving 0.69 and 3.8 mg/kg/day, respectively, from the feed for up to 26 weeks and reductions of 20–43 and 86–92% were observed in female dogs receiving 0.78 and 4.3 mg/kg/day, respectively, for 26 weeks (Allen et al. 1990). Clinical signs such as tremors, salivation, uncoordinated gait, and diarrhea were observed in rats administered guthion in the feed at ≥3.2 mg/kg/day guthion for 13 weeks (Sheets et al. 1997), in rats administered 5 mg/kg/day during gestation (Short et al. 1980), or in dogs receiving ≥0.69 mg/kg/day for 26 weeks (Allen et al. 1990). The available data suggest that reduction in erythrocyte AChE activity is the most sensitive end point following intermediate-duration oral exposures to guthion. The studies by Allen et al. (1990) and Sheets et al. (1997) identified LOAELs of 0.69–0.78 mg/kg/day in dogs and 0.91–1.1 mg/kg/day in rats, respectively, for reductions in erythrocyte AChE activity; however, the study by Allen et al. (1990) showed that dogs were more sensitive than rats to the anticholinesterase effects of guthion and thus, it was selected for derivation of the intermediate-duration oral MRL.

Technical-grade guthion (91.9% a.i.) was given to beagle dogs (4/sex/group) in the food at concentrations of 5.0, 25.0, or 125.0 ppm; these concentrations are equivalent to guthion doses of 0.15, 0.69, and 3.8 mg/kg/day, respectively, in the males, and 0.16, 0.78, and 4.3 mg/kg/day, respectively, in the females (Allen et al. 1990). Dose-related reductions in erythrocyte AChE activity were evident at the week 4 sampling time. Erythrocyte AChE activity was further reduced from week 4 to 13, but remained relatively constant from week 13 to week 26. Statistically nonsignificant reductions in erythrocyte AChE activity during the 26-week period were ≤8% in males at 0.15 mg/kg/day and 11–21% in females at 0.16 mg/kg/day. Reductions in erythrocyte AChE activity were 22–40% in males at 0.69 mg/kg/day and 20–43% in females at 0.78 mg/kg/day. Reductions in erythrocyte AChE activity from weeks 4 to 26 were 66–88% in males (3.8 mg/kg/day) and 86–92% in females (4.3 mg/kg/day). Male and female dogs receiving guthion doses of 3.8 and 4.3 mg/kg/day, respectively, suffered from an increased incidence of

mucoid diarrhea and occasional emesis. The same signs, but with a greater severity, were observed in male dogs at 0.69 mg/kg/day. These signs were related to treatment with guthion. Terminal body weights were reduced by 12 and 16% in male and female dogs of the 3.8 and 4.3 mg/kg/day dose groups, respectively, although there was no difference in food consumption among treated and control animals. There were no treatment-related hematological effects or changes in urinalysis parameters. Findings were negative in hearing and ophthalmoscopic tests on weeks 13 and 26 and there was no treatment-related increase in mortality in any dose group (Allen et al. 1990). Clinical chemistry tests showed that albumin and albumin/globulin values were significantly reduced in males by 13 and 20%, respectively, in the 3.8 mg/kg/day group.

In order to derive a point of departure to calculate an intermediate-duration oral MRL, a BMD approach was applied to the changes in erythrocyte AChE activity observed in male and female dogs exposed to guthion in the diet for 26 weeks (Allen et al. 1990). BMDs and BMDLs were calculated using the EPA Benchmark Dose Software (BMDS version 1.3.2). The BMDs and BMDLs are estimates of the doses associated with a 20% change in erythrocyte AChE activity. Reductions in erythrocyte AChE activity of magnitude <20% are not considered to be biologically significant. The BMD modeling is described in greater detail in Appendix A. A nonhomogeneous variance linear model predicted a BMD and BMDL of 0.44 and 0.29 mg/kg/day, respectively.

An intermediate-duration oral MRL of 0.003 mg/kg/day was calculated by dividing the BMDL of 0.29 mg/kg/day by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

- An MRL of 0.003 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to guthion.

Dose-related reductions in erythrocyte AChE activity were observed in rats and dogs administered guthion in the feed for chronic durations. Statistically significant reductions in erythrocyte AChE activity were observed in male and female rats receiving 0.75 and 0.96 mg/kg/day guthion, respectively, from the feed for 2 years; however, these were only 10–22% reductions. Biologically significant reductions were mainly restricted to doses of 2.33 and 3.11 mg/kg/day in male (20–37% reduction) and female (23–31% reduction) rats, respectively (Schmidt and Chevalier 1984). Dogs appeared to be more sensitive to guthion. After 1 year, male dogs receiving 0.69 or 3.8 mg/kg/day showed reductions in erythrocyte AChE activity of 27 and 86%, respectively, while females receiving 0.78 or 4.3 mg/kg showed reductions in erythrocyte AChE activity of 35 and 86%, respectively (Allen et al. 1990). Significant reductions (19–

67%) in plasma ChE activity were observed in female rats at doses ≥0.96 mg/kg/day and in male rats at 2.3 mg/kg/day (Schmidt and Chevalier 1984). In male dogs fed guthion for 1 year, reductions in plasma ChE activity were 53% at 3.8 mg/kg/day while female dogs showed reductions of 30 and 53% at 0.78 and 4.3 mg/kg/day, respectively (Allen et al. 1990). Plasma ChE inhibition is used as an indicator of exposure, but does not serve as a reliable indicator of a neurotoxic effect. However, inhibition of red blood cell AChE and brain AChE represents a relevant neurological effect. Increased relative brain and liver weights, lower terminal body weight, and alopecia were observed in rats at 2.3 mg/kg/day (Schmidt and Chevalier 1984). Increased incidence of diarrhea and occasional emesis were observed in male dogs at 0.69 mg/kg/day. Diarrhea, occasional emesis, and reductions in terminal body weight were also observed in male and female dogs receiving guthion at 3.8 and 4.3 mg/kg/day, respectively, from the feed for 1 year (Allen et al. 1990). The available chronic-duration data indicate that reduction in erythrocyte AChE activity is the most sensitive end point following chronic-duration oral exposures to guthion. The 52-week study in dogs (Allen et al. 1990) was selected to derive the chronic-duration oral MRL because, at similar doses (0.69–0.78 mg/kg/day in dogs after 52 weeks and 0.75–0.96 mg/kg/day in rats after 2 years), there was a more marked reduction in erythrocyte AChE activity in dogs (20–43%) than in rats (10–22%).

Technical-grade guthion (91.9% a.i.) was administered in the feed at 5, 25, or 125 ppm to beagle dogs (4/sex/group) for 52 weeks (Allen et al. 1990). These dietary levels provided guthion doses of 0.15, 0.69, and 3.8 mg/kg/day, respectively, to the males, and 0.16, 0.78, 4.3 mg/kg/day, respectively, to the females. Erythrocyte AChE and plasma ChE activities were determined prior to treatment and periodically until study termination. Dose-related reductions in erythrocyte AChE activity were evident on week 52. A statistically nonsignificant reduction of 15% in erythrocyte AChE activity was observed in females at 0.16 mg/kg/day on week 52, but there was no effect in males. On week 52, reductions in erythrocyte AChE activity in males at 0.69 and 3.8 mg/kg/day were 27 and 86%, respectively. Females in the 0.78 and 4.3 mg/kg/day groups showed 35 and 86% reductions, respectively, in erythrocyte AChE activity. Brain AChE activity on week 52 in the 3.8 and 4.3 mg/kg/day groups was reduced by 27 and 20% in males and females, respectively. Reductions in brain AChE activity were 1 and 10% in female and male dogs receiving administered 0.78 and 0.69 mg/kg/day, respectively. No effect on brain AChE activity was observed in males administered 0.15 mg/kg/day or females administered 0.16 mg/kg/day. Plasma ChE activity was reduced by 53% in males and females administered 3.8 and 4.3 mg/kg/day, respectively. No statistically significant reductions in plasma ChE activity were observed in male or female dogs administered ≤0.69 or ≤0.78 mg/kg/day, respectively. Terminal body weights were reduced by 12% in males in the 3.8 mg/kg/day group and by 16% in females in the 4.3 mg/kg/day group, although

there was no difference in food consumption among treated and control animals. There were no treatment-related hematological effects or changes in urinalysis parameters. Findings were negative in hearing and opthalmoscopic tests conducted at study termination and there was no treatment-related increase in mortality in any dose group. There were no changes in absolute or relative organ weights in females at the doses tested. Absolute and relative spleen weights were reduced in males in a dose-related manner with significant reductions in relative spleen weight at doses ≥0.69 mg/kg/day; however, congestion of the spleen and increased absolute spleen weight were observed in 4/4 male dogs of the control group. A 7–17% decrease in albumin and albumin/globulin values were observed on week 52 in males of the 3.8 mg/kg/day group. A 39 and 15% increase in P450 activity was observed in male dogs at 3.8 mg/kg/day and in female dogs at 4.3 mg/kg/day, respectively. A 34 and 30% increase in N-demethylase activity was observed in male dogs at 3.8 mg/kg/day and in female dogs at 4.3 mg/kg/day, respectively. Other effects were restricted to the high dose groups (Allen et al. 1990).

In order to derive a point of departure to calculate a chronic-duration oral MRL, a BMD approach was applied to the changes in erythrocyte AChE activity observed in male and female dogs exposed to guthion in the diet for 52 weeks (Allen et al. 1990). BMDs and BMDLs were calculated using the EPA Benchmark Dose Software (BMDS version 1.3.2). The BMDs and BMDLs are estimates of the doses associated with a 20% change in erythrocyte AChE activity. Reductions in erythrocyte AChE activity of magnitude <20% are not considered to be biologically significant. The BMD modeling is described in greater detail in Appendix A. BMDs of 0.48 and 0.50 mg/kg/day in male and female dogs, respectively, and BMDLs of 0.30 and 0.32 mg/kg/day in male and female dogs, respectively, were obtained by analysis of the low-dose region of the dose-response curve for dogs exposed to guthion in the diet for 52 weeks. The lowest BMDL (0.30 mg/kg/day) was selected as the point of departure.

A chronic-duration oral MRL of 0.003 mg/kg/day was calculated by dividing the BMDL of 0.30 mg/kg/day by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

2. RELEVANCE TO PUBLIC HEALTH

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

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

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

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.

The principal toxic effect of guthion in humans and laboratory animals is inhibition of AChE, which results in the accumulation of acetylcholine at acetylcholine receptors leading to cholinergic responses in the peripheral (muscarinic and nicotinic) and central nervous system and neuromuscular junctions. In this Toxicological Profile for Guthion, AChE inhibition of magnitude 20–59% is considered a less serious adverse effect in the absence of more serious signs of neurotoxicity. AChE inhibition ≥60% is considered a more serious effect independent of the presence or absence of other neurotoxicity indicators.

3.2.1 Inhalation Exposure

Guthion has a low volatility; thus, inhalation exposure is likely to be to guthion aerosols rather than vapor. It is possible that some of the exposure under these conditions was by the dermal route and/or the oral route (grooming).

3.2.1.1 Death

No information was located regarding mortality in humans following inhalation exposure to guthion.

The 1-hour LC_{50} values and 95% confidence intervals in male and female rats were 69 (62–77) mg/m^3 and 79 (68–93) mg/m^3, respectively (EPA 1978a). There were no mortalities in male or female rats exposed to guthion aerosols at concentrations as high as 4.72 mg/m^3 for 6 hours/day, 5 days/week for 12 weeks (Kimmerle 1976).

The LC_{50} values for each species and duration category are shown in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No information was located regarding systemic effects in humans following inhalation exposure to guthion. Available information in animals is restricted to a single report of male and female Wistar rats exposed to guthion by inhalation at concentrations as high as 4.72 mg/m^3 for 6 hours/day, 5 days/week for 12 weeks (Kimmerle 1976). No significant effects on absolute or relative weights of the thyroid, adrenals, heart, lungs, liver, or kidneys were observed and there were no indications of exposure-related histopathological effects. No significant changes were seen regarding hemoglobin concentration, red blood cell concentration, thrombocyte concentration, percent packed cell volume, or leucocyte differentials.

Body Weight Effects. A 19.7% reduction in body weight gain was observed in male, but not female, Wistar rats exposed by inhalation to guthion at 4.72 mg/m^3, 6 hours/day, 5 days/week for 12 weeks (Kimmerle 1976). Weight gain was not affected at 1.24 mg/m^3.

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

3.2.1.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological or lymphoreticular effects in humans following inhalation exposure to guthion. Available information in animals is restricted to a single report of male and female Wistar rats exposed to guthion by inhalation at concentrations as high as 4.72 mg/m^3 for 6 hours/day, 5 days/week for 12 weeks (Kimmerle 1976). No significant effects on absolute or relative weights of the thymus or spleen were observed and there were no indications of exposure-related histopathological effects.

Table 3-1 Levels of Significant Exposure to Guthion - 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				69[b] M (LC50) 79 F (LC50)	EPA 1978a	
Neurological								
2	Rat (Sprague-Dawley)	1 hr			39 M (41% reduction in blood ChE)		EPA 1978a	
3	Rat (Wistar)	6 hr/d 5 d/wk 2 wk		1.24[c] M	4.72 M (25% reduction in erythrocyte ChE activity)		Kimmerle 1976	
INTERMEDIATE EXPOSURE								
Systemic								
4	Rat (Wistar)	6 hr/d 5 d/wk 12 wk	Bd Wt	1.24 M	4.72 M (19.7% reduction in body weight gain)		Kimmerle 1976	

Table 3-1 Levels of Significant Exposure to Guthion - 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
5	Rat (Wistar)	6 hr/d 5 d/wk 12 wk	Resp	4.72			Kimmerle 1976	No treatment-related effects on weight or morphology in thyroid, adrenals, heart, lung, liver, gonads, or kidneys.
			Cardio	4.72				
			Hemato	4.72				
			Hepatic	4.72				
			Renal	4.72				
			Endocr	4.72				
Immuno/ Lymphoret								
6	Rat (Wistar)	6 hr/d 5 d/wk 12 wk		4.72			Kimmerle 1976	No treatment-related effects on weight or morphology in thymus or spleen.
Neurological								
7	Rat (Wistar)	6 hr/d 5 d/wk 12 wk		1.24[d]	4.72	(29-48% reduction in erythrocyte ChE activity for males; 26-39% for females)	Kimmerle 1976	

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

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Used to derive an acute-duration inhalation minimal risk level (MRL) of 0.02 mg/m3; the MRL was derived by dividing the NOAEL[HEC] of 0.50 mg/m3 by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability).

d Used to derive an intermediate-duration and chronic-duration inhalation minimal risk level (MRL) of 0.01 mg/m3; the MRL was derived by dividing the NOAEL[HEC] of 0.37 mg/m3 by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; ChE = cholinesterase; d = day(s); Endocr = endocrine; F = Female; hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

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

Acute (≤14 days)

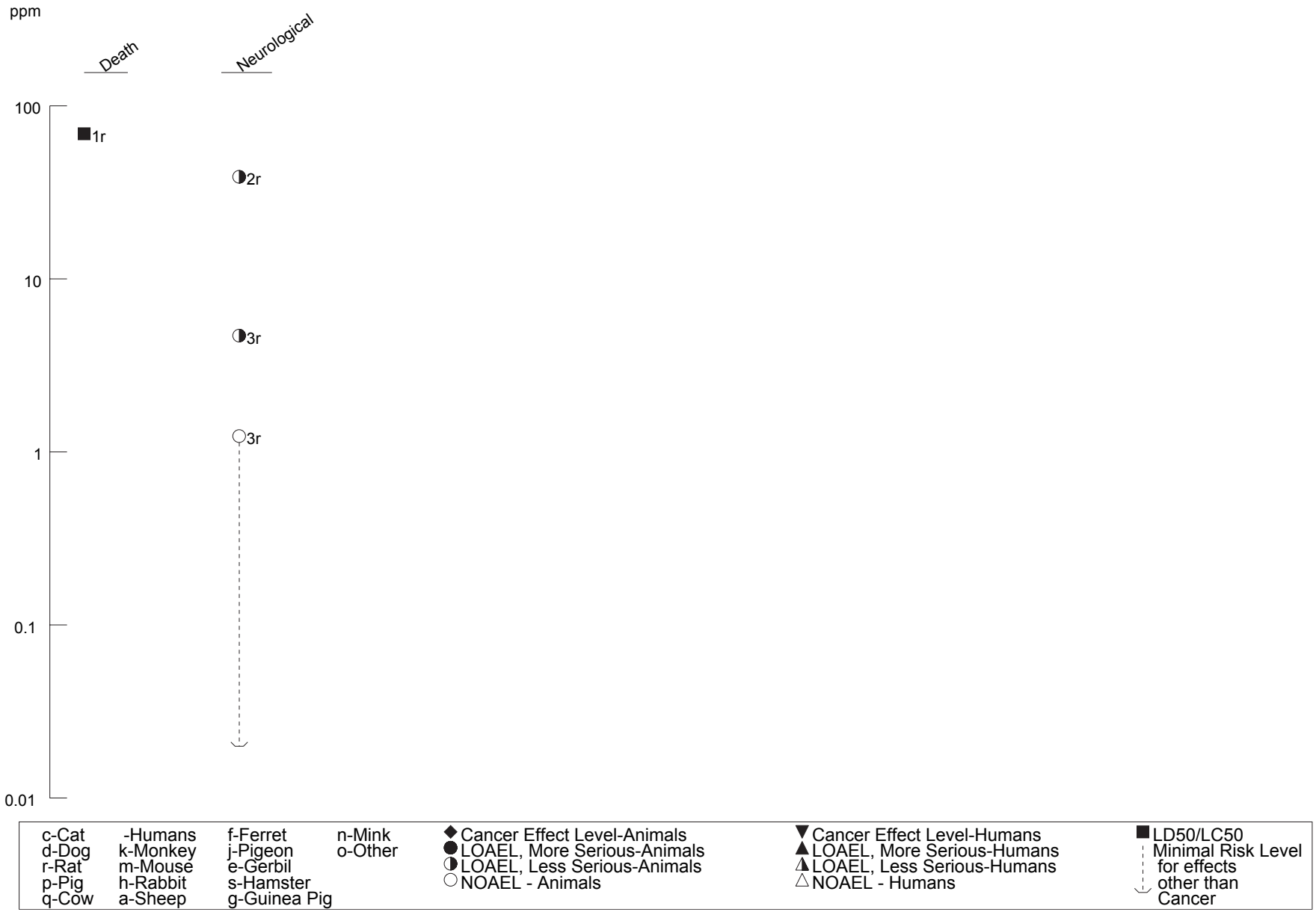
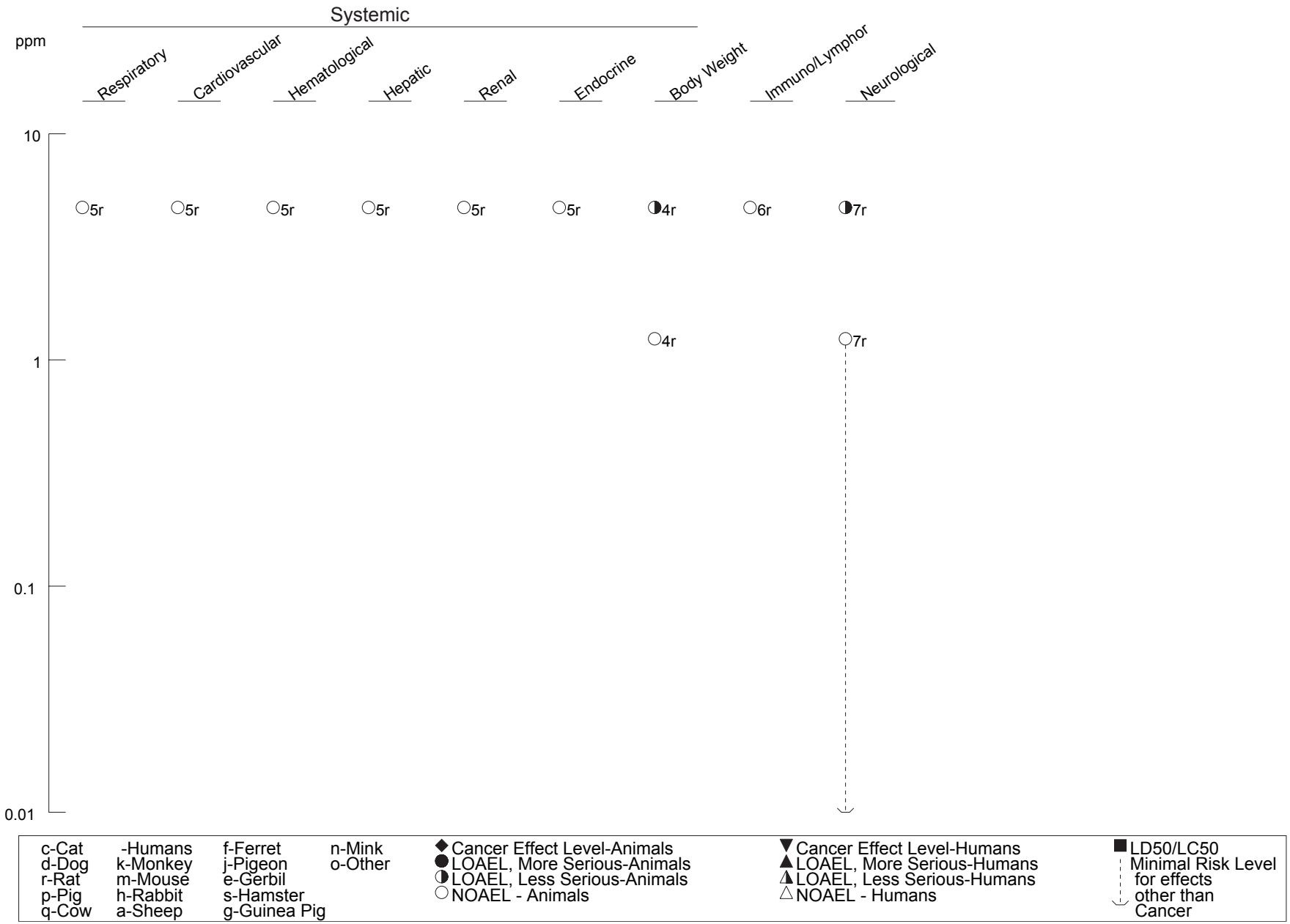


Figure 3-1 Levels of Significant Exposure to Guthion - Inhalation *(Continued)*

Intermediate (15-364 days)



The NOAEL for immunological and/or lymphoreticular effects in Wistar rats for intermediate-duration exposure is recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

Guthion, an AChE organophosphate, inhibits AChE in the central and peripheral nervous systems. Inhibition of AChE results in accumulation of acetylcholine at muscarinic and nicotinic receptors leading to peripheral and central nervous system effects. These effects usually appear within a few minutes to 24 hours after exposure, depending on the extent of exposure. Occupational exposure to guthion via inhalation would likely involve oral and dermal exposure routes as well. However, no information was located regarding associations between neurological effects in humans and inhalation exposure to guthion specifically.

EPA (1978a) reported a 41% (range 27–59%) reduction in blood plasma cholinesterase (plasma ChE) activity in rats exposed to guthion aerosols at 39 mg/m^3 for 1 hour. Erythrocyte AChE activity was reduced by >20% (range 25–44%) in male Wistar rats following exposure to guthion aerosols at 4.72 mg/m^3, 6 hours/day, 5 days/week, for 2–12 weeks; similarly-exposed female Wistar rats exhibited 26–39% reduced erythrocyte AChE activity after 4–12 weeks of exposure (Kimmerle 1976). The reductions in erythrocyte AChE activity were not associated with changes in appearance or behavior of the exposed animals. There were no biologically significant changes in erythrocyte AChE activity at ≤1.24 mg/m^3. The study investigators noted that brain cholinesterase activity was not reduced at any of the concentrations tested.

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

3.2.1.5 Reproductive Effects

No information was located regarding reproductive effects in humans following inhalation exposure to guthion. Available information in animals is restricted to a single report of male and female Wistar rats exposed to guthion by inhalation at concentrations as high as 4.72 mg/m^3 for 6 hours/day, 5 days/week for 12 weeks (Kimmerle 1976). No significant effects on absolute or relative weights of the gonads were observed and there were no indications of exposure-related histopathological effects.

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

3.2.1.6 Developmental Effects

No information was located regarding developmental effects in humans or animals following inhalation exposure to guthion.

3.2.1.7 Cancer

No information was located regarding cancer in humans or animals following inhalation exposure to guthion.

3.2.2 Oral Exposure

3.2.2.1 Death

No information was located regarding mortality in humans following oral exposure to guthion. A number of studies have examined the acute lethality of guthion in laboratory animals. Single-dose, oral toxicity studies with guthion administered to male or female rats reported LD_{50} values in the range of 11–26 mg/kg (DuBois et al. 1957; Gaines 1960; EPA 1978a; Pasquet et al. 1976). These studies suggest that male and female rats have similar susceptibilities to the acute lethal toxicity of guthion administered orally.

Single or repeated oral doses of guthion at ≥8 mg/kg/day killed all treated virgin female mice or rats and pregnant mice (Kavlock et al. 1985; Short et al. 1980). Elevated mortality rates in the 15–62% range were also observed in pregnant rats administered guthion at ≥4.9 mg/kg/day (Holzum 1990; Short et al. 1980). No significant increases in mortality were observed in male or female mice or rats after acute-, intermediate-, or chronic-duration oral exposures to ≤4 mg/kg/day (Allen et al. 1990; Holzum 1990; Schmidt and Chevalier 1984; Short et al. 1980).

No treatment-related increased mortality was observed in male or female rats receiving up to 2.3 or 3.1 mg guthion/kg/day, respectively, from the diet for up to 2 years (Schmidt and Chevalier 1984) or in male and female dogs receiving up to 3.8 or 4.3 mg guthion/kg/day, respectively, from the diet for 52 weeks (Allen et al. 1990).

The LD_{50} values for each species and duration category are shown in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No information was located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, or metabolic effects in humans. No information was located regarding dermal or metabolic effects in animals following oral exposure to guthion.

Respiratory Effects. Information regarding respiratory effects following oral exposure to guthion is limited. There were no gross or histopathological signs of treatment-related respiratory effects in male and female Osborne-Mendel rats receiving up to 10.9 and 9.6 mg guthion/kg/day, respectively, from the diet for up to 80 weeks or in male and female B6C3F1 mice receiving up to 10.7 and 21.6 mg guthion/kg/day, respectively, from the diet for 80 weeks (NCI 1978).

Cardiovascular Effects. Information regarding cardiovascular effects following oral exposure to guthion is limited. There were no gross or histopathological signs of treatment-related cardiovascular effects in male and female Osborne-Mendel rats receiving up to 10.9 and 9.6 mg guthion/kg/day, respectively, from the diet for up to 80 weeks or in male and female B6C3F1 mice receiving up to 10.7 and 21.6 mg guthion/kg/day, respectively, from the diet for 80 weeks (NCI 1978).

Gastrointestinal Effects. Treatment-related increased incidences of mucoid feces and diarrhea were reported in male dogs receiving 0.69 or 3.8 mg guthion/kg/day or female dogs receiving 4.3 mg guthion/kg/day from the diet for up to 1 year (Allen et al. 1990). There were no gross or histopathological signs of treatment-related gastrointestinal effects in male and female Osborne-Mendel rats receiving up to 10.9 and 9.6 mg guthion/kg/day, respectively, from the diet for up to 80 weeks or in male and female B6C3F1 mice receiving up to 10.7 and 21.6 mg guthion/kg/day, respectively, from the diet for 80 weeks (NCI 1978).

Hematological Effects. No biologically significant hematological effects were observed in male or female rats receiving up to 2.3 and 3.1 mg guthion/kg/day, respectively, from the diet for up to 2 years; significantly elevated thrombocyte counts in high-dose female rats at 6–24 months were found to be within the normal range of variability (Schmidt and Chevalier 1984). No treatment-related hematological

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	Once (G)				16[b] M (14 day LD50) 18 F (14 day LD50)	EPA 1978a	
2	Rat (Sherman)	Once (GO)				13 M (14 day LD50) 11[b] F (14 day LD50)	Gaines 1960	
3	Rat (CD)	Once (G)				26 M (10 day LD50) 24[b] F (10 day LD50)	Pasquet et al. 1976	
4	Rat (CD)	35 d 1 x/d (GO)				8 F (100% mortality)	Short et al. 1980	
5	Mouse (CD-1)	Once Gd 8 (GO)				20 F (21/40 maternal death)	Kavlock et al. 1985	
6	Mouse (CD)	10 d 1 x/d (GO)				8 F (100% mortality)	Short et al. 1980	
Systemic								
7	Rat (Sprague-Dawley)	Gd 6-15 (GO)	Bd Wt	2 F			Astroff and Young 1998	

Table 3-2 Levels of Significant Exposure to Guthion - 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
8	Rat (CD)	Gd 6-15 (GO)	Bd Wt	2.5 F		5 F (50% reduction in maternal weight gain)	Short et al. 1980	
9	Mouse (CD-1)	Once Gd 8 (GO)	Bd Wt	16 F	20 F (19% reduction in maternal weight gain)		Kavlock et al. 1985	
10	Mouse (CD-1)	Gd 6-15 (GO)	Bd Wt	5 F			Short et al. 1980	
Neurological								
11	Rat (Sprague-Dawley)	Gd 6-15 (GO)		1 F[c]	2 F (40% reduction in maternal brain ChE activity on gestation day 16)	2 F (75% reduction in maternal erythrocyte ChE activity on gestation day 16)	Astroff and Young 1998	
12	Rat (Sprague-Dawley)	Once (G)				16 M (signs of cholinergic poisoning: salivation, lacrimation, exophthalmus, defecation, urination, and muscle fasciculations)	EPA 1978a	
13	Rat (CD)	Once (G)			2 F (21-24% reduction in erythrocyte and brain ChE activity)	18 F (65-82% reduction in brain and erythrocyte ChE activity)	Pasquet et al. 1976	

Table 3-2 Levels of Significant Exposure to Guthion - 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
14	Rat (CD)	35 d 1 x/d (GO)		4 F		8 F (salivation, urination, lacrimation, and tremors)	Short et al. 1980	
15	Rat (Holtzman)	1 wk (F)		2.8 F		5.7 F (78.2% reduction in brain ChE activity)	Su et al. 1971	
16	Mouse (CD-1)	10 d 1 x/d (GO)		4 F		8 F (salivation, urination, lacrimation, and tremors)	Short et al. 1980	
17	Mouse (CD-1)	Gd 6-15 (GO)		2.5 F		5 F (tremors, salivation, and urination observed in some pregnant mice)	Short et al. 1980	
Reproductive								
18	Rat (Sprague-Dawley)	Gd 6-15 (GO)		2 F			Astroff and Young 1998	
19	Mouse (CD-1)	Once Gd 8 (GO)		16 F	20 F (reduced incidence of viable litters)		Kavlock et al. 1985	
Developmental								
20	Rat (Sprague-Dawley)	Gd 6-15 (GO)		2			Astroff and Young 1998	

Table 3-2 Levels of Significant Exposure to Guthion - 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
21	Mouse (CD-1)	Once Gd 8 (GO)		16	20 (11% reduction in fetal body weight)		Kavlock et al. 1985	This dose level was associated with an increase in maternal mortality.
22	Mouse (CD-1)	Once Gd 8 (GO)			16 (increased incidence of supernumerary ribs)		Kavlock et al. 1985	
23	Mouse (CD-1)	Gd 6-15 (GO)		2.5	5 (increased incidence of malaligned sternebrae in fetuses)		Short et al. 1980	
INTERMEDIATE EXPOSURE								
Death								
24	Rat (Wistar)	14 wk before mating to ppd 5 or 28 (F)				4.9 F (7/46 rats died or were moribund and sacrificed)	Holzum 1990	
25	Rat (CD)	Gd 6-ppd 21 (GO)				5 F (62% mortality in dams)	Short et al. 1980	
26	Rat (Wistar)	3 wk (F)				11.5 M (increased mortality, incidence not provided)	Vos et al. 1983	

Table 3-2 Levels of Significant Exposure to Guthion - 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
27	Dog Cocker spaniel	26 wk (F)		3.8[b] M 4.3 F			Allen et al. 1990	
Systemic								
28	Rat (Wistar)	8 wk (F)	Other	0.75 M	2.3 M (15/60 increased incidence of alopecia)		Schmidt and Chevalier 1984	
29	Rat (Fischer- 344)	13 wk (F)	Bd Wt	2.8[b] M 3.2 F	7.9 M (unspecified reduction in terminal body weight)		Sheets et al. 1997	
30	Rat (Wistar)	3 wk (F)	Bd Wt	2.3 M	11.5 M (decreased terminal body weight, magnitude not provided)		Vos et al. 1983	
31	Rat (Wistar)	3 wk (F)	Endocr	2.3 M	11.5 M (decreased relative pituitary weight; unspecified histopathologic findings in the pituitary and adrenals; quantitative results not provided)		Vos et al. 1983	

Table 3-2 Levels of Significant Exposure to Guthion - 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
32	Dog Cocker spaniel	8 wk (F)	Gastro	0.15[b] M 0.78 F	0.69[b] M (increased incidence of mucoid diarrhea and emesis) 4.3 F (increased incidence of mucoid diarrhea and emesis)		Allen et al. 1990	
33	Dog Cocker spaniel	26 wk (F)	Ocular	3.8[b] M 4.3 F			Allen et al. 1990	
34	Dog Cocker spaniel	26 wk (F)	Hemato	3.8[b] M 4.3 F			Allen et al. 1990	
Immuno/ Lymphoret								
35	Rat (Wistar)	3 wk (F)		2.3 M	11.5 M (decreased relative spleen and mesenteric lymph node weights, as well histopathologic findings in the thymus; quantitative results not provided)		Vos et al. 1983	

Table 3-2 Levels of Significant Exposure to Guthion - 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								
36	Rat (Wistar)	14 wk before mating to ppd 5 or 28 (F)			0.55 F (25 and 47% reductions in erythrocyte ChE activity on lactation days 5 and 28, respectively)	1.5 F (75 and 84% reductions in erythrocyte ChE activity on lactation days 5 and 28, respectively)	Holzum 1990	
37	Rat (Fischer- 344)	13 wk (F)			0.91 M (37% reduction in erythrocyte ChE activity on week 13)	2.8 M (84% reduction in erythrocyte ChE activity on week 13)	Sheets et al. 1997	
38	Rat (Fischer- 344)	13 wk (F)		1.1 F		3.2 F (tremors, incoordinated gait, and perianal staining)	Sheets et al. 1997	
39	Rat (CD)	Gd 6-ppd 21 (GO)		2.5 F		5 F (tremors, salivation, and urination were observed in some pregnant CD rats)	Short et al. 1980	
40	Dog Cocker spaniel	26 wk (F)		0.15[d] M	0.69 M (22-40% reduction in erythrocyte ChE activity)	3.8 M (66-88% reduction in erythrocyte ChE activity; 37-58% reduction in plasma ChE activity; 27% reduction in brain ChE)	Allen et al. 1990	

Table 3-2 Levels of Significant Exposure to Guthion - 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
Reproductive								
41	Rat (Wistar)	14 wk before mating to ppd 5 or 28 (F)		3.7[b] M 4.9 F			Holzum 1990	Insemination, fertility, or gestation indices or duration of gestation were not affected.
42	Rat (Wistar)	3 wk (F)		2.3 M	11.5 M (unspecified histopathologic findings in the testes)		Vos et al. 1983	
Developmental								
43	Rat (Wistar)	14 wk before mating to ppd 5 or 28 (F)		0.43[b] M 0.55 F	1.3[b] M (statistically significant reduction in viability of pups on ppd 5) 1.5 F (statistically significant reduction in viability of pups on ppd 5)		Holzum 1990	
44	Rat (Wistar)	14 wk before mating to ppd 5 or 28 (F)		1.5 F	4.9 F (significantly lower (19-25%) pup weight, relative to controls, on ppd 14 and 21)		Holzum 1990	
45	Rat (Wistar)	14 wk before mating to ppd 5 or 28 (F)		3.8 M			Holzum 1990	No reduction in viability when treated males were mated with untreated females.

Table 3-2 Levels of Significant Exposure to Guthion - 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
46	Rat (Wistar)	14 wk before mating to ppd 5 or 28 (F)		1.5 F	4.9 F (in pups: significant (19%) reduction in brain weight on ppd 5 and 46% reduction in brain ChE activity on ppd 28)		Holzum 1990	
47	Rat (CD)	Gd 6-ppd 21 (GO)		2.5		5 (34% reduction in pup weight; 85% reduction in pup survival)	Short et al. 1980	This exposure level was also associated with an increase in maternal mortality.
48	Rat (CD)	Gd 6-ppd 21 (GO)		2.5	5 (in pups in the surviving litter: rear legs were stiff, at right angles to the body; pups lacked neuromuscular coordination of hind legs; muscle tremors in the tail and upturned snouts)		Short et al. 1980	The 5 mg/kg/day dose was associated with an increase in maternal mortality.
CHRONIC EXPOSURE								
Death								
49	Rat (Wistar)	2 yr (F)		2.3[b] M 3.1 F			Schmidt and Chevalier 1984	
Systemic								
50	Rat (Wistar)	2 yr (F)	Bd Wt	0.75[b] M 3.11 F	2.33 M (10% reduction in body weight)		Schmidt and Chevalier 1984	

Table 3-2 Levels of Significant Exposure to Guthion - 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
51	Rat (Wistar)	2 yr (F)	Dermal	0.75 M	2.3 M (15/60 increased incidence of alopecia)		Schmidt and Chevalier 1984	
52	Rat (Wistar)	2 yr (F)	Ocular	2.3[b] M 3.1 F			Schmidt and Chevalier 1984	
53	Rat (Wistar)	2 yr (F)	Hemato	2.3 M 0.96[b] F	3.1 F (thrombocyte values significantly elevated by 20-25%)		Schmidt and Chevalier 1984	
54	Rat (Wistar)	2 yr (F)	Hepatic	2.3 M 0.96[b] F			Schmidt and Chevalier 1984	
55	Rat (Wistar)	2 yr (F)	Renal	2.3[b] M 3.1 F			Schmidt and Chevalier 1984	

Table 3-2 Levels of Significant Exposure to Guthion - 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
56	Dog Cocker spaniel	52 wk (F)	Gastro	0.15[b] M 0.78 F	0.69[b] M (increased incidence of mucoid diarrhea and emesis) 4.3 F (increased incidence of mucoid diarrhea and emesis)		Allen et al. 1990	
57	Dog Cocker spaniel	52 wk (F)	Ocular	3.8[b] M 4.3 F			Allen et al. 1990	
58	Dog Cocker spaniel	52 wk (F)	Hemato	3.8[b] M 4.3 F			Allen et al. 1990	
59	Dog Cocker spaniel	52 wk (F)	Hepatic	0.69[b] M 0.78 F			Allen et al. 1990	
60	Dog Cocker spaniel	52 wk (F)	Bd Wt	0.69 M	3.8 M (12% decrease in terminal body weight)		Allen et al. 1990	

Table 3-2 Levels of Significant Exposure to Guthion - 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
61	Dog Cocker spaniel	52 wk (F)	Renal	3.8[b] M 4.3 F			Allen et al. 1990	
Neurological								
62	Rat (Wistar)	2 yr (F)		0.25 M	2.3 M (38-49% reduction in plasma ChE activity; 32% reduction in brain ChE activity; 7-11% increase in relative brain weight) 0.75 M (10-22% reduction in erythrocyte ChE activity)		Schmidt and Chevalier 1984	
63	Dog Cocker spaniel	52 wk (F)		0.15[e] M	0.69 M (27% reduction in erythrocyte ChE activity)	3.8 M (86% reduction in erythrocyte ChE activity)	Allen et al. 1990	

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

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Used to derive an acute-duration oral minimal risk level (MRL) of 0.01 mg/kg/day; the MRLs were derived by dividing the BMDL of 1.04 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 to protect sensitive subpopulations).

d Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.003 mg/kg/day; the MRL was derived by dividing the BMDL of 0.29 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 to protect sensitive subpopulations).

e Used to derive a chronic-duration oral minimal risk level (MRL) of 0.003 mg/kg/day; the MRL was derived by dividing the BMDL of 0.30 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 to protect sensitive subpopulations).

ChE = cholinesterase; Bd Wt = body weight; d = day(s); (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; ppd = post-parturition day; x = time(s); wk = week(s); yr = year(s)

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

Acute (≤14 days)

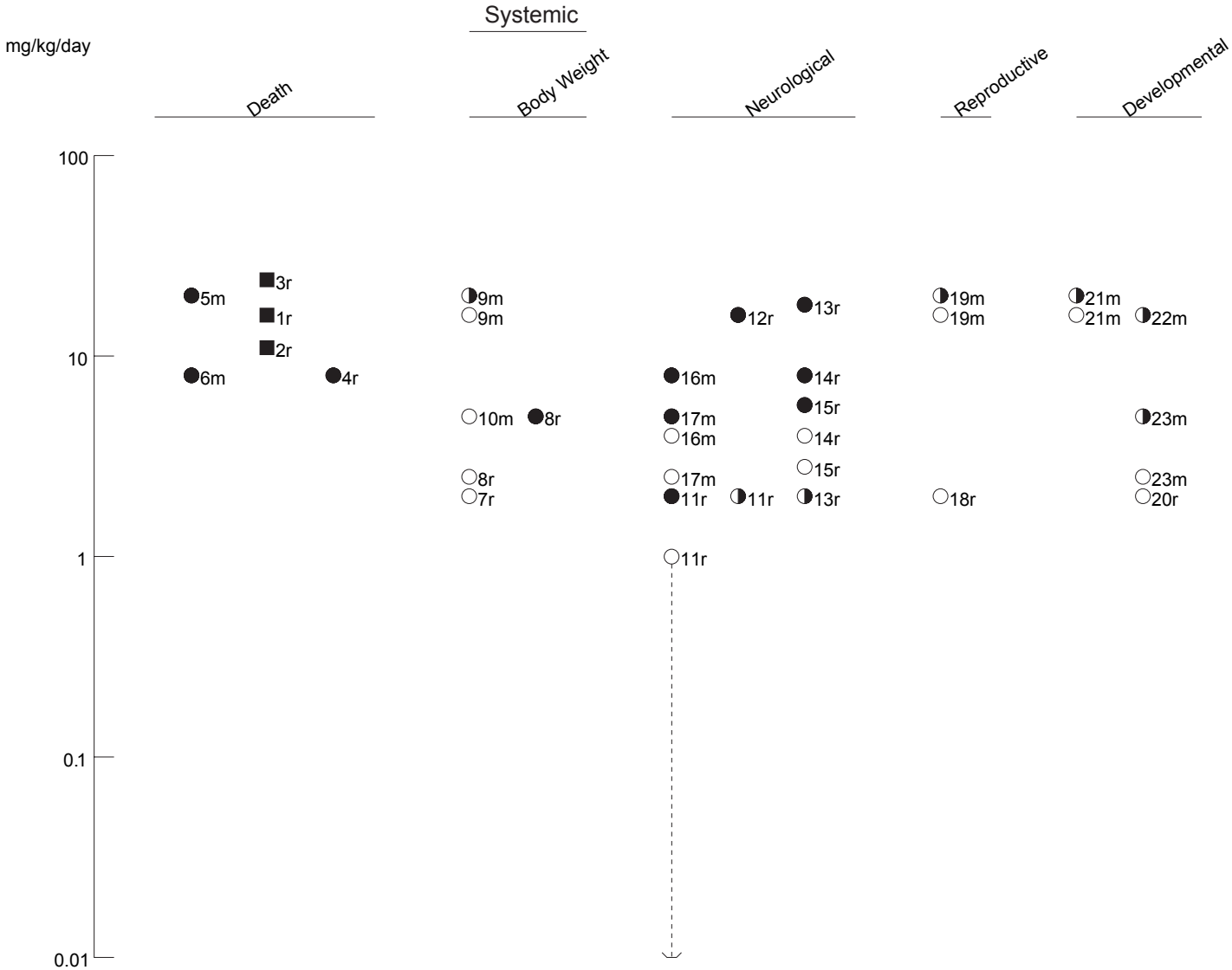


Figure 3-2 Levels of Significant Exposure to Azinphos-methyl - Oral *(Continued)*

Intermediate (15-364 days)

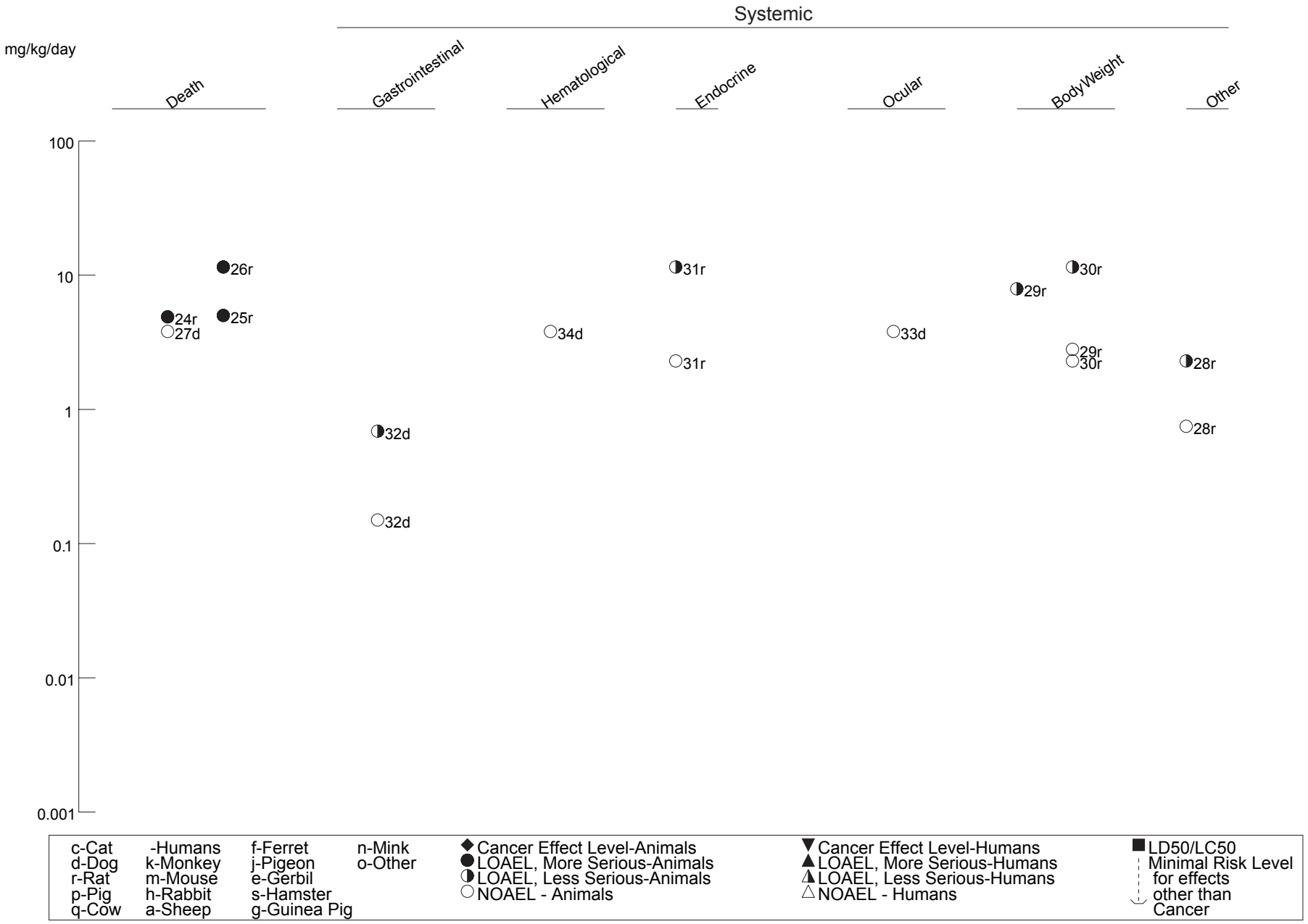
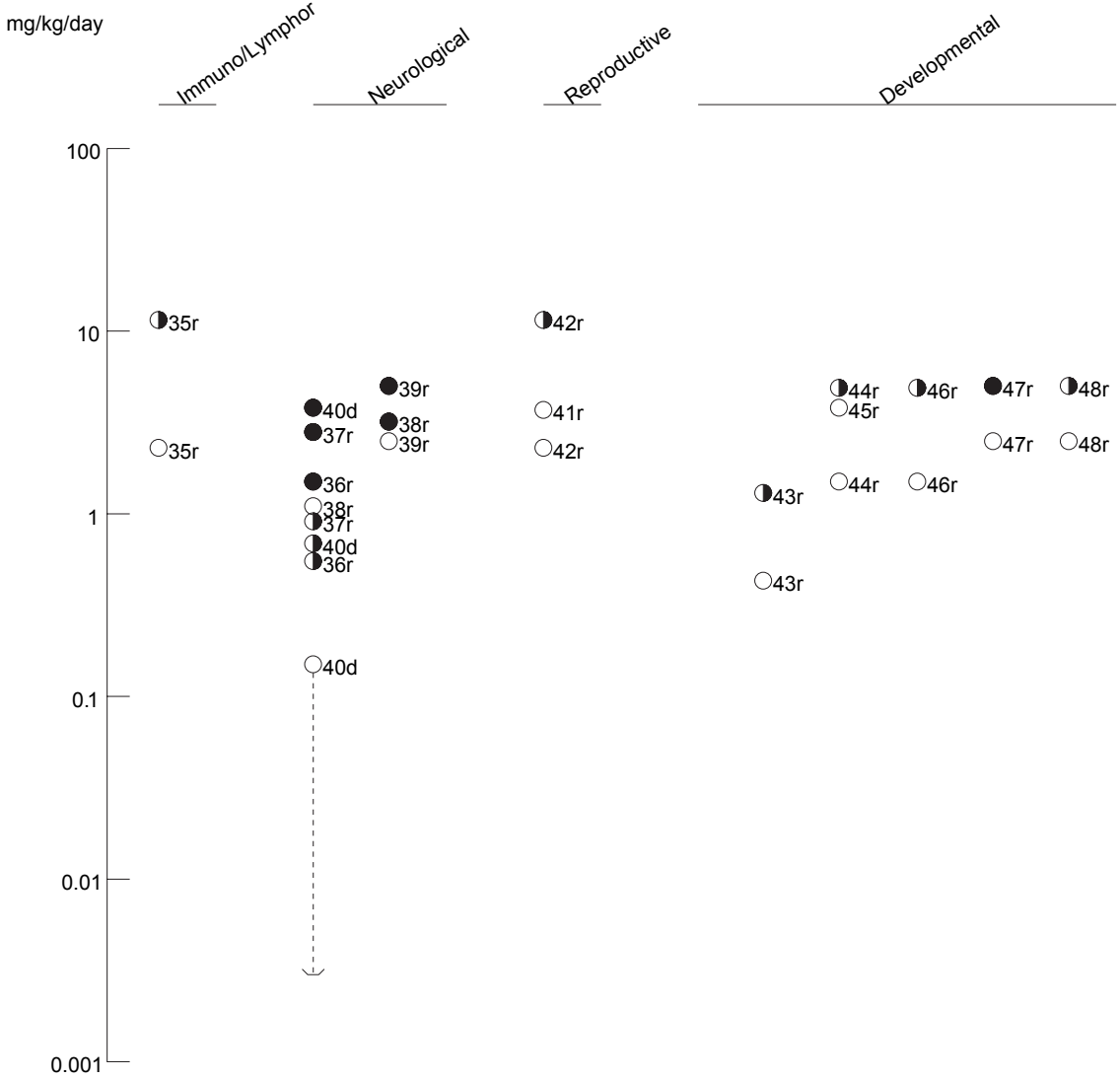


Figure 3-2 Levels of Significant Exposure to Guthion - Oral *(Continued)*

Intermediate (15-364 days)



c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

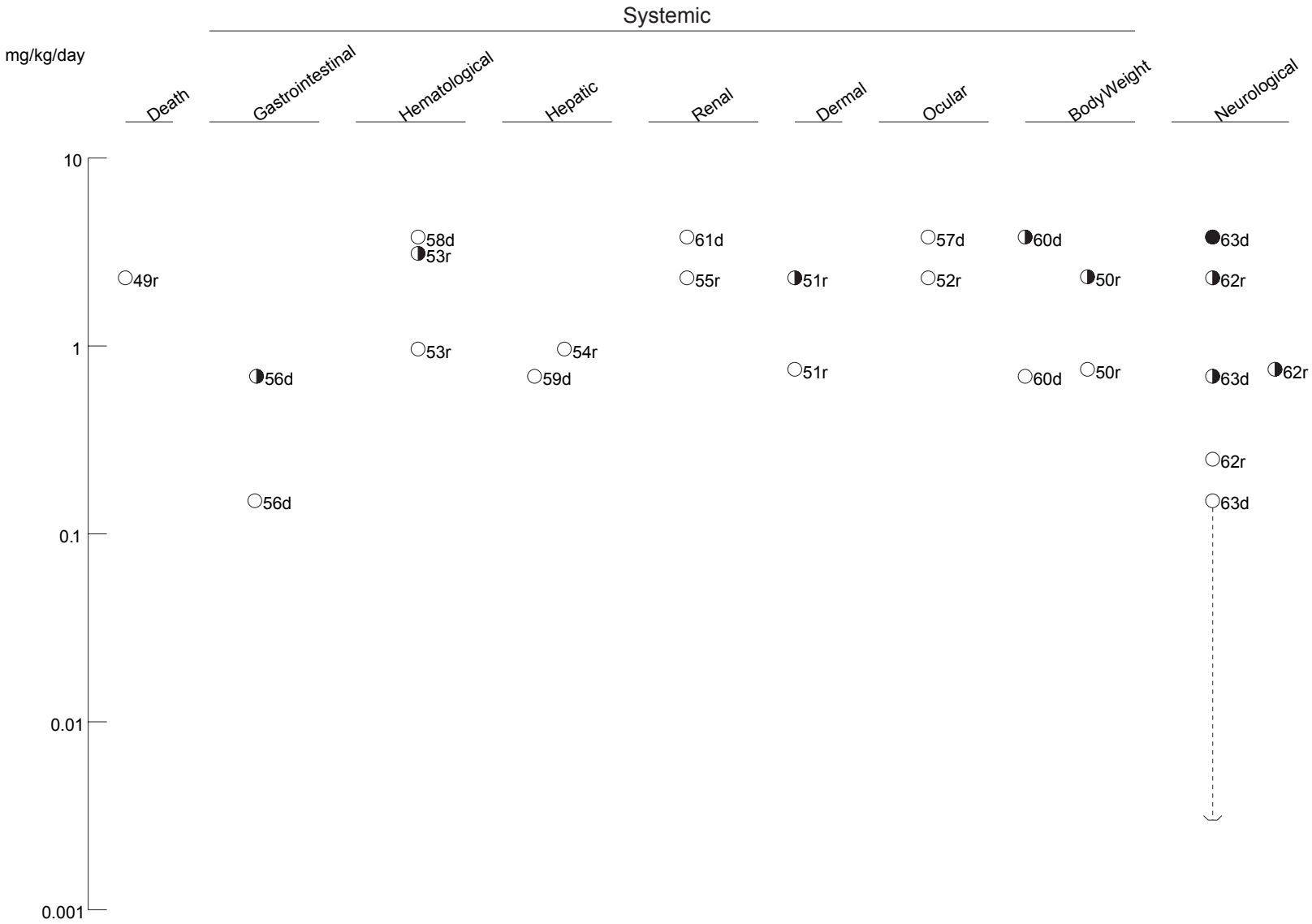
◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

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

Chronic (≥365 days)



effects were observed in male or female dogs receiving as much as 3.8 or 4.3 mg guthion/kg/day, respectively, from the diet for up to 12 months (Allen et al. 1990).

Musculoskeletal Effects. Information regarding musculoskeletal effects following oral exposure to guthion is limited. There were no gross or histopathological signs of treatment-related musculoskeletal effects in male and female Osborne-Mendel rats receiving up to 10.9 and 9.6 mg guthion/kg/day, respectively, from the diet for up to 80 weeks or in male and female B6C3F1 mice receiving up to 10.7 and 21.6 mg guthion/kg/day, respectively, from the diet for 80 weeks (NCI 1978).

Hepatic Effects. Information regarding hepatic effects following oral exposure to guthion is limited. There were no gross or histopathological signs of treatment-related hepatic effects in male and female Osborne-Mendel rats receiving up to 10.9 and 9.6 mg guthion/kg/day, respectively, from the diet for up to 80 weeks or in male and female B6C3F1 mice receiving up to 10.7 and 21.6 mg guthion/kg/day, respectively, from the diet for 80 weeks (NCI 1978).

Renal Effects. Urinalysis did not reveal evidence of exposure-related renal effects in male or female rats receiving 2.3 or 3.1 mg guthion/kg/day, respectively, from the diet for up to 2 years (Schmidt and Chevalier 1984) or in male and female dogs receiving 3.8 or 4.3 mg guthion/kg/day, respectively, from the diet for 52 weeks (Allen et al. 1990). Pathologic examinations of the guthion-exposed rats and dogs revealed no signs of treatment-related adverse renal effects (Allen et al. 1990; Schmidt and Chevalier 1984). There were no gross or histopathological signs of treatment-related renal effects in male and female Osborne-Mendel rats receiving up to 10.9 and 9.6 mg guthion/kg/day, respectively, from the diet for up to 80 weeks or in male and female B6C3F1 mice receiving up to 10.7 and 21.6 mg guthion/kg/day, respectively, from the diet for 80 weeks (NCI 1978).

Endocrine Effects. Vos et al. (1983) reported decreased relative pituitary weight as well as unspecified histopathologic findings in the pituitary and adrenals of male Wistar rats receiving 11.5 mg/kg/day guthion from the diet for 3 weeks. This effect was not seen in rats receiving 2.3 mg/kg/day. There were no histopathological indications of treatment-related effects on thyroid, parathyroid, pituitary, or adrenal tissues among male and female rats receiving up to 2.3 or 3.1 mg guthion/kg/day, respectively, from the diet for up to 2 years (Schmidt and Chevalier 1984), male and female dogs receiving up to 3.8 or 4.3 mg guthion/kg/day, respectively, from the diet for 52 weeks (Allen et al. 1990), male and female Osborne-Mendel rats receiving up to 10.9 and 9.6 mg guthion/kg/day,

respectively, from the diet for up to 80 weeks (NCI 1978), or male and female B6C3F1 mice receiving up to 10.7 and 21.6 mg guthion/kg/day, respectively, from the diet for 80 weeks (NCI 1978).

Ocular Effects. No treatment-related ocular effects were observed in male or female rats receiving up to 2.3 or 3.1 mg guthion/kg/day, respectively, from the diet for up to 2 years (Schmidt and Chevalier 1984). No treatment-related effects were observed in opthalmoscopic examinations conducted in male and female dogs receiving up to 3.8 or 4.3 mg guthion/kg/day, respectively, from the diet for 52 weeks (Allen et al. 1990).

Body Weight Effects. Reductions in body weight gain or terminal body weights have been observed following acute, intermediate, and chronic oral exposure to guthion. A 19% decrease in maternal body weight gain was observed in mouse dams administered a single gavage dose of 20 mg guthion/kg/day on gestational day 8 (Kavlock et al. 1985). A 50% reduction in maternal body weight gain was observed in rat dams administered 5 mg guthion/kg/day by gavage on gestational days 6–15; the 5 mg/kg/day dose level also resulted in 25% decreased food consumption and clinical signs of AChE inhibition (tremors and salivation) (Short et al. 1980). Maternal body weight was not adversely affected in other rats or mice administered 2 or 2.5 mg guthion/kg/day, respectively, by gavage on gestational days 6–15 (Astroff and Young 1998; Short et al. 1980). Male and female dogs receiving 3.8 and 4.3 mg guthion/kg/day, respectively, from the diet for 52 weeks exhibited 12 and 16% lower mean final body weights than their respective controls in the absence of a treatment-related effect on food consumption; no significant body weight effects were seen in the male or female dogs receiving doses ≤0.69 and 0.78 mg/kg/day, respectively (Allen et al. 1990). Body weights of male rats receiving 2.3 mg guthion/kg/day from the diet were approximately 10% lower than controls throughout 2 years of treatment in the absence of a treatment-related effect on food consumption; no significant treatment-related effects on body weight were seen at lower doses in males or in females receiving up to 3.1 mg guthion/kg/day (Schmidt and Chevalier 1984). Significantly decreased growth (approximately 10–15% lower than controls) was observed consistently during 80 weeks of dietary exposure of Osborne-Mendel rats receiving 5.5 or 10.9 mg guthion/kg/day (males) and 9.6 mg/kg/day (females) (NCI 1978). There were no indications of treatment-related body weight effects in similarly-exposed male and female B6C3F1 mice receiving up to 10.7 and 21.6 mg guthion/kg/day, respectively (NCI 1978). An unspecified decrease in body weight (investigators noted that most body weight changes observed in this study of several compounds were 5–15%) was observed in male rats following 13 weeks of exposure to 7.9 mg/kg/day, but not after exposure to 2.8 mg/kg/day (Sheets et al. 1997); decreases in body weight and food consumption were observed in females at 7 mg/kg/day but not at 3.2 mg/kg/day.

Other Systemic Effects. Among male and female rats receiving 2.3 and 3.1 mg guthion/kg/day, respectively, from the diet for up to 2 years, chronic alopecia was noted. Clinical chemistry performed on these rats did not reveal signs of treatment-related effects (Schmidt and Chevalier 1984). Serum albumin and albumin/globulin values were significantly reduced in male dogs receiving 3.8 mg guthion/kg/day from the diet for 52 weeks; the magnitudes of these reductions in albumin and albumin/globulin ranged from 7 to 13% and from 17 to 20%, respectively, from weeks 13 to 52 (Allen et al. 1990). Dietary administration of guthion to male and female dogs for 52 weeks at concentrations resulting in doses of 3.8 mg/kg/day (males) and 4.3 mg/kg/day (females) resulted in 39 and 15% increased cytochrome P-450 activity (males and females, respectively) (Allen et al. 1990).

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

3.2.2.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological or lymphoreticular effects in humans following oral exposure to guthion. Vos et al. (1983) reported decreased relative spleen and mesenteric lymph node weights, as well as unspecified histopathologic findings in the thymus in male Wistar rats receiving 11.5 mg guthion/kg/day from the diet for 3 weeks; no effects were seen at a dose level of 2.3 mg/kg/day. No evidence of treatment-related histopathological effects were seen in sections of spleens from male and female rats receiving up to 2.3 and 3.1 mg guthion/kg/day, respectively, from the diet for up to 2 years (Schmidt and Chevalier 1984). Significantly lower mean relative spleen weights (0.29 and 0.26% of body weight, compared to 0.63% in controls) were noted in male dogs receiving 0.69 and 3.8 mg guthion/kg/day from the diet for 52 weeks (Allen et al. 1990). However, the study authors considered this effect to have been the result of an unusually high incidence of congested spleen in the control dogs rather than a treatment-related effect. No significant treatment-related effect on spleen weight was seen in similarly-exposed female dogs at doses as high as 4.3 mg/kg/day (Allen et al. 1990). There were no gross or histopathological signs of treatment-related immunological or lymphoreticular effects in spleen and lymph nodes of male and female Osborne-Mendel rats receiving up to 10.9 and 9.6 mg guthion/kg/day, respectively, from the diet for up to 80 weeks or in male and female B6C3F1 mice receiving up to 10.7 and 21.6 mg guthion/kg/day, respectively, from the diet for 80 weeks (NCI 1978).

3.2.2.4 Neurological Effects

Available human data are limited to observations of the lack of significant changes in plasma ChE or erythrocyte AChE activity in a group of five subjects receiving guthion orally at up to 0.29 mg/kg/day for 4 weeks (Rider and Puletti 1969; Rider et al. 1970, 1971, 1972).

As discussed in detail in Section 3.5. Mechanisms of Action, guthion poisoning is characterized by the inhibition of AChE in the central and peripheral nervous system. AChE is also present in erythrocytes. In *in vitro* assays, roughly equivalent inhibition of AChE in erythrocytes and neural tissues is produced by a given concentration of organophosphates such as guthion (Iyaniwura 1991). Therefore, inhibition of erythrocyte AChE can be used as a surrogate indicator of the extent of inhibition of neural AChE. Blood plasma also contains other cholinesterases (ChEs). In humans, plasma ChE is almost exclusively composed of butyrylcholinesterase, which is capable of hydrolyzing acetylcholine and butyrylcholine *in vitro*. The *in vivo* substrate of plasma ChE is unknown. In general, plasma ChE can be inhibited by guthion at lower levels of exposure than those required to inhibit neural or erythrocyte AChE. Plasma ChE activity is considered to be a sensitive indicator of exposure to organophosphates such as guthion, but not an indicator of a neurologic effect.

The most commonly observed neurological effects in laboratory animals treated orally with guthion are the inhibition of erythrocyte AChE activity and clinical signs of cholinesterase inhibition (Allen et al. 1990; Astroff and Young 1998; Holzum 1990; Pasquet et al. 1976; Schmidt and Chevalier 1984; Sheets et al. 1997; Short et al. 1980; Su et al. 1971). Treatment-related decreased erythrocyte AChE activity is generally the most sensitive end point. Reductions in brain AChE activity are observed at somewhat higher doses than those affecting erythrocyte AChE. Clinical signs are only evident in animals at doses several times higher than those eliciting reductions in AChE activity. Cholinergic signs such as salivation, lacrimation, exophthalmus, defecation, urination, and muscle fasciculations have been observed in rats and mice administered lethal oral doses of guthion (EPA 1978a; Pasquet et al. 1976; Short et al. 1980) and in rats and mice administered guthion doses ≥3.2 mg/kg/day (Sheets et al. 1997; Short et al. 1980). Reductions in erythrocyte AChE activity of ≥75% (considered a serious adverse effect) were observed in rats and dogs after acute, intermediate, or chronic oral exposures to guthion at doses ≥2 mg/kg/day (Allen et al. 1990; Astroff and Young 1998; Pasquet et al. 1976; Sheets et al. 1997) and reductions in the range of 20–50% have been observed in rats or dogs after acute-to-chronic oral exposure to guthion at doses ranging from 0.55 to 2 mg/kg/day (Allen et al. 1990; Holzum 1990; Pasquet et al. 1976; Schmidt and Chevalier 1984; Sheets et al. 1997). No biologically significant changes in

erythrocyte AChE activity were seen in rats receiving 0.43 mg guthion/kg/day for at least 14 weeks (Holzum 1990), dogs receiving 0.15–0.16 mg guthion/kg/day for 52 weeks (Allen et al. 1990), or rats receiving 0.25–0.31 mg guthion/kg/day for 2 years (Schmidt and Chevalier 1984).

Brain AChE activity was reduced by 20–78% in rats and dogs receiving acute or chronic oral doses of guthion ranging from 0.96 to 5.7 mg/kg/day; lower oral doses failed to elicit levels of biologically significant (≥20%) brain AChE inhibition (Allen et al. 1990; Astroff and Young 1998; Pasquet et al. 1976; Schmidt and Chevalier 1984; Su et al. 1971).

Reductions of 35–58% in plasma ChE activity were observed in rats and dogs receiving at 0.96–4.3 mg guthion/kg/day orally for up to 2 years and 52 weeks, respectively (Allen et al. 1990; Schmidt and Chevalier 1984). However, guthion-induced reductions in plasma ChE activity are of questionable biological significance.

No effect on hearing was evident in male or female dogs receiving up to 3.8 and 4.3 mg guthion/kg/day, respectively, from the diet for up to 52 weeks (Allen et al. 1990).

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

Neurological effects associated with perinatal exposure are presented in Section 3.2.2.6 (Developmental Effects).

3.2.2.5 Reproductive Effects

No information was located regarding reproductive effects in humans following oral exposure to guthion.

Unspecified histopathologic findings were observed in the testes of Wistar rats receiving 11.5 mg guthion/kg/day from the diet for 3 weeks; no indications of treatment-related reproductive effects were seen at a dose level of 2.3 mg/kg/day (Vos et al. 1983). No treatment-related effects on insemination, fertility, or gestation indices were seen in male and female rats receiving guthion from the diet for 14 weeks before mating and throughout mating, gestation, and lactation at doses ranging from 0.43 to 4.9 mg/kg/day (Holzum 1990). There were no indications of treatment-related effects on reproductive organ weights or pathology among male and female rats receiving up to 2.3 or 3.1 mg guthion/kg/day,

respectively, from the diet for up to 2 years (Schmidt and Chevalier 1984) or in male and female dogs receiving up to 3.8 or 4.3 mg guthion/kg/day, respectively, from the diet for 52 weeks (Allen et al. 1990). There were no gross or histopathological signs of treatment-related effects on reproductive tissues of male and female Osborne-Mendel rats receiving up to 10.9 and 9.6 mg guthion/kg/day, respectively, from the diet for up to 80 weeks or male and female B6C3F1 mice receiving up to 10.7 and 21.6 mg guthion/kg/day, respectively, from the diet for 80 weeks (NCI 1978).

3.2.2.6 Developmental Effects

No information was located regarding developmental effects in humans following oral exposure to guthion.

Neurological effects were observed in offspring from pregnant rats administered guthion at 5 mg/kg/day from gestation day 6 to postparturition day 21 by gavage (Short et al. 1980). One day after weaning, pups in the surviving litter presented stiff rear legs at right angles to the body and lack of neuromuscular coordination in the use of the hind legs, as well as muscle tremors in the tail and upturned snouts (Short et al. 1980). These effects were not observed at 2.5 mg/kg/day. Fetal brain cholinesterase activity on gestation day 20 was unaffected in pups from Sprague-Dawley rats administered guthion at 2 mg/kg/day on gestation days 6–15 (Astroff and Young 1998).

A marked increase in the incidence of supernumerary ribs was observed in the offspring of pregnant mice administered 16 or 20 mg guthion/kg by gavage on gestation day 8; the 20 mg/kg dose level was also fatal to 21 of 40 treated dams (Kavlock et al. 1985). The incidence of supernumerary ribs was 3% in the control group, and approximately 24 and 58% in the 16 and 20 mg/kg groups, respectively; however, the authors reported an inverse correlation between maternal weight gain and the incidence of supernumerary ribs and suggested that there was an association between nonspecific adverse health effects in the dams and the development of supernumerary ribs in fetuses.

An 11% reduction in fetal weight was observed at gestation day 18 in the offspring of pregnant mice administered 20 mg guthion/kg by gavage on gestation day 8; this dose level was also associated with 53% maternal mortality (21/40 dams) (Kavlock et al. 1985). An apparently maternally-nontoxic gavage dose of 16 mg guthion/kg/day did not affect fetal weight. Significantly reduced pup weight (34% lower than controls) and perinatal survival (85% lower than controls) were noted in the offspring of rat dams administered 5 mg guthion/kg/day by gavage on gestation day 6 through postpartum day 21 (Short et al.

1980). However, this dosing regimen also resulted in 62% maternal death, depressed maternal body weight gain, and neurological signs of cholinesterase inhibition. There were no significant maternal or fetal effects at dose levels ≤2.5 mg/kg/day. No effects on fetal body weights were seen following administration of 2.0 mg guthion/kg/day to pregnant rats on gestation days 6–15 (Astroff and Young 1998), or 5.0 mg/guthion/kg/day to pregnant rats or mice on gestation days 6–15 (Short et al. 1980). Significantly decreased survival was observed in the 5-day-old offspring of male and female rats administered 1.3 and 1.5 mg guthion/kg/day in the diet for 14 weeks prior to mating and throughout mating, gestation, and postparturition day 5 (Holzum 1990). These doses were associated with 69 and 75% reductions in erythrocyte AChE in the parental rats (Holzum 1990).

Guthion exposure did not elicit external, visceral, or skeletal malformations or variations in offspring of rats administered guthion at 2.0 mg/kg/day on gestation days 6–15 (Astroff and Young 1998) or skeletal anomalies in pups from mice administered guthion at 2.5 mg/kg/day on gestation days 6–15 (Short et al. 1980); however, pups of the 5 mg/kg/day dose group exhibited increased incidence of malaligned sternbrae (Short et al. 1980).

3.2.2.7 Cancer

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

The carcinogenicity of guthion was assessed in groups of male and female rats and mice orally exposed for a lifetime (NCI 1978; Schmidt and Chevalier 1984). No treatment-related effects on incidence of histopathologic neoplastic lesions were seen in male or female Wistar rats exposed to guthion doses as high as 3.11 mg/kg/day in the diet for 2 years (Schmidt and Chevalier 1984). The NCI (1978) reported significant increases in incidences of benign thyroid tumors, malignant thyroid tumors, or combined follicular cell tumors in male Osborne-Mendel rats receiving estimated doses of 5.5 or 10.9 mg guthion/kg/day from the diet for 80 weeks followed by a 35-week observation period and significant increases in the combined incidence of islet cell carcinoma or carcinomas in the pancreas of the 10.9 mg/kg/day male rats. However, it was noted that these tumor incidences could not be clearly attributed to treatment with guthion due to high spontaneous incidences of these tumors in male Osborne-Mendel rats at the laboratory where the study was performed. There was no evidence of treatment-related increased tumors in the guthion-treated female rats receiving estimated oral doses as high as 9.6 mg/kg/day (NCI 1978).

Benign and malignant neoplasms were observed among dosed and control B6C3F1 mice (NCI 1978); however, in previous studies, each type has been observed as spontaneous lesions (NCI 1978). The incidence of hepatocellular adenomas (2/8, 11/49, and 19/50 in the 0, 5.4, and 10.7 mg/kg/day groups, respectively) in male mice provide equivocal evidence of an association between these lesions and guthion exposure. There were no statistically significant associations between tumor incidence and guthion exposure in female mice (NCI 1978).

Under the conditions of the bioassay, NCI (1978) concluded that the incidences of neoplasms of the pancreatic islets and of the follicular cells of the thyroid in male rats provide suggestive, but insufficient, evidence of the carcinogenic potential of guthion in male rats. NCI (1978) concluded that guthion was not carcinogenic in male or female B6C3F1 mice or female Osborne-Mendel rats. The EPA Integrated Risk Information System of EPA (IRIS 2008) does not include an assessment for guthion. The International Agency for Research on Cancer (IARC) has not classified guthion as to its carcinogenicity (IARC 2006).

3.2.3 Dermal Exposure

The highest NOAEL values and all LOAEL values from each reliable study for appropriate end points in each species and duration category are recorded in Table 3-3.

3.2.3.1 Death

No information was located regarding mortality in humans following dermal exposure to guthion.

Available acute dermal toxicity studies in animals indicate a wide range of LD_{50} values. For instance, Pasquet et al. (1976) calculated a dermal LD_{50} of 90 mg/kg for female rats administered receiving a single application of guthion. Gaines (1960) reported the same acute dermal LD_{50} value of 220 mg/kg for both male and female Sherman rats. In contrast, EPA (1978a) reported acute dermal LD_{50} values of 455 and 222 mg/kg for male and female Sprague-Dawley rats, respectively. The highest reported acute dermal LD_{50} was 6,000 mg/kg reported by Skinner and Kilgore (1982) after a single dose of guthion was applied to the hind feet of male Swiss Webster mice.

Table 3-3 Levels of Significant Exposure to Guthion - 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				455 M mg/kg (14 day LD50)	EPA 1978a	
					222 F mg/kg (14 day LD50)		
Rat (Sherman)	Once				220 M mg/kg (14 day LD50)	Gaines 1960	
					220 F mg/kg (14 day LD50)		
Rat (CD)	Once				90 F mg/kg (10 day LD50)	Pasquet et al. 1976	
Mouse (Swiss-Webster)	Once				6000 M mg/kg (24 hour LD50)	Skinner and Kilgore 1982	
Immuno/ Lymphoret							
Human	Once		1 %volume			Lisi et al. 1987	Patch test with 1% guthion solution.
Human	Once			1 F %volume (allergic reaction to guthion in 1/64 fruit harvest workers)		Sartorelli et al. 1999	

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

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Neurological							
Human	Once		0.0007 mg/kg			Franklin et al. 1981	Erythrocyte ChE activity.
Human	1 x/d		0.46 M mg/kg/day			Schneider et al. 1994	Reductions in erythrocyte ChE activity were 16% or less.
Rat (Sprague-Dawley)	Once				222 F mg/kg (signs of cholinergic poisoning: salivation, lacrimation, exophthalmus, defecation, urination, muscle fasciculations)	EPA 1978a	
Mouse (Swiss-Webster)	Once			600 M mg/kg (24 hour ED50 for erythrocyte ChE activity)		Skinner and Kilgore 1982	

ChE = cholinesterase; d = day(s); ED50 = median effective dose, 50% effect in population; F = Female; Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; x = time(s)

3.2.3.2 Systemic Effects

No information was located regarding systemic effects in humans following dermal exposure to guthion. No information was located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, endocrine, dermal, ocular, or metabolic effects in animals following dermal exposure to guthion.

Hematological Effects. A 10% reduction in erythrocyte count was observed in male New Zealand white rabbits administered 20 mg guthion/kg/day, 5 days/week for 21 days; this effect was not seen at a dose level of 2 mg/kg/day in males or at doses up to and including 20 mg/kg/day in similarly-treated females (EPA 1999b).

Renal Effects. Treatment-related increases in kidney weight and incidence of inflammatory renal changes were observed in male New Zealand white rabbits administered 20 mg guthion/kg/day, 5 days/week for 21 days; these effects were not seen at a dose level of 2 mg/kg/day in males or at doses up to and including 20 mg/kg/day in similarly-treated females (EPA 1999b).

Body Weight Effects. A 40–70% reduction in body weight gain was observed in female rabbits administered 20 mg guthion/kg/day, 5 days/week for 3 weeks; this effect was not seen at a dose level of 2 mg/kg/day in females or at doses up to and including 20 mg/kg/day in similarly-treated males (EPA 1999b).

3.2.3.3 Immunological and Lymphoreticular Effects

Patch tests were performed on 64 female workers (aged 17–59 years; mean, age 35 years) involved for an average of 11 years in the harvesting of cherries, peaches, olives, and grapes in Italy (Sartorelli et al. 1999). Only one subject, who was without symptoms, showed a positive allergic reaction to guthion. In another study of 180 agricultural workers, 43 former agricultural workers, and 429 patients admitted to the clinic for nonallergic skin disorders, none of the subjects showed allergic or irritant reactions to 1% guthion patches applied to the upper back (Lisi et al. 1987).

3.2.3.4 Neurological Effects

Blood AChE activity was determined in approximately 34 peach harvest workers in California in 1991 (Schneider et al. 1994). Workers were classified as “harvesters” (approximately 10) or “sorters” (approximately 24). Harvesters (all were male) entered orchards to pick fruit 51 days after treatment with

guthion (50% active ingredient at 1.5 pounds active ingredient per 100 gallons of water per acre) and worked for 10 of the next 17 days, while sorters (males and females) went through fruit bins removing culls or fruit that was too green. The latter group was considered to have minimal exposure to foliar residues and served as a control group. There were no differences among harvesters or sorters in their whole blood AChE before workers entered the orchards; however, 14 and 23 days after entering the field, significant differences in AChE levels among these two groups were evident. The largest reduction in AChE observed in harvesters 14 days after entering the orchard was of approximately 16%. Similar reductions were reported 23 days after exposure, but conflicting data were offered by two separate laboratories. During the study period, there were no statistically significant ($p>0.05$) reductions in AChE in sorters, whereas two of four measurements showed significant ($p<0.05$) reductions in AChE in harvesters. No symptoms of organophosphorus insecticide poisoning were reported by any of the workers.

A study was conducted with 17 orchardists who applied a single treatment of guthion in a wettable powder formulation (50% a.i.) in the South Okanagan Valley, British Columbia (Franklin et al. 1981). The amounts of guthion applied in this study ranged from approximately 1 to 5 kg. Respirators were worn by applicators. Based on analysis of guthion residues on patches, dermal exposure was estimated to range from 9 to 43 µg guthion/kg applied. A mean dermal exposure dose of 0.7 µg/kg was estimated based on anatomical regional deposition of guthion on the bodies of subjects, surface area estimates of these anatomical regions, and a reference body weight of 70 kg. Postexposure erythrocyte AChE activity appeared to be reduced 15% in the exposed workers; however, these alterations did not exceed the variation observed in the group of unexposed individuals (n=10) in the control group (Franklin et al. 1981).

A study was conducted of 21 male agricultural workers (ages 21–63; mean age 35.5 years) exposed to foliage-borne residues of guthion during peach-thinning operations in California (Kraus et al. 1977). Workers entered the peach orchards 14 days after they had been treated with a 50% wettable powder of guthion (50% a.i.) at a rate of 2 pounds a.i. per 100 gallons of water per acre. Mean whole blood ChE activity levels during the 5-day exposure period ranged from 90.1 to 95.6% of mean baseline (3-day preexposure) levels (Kraus et al. 1977). Erythrocyte AChE activity was not measured. Although postexposure examinations indicated a reduction in upper body reflex activity, it seems likely that the observation was due to fatigue from work-related exertion during thinning. There was no reduction in reflexes in the lower extremities (Kraus et al. 1977).

Reductions in erythrocyte AChE activity were observed in a group of 20 agricultural workers (ages 18–58; median age 28.5 years) who entered California peach orchards 30 days after they had been treated with guthion (1.5 pounds a.i. per acre) (McCurdy et al. 1994). Three days after entering the treated fields, erythrocyte AChE activity was 7% lower than baseline levels in the same workers. After 44 days of fieldwork, erythrocyte AChE activity had decreased 19% from baseline levels (McCurdy et al. 1994). No clinical signs were reported by the authors.

EPA (1978a) reported signs of cholinergic poisoning, such as salivation, lacrimation, exophthalmus, defecation, urination, and muscle fasciculations in male and female Sprague-Dawley rats administered lethal doses of guthion dermally. Although the precise doses at which these effects were observed were not provided, it was reported that the 14-day dermal LD_{50} values in male and female rats were 455 mg/kg (95% confidence interval [CI]: 301–687) and 222 mg/kg (95% CI 181–271), respectively. Skinner and Kilgore (1982) estimated that a single, dermal exposure to 600 mg/kg would elicit a 50% reduction in erythrocyte AChE activity in male Swiss-Webster mice.

A 24–38% reduction in erythrocyte AChE activity was observed in male and female rabbits administered 20 mg/kg/day dermally 5 days/week for 3 weeks; this effect was seen as early as day 10 following the initiation of treatment (EPA 1999b).

Male rats were treated dermally with A 16–17% reduction in erythrocyte AChE activity (relative to control animals) was observed within 10–24 hours in male rats administered dermal applications of a 35% wettable powder formulation of guthion at a guthion equivalent dose of 5.6 mg/kg for up to 1 week (EPA 1999b). There was no effect on erythrocyte AChE activity in rats of a 0.56 mg/kg group and no effect on plasma ChE activity at either dose level.

3.2.3.5 Reproductive Effects

No information was located regarding reproductive effects in humans or animals following dermal exposure to guthion.

3.2.3.6 Developmental Effects

García et al. (1998) studied the incidence of congenital malformations (nervous system defects, cardiovascular defects, oral clefts, epispadia or hypospadia, and musculoskeletal defects) in children born of fathers with occupational exposures to pesticides. Exposure was assessed via questionnaire. The odds

ratio for the occurrence of birth defects in fathers (6 cases and 8 referent cases) exposed to guthion was 0.71 (0.23–2.25), indicating that there was no evident association between the occurrence of birth defects and paternal exposure to guthion.

3.2.3.7 Cancer

No information was located regarding cancer in human or animals following dermal exposure to guthion.

3.3 GENOTOXICITY

In vivo evaluations of genotoxicity in humans were not located. The results of all available *in vivo* animal studies and *in vitro* tests are presented in Tables 3-4 and 3-5, respectively. Negative results were reported in a study of recessive lethality in *Drosophila* and two studies of micronuclei formation and dominant lethality in mice (Waters et al. 1982). The available *in vitro* genotoxicity data suggest that guthion is not genotoxic to prokaryotic organisms (Carere et al. 1978; Hrelia et al. 1990; Waters et al. 1982; Zeiger et al. 1987). Six available *in vitro* studies with eukarytotic organisms (fungi and mammalian cells) showed positive results for genotoxic effects (Alam and Kasatiya 1976; Alam et al. 1974; Bianchi-Santamaria et al. 1997; Waters et al. 1982); results of five other *in vitro* assays were negative (Chen et al. 1982a, 1982b; Waters et al. 1982).

3.4 TOXICOKINETICS

3.4.1 Absorption

No information was located regarding possible age-related differences in absorption of guthion following inhalation, oral, or dermal exposure.

3.4.1.1 Inhalation Exposure

Absorption of guthion via the inhalation pathway can be inferred from a study demonstrating reductions in erythrocyte AChE activity in rats exposed to guthion aerosols at 4.72 mg/m^3 for 2 weeks (Kimmerle 1976). Absorption via the inhalation pathway appears to be rapid. Whole blood ChE activity was reduced by an average of 41% in male Sprague-Dawley rats following a 1-hour exposure to 39 mg/m^3 (EPA 1978a).

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

Species (test system)	End point	Results	Reference
Drosophila melanogaster	Recessive lethality	–	Waters et al. 1982
Mammalian cells			
Mouse	Micronuclei formation	–	Waters et al. 1982
Mouse	Dominant lethal	–	Waters et al. 1982

– = negative result

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

Species (test system)	End point	Results	Reference
Prokaryotic organisms			
Salmonella typhimurium (TA1535, TA1536, TA1537, TA1538)	Reverse mutation	–	Carere et al. 1978
S. typhimurium ((TA98, TA100, TA1535, TA1537, TA1538)	Reverse mutation	– (with or without metabolic activation)	Waters et al. 1982
S. typhimurium	Reverse mutation	– (with or without metabolic activation)	Hrelia et al. 1990
S. typhimurium (TA98, TA100, TA1535, TA1537)	Reverse mutation	+ (weakly mutagenic in TA98; negative in others)	Zeiger et al. 1987
Streptomyces coelicolor	Forward mutation	–	Carere et al. 1978
Escherichia coli	Reverse mutation	– (with and without metabolic activation)	Waters et al. 1982
Eukaryotic organisms			
Fungi			
Saccharomyces cerevisiae	Enhanced mitotic recombination	+ (with and without metabolic activation)	Waters et al. 1982
S. cerevisiae	Gene conversion; crossing over	– (with and without metabolic activation)	Waters et al. 1982
S. cerevisiae	Enhanced mitotic crossing over	+ (with metabolic activation)	Hrelia et al. 1990
Mammalian cells			
Human cell lines WI–38 and HEp-2	Chromosome breaks	+	Alam and Kasatiya 1976
Human lymphocytes	Micronucleus formation	+	Bianchi-Santamaria et al. 1997
Chinese hamster ovary cells (KI cell line)	Chromosome breaks	+	Alam et al. 1974
Chinese hamster ovary cells	Sister chromatid exchange	– (with and without metabolic activation)	Waters et al. 1982

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

Species (test system)	End point	Results	Reference
Chinese hamster ovary cells (V79 line)	Sister chromatid exchange	– (without metabolic activation)	Chen et al. 1982a
Chinese hamster ovary cells (V79 line)	Sister chromatid exchange	– (with metabolic activation)	Chen et al. 1982b
Mouse lymphoma cells	Forward mutation	+ (with and without metabolic activation)	Waters et al. 1982
Human fetal lung fibroblasts	Unscheduled DNA synthesis	– (with and without metabolic activation)	Waters et al. 1982

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

3.4.1.2 Oral Exposure

No information was located regarding absorption of guthion in humans after oral exposure. Animal studies suggest that gastrointestinal absorption of guthion is rapid. Greater than 80% of the radioactivity from an 8 mg/kg oral dose of radiolabeled guthion was detected in the internal organs (other than gastrointestinal tract), urine, and exhaled air of rats at 6 hours posttreatment (Fakhr et al. 1996).

3.4.1.3 Dermal Exposure

Guthion is absorbed through the skin, as demonstrated by the urinary excretion of radiolabeled metabolites of guthion after the application of 4 μg guthion/cm^2 to forearms of six volunteers (Feldmann and Maibach 1974). Radiolabeled metabolites were detected in the urine as early as 4 hours postapplication; approximately 16% of the dose was excreted during 5 days postapplication.

Dermal absorption of guthion has also been demonstrated in animals, as evidenced by excretion of guthion urinary metabolites following dermal exposure. Franklin et al. (1983) estimated 60% absorption of guthion from 24-hour dermal application (100–400 μg guthion) to the dorsal skin of male Sprague-Dawley rats, based on urinary recovery of dimethyl thiophosphate (DMTP); most of the urinary DMTP had been recovered by 24 hours postapplication. Nearly 5% of the radioactivity from a 35% wettable powder formulation of ^{14}C-guthion, applied dermally to rats at a concentration resulting in an estimated dermal dose of 0.056 mg (a.i.)/kg, was recovered in the urine during 10 hours postdosing, indicating that the material was readily absorbed through the skin (Schroeder 1992). Based on measurements of total radioactivity recovered at 10 hours postdosing, it was estimated that >50% of the applied dose had been absorbed.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No human or animal data were located regarding distribution following inhalation exposure to guthion. No information was located regarding possible age-related differences in the distribution of absorbed guthion.

3.4.2.2 Oral Exposure

No data were located regarding distribution in humans following oral exposure to guthion. At 6 hours following single oral dosing of ^{14}C-guthion (8 mg/kg) to rats, >50% of the radioactivity was detected in muscle tissue, approximately 2.4% in the liver, and 1% in the blood; other tissues and organs accounted for 0.1–0.8% of the radioactivity (Fakhr et al. 1996). By 48 hours postdosing, radioactivity was no longer detected in organs or tissues and approximately 71, 13, and 6 % of the administered radioactivity had been recovered in expired CO_2, feces, and urine, respectively.

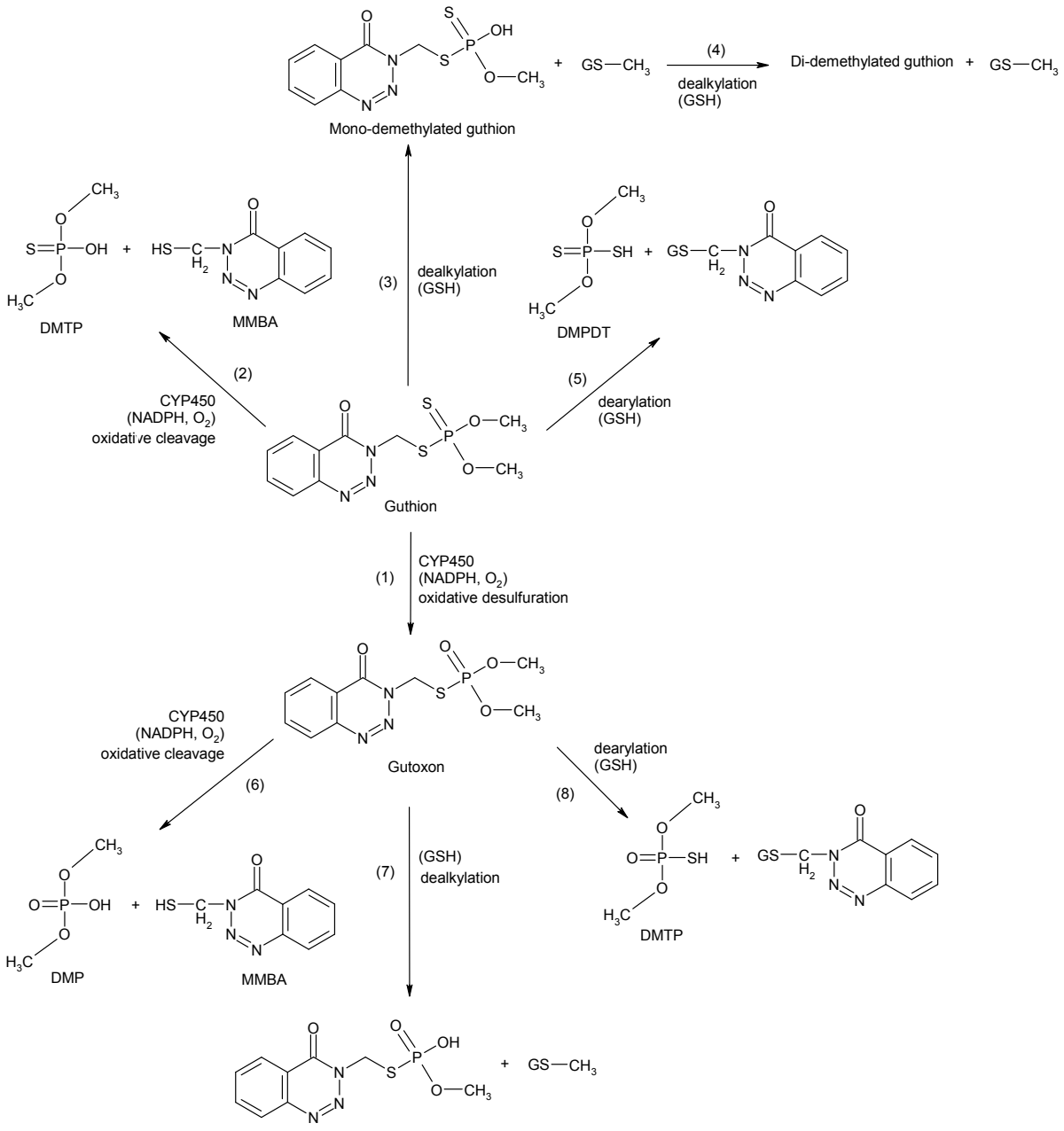
3.4.2.3 Dermal Exposure

Based on urinary excretion of radiolabeled metabolites of guthion following dermal application of guthion to volunteers (Feldmann and Maibach 1974), absorption, distribution, and metabolism of guthion is inferred. Similarly, distribution of guthion and its metabolites can be inferred based on recovery of radioactivity from urine and body tissues of laboratory animals following dermal application of ^{14}C-guthion (Franklin et al. 1983; Zendzian 2003).

3.4.3 Metabolism

A proposed metabolic scheme for guthion is presented in Figure 3-3. Although guthion (as parent compound) can function as an AChE inhibitor at relatively high concentrations (Buratti et al. 2003), its oxygenated metabolite (gutoxon) has long been considered to be the major source of AChE inhibition (Murphy and DuBois 1957). Results of *in vitro* studies using human liver microsomes indicate that the bioactivation of guthion to gutoxon (reaction 1 in Figure 3-3) is a two-phase process, characterized by separate low- and high-affinity constants, and catalyzed by cytochrome P450 isozymes CYP1A2, CYP3A4, and CYP 2B6 (Buratti et al. 2003). The CYP1A2 isozyme appears to be mainly involved in the high-affinity phase of desulfuration observed at relatively low guthion concentrations, whereas CYP3A4 is closely related to the low-affinity phase and CYP2B6 is associated with both high- and low-affinity phases at a wide range of guthion concentrations. The efficient activation of guthion to gutoxon in whole liver homogenates of rat, mouse, or guinea pig requires NAD or NADP+G-6-P (Hitchcock and Murphy 1971). The amounts of gutoxon equivalents formed in 15 minutes following the addition of guthion to whole liver homogenates (amended with NADP and G-6-P) of rats, mice, and guinea pigs were 0.69, 0.59, and 0.66 nmol/10 mg liver tissue, respectively, indicating that these three species are similar in guthion activation efficiency.

Figure 3-3. Proposed Metabolism of Guthion



DMP = dimethyl phosphate; DMPDT = dimethyl phosphorodithioate; DMTP = dimethyl thiophosphate; MMBA = mercaptomethyl benzazimide

Sources: adapted from Fakhr et al. 1996; Motoyama and Dauterman 1972

Major metabolites of guthion in the 48-hour urine of rats orally administered parent compound include mercaptomethyl benzazimide (MMBA), mono- and di-demethylated guthion, benzazimide, dimethyl phosphorodithioate (DMPDT), DMTP, and two unknown metabolites (Fakhr et al. 1996). Neither guthion (as parent compound) nor gutoxon were detected in the urine of these rats. Analysis of the urinary metabolites indicates that guthion is detoxified via two major pathways. One pathway involves CYP450-mediated cleavage of the P-S-C bond to yield DMTP and MMBA (reaction 2 in Figure 3-3). The other pathway involves glutathione-mediated dealkylation via cleavage of the P-O-CH_3 bond to yield mono-demethylated guthion and GS-CH_3 (*S*-methyl glutathione) (reaction 3 in Figure 3-3), which may be further demethylated to di-demethylated guthion and *S*-methyl glutathione (reaction 4 in Figure 3-3). *S*-methyl glutathione may be further degraded to CO_2, which may explain the relatively large amounts of $^{14}CO_2$ in expired air following oral administration of radiolabeled guthion to laboratory animals (see Section 3.4.4.2). The presence of DMPDT in the rat urine indicates that guthion may undergo glutathione-catalyzed dearylation to form DMPDT and glutathione-conjugated mercaptomethyl benzazimide (reaction 5 in Figure 3-3). Likely metabolic steps involved in the detoxification of gutoxon include CYP450-mediated cleavage of the P-S-C bond to yield dimethyl phosphate (DMP) and MMBA (reaction 6 in Figure 3-3), glutathione-mediated dealkylation via cleavage of the P-O-CH_3 bond to yield demethylated guthion and *S*-methyl glutathione (reaction 7 in Figure 3-3), and glutathione-catalyzed dearylation to form DMTP and glutathione-conjugated mercaptomethyl benzazimide (reaction 8 in Figure 3-3).

Glutathione has been implicated in the detoxification of guthion in mammals (Levine and Murphy 1977; Motoyama and Dauterman 1972; Sultatos and Woods 1988); however, some studies contradict this role (Sultatos and Woods 1988). Support for the role of glutathione in detoxification comes from the observations that, in mice and rats, the depletion of glutathione, such as by pretreatment with methyl iodide or diethyl maleate, potentiates the toxicity of many dimethyl-substituted organothiophosphate insecticides and that the administration of large doses of certain dimethyl-substituted organothiophosphates elicits decreases in hepatic glutathione content (Sultatos and Woods 1988). Incubation of guthion in mouse liver homogenates reduced glutathione levels by 25% (Levine and Murphy 1977), but when the oxidative cofactors NADP and G-6-P were added to the medium, glutathione levels remained at control levels during 90 minutes of incubation. However, when guthion and the oxidative cofactors were added to liver homogenates from mice that were treated with piperonyl butoxide (an inhibitor of microsomal mixed function oxidases), levels of glutathione were reduced to approximately 80% of control values. These data suggest that glutathione is significantly involved in the detoxification of guthion when oxidative metabolism is inhibited (Levine and Murphy 1977). Other

results indicate that glutathione may not be required for detoxication of guthion. Sultatos and Woods (1988) demonstrated that, although depletion of hepatic glutathione in the mouse by pretreatment with diethyl maleate potentiated the acute toxicity of guthion, depletion of hepatic glutathione by pretreatment with buthionine sulfoximine did not (Sultatos and Woods 1988).

Paraoxonase (PON1; serum A-esterase), an enzyme found in humans and other mammals, can hydrolyze the oxygen analogues of organophosphate insecticides such as parathion, chlorpyrifos, and diazinon, thereby reducing their toxicity (Costa et al. 1999). In humans, serum PON1 is a polymorphic enzyme that shows low, intermediate, or high activity based on the hydrolysis of paraoxon (Akgür et al. 1999). However, PON1 does not appear to be involved in the hydrolysis of gutoxon because there was no difference in the inhibition of brain cholinesterase among homozygous wild (*PON1* +/+) or knockout (*PON1* -/-) mice treated with guthion (Costa et al. 1999).

No information was located regarding possible age-related differences in guthion metabolism.

3.4.4 Elimination and Excretion

The urinary metabolites, DMPDT, DMTP, and DMP, were detected in the urine of individuals (88 men, 11 women; ages 16–59 years) who resided near an area where guthion was used but who were not known to be occupationally exposed to guthion (Aprea et al. 1994). The total excretion of these urinary metabolites (DMPDT + DMTP + DMP) had a geometric mean and standard deviation of 145 and 2.3 nmol/g creatinine, respectively, with a range of values of 5.5–884.5 nmol/g creatinine (Aprea et al. 1994). However, these metabolites are not specific to guthion exposure.

No information was located regarding possible age-related differences in elimination and excretion of guthion and its metabolites.

3.4.4.1 Inhalation Exposure

No information was located on the elimination and excretion of guthion in human or animals following inhalation exposure.

3.4.4.2 Oral Exposure

Guthion is rapidly metabolized and eliminated, as evidenced by the appearance of 22, 7.5, and 2.3% of the radioactivity from a single oral dose of 8 mg/kg of ^{14}C-guthion (labeled at the two methyl groups) in expired air (as $^{14}CO_2$), feces, and urine of rats by 6 hours postdosing (Fakhr et al. 1996). Approximately 63, 11, and 6%, respectively, had been excreted by 24 hours postdosing; by 48 hours postdosing, total excretion of radioactivity by these routes had accounted for 90% of the administered dose. Major metabolites of guthion in the 48-hour urine included MMBA, mono- and di-demethylated guthion, benzazimide, DMPDT, DMTP, and two unknown metabolites. A total of seven urinary metabolites contained radioactivity from labeled methyl groups. Several urinary metabolites were not radiolabeled; these included MMBA, di-demethylated guthion, benzazimide, and other compounds. Neither guthion (as parent compound) nor gutoxon were detected in the urine.

3.4.4.3 Dermal Exposure

Urinary excretion of radiolabeled metabolites of guthion was detected after application of 4 μg guthion/cm^2 to the ventral forearm of six volunteers (Feldmann and Maibach 1974). The treated areas of the forearms were not protected and the subjects were asked not to wash the area for 24 hours. Radiolabeled metabolites could be detected in the urine ≤4 hours after application of the insecticide. The urinary excretion rate of guthion metabolites increased from 0.04% dose/hour in the first 4 hours after dosing to a maximum of 0.29% dose/hour at 8–12 hours after the dose had been applied (Feldmann and Maibach 1974). After that time, the excretion rate decreased until it reached 0.04% dose/hour 96–120 hours after the dose had been applied. Approximately 16% of the dose was excreted within the 120-hour urinary sampling period (Feldmann and Maibach 1974). The urinary excretion values were corrected for guthion absorption efficiency as determined in a preliminary study where the subjects were administered a single, intravenous dose of 1 μCi of radiolabeled guthion (Feldmann and Maibach 1974). The latter study showed that approximately 70% of the intravenous dose was excreted within 120 hours, with a half-life of 30 hours. Urinary excretion of the radiolabeled residues of intravenously-administered guthion was faster than observed with the dermally-applied insecticide, the former reaching 1.6% dose/hour 8–12 hours after administration (Feldmann and Maibach 1974).

Approximately 60% of the guthion doses (100–400 μg/rat) applied to a shaved area (2.6 cm^2) of the dorsal skin of male Sprague-Dawley rats was recovered in urine as DMTP (Franklin et al. 1983). The authors speculated that the calculation of dermal absorption of guthion based on the detection of DMTP in urine may lead to underestimates of absorption because DMTP constitutes only about 30% of the total

alkyl phosphates excreted in urine after exposure to guthion. A linear relationship (r=0.943) between guthion doses and total DMTP output suggests that the capacity of the metabolic pathways was not exceeded at the doses administered. Franklin et al. (1986) briefly presented the results of a study with human subjects (two subjects per dose) who were administered guthion on the forehead at 500–6,000 μg/person (approximately 7–86 μg/kg). By 72 hours postdosing, the urinary excretion of DMTP had accounted for 5–17% of the administered dose. In general, increasing cumulative excretion was observed with increasing doses. Approximately 26 and 10% of the radioactivity from a 35% wettable powder formulation of ^{14}C-guthion, applied dermally to rats at a concentration resulting in an estimated dermal dose of 0.056 mg (a.i.)/kg and rinsed 10 hours later, was recovered in the 7-day urine and feces, respectively (Schroeder 1992).

3.4.4.4 Other Routes of Exposure

The urinary recovery of metabolites observed in a study with human subjects administered a single intravenous dose of radiolabeled guthion (1 μCi) showed an initial peak (1.5% dose/hour) during 4 hours postdosing, which was followed by a drop in excretion and a second peak (1.6% dose/hour) 812 hours postdosing (Feldmann and Maibach 1974). The urinary output of radiolabeled guthion metabolites after a 1 μCi intramuscular dose in rats showed two peaks in urinary excretion of the administered dose, one 4 hours postdosing (approximately 13% of the dose) and a higher peak (approximately 20% of the dose) at 24 hours postdosing, followed by a rapid decrease in output to very low levels after 120 hours (Franklin et al. 1983).

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.

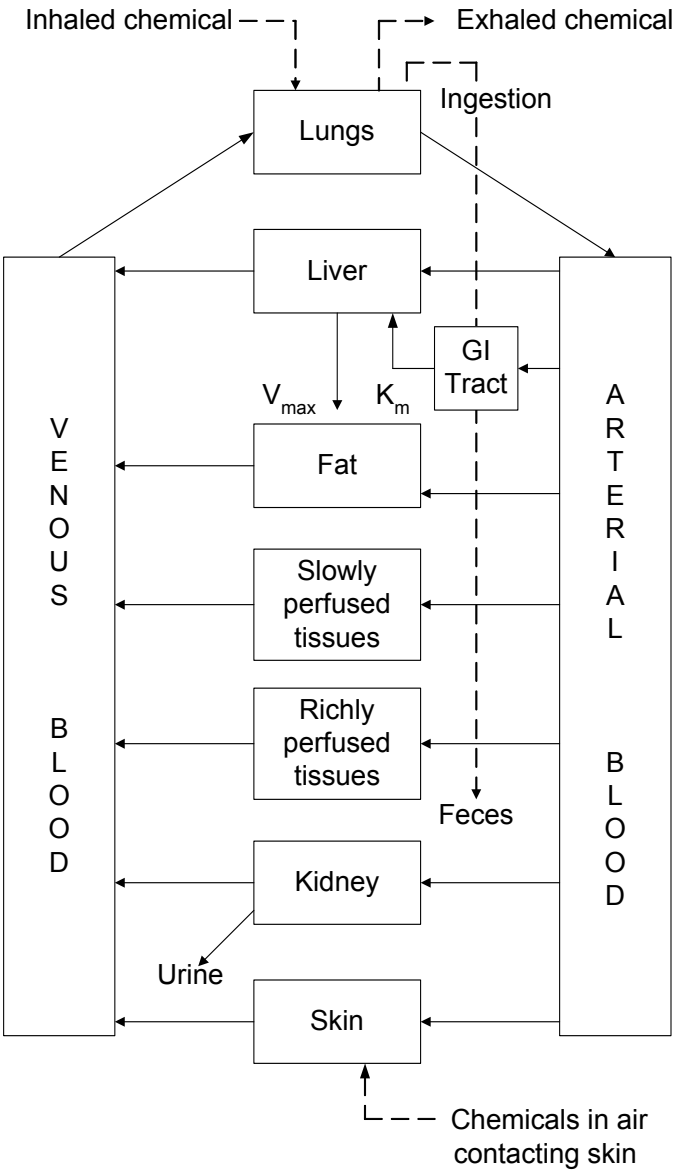
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically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

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 et al. 1994

A PBPK model for guthion was not located. Feldmann and Maibach (1974) conducted a study of the urinary excretion of radiolabeled metabolites of guthion after application of 4 μg guthion/cm^2 to the ventral forearm of six volunteers. These data were used to develop a toxicokinetic model of the elimination of guthion based on the urinary elimination of alkylphosphate metabolites (Carrier and Brunet 1999). The model, which does not include physiological details, predicted that the maximum body burdens of guthion after a single, 5-hour exposure or after repeated daily exposures for nine consecutive days were 73 and 208%, respectively, of the absorbed daily dose. The maximum body burden after a single exposure was predicted to occur 17 hours after the dose was administered. In the case of repeated doses, the body burden increased at an initially rapid rate and continued to increase until it reached steady-state after approximately nine daily doses; the rate of urinary excretion of guthion metabolites was predicted to reach steady state by day 9 as well. The rate of urinary excretion of metabolites after repeated doses was 3 times higher than after a single dose. The model was also used to estimate that 76% of the administered dose of guthion is excreted in the urine within 20 days after a single, 5-hour exposure.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

As discussed in detail in Section 3.4 (Toxicokinetics), guthion is readily absorbed and rapidly metabolized and eliminated following inhalation, oral, or dermal exposure. No studies were located in which mechanisms of absorption were assessed for guthion. It is expected that absorption is accomplished via passive diffusion. No information was located regarding mechanisms of distribution of absorbed guthion. However, other organophosphorus pesticides, such as diazinon, parathion, and methyl parathion, are known to bind reversibly to plasma proteins. It is generally understood that guthion does not appreciably accumulate in any specific body tissues and that absorbed guthion is rapidly metabolized and eliminated. No information was located regarding mechanisms of elimination and excretion of parent compound or metabolites of guthion.

3.5.2 Mechanisms of Toxicity

The most salient systemic effects of exposure to guthion are related to its direct effect on the nervous system and the secondary effects that result from it. The direct manner in which guthion exerts its systemic effects is through inhibition of ChE, specifically AChE in the central and peripheral nervous system. 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 ChE is almost exclusively composed of butyrylcholinesterase. Although butyrylcholinesterase is capable of hydrolyzing acetylcholine and butyrylcholine *in vitro*, the *in vivo* substrate of plasma ChE is unknown. Guthion is bioactivated *in vivo* and *in vitro* to its oxygen analog form, variably referred to as gutoxon or azinphos-methyl oxon (Buratti et al. 2003; Hitchcock and Murphy 1971; Sultatos and Woods 1988). Gutoxon reacts with a serine hydroxyl group at the active site of AChE, rendering it largely inhibited and unreactive. 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 inhibited AChE enzyme cannot degrade acetylcholine and the neurotransmitter accumulates at the ending of cholinergic nerves with the ensuing continual stimulation of electrical activity (Carrier and Brunet 1999). Cholinergic nerves 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 gutoxon may have profound and wide-ranging systemic effects. Acetylcholine can be found in the autonomic nervous system, the somatic motor nervous system, and in the central nervous system. 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, and tightness of chest), and cardiovascular system (bradychardia, decrease in blood pressure) (Ecobichon 1995). 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 (Ecobichon 1995). It has been recognized that, after repeated exposures to organophosphate insecticides, humans and other animal species may develop 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).

Other esterases, such as carboxylesterase, may be involved in the toxicity of organophosphate insecticides. For instance, malaoxon, the oxon form of malathion, is hydrolyzed by a carboxylesterase. When the carboxylesterase is inhibited, the acute toxicity of malaoxon increases (Agency for Toxic Substances and Disease Registry 2003); however, no data were located to suggest a similar role for carboxylesterases in guthion toxicity.

3.5.3 Animal-to-Human Extrapolations

No studies were located that directly studied the comparative toxicokinetics of guthion in animals and humans. Nevertheless, available information suggests that the toxicokinetics of guthion in animals and humans are generally similar. Recent work suggests that the desulfuration of guthion to gutoxon in human liver microsomes is largely effected by at least three cytochromes (CYP1A2, CYP3A4, and CYP2B6), which show different affinities for the substrate (Buratti et al. 2003). Significant variations in the activities of these cytochromes among humans and laboratory animal species would be expected to result in notable differences in guthion metabolism.

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).

Although no studies were located regarding endocrine disruption in humans or animals after exposure to guthion, the studies discussed in this toxicological profile (Holzum 1990; Kavlock et al. 1985; NCI 1978; Short et al. 1980; Vos et al. 1983) do not suggest that guthion exerts consistent, clinically-evident effects on the neuroendocrine axis.

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics

and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

No human data are available regarding possible age-related differences in susceptibility to guthion toxicity. Developmental toxicity studies in rats and rabbits have shown no evidence of increased sensitivity of fetuses as compared to maternal animals following *in utero* exposure. Furthermore, single- and two-generation reproductive toxicity studies in rats showed no increased susceptibility of pups versus adults (EPA 1999b). Additional relevant information from other organophosphorus pesticides is presented below in order to draw inferences as the data allow. Acute dermal, inhalation, and oral exposures to the organophosphorus pesticide methyl parathion has resulted in typical signs of organophosphate poisoning including reductions in plasma and erythrocyte AChE activity, alterations in

the function of nervous, cardiac, pulmonary, and gastrointestinal systems, and deaths in adults (Fazekas 1971; Fazekas and Rengei 1964) as well as in children (Dean et al. 1984). These findings suggest that adults and children share similar targets of toxicity from exposure to methyl parathion. These findings might apply to guthion given the similarities in the mode of action between the two pesticides; however, it should be noted that there are no reported poisonings of children exposed to guthion. The neurotoxicity of guthion is dependent on its bioactivation via a cytochrome P450 mediated desulfuration to the oxon form (Buratti et al. 2003). Recent work suggests that the desulfuration of guthion to the oxon form by cytochromes in human liver microsomes proceeds via two steps, each characterized by high and low affinities; that more than one cytochrome may be involved in the desulfuration process; and that the role of different cytochromes in desulfuration may be dependent on the guthion concentration (Buratti et al. 2003). Some P450 isozymes are regulated differently during development than during adulthood (Leeder and Kearns 1997), but information specific to guthion is not available. Nevertheless, it is conceivable that developmental differences in the regulation of P450 isozymes could lead to differences in the susceptibility of children to guthion toxicity. It is known that acetylcholine, acetylcholinesterase, and butyrylcholinesterase are involved in the development of the nervous system (Brimijoin and Koenigsberger 1999; Layer 1990; Layer and Willbold 1994) and that some of this development is not completed until adulthood. Thus, it is plausible that by interfering with the normal ChE function, guthion might elicit adverse developmental effects. Garcia-Lopez and Monteoliva (1988) showed that erythrocyte AChE activity increases with increasing age, starting at birth and until >60 years of age. It is conceivable that these changes in AChE activity could elicit age-related differences in responses to guthion poisoning.

Although some studies have reported reductions in pup weight and survival, brain weight, and ChE activity, and increased incidence of supernumerary ribs and malaligned sternebrae in offspring of pregnant mice or rats (Holzum 1990; Kavlock et al. 1985; Short et al. 1980), these effects are typically observed at maternally toxic doses.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic

substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, 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 guthion 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 guthion 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 Guthion

The ideal biomarker for the quantification of exposure to guthion would be specific to the chemical of interest and would probably be the insecticide itself or a metabolite that could only be detected after exposure to guthion. It has been shown that DMPDT, DMTP, and DMP are metabolic products of the *in vivo* degradation of guthion (Carrier and Brunet 1999) and have been detected in urine of humans under

field and experimental conditions after dermal or otherwise unspecified exposure. For instance, Franklin et al. (1986) detected DMTP in the urine of volunteers 72 hours after they were administered guthion at 500–6,000 µg/person (approximately 7–86 µg/kg) on the forehead. Urinary excretion of the metabolites DMPDT, DMTP, and DMP was detected in a group (n=99) of individuals not known to be occupationally exposed to guthion (Aprea et al. 1994). These individuals may have been exposed to guthion from the diet, but exposure estimates were not provided. The total excretion of DMPDT + DMTP + DMP exhibited a range of 5.5–884.5 nmol/g creatinine, a geometric mean of 145 nmol/g creatinine, and a standard deviation of 2.3 (Aprea et al. 1994). Unfortunately, these metabolites are of limited use as biomarkers of exposure because they can be detected after exposure to other organophosphate insecticides as well. Neither guthion nor gutoxon were detected in urine collected during 48 hours from rats administered a single oral dose of guthion at 8 mg/kg (Fakhr et al. 1996). No studies were located regarding the usefulness of guthion or gutoxon in blood of exposed animals or humans as biomarkers of exposure.

3.8.2 Biomarkers Used to Characterize Effects Caused by Guthion

Guthion-induced changes in erythrocyte AChE and plasma ChE activity do not serve as biomarkers of effect that are specific to guthion poisoning because such changes are common to numerous organophosphorus and carbamate ester insecticides. In addition, the large degree of variability in ChE activity in human populations suggests that caution should be exercised when comparing ChE activities from exposed populations, such as agricultural workers, and reference populations. For example, activity levels at the upper limit of the normal range may be 200% higher than those at the lowest level (Maroni et al. 2000). Long-term sequential monitoring of ChE activity in populations of interest may allow a more accurate confirmation of enzyme inhibition (Coye et al. 1987).

Organophosphate poisoning may be categorized as mild, moderate, or severe based on the clinical signs and symptoms of poisoning and the measured reductions in ChE activity. Mild cases of poisoning, in which the patient retains the ability to move, may occur when plasma ChE activity levels are 50–80% below normal; moderate cases of poisoning in which the patient has lost the ability to walk can be seen with activity levels 80–90% below normal; and severe poisoning with respiratory distress and unconsciousness may be seen at plasma ChE activity levels >90% below normal (Tafuri and Roberts 1987). Methods for measuring erythrocyte and plasma cholinesterase are presented in Chapter 7.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Chemicals that alter the metabolism of guthion, particularly its activation to gutoxon and the degradation of guthion or gutoxon, can be expected to alter the toxicity of guthion. Piperonyl butoxide, an inhibitor of microsomal mixed function oxidases, inhibited the activation of guthion to gutoxon *in vitro* (Levine and Murphy 1977). Although the activation and detoxification of guthion *in vivo* interact in complex ways, it would be expected that inhibition of the activation of guthion to its oxygen analog would result in a reduction of the anticholinesterase toxicity of guthion.

Given that guthion shares essential aspects of its mechanism of toxic action with many other organophosphate (and carbamate ester) insecticides, it is reasonable to expect that the toxicity of guthion and other organophosphate insecticides would show at least additive effects under concurrent exposure conditions. Dose additivity for anticholinesterase effect was observed *in vitro* when rat brain AChE was incubated with the guthion oxygen analog and chlorpyrifos-oxon simultaneously (Richardson et al. 2001). The anticholinesterase effect was nonlinear when the two chemicals were added to serum ChE. Greater-than-additive effects were observed when the two bioactive chemicals were added sequentially at high concentrations to rat serum or brain incubation media. In 2002, the EPA completed a Revised OP Cumulative Risk Assessment (EPA 2002) to address cumulative risk from exposure to organophosphate insecticides in food, water, and domestic applications. The reader should refer to that document, available on-line, for an in-depth discussion of the issue of cumulative risk from exposure to organophosphate insecticides.

Pyridostigmine is an anticholinesterase drug used in the treatment of symptoms of myasthenia gravis (Taylor 2001). Individuals who are undergoing medical treatment with pyridostigmine or other anti-ChE drugs on an ongoing basis and are concurrently exposed to guthion might experience an additional inhibition of AChE elicited by guthion; however, the extent of the additional reduction in AChE activity elicited by guthion and the clinical neurotoxic effects, if any, of this additional reduction in AChE activity are uncertain. Pyridostigmine was also used in 1990 during the Persian Gulf War to protect troops from poisoning with the nerve agent Soman (Taylor 2001). However, when administered prophylactically to U.S. troops, treatment with pyridostigmine would be discontinued upon exposure to Soman and the exposed personnel would be treated immediately with the antidotes atropine and pralidoxime.

The antagonistic effect of some drugs on the anticholinesterase action of organophosphates has been applied to great advantage in the emergency treatment of acute organophosphate intoxications in humans.

Atropine, for instance, is a potent blocker of the activity of acetylcholine at muscarinic nerve receptors. Atropine reduces the clinical effects associated with the stimulation of the parasympathetic nervous system by excess acetylcholine. The antidote pralidoxime (2-PAM), can not only reverse the effect of cholinergic nicotinic overstimulation (such as skeletal muscle fasciculation, muscle weakness, and paralysis of respiratory muscles), but can also reactivate phosphorylated cholinesterase (Tafuri and Roberts 1987).

In vitro studies showed that guthion activation proceeded more rapidly and gutoxon degradation was markedly reduced when fluoride (0.01 M) was added to rat liver microsomes amended with cofactors and either guthion or gutoxon (Dahm et al. 1962). It has been postulated that fluoride interferes with the activity of phosphatases (Murphy and Dubois 1957). These studies indicate that alterations in the balance between the activation of guthion and the degradation of guthion and gutoxon can be elicited *in vitro*. It may reasonably be expected that these alterations might also affect the anticholinesterase activity of gutoxon *in vivo*.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

No information was located regarding variability in susceptibility among different populations exposed to guthion. However, individuals who respond to the anticholinesterase effects of organophosphates more rapidly and with greater reductions in ChE activity might be expected to be more susceptible to the neurotoxic effects of guthion. These responses may be genetic in origin or may be due to differences in development or life style factors, such as nutrition or behavior, or to preexisting disease states. Individuals with hereditary low plasma ChE levels (Kalow 1956; Lehmann and Ryan 1956) and those with unusually low levels of erythrocyte acetylcholinesterase, such as individuals with paroxysmal nocturnal hemoglobinuria (Auditore and Hartmann 1959), would have increased susceptibility to the effects of anticholinesterase agents such as guthion. During pregnancy, women have exhibited significantly decreased plasma ChE activity levels (De Peyster et al. 1993; Evans and Wroe 1980; Evans

et al. 1988; Howard et al. 1978; Sanz et al. 1991; Venkataraman et al. 1990) and significantly increased erythrocyte AChE levels (De Peyster et al. 1993; Sanz et al. 1991; Venkataraman et al. 1990), but it is not known whether these differences might make pregnant women more susceptible to guthion 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 guthion. 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 guthion. 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:

Carlton FB, Simpson WM, Haddad LM. 1998. The organophosphates and other insecticides. In: Haddad LM, Shannon MW, Winchester JF, eds. Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: W B Saunders Company, 836-845.

Goldfrank LR, Flomenbaum NE, Lewin NA, et al., eds. 1998. Goldfrank's toxicologic emergencies. 6th ed. Stamford, CT: Appleton and Lange, 836-843.

Osmundson M. 1998. Insecticides and pesticides. In: Viccellio P, ed. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers, 401-413.

3.11.1 Reducing Peak Absorption Following Exposure

No information specific to guthion was located regarding methods for reducing guthion toxicity. The following information for reducing the toxicity of organophosphates in general is considered relevant to guthion and was obtained from the texts listed above. Respiratory distress is a common effect of poisoning after inhalation of organophosphates and its treatment is mostly supportive. Under some circumstances intubation may be necessary to facilitate control of secretions. Washing the skin with copious amounts of soap and water is recommended in cases of dermal contamination with organophosphates. This first wash may be followed by a second washing with ethyl alcohol. Exposure of the eyes should be immediately treated by copious irrigation of the eye with normal saline or lactated Ringer’s solution (Aaron and Howland 1998). Contaminated clothing including leather garments should be destroyed. Activated charcoal is recommended for many organophosphates after oral exposure; however, Carlton et al. (1998) pointed out that this treatment may lack efficiency with some organophosphates. Ipecac should not be used for organophosphate poisoning (Osmundson 1998).

Cathartics may be unnecessary as intestinal motility is greatly increased. Gastric lavage may be performed with care, as organic solvent vehicles may cause pneumonitis if inhaled during the procedure.

3.11.2 Reducing Body Burden

No information was located regarding the reduction of the body burden of guthion. However, it should be pointed out that the body burden of guthion is expected to be rapidly reduced upon cessation of exposure to the insecticide. There were no detectable guthion metabolites in muscle or internal organs in rats 48 hours after being administered an 8 mg/kg dose of radiolabeled guthion by gavage (Fakhr et al. 1996).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Information on the interference with the mechanism of action for toxic effects of guthion was not located. Thus, information pertinent to organophosphate pesticides in general was extracted from the texts listed above. Organophosphate poisoning is commonly treated by administration of atropine and pralidoxime (2-PAM). Atropine is a competitive antagonist at muscarinic receptor sites and is helpful in drying excessive secretions, especially from the tracheobronchial tree. Although atropine crosses the blood-brain barrier and thus also treats the central nervous system effects, it does not antagonize nicotinic effects. Initial doses of 1–2 mg for an adult and 0.05 mg/kg for children, preferably by the intravenous route, have been recommended. Treatment may be repeated every 15–30 minutes until signs of atropinization occur. Glycopyrrolate, a quaternary ammonium compound, has also been used instead of atropine (Bardin and Van Eeden 1990). Glycopyrrolate does not cross the blood-brain barrier and has fewer central nervous system effects than atropine. Nicotinic effects such as muscle weakness and respiratory depression from organophosphate poisoning are commonly treated by administration of 2-PAM. 2-PAM is a quaternary amine oxime that can restore enzymatic activity by reversing the phosphorylation of acetylcholinesterase. 2-PAM and other oximes function by nucleophilic attack on the phosphorylated enzyme; the oxime-phosphonate is then split off, leaving the regenerated enzyme. Moreover, 2-PAM has an anticholinergic effect and may prevent continued toxicity by detoxifying the organophosphate molecule (Carlton et al. 1998). 2-PAM should be administered as soon as a diagnosis of poisoning 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. Since enzyme regeneration depends on plasma levels of the organophosphate, some patients may require multiple doses. A 2-PAM serum level of 4 μg/L is suggested as the minimum therapeutic threshold. 2-PAM is considered a safe drug with few side effects; however, high doses of 2-PAM can cause neuromuscular blockade and inhibition of AChE, although these effects are minimal at

the recommended antidotal doses (Taylor 2001). An intravenous administration rate of 2-PAM >500 mg/minute can result in mild weakness, blurred vision, diplopia, dizziness, headache, nausea, and tachycardia (Taylor 2001).

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 guthion 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 guthion.

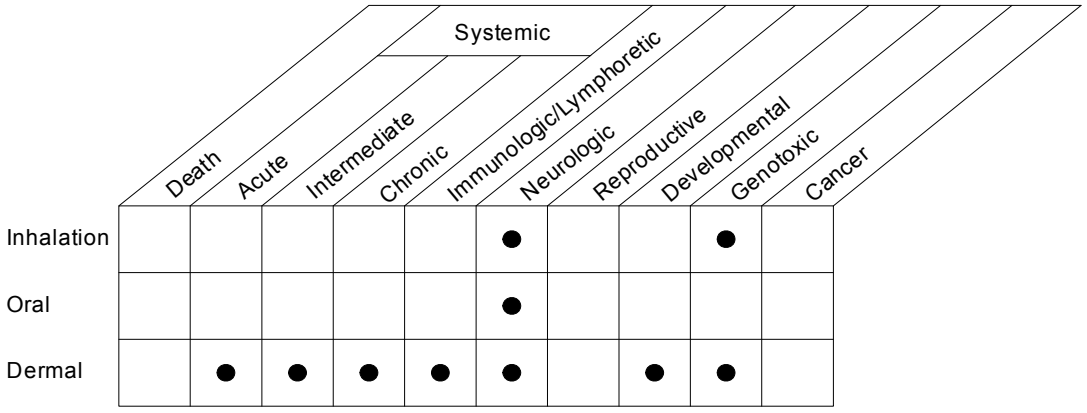
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

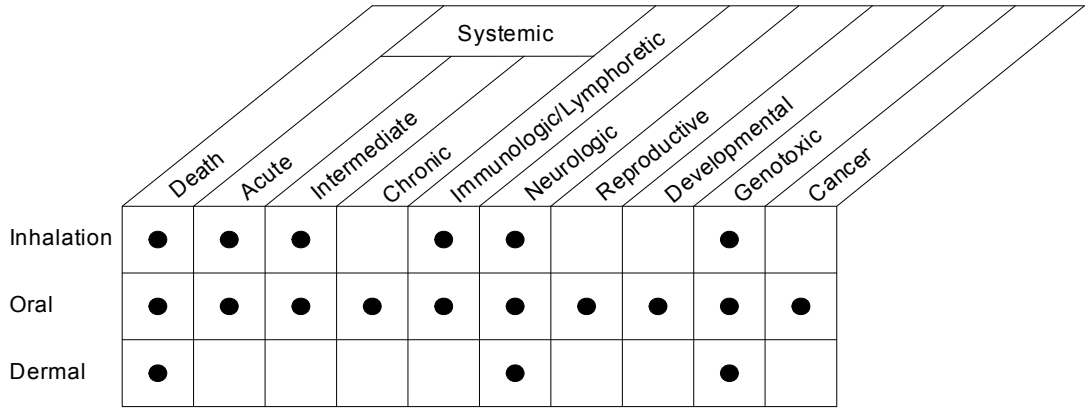
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to guthion are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of guthion. Each dot in the figure indicates that one or more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

Human and animal studies suggest that inhibition of AChE activity is the most sensitive end point of guthion toxicity. Inhibition of AChE activity has been observed after inhalation, oral, and dermal exposures to guthion. The inhibition of AChE activity by guthion is dose-related, but is not strongly

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



Human



Animal

● Existing Studies

influenced by duration of exposure. The inhibition of nervous system AChE leads to the accumulation of the neurotransmitter acetylcholine at the ending of cholinergic nerves with the ensuing continual stimulation of electrical activity (Carrier and Brunet 1999). Erythrocyte AChE is analogous to nervous system AChE and inhibition of the former is correlated with clinical toxicity in the nervous system (Carrier and Brunet 1999). In humans and animals, significant inhibition of erythrocyte AChE activity occurs at doses that are several times lower than doses eliciting clinical signs and symptoms.

In humans, mild, moderate, and severe poisoning with organophosphate insecticides corresponds to ChE activity reductions to 20–50, 10–20, and <10% of normal levels, respectively (Aaron and Howland 1998). Despite these general guidelines, it should be kept in mind that a single ChE activity measurement cannot confirm or exclude exposure to organophosphate insecticides given the large variation in the normal levels of ChE activity in the general population.

There is a paucity of controlled studies of humans exposed to guthion. The only controlled studies of humans exposed orally to guthion (Rider and Puletti 1969; Rider et al. 1970, 1971, 1972) remain unpublished, and limited information from them is available only in abstracts; however, a small number of dermal absorption and dermatologic studies in humans and studies of agricultural workers exposed to guthion during application are available.

Neurological, systemic, reproductive, and developmental effects have been evaluated in dogs, rats, or mice after acute-, intermediate-, and chronic-duration exposures to guthion by inhalation, oral, and dermal routes. The potential carcinogenicity of guthion has also been evaluated.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. No controlled, acute toxicity studies in humans exposed to guthion orally or by inhalation were available. Studies of agricultural workers exposed to guthion were located (Franklin et al. 1981; Kraus et al. 1977; Schneider et al. 1994) as were studies of the dermal absorption of guthion in volunteers (Feldmann and Maibach 1974). Guthion is absorbed when applied dermally in humans as demonstrated by the urinary excretion of radiolabeled metabolites of guthion after a single application of guthion to the forearms of volunteers (Feldmann and Maibach 1974). Feldmann and Maibach (1974) examined the excretion of radiolabeled guthion metabolites, but the study was not designed to identify toxic end points. Acute-duration studies in rats and mice evaluated the neurotoxic, systemic, reproductive, and developmental effects of guthion following inhalation, oral, and dermal

exposure (Astroff and Young 1998; EPA 1978a; Gaines 1960; Kavlock et al. 1985; Kimmerle 1976; Pasquet et al. 1976; Short et al. 1980; Skinner and Kilgore 1982; Su et al. 1971). ATSDR derived an acute-duration inhalation MRL based on the study by Kimmerle (1976), which is the only available acute-duration inhalation study with guthion in which activity levels of erythrocyte AChE were determined. Clinical signs at lethal doses were reported after a 1-hour exposure of rats to guthion, but erythrocyte AChE activity was not determined (EPA 1978a). An additional acute-duration inhalation study in mice or rats conducted at doses ranging from the low doses in Kimmerle (1976) to the higher doses used in EPA (1978a) would be useful to confirm the results of Kimmerle (1976) and to allow a better understanding of the dose-response curve for reductions in erythrocyte AChE activity and the onset of clinical signs of neurotoxicity. ATSDR derived an acute-duration oral MRL based on the study of Astroff and Young (1998). Additional acute-duration studies of the oral toxicity of guthion are not considered necessary at this time. The large variation in dermal LD_{50} values (EPA 1978a; Gaines 1960; Pasquet et al. 1976; Skinner and Kilgore 1982) could be due to differences in absorption related to experimental methods. An additional acute-duration dermal study in mice or rats would be useful to better understand the dose response curve for reductions in erythrocyte AChE activity and the onset of clinical signs of neurotoxicity.

Intermediate-Duration Exposure. Limited data are available regarding guthion-induced effects on ChE activity following repeated oral exposure of volunteers for 4 weeks (Rider and Puletti 1969; Rider et al. 1970, 1971, 1972). There was no effect on erythrocyte AChE or plasma ChE activity at the doses tested. No intermediate-duration inhalation or dermal studies were located regarding guthion toxicity in humans. No intermediate-duration dermal studies were located regarding guthion toxicity in animals; however, the effects elicited by exposure to guthion are not expected to be route-dependent and the effects from dermal exposure are expected to be similar to those observed after oral or inhalation exposure. Intermediate-duration studies have evaluated the neurotoxic, systemic, reproductive, and developmental effects of guthion administered orally or by inhalation to rats and dogs (Allen et al. 1990; Holzum 1990; Kimmerle 1976; Schmidt and Chevalier 1984; Sheets et al. 1997; Short et al. 1980; Vos et al. 1983). A number of studies have demonstrated that neurotoxicity, exhibited as significant reductions in erythrocyte AChE or clinical signs of neurotoxicity, is the most sensitive end point following intermediate-duration exposures to guthion. Increased mortality was observed in rats administered guthion by gavage (Short et al. 1980) or in the diet (Holzum 1990). The available experimental data suggest that developmental and reproductive effects are evident mostly at doses that are maternally toxic or that elicit significant reductions in parental erythrocyte AChE. ATSDR derived an intermediate-

duration inhalation MRL based on the study by Kimmerle (1976) and an intermediate-duration oral MRL based on the study by Allen et al. (1990).

Chronic-Duration Exposure and Cancer. No controlled studies were located regarding guthion-induced toxicity following chronic-duration inhalation or dermal exposure of humans or animals. No studies of chronic, oral exposure to guthion in humans were located. Information from chronic toxicity studies is important because people working with guthion might be exposed to this pesticide for many years. The study by Weinbaum et al. (1997) suggests that dermal, and perhaps inhalation, exposures of workers to guthion may lead to adverse health effects. An increased association was observed between the occurrence of systemic illness (defined as an acute illness following pesticide exposure, with symptoms and signs not restricted to the eyes or skin) in workers and agricultural use of guthion (Weinbaum et al. 1997). Chronic-duration studies in dogs and rats have evaluated the systemic and neurological effects of guthion administered in the diet for up to 2 years (Allen et al. 1990; Schmidt and Chevalier 1984). ATSDR derived a chronic-duration inhalation MRL based on Kimmerle (1976) and a chronic-duration oral MRL based on Allen et al. (1990). A study of the long-term neurological effects of exposure to guthion is warranted.

No studies were located regarding cancer in humans following oral exposure to guthion. A 2-year carcinogenicity study in rats and mice showed an increased combined incidence of islet cell carcinoma or carcinomas of the pancreas in male rats exposed to 10.9 mg/kg/day guthion in the diet for 80 weeks followed by a 35-week observation period (NCI 1978). However, this lesion occurs at a high spontaneous incidence in the animals used in this study and the increased incidence in the treated males could not be unequivocally attributed to treatment with guthion (NCI 1978). Similarly, the increases in the incidence of benign thyroid tumors, malignant thyroid tumors, or combined follicular cell tumors observed in male rats exposed to 5.5 or 10.9 mg/kg/day (NCI 1978) could not be attributed to treatment with guthion due to the historically high spontaneous incidence of these neoplasms in male rats in this laboratory (NCI 1978). There was no evidence of the occurrence of treatment-related tumors in female rats in this study or in another study of male and female Wistar rats exposed to 0.25–3.11 mg/kg/day for 2 years (Schmidt and Chevalier 1984). Benign and malignant neoplasms were observed among dosed and control B6C3F1 mice, but these lesions appear to occur spontaneously in mice in this laboratory and the effect could not be attributed to guthion (NCI 1978). The incidences of neoplasms of the pancreatic islets and of the follicular cells of the thyroid in male rats provide suggestive but insufficient evidence of a carcinogenic potential of guthion in male rats (NCI 1978). There was no significant increase in the incidence of tumors in female rats. The results of these studies led NCI (1978) to conclude that, under the

conditions of this bioassay, guthion was not carcinogenic in male or female mice or female rats. There was suggestive but insufficient evidence to conclude that guthion was carcinogenic in male rats. Additional carcinogenicity studies with guthion are not needed at this time.

Genotoxicity. No *in vivo* studies of genotoxic effects in humans were located. Six of the 11 *in vitro* studies with eukaryotic organisms (fungi and mammalian cells) that were located showed positive results for genotoxic effects (Alam and Kasatiya 1976; Alam et al. 1974; Bianchi–Santamaria et al. 1997; Hrelia et al. 1990; Waters et al. 1982; Zeiger et al. 1987), but the remaining studies (Carere et al. 1978; Hrelia et al. 1990; Waters et al. 1982) did not. An *in vivo* genotoxicity evaluation of persons exposed to guthion, particularly agricultural workers, would provide data that could assist in establishing the genotoxic potential of this insecticide in humans.

Reproductive Toxicity. No studies are available on the reproductive toxicity of guthion in humans through any route of exposure or in animals exposed dermally or by inhalation. The reproductive toxicity of guthion has been evaluated in mice and rats administered guthion orally. Reductions in the incidence of viable litters were observed in the offspring of pregnant mice administered 20 mg/kg guthion orally once on gestation day 8 (Kavlock et al. 1985). Astroff and Young (1998) did not observe reproductive effects in pregnant rats administered guthion at 2 mg/kg/day on gestation days 6–15. Insemination, fertility, or gestation indices or duration of gestation were not affected in male and female rats administered guthion at 0.43 to 4.9 mg/kg/day in the diet for 14 weeks before mating and continuously through gestation (Holzum 1990). The available evidence suggests that adverse reproductive effects are observed at doses that are higher than doses eliciting maternal toxicity. Thus, an additional study of the reproductive toxicity of guthion in animals after intermediate-duration exposure is not needed at this time.

Developmental Toxicity. No controlled studies are available on the developmental toxicity of guthion in humans by any route of exposure. No association was observed between occupational exposure to guthion and the occurrence of congenital malformations in a study of male agricultural workers conducted in Spain during 1993 and 1994 (García et al. 1998). Increased incidences of supernumerary ribs and reduced fetal body weight gain were observed in the offspring of pregnant mice administered a single oral dose of guthion at 16 and 20 mg/kg, respectively (Kavlock et al. 1985). Increased incidences of malaligned sternbrae and reduced body weight gain, brain weight, brain AChE activity, and survival were observed in the pups of pregnant rats administered 1.3–5 mg/kg/day during gestation (Holzum 1990; Short et al. 1980). The available experimental data suggest that in most studies developmental effects are evident only at doses that are maternally toxic. Thus, additional studies of the

in utero developmental toxicity of guthion do not seem necessary at this time; however, information is lacking regarding the developmental effects of exposures of juvenile animals or children to guthion and a study to fill this data gap is warranted.

Immunotoxicity. No studies were located on the immune toxicity in humans exposed to guthion by inhalation or oral exposure. Two studies examined the incidence of allergic responses in volunteers who were administered skin patches. In one of these studies guthion did not elicit a dermal immune response (Lisi et al. 1987), while in the other study, 1 of 63 workers showed an allergic reaction to guthion (Sartorelli et al. 1999). Vos et al. (1983) reported decreased relative spleen and mesenteric lymph node weights, as well as unspecified histopathologic findings in the thymus in male Wistar rats exposed to guthion in the diet at 11.5 mg/kg/day for 3 weeks. An increase in mortality was also observed at 11.5 mg/kg/day; no effects were observed at 2.3 mg/kg/day (Vos et al. 1983). Thymus and spleen morphology were not affected in rats exposed to guthion by inhalation for up to 12 weeks (Kimmerle 1976). The available evidence suggests that guthion elicits an unspecified immune response only at levels that also increase mortality. Thus, additional immunotoxicity studies are not warranted at this time.

Neurotoxicity. Available studies strongly suggest that adverse effects on the nervous system are the most sensitive end points of guthion toxicity and these effects are well characterized. Although no significant changes in plasma ChEor erythrocyte AChE activity were observed in a small group of subjects who took guthion orally at 0.057–0.086 mg/kg/day for 4 weeks (Rider and Puletti 1969; Rider et al. 1970, 1971, 1972), studies of agricultural workers have demonstrated 10–20% reductions in erythrocyte AChE or whole blood ChE activity after a single air-blast application of guthion (Franklin et al. 1981) or after entering field treated with guthion (Kraus et al. 1977; McCurdy et al. 1994; Schneider et al. 1994). Despite the reductions in erythrocyte AChE activity, workers did not exhibit clinical signs of neurotoxicity. A number of animal studies have demonstrated marked reductions in erythrocyte, brain, or plasma AChE activity, or whole blood ChE activity as well as clinical signs of neurotoxicity after acute-, intermediate-, or chronic-duration exposures to guthion by inhalation (Kimmerle 1976), oral (Allen et al. 1990; Astroff and Young 1998; EPA 1978a; Holzum 1990; Pasquet et al. 1976; Schmidt and Chevalier 1984; Sheets et al. 1997; Short et al. 1980; Su et al. 1971), or dermal (EPA 1978a; Skinner and Kilgore 1982) exposure routes. No data are currently available to address the possibility of long-term neurological effects of repeated exposure to guthion. Thus, it is recommended that a battery of tests designed to detect subtle neurological effects be conducted among workers involved in the application of guthion or who enter fields treated with guthion.

Epidemiological and Human Dosimetry Studies. Agricultural workers face the highest risk of exposure to guthion. Studies of agricultural workers who applied guthion (Franklin et al. 1981) or entered fields treated with guthion (Kraus et al. 1977; McCurdy et al. 1994; Schneider et al. 1994) showed reductions in erythrocyte AChE activity or whole blood ChE activity, but did not exhibit clinical signs of neurotoxicity. These studies have examined changes in erythrocyte AChE activity over brief exposure durations and have generally not addressed systemic effects. Thus, an epidemiological study of agricultural workers exposed chronically to guthion would help evaluate the suggested association between the incidence of systemic illness and agricultural use of guthion (Weinbaum et al. 1997). An accurate quantification of exposure to guthion would be necessary to derive useful data from such a study.

Biomarkers of Exposure and Effect.

Exposure. The ideal biomarker for the quantification of exposure to guthion would be specific to the chemical of interest and would probably be the insecticide itself or a metabolite that could only be detected after exposure to guthion. It has been shown that DMPDT, DMTP, and DMP are metabolic products of the *in vivo* degradation of guthion (Carrier and Brunet 1999) and have been detected in urine of humans exposed to guthion under field and experimental conditions (Aprea et al. 1994; Franklin et al. 1986); however, these metabolites are not specific to guthion, but indicate potential exposure to a variety of organophosphate pesticides. Direct monitoring data of guthion in humans is rare since its biological half-life is short. No studies were located that detected guthion or gutoxon in blood of exposed animals or humans. Reductions in plasma ChE and erythrocyte AChE activity and clinical symptoms of neurotoxicity are reliable biomarkers of exposure to guthion; however, it is currently not possible to use these biomarkers to distinguish between exposure to guthion and other organophosphorus insecticides. Development of a biomarker of exposure specific to guthion would be useful in conducting exposure assessments and epidemiological studies.

Effect. Cholinergic symptoms of neurotoxicity and reductions in erythrocyte AChE activity (a surrogate for nervous system AChE activity) provide reliable biomarkers for the effect of guthion; however, these effects are not unique to guthion exposure and are elicited by other organophosphate and carbmamate ester insecticides as well. In addition, the large degree of variability in ChE activity in human populations suggests that caution should be exercised when comparing ChE activities from exposed populations, such as agricultural workers, and reference populations (Coye et al. 1987; Maroni et al. 2000). Development of a biomarker of effect specific to guthion would be useful in conducting exposure assessments and epidemiological studies.

Absorption, Distribution, Metabolism, and Excretion. Animal studies have demonstrated that guthion is absorbed via the inhalation pathway, as can be inferred from the observed reductions in erythrocyte AChE activity (Kimmerle 1976) and whole blood ChE activity (EPA 1978a) following acute- or intermediate-duration exposure. No human data are available from which to estimate the absorption of guthion after oral exposure, but animal studies suggest that guthion is rapidly absorbed after oral exposure (Fakhr et al. 1996). The detection of urinary metabolites of guthion in dermally-exposed humans and rats serves as indication that dermally applied guthion is absorbed (Feldmann and Maibach 1974; Franklin et al. 1983).

No studies are available regarding the distribution of guthion in exposed humans or animals following inhalation exposure; however, the distribution of guthion in exposed animals or humans is not expected to be route-dependent. A study on the distribution of guthion administered orally to rats was located (Fakhr et al. 1996). The bioactivation of guthion to gutoxon and the detoxication of guthion is understood (Dahm et al. 1962; Hitchcock and Murphy 1971; Levine and Murphy 1977; Motoyama and Dauterman 1972; Sultatos and Woods 1988). Studies suggest that the role of different cytochromes in the bioactivation process may be dependent on the guthion concentration (Buratti et al. 2003).

Urinary excretion of guthion metabolites has been demonstrated in humans (Aprea et al. 1994); however, the detected metabolites are not unique to guthion. No information was located on the elimination and excretion of guthion in human or animals following inhalation exposure. Elimination of guthion is not expected to be route dependent. Radiolabeled guthion metabolites were eliminated largely in expired air, and feces of rats after a single oral dose; neither guthion nor its oxon metabolite were detected by chromatographic analysis of the urine (Fakhr et al. 1996). Urinary excretion of radiolabeled metabolites of guthion (predominantly DMTP) has been examined in dermally exposed human subjects (Feldmann and Maibach 1974; Franklin et al. 1986) and laboratory animals (Franklin et al. 1983). The urinary output of radiolabeled guthion metabolites after an intramuscular injection to rats showed two peaks in urinary excretion of the administered dose, one 4 hours after the dose (approximately 13% of the dose) and a higher peak (approximately 20% of the dose) after 24 hours, which was followed by a rapid decrease in output (Franklin et al. 1983). Urinary recovery of metabolites observed in a study with human subjects administered a single intravenous dose of radiolabeled guthion also showed an initial peak (1.5% dose/hour) 0–4 hours after the dose was administered, which was followed by a drop in excretion and a second peak (1.6% dose/hour) 812 hours after the dose was administered (Feldmann and Maibach 1974).

The pharmacokinetics of guthion are fairly well understood; additional pharmacokinetic studies are not considered necessary at this time.

Comparative Toxicokinetics. No studies were located that directly evaluated the comparative toxicokinetics of guthion in animals and humans. Nevertheless, available studies suggest that the toxicokinetics of guthion in animals and humans are generally similar (EPA 1999b; Feldmann and Maibach 1974, Zendzian 2003) and that neural AChE is the critical target of guthion toxicity in animals and humans (Buratti et al. 2003; Hitchcock and Murphy 1971). Recent work suggests that the desulfuration of guthion to gutoxon in human liver microsomes is largely effected by at least three cytochromes (CYP1A2, CYP3A4, and CYP2B6), which show different affinities for the substrate (Buratti et al. 2003). If the spectrum of activities of these cytochromes in animals varies markedly from that in humans, notable differences in animals and humans might be expected. No data are available to determine whether such differences exist. A study of the comparative toxicokinetics of guthion in animals and humans may be warranted.

Methods for Reducing Toxic Effects. Guthion exerts its systemic effects through inhibition of AChE in the central and peripheral nervous systems. Guthion is bioactivated *in vivo* and *in vitro* to its oxygen analog form, gutoxon (Buratti et al. 2003; Hitchcock and Murphy 1971; Sultatos and Woods 1988), which reacts with a serine hydroxyl group at the active site of AChE, rendering it largely inhibited and unreactive. The inhibited AChE enzyme cannot degrade acetylcholine and the neurotransmitter accumulates at the ending of cholinergic nerves with the ensuing continual stimulation of electrical activity (Carrier and Brunet 1999). Intoxications with guthion are managed as are intoxications caused by other organophosphate insecticides, namely, by administering respiratory support, atropine treatment, and reactivation of neural AChE with 2-PAM (Carlton et al. 1998; Tafuri and Roberts 1987). The mechanism of inhalation, oral, or dermal absorption of guthion is not known. Research is needed to develop an understanding of the mechanisms of route-specific absorption of guthion. Currently, no methods exist to promote the excretion of guthion or its active metabolite, gutoxon. Research is needed to develop methods to promote the excretion of guthion and the active metabolite gutoxon.

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.

No information is available for any route of exposure regarding potential age-related differences in guthion toxicity in humans or animals. No cases of children poisoned by exposure to guthion were located. Nevertheless, the critical targets of guthion toxicity can be expected to be similar in children and adults. Comparative studies of the toxicity and toxicokinetics of guthion in juvenile and adult animals are needed.

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

One ongoing study pertaining to the health effects of guthion has been identified in the Federal Research in Progress (FEDRIP) database. J.E. Chambers, J.S. Boone, and R.L. Carr of the College of Veterinary Medicine at Mississippi State University are conducting an investigation of the biochemical and physiological factors contributing to the age-related differences in responses of mammals to insecticides (FEDRIP 2006).

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4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

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

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Guthion is a nonsystemic organophosphate insecticide. Pure guthion is a colorless to white, odorless, crystalline solid with a melting point range of 72–74 °C, while the technical-grade material is a cream to yellow-brown, granular solid with a melting point of 67–70 °C (EPA 2001b). Guthion is readily soluble in most organic solvents (acetone, toluene, chloroform, acetonitrile, benzene, xylene, carbon tetrachloride, and chlorobenzene), slightly soluble in methanol, ethanol, and propanol, and poorly soluble in water. Information regarding the physical and chemical properties of this compound is located in Table 4-2.

Table 4-1. Chemical Identity of Guthion

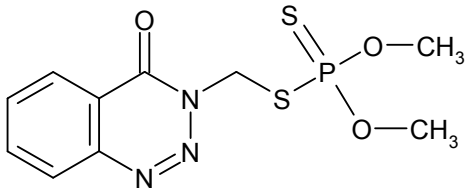
Characteristics	Guthion	References
Chemical name	S-(3,4-Dihydro-4-oxobenzo[d]-[1,2,3]-triazin-3-yl-methyl)O,O-dimethylphosphorodithioate	Tomlin 2003
Synonyms	O,O-Dimethyl S-[(4-oxo-1,2,3-benzotriazin-3(4H)-yl)-methyl]; Azinphos-methyl	Tomlin 2003
Trade names	Guthion; Aziflo; Azin-PB; Crysthyon; Mezyl; Sniper; Supervalex	Tomlin 2003
Chemical formula	$C_{10}H_{12}N_3O_3PS_2$	Tomlin 2003
Chemical structure		Tomlin 2003
Identification numbers:		
CAS registry	86-50-0	Tomlin 2003
NIOSH RTECS	TE1925000	NIOSH 2005
EPA hazardous waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	NA 2783; Guthion mixture, liquid	HSDB 2008
HSDB	1171	HSDB 2008
NCI	No data	

Table 4-2. Physical and Chemical Properties of Guthion

Property	Information	References
Molecular weight	317.3	Tomlin 2003
Color	Colorless to white (pure material); cream to yellow brown (technical grade material)	EPA 2001b
Physical state	Crystalline	Tomlin 2003
Melting point	72–74 °C (pure material); 67–70 °C (technical-grade material)	EPA 2001b
Boiling point	Decomposes above 200 °C	Tomlin 2003
Specific gravity (20 °C)	1.518	Tomlin 2003
Odor	Odorless	EPA 2001b
Odor threshold		
Water	0.0002 mg/kg	Verschueren 2001
Air	No data	
Solubility		
Water at 25 °C	28 mg/L	Tomlin 2003
Organic solvents	>250 g/L in dichloroethane, acetone, acetonitrile, ethyl acetate, and DMSO; 1.2 g/L in n-heptane and 170 g/L in xylene (all at 20 °C)	Tomlin 2003
Partition coefficients		
Log K_{ow}	2.75	Hansch et al. 1995
Log K_{oc}	2.69–3.67	Gawlik et al. 1998
Vapor pressure		
20 °C	$3x10^{-5}$ Pa ($2.2x10^{-7}$ mm Hg)	Suntio et al. 1988
Henry's law constant	$3.7x10^{-9}$ atm-m^3/mol	EPA 1999a
Flashpoint (closed cup)	No data	
Flammability limits		
Air	No data	
Conversion factors[a]		
ppm (v/v to mg/m^3 in air (20 °C)	1 ppm = 13.2 mg/m^3	Verschueren 2001
mg/m^3 to ppm (v/v) in air (20 °C)	1 mg/m^3 = 0.076 ppm	Verschueren 2001
Explosive limits	No data	

[a]Guthion exists partially in the particulate-phase in the atmosphere. This conversion is only applicable to vapor-phase guthion.

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

5.1 PRODUCTION

Guthion is produced by the reaction of N-bromethylazimidobenzoyl with sodium dimethyldithio-phosphoric acid (NRC 1977). Current production volumes are not known. In 1997, 2,091,014 pounds of guthion were used on crops throughout the United States with the vast majority being applied to apple orchards (USDA 2000). This represented an 18% decrease from national usage data compiled for 1992 in which 2,548,867 pounds were used. In the Interim Registration Eligibility Decision (interim RED) document for guthion, EPA estimated that <2 million pounds are used annually (EPA 2001b). Current use volumes of guthion throughout the United States are expected to be considerably lower than in previous years since many of the registered uses for this insecticide have been cancelled or are expected to be cancelled in upcoming years (see Section 5.3). For example, according to the State of California Department of Pesticide Regulation, use of guthion has decreased in California from over 400,000 pounds in 1994, to slightly over 50,000 pounds used in 2004 (CDPR 2006). The SRI Directory of Chemical Producers lists Bayer Crop Science as the only manufacturer of guthion in 2005 (SRI 2005); however, according to the National Pesticide Information Retrieval System, there are currently four active registrants manufacturing formulated products or technical-grade guthion (NPIRS 2006). These companies and the products produced are described in Table 5-1.

No information is available in the TRI database on facilities that manufacture or process guthion because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 1998c).

5.2 IMPORT/EXPORT

No current data are available regarding the volume of guthion imported or exported to and from the United States. As with many pesticides with production or uses involving proprietary information, quantitative estimates of production, import, and export volumes are not publicly available (Bason and Colborn 1992).

Table 5-1. Manufacturers of Technical-Grade or Formulated Products Containing Guthion

Company name and address	Number of active products	Product description(s)
Bayer CropScience Research Triangle Park, North Carolina 27709 (919)549-2000	2	Technical-grade powder and 50% wettable powder
Gowan Company Yuma, Arizona 85366-5569 (928)783-8844	5	Technical-grade powder, 50% water soluble bags, 35% water soluble bags, 35% wettable powder, and 50% polyvinyl acetate bags
Makhteshim Chemical Works, Ltd. Makhteshim-Agan of North America, Inc. Raleigh, North Carolina 27609 (919)256-9300	1	Technical-grade powder
Micro-Flo Company, LLC Memphis, Tennessee 38117 (901)432-5118	3	35% Emulsifiable concentrate, 35% wettable powder, 50% wettable powder

Source: NPIRS 2006

5.3 USE

Guthion is a broad spectrum organophosphate insecticide, acaricide, and molluscacide that has been used to control a wide variety of insects including codling moths, plum curculios, apple maggots, aphids, leafrollers, mites, mealybugs, moths, and boll weevils (EPA 2001b). It has been used on a variety of crops; however, its major use has been on tree crops, including pome and stone fruit and nut crops (EPA 2001b).

In 2001, the EPA published its interim RED for guthion, in which it concluded that all uses of guthion were ineligible for re-registration based on their currently approved labeling (EPA 2001b). The EPA proposed the immediate cancellation of 28 Group 1 uses of guthion (alfalfa, beans—succulent or snap, birdsfoot trefoil, broccoli, cabbage including Chinese, caneberries—foliar application only, cauliflower, citrus, celery, clover, cucumbers, eggplants, filberts, grapes, melons, nectarines, nursery stock other than quarantine use, onions—green, onions—dry bulb, parsley, pecans, peppers, plums and dried plums, potatoes, quince, spinach, strawberries, and tomatoes), which were deemed to have little use and/or low benefits. Another seven uses were allowed to continue with a 4-year phase out since these uses were considered to have moderately high economic benefit. The remaining uses were considered to have significant economic benefits for which no adequate pesticide could be used in place of guthion (California EPA 2004). These uses were considered eligible for re-registration with 4-year time limited tolerances. If no request was made for re-registration these uses were set to expire in October 2005. In July 2004, the guthion registrants submitted applications to extend the registrations for the remaining 10 uses of guthion (Group 3 uses). These uses include almonds; apples/crabapples; blueberries, lowbush and highbush; Brussels sprouts; cherries, sweet and tart; nursery stock; parsley; pears; pistachios; and walnuts. On March 29, 2006, EPA amended the registrations of guthion products to terminate the Group 2 uses, which include caneberries, cotton, cranberries, peaches/nectarines, potatoes, and Southern pine seed orchards (EPA 2006j). This order follows up on an August 2005 notice of receipt of requests from the registrants to voluntarily cancel the Group 2 uses. Under the existing stocks provisions, distribution or sale of these products for these uses is allowed until March 31, 2006, and use of these products is allowed until September 30, 2006. On June 9, 2006, EPA proposed the cancellation of guthion usage for apples, blueberries, cherries, parsley, and pears by 2010 and cancellation of its uses on almonds, Brussels sprouts, pistachios, walnuts, and nursery stock by 2007 (EPA 2006l).

5.4 DISPOSAL

The two methods most frequently employed for the disposal of organophosphate pesticides such as guthion are incineration and alkaline hydrolysis (NIOSH 1981). Incineration involves dissolving guthion in a flammable solvent such as alcohol followed by atomization in a suitable combustion chamber equipped with an appropriate effluent gas cleaning device.

Guthion is listed as toxic substances under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA). Disposal of wastes containing these compounds is controlled by a number of federal regulations (see Chapter 8). The EPA Office of Pesticide Programs has detailed labels for the use, storage, and disposal of all pesticides, including registered products containing guthion. All pesticide products are required to bear instructions for the storage and disposal of the pesticides and the pesticide containers. Storage and disposal instructions cover the appropriate storage of the pesticide product; disposal of any unused pesticide product or any rinse liquids resulting from cleaning of pesticide application equipment; and the disposal of the pesticide container. State and local regulations may be stricter than the federal requirements listed on the label.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

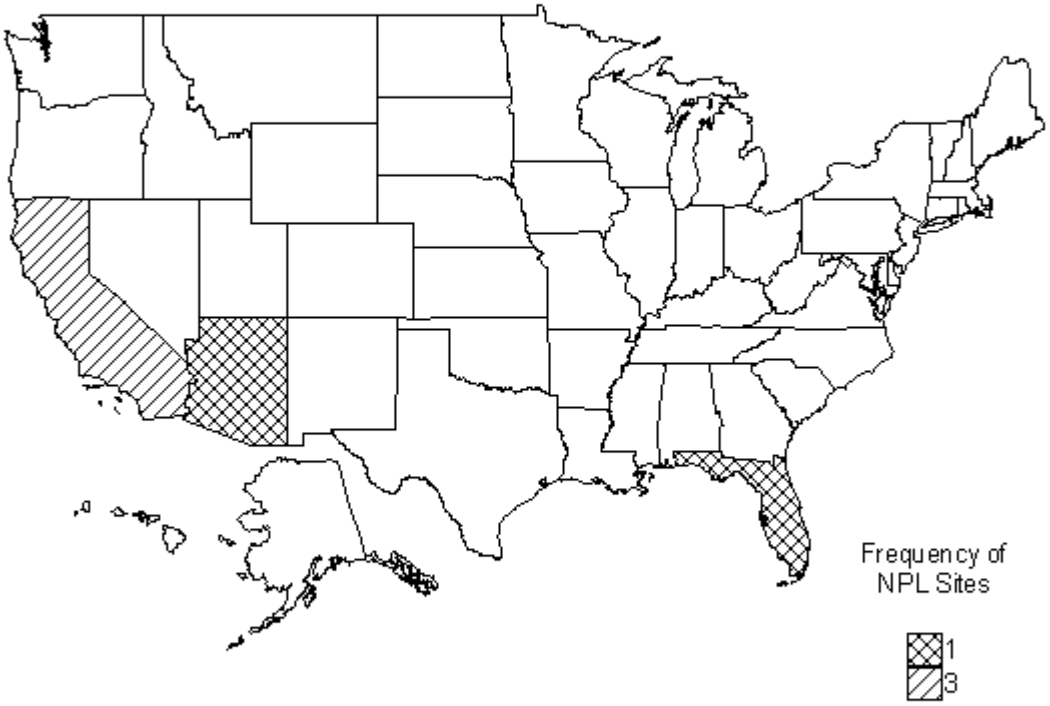
Guthion has been identified in at least 5 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2008). However, the number of sites evaluated for guthion is not known. The frequency of these sites can be seen in Figure 6-1.

Guthion is a restricted use organophosphate insecticide that is primarily used as a foliar application against phytophagous insect pests on fruit, field, or vegetable crops and works as both a contact insecticide and a stomach poison. In 2001, the EPA proposed the immediate cancellation of most uses of guthion. The only crops that guthion can still be applied to are almonds; apples/crabapples; blueberries, lowbush and highbush; Brussels sprouts; cherries, sweet and tart; nursery stock; parsley; pears; pistachios; and walnuts. On August 8, 2007, the companies that produce guthion voluntarily requested to amend their registrations which would effectively terminate certain uses (Brussels sprouts and nursery stock) of guthion by September 30, 2007 (EPA 2007). Uses on walnuts, almonds, and pistachios are scheduled to cease by October 30, 2009, and all other uses would be terminated by September 30, 2012 (EPA 2007). The application rate of guthion varies depending upon which crop it is applied to, but is typically in the range of 0.3–1.4 pounds a.i./A (EPA 1999a).

Guthion is not considered highly persistent in the environment, and degrades by a combination of biotic and abiotic mechanisms. Biodegradation occurs readily in soils and water under aerobic conditions with half-lives on the order of several days to a few weeks. Hydrolysis and photolysis are also important degradation pathways for guthion in water, foliage, and soils. In the atmosphere, vapor-phase guthion is quickly degraded by photochemically produced hydroxyl radicals; the half-life for this reaction in air is on the order of a few hours. Particulate-phase guthion is removed from the atmosphere by wet and dry deposition processes. Guthion has moderate to low mobility in soils. Its leaching potential is considered low, and therefore, guthion is only occasionally detected in groundwater.

Levels of guthion in the environment can vary considerably. In areas where it is not used, it is rarely detected, suggesting that long-range transport of this chemical does not occur. However, guthion is frequently detected in surface water bodies near fields or orchards where it has been applied as an insecticide. The most important route of exposure to guthion for the general population is through the ingestion of foods, especially vegetables and fruits that have been sprayed with this insecticide. Ingestion of contaminated drinking water, inhalation exposure, and dermal exposure to guthion are expected to be

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



Derived from HazDat 2008

low for the general population. Agricultural workers, their families, and persons residing near crops that are treated with guthion are expected to have much greater frequency of exposure and the potential to be exposed to higher levels of guthion than the general population.

6.2 RELEASES TO THE ENVIRONMENT

The amount of guthion used in the United States, and thus released to the environment, appears to be declining. The total amount of guthion used in 1997 was reported as 2,091,014 pounds, which was an 18% decrease from the amount used (2,548,867 pounds) in 1992 (USDA 2000). In 2002, the estimated annual agricultural use of guthion had declined to about 1.2 million pounds, nearly a 50% decline from 1997 (USGS 2007). Recent restrictions on the crops that guthion can be applied to are likely to result in lower emissions in future years.

There is no information on releases of guthion to the environment from manufacturing and processing facilities because these releases are not required to be reported (EPA 1998c).

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).

6.2.1 Air

There is no information on releases of guthion to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 1998c).

Guthion releases to the atmosphere arise from its use as an insecticide where it is applied to crops by aerial application or with ground-based boom sprayers. Guthion was detected in air samples at one of the five current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2008).

6.2.2 Water

There is no information on releases of guthion to the water from manufacturing and processing facilities because these releases are not required to be reported (EPA 1998c).

Guthion is released to water from point source discharges, spray drift from aerial applications, and runoff and erosion of treated soils. A multi-year study from 1981 to 1984 was conducted to determine the loadings of carbofuran, fenvalerate, and guthion to Lake Oconee in Georgia from the treatment of a pine seed orchard adjacent to the lake (Bush et al. 1986). A series of approximately 85 rainfall events over a 49 month period produced varying amounts of runoff and erosion loadings into the lake. For example, guthion was applied aerially in April of 1981 and a rainfall event 10 days postapplication produced 1,540 µg/L of guthion in the resultant runoff water (Bush et al. 1986). The amount of spray drift entering the lake was estimated by placing a series of 9 glass fiber disks within the treatment zone of the orchard and 12 discs along the edge of the lake. The discs within the treatment zone averaged 1,201 µg of guthion per disc, while the discs adjacent to the lake averaged 1.2 µg of guthion per disc (Bush et al. 1986).

Two field runoff studies were submitted by the Bayer Corporation to the EPA in support of the registration of guthion (EPA 1999a). These two studies were conducted on cotton fields in Colquitt County, Georgia and Benoit, Mississippi. A single application of guthion at an application rate of 0.25 pounds a.i./A was made in August 1989 to the Mississippi field. Eight applications of guthion (0.25 pounds a.i./A) were made at 3-day intervals starting on August 1 at the Georgia location. At the Mississippi site, a total of 14.9 g of guthion was released in runoff from the 5.2-acre plot during a heavy rainfall event that produced 3.08 inches of precipitation 2 days postapplication. Approximately 31.5% of the precipitation was accounted for in runoff from the plot during the rainfall event (EPA 1999a). A total of 13.3 g of guthion was released in runoff from the 9-acre portion of the Georgia field in four storms which occurred on August 8 (32 mm of precipitation), August 26 (61 mm of precipitation), August 31 (37 mm of precipitation), and October 1 (33 mm of precipitation). These produced 3.6, 8.3, 1.3, and 0.0012 g of guthion in the collected runoff, respectively (EPA 1999a).

Guthion was detected in the groundwater at one of the five current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2008). There were no detections of guthion in surface water at any of these sites.

6.2.3 Soil

There is no information on releases of guthion to the soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 1998c).

Guthion is released directly to soils from its registered use as an insecticide (EPA 1999a). Deposition to the ground following aerial spraying or direct applications via chemigation or sprinkler irrigation systems is common. Guthion was detected in soil samples at three of the five current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2008). There were no detections of guthion in sediment at any of these sites.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

The vapor pressure of guthion is 2.2×10^{-7} mm Hg (Suntio et al. 1988) and its estimated Henry's law constant is 3.7×10^{-9} atm-m^3/mol, calculated from its vapor pressure and water solubility (EPA 1999a). These values suggest that guthion is essentially nonvolatile from water and soil surfaces. The volatilization flux of guthion from treated walnut orchards was estimated using the EPA's SCREEN-2 dispersion model (Woodrow et al. 1997). The estimated volatilization flux from the surface of the walnut tree leaves was 0.067 μg/m^2-second, which resulted in an estimated atmospheric concentration of approximately 0.23 μg/m^3 15 m downwind from the application site.

In the atmosphere, postapplication spray drift is an important source of environmental contamination and is responsible for much of guthion's transport outside of its target zone. The amount of spray drift is influenced by meteorological conditions such as wind speed and method of application (e.g., aerial or ground spraying). Droplet size, humidity, and temperature are also important factors that can affect spray drift. In general, fine droplet size, low humidity, and warm temperatures enhance the likelihood of increased spray drift. For most spray applications of pesticides, buffer zones are required between the target crop and any permanent water bodies. These buffer zones for guthion typically range from 25 feet for ground applications using boom sprayers to 150 feet for aerial applications to certain crops. Guthion

may be removed from the atmosphere by wet and dry deposition. This is confirmed by the detection of guthion in atmospheric rainwater samples (Section 6.4.1). The short atmospheric residence time of guthion suggests that it will not be transported long distances from its initial release point.

Adsorption/desorption experiments using three different soils suggest that guthion has moderate to low mobility in soil and the potential to leach into groundwater is considered low. The K_{oc} values of guthion in a sandy loam (1.6% organic carbon), silt loam (2.9% organic carbon), and clay loam (0.3% organic carbon) were calculated as 475, 579, and 3,266, respectively from the Freundlich adsorption coefficients (EPA 1999a). The adsorption characteristics of guthion in five standard European soils have also been studied (Gawlik et al. 1998). The K_{oc} values in these five reference soils ranged from 534 to 4,644. The physical properties of these soils and corresponding adsorption coefficients are shown in Table 6-1.

The mobility of guthion in soils under field conditions has been studied in two alfalfa fields located in California (EPA 1999a). In the first field, a single application of guthion was made to a portion of the field at 3 pounds a.i./A. In another section of the field, two applications of 3 pounds a.i./A were made 7 days apart. The soil type of the field was described as Salinas silt that was slightly alkaline (pH 6.9–8.0). Over the course of 60 days, guthion was only detected in one soil sample below a depth of 6 inches, suggesting very limited mobility in the field. The same experimental protocol was employed in the second field located in Fresno, California. Guthion was not detected in any soil samples below a sampling depth of 6 inches in this field (EPA 1999a). Guthion was not detected below a depth of 30 cm when applied at an application rate of 9 pounds/A to a potato field with a soil texture that was described as a sandy loam and irrigated with 27.6 cm of water (Yaron et al. 1974). An aged soil column leaching study indicated that guthion and its degradation products are not particularly mobile in soils and the potential to leach into groundwater is low (EPA 1999a). Following application of an unspecified amount of ^{14}C labeled guthion to a soil that was aged for 28 days and then dried before being packed into the column, 90% of the radioactivity was located in the top 5 cm of the column after application of 35.5 cm of water over 45 days. A total of 4.4% of the radioactivity leached from the bottom of the 30.5 cm column.

The uptake and translocation of guthion in bean plants and barley has been demonstrated (Al-Adil et al. 1973). The authors reported that guthion was readily absorbed through the roots and transported undegraded to other parts of the plant following incorporation into the soil or during direct application to the leaves. The assimilation of guthion by the roots and the translocation of the radiocarbon into the aerial parts of both plant species were most rapid during the first 24 hours. On day 8, the majority of the

Table 6-1. Soil Adsorption Characteristics of Guthion in Five European Soils

Property	Vertic Cambisol (Italy)	Rendzina silt loam (Greece)	Dystric Cambisol loam (Wales)	Orthic Luvizol silt (France)	Orthic Podzol loamy sand (Germany)
pH	5.1	7.4	5.2	6.5	3.2
Percent clay	75%	22.6%	17%	20.3%	6%
Percent organic carbon	1.3%	3.7%	3.45%	1.55%	9.25%
K_d	60.37	19.0	18.4	8.6	75.4
1/n[a]	0.82	0.90	0.91	0.88	0.81
K_{oc}	4,644	487	534	556	815

[a]The parameter 1/n relates to the linearity of the adsorption isotherm. Generally, values close to 1 indicate a highly linear adsorption isotherm.

Source: Gawlik et al. 1998

residues (98%) identified were of the undegraded parent compound. Topical application to the stem and seed injection with guthion also indicated translocation of the residues throughout the plant system.

Based on its low mobility in soil, guthion is expected to adsorb to suspended solids and sediment in the water column. Guthion applied at a nominal application rate of 20 µg/L to the surface of a 2 ha pond was not detected in sediment samples 3 hours postapplication; however, guthion levels in sediment gradually increased to a maximum concentration of 62.7 µg/kg 4 days postapplication (Knuth et al. 2000). The levels gradually decreased to 11.9 µg/kg 8 days postapplication and then continued to decrease at a near constant rate to 2.05 µg/kg 50 days postapplication. Sediment samples collected at days 92, 120, and 366 had no measurable levels of guthion (detection limits 0.20 µg/kg). Accounting for the total mass balance in the pond, the authors concluded that both the aqueous phase and the sediment compartment are important environmental sinks for guthion applied to the water surface.

There are little data regarding guthion's potential to bioconcentrate in aquatic organisms, and conflicting conclusions have been reported. According to an environmental fate and exposure assessment for guthion conducted by the EPA, bioconcentration and bioaccumulation are not expected based upon the log K_{ow} value of guthion. An estimated bioconcentration factor (BCF) of 26 was calculated from a log K_{ow} of 2.75 (Hansch et al. 1995) and a regression-derived equation (Meylan et al. 1999). This BCF value suggests that the potential for guthion to bioconcentrate and biocaccumulate in aquatic organisms is low. However, experimental studies using constructed ecosystems indicate that guthion may bioconcentrate in aquatic organisms. Guthion formulated as an emulsifiable concentrate and applied to the surface of a 2-ha pond near Duluth, Minnesota at a nominal application rate of 20 µg/L showed accumulation in fathead minnows (Knuth et al. 2000). The level of dissolved guthion in the water column and the amount of guthion in adult fathead minnows were used to calculate lipid corrected BCF values. A maximum lipid corrected BCF value of 3,003 was observed 3 hours postapplication, while a minimum value of 1,027 was observed 1 day postapplication. Eight days postapplication, the BCF gradually increased to 2,254 (Knuth et al. 2000). Although these data indicate a high degree of bioconcentration, the whole-body BCF values in the minnows are substantially lower. Using the author-reported mean lipid content of 2.12% in the fathead minnows, the maximum whole-body BCF value is approximately 64 (3 hours postapplication), and the minimum value is approximately 22. These whole-body BCF values indicate that bioconcentration in aquatic organisms is low to moderate. These data are consistent with the findings of uptake and accumulation studies conducted using catfish. Catfish exposed to guthion had a relatively low magnitude of accumulation with rapid uptake and excretion (California EPA 2004). The accumulation factor was approximately 60 during the last 21 days of the 28-day exposure period. Guthion and the

desmethyl oxygen analog were observed in fish tissue. Approximately 67 and 85% of the residues were excreted within 5 hours and 4 days, respectively, after exposure was discontinued.

6.3.2 Transformation and Degradation

In general, guthion is not considered highly persistent in the environment. The dominant degradation mechanism in air is reaction with photochemically produced hydroxyl radicals and direct photolysis. In water, a combination of biodegradation, hydrolysis, and photolysis is expected to result in the degradation of guthion. Biodegradation appears to be the dominant degradation process for guthion in soils, and foliar degradation by photolysis is likely to limit the persistence of guthion on treated crops.

6.3.2.1 Air

Guthion has a vapor pressure of 2.2×10^{-7} mm Hg at 20 °C (Suntio et al. 1988), which suggests that it will exist in both the vapor and particulate phases in the ambient atmosphere. Vapor-phase guthion is expected to be rapidly degraded through reaction with photochemically produced hydroxyl radicals and direct photolysis. An estimated hydroxyl radical rate constant of 1.5×10^{-10} cm^3/molec-second was estimated for guthion using a structure-estimation method (Meylan and Howard 1993). This corresponds to an atmospheric half-life of approximately 2.5 hours, assuming an atmospheric hydroxyl radical concentration of 5×10^5 molec/cm^3 (Atkinson 1985). In a direct photolysis study, thin films of guthion exposed to summer sunlight at Riverside, California degraded with an approximate half-life of 8.2 hours calculated using data by Chukwudebe et al. (1989). Three photodegradation products were observed including thiophosphoric acid O,S,O'-trimethyl ester, dithiophosphoric acid O,S,S'-trimethyl ester, and dithiophosphoric acid O,S,O'-trimethyl ester.

6.3.2.2 Water

Guthion is degraded through a combination of biotic and abiotic mechanisms in water, and is not considered persistent under environmental conditions. The hydrolysis half-lives of guthion at 30 °C in aqueous buffered solutions at pH 4, 7, and 9 were 49, 26, and 3.7 days, respectively (EPA 1999a). At 40 °C the half-lives were 23, 13, and 1.8 days at pH 4, 7, and 9, respectively. A wide variety of metabolites were formed during these experiments and in general, initial concentration and temperature did not appear to affect the amount of each degradation product that was produced. Mercaptomethyl benzazimide was formed at 4.9–10.4% after 30 days at pH 7. Hydroxymethyl benzazimide and benzazimide, which were measured as a single analyte, were found after 30 days at 8.1–12.2% at pH 4,

6.0–14.2% at pH 7, and 32.4–38.9% at pH 9. Anthranilic acid was also identified as a degradation product of guthion. Anthranilic acid was formed at 18.1–22.8% of the parent at 30 days in the pH 9 test systems. An unidentified metabolite was observed in the pH 9 test systems at 7.4–14.5% of the initially applied amount. Bismethyl benzazamide sulfide was also found at concentration <10% of the applied radioactivity.

The aqueous photolysis half-life of guthion maintained at pH 4.35 and 30 °C and exposed to natural sunlight conditions in Kansas City, Missouri was calculated as 76.7 hours (EPA 1999a). Two major degradation products were identified, benzazimide and anthranilic acid. It was noted that each metabolite is actually a complex of two degradates that could not be separately identified by the analytical procedure used in the study. The benzazimide complex consisted of benzazimide and (1N)-methoxybenzazimide, while the anthranilic acid complex consisted of anthranilic acid and methyl anthranilate ester. Benzazimide complex represented 39.1% of the radiolabeled residues at the end of the experiment, while the anthranilic acid complex reached 7.2% of the radiolabeled residues at the end of experiment.

An aerobic aquatic metabolism study was described that resulted in the formation of several degradation products of guthion; however, no rate data were supplied with this study (EPA 1999a). The degradation products identified were: des-methyl guthion, des-methyl guthion S-methyl isomer, methyl benzazimide, methylsulfinyl methyl benzazimide, methylsulfonyl methyl benzazimide, methyl benzazimide sulfonic acid, methylthiomethyl benzazimide, and either/or hydroxy-methyl benzazimide/benzazimide. The last two degradates were unresolved by the chromatographic method used for analysis. The only metabolite observed at >10% of the nominal concentration was methyl benzazimide sulfonic acid (EPA 1999a).

The degradation kinetics of guthion in a mixture of 19 organophosphate and organonitrate pesticide solutions at the ppb level was measured in ultra-pure distilled water, natural seawater, river water, and filtered river water (Lartiges and Garrigues 1995). The experiments were conducted at two temperatures (6 and 22 °C), three pH levels (pH 6.1, 7.3, and 8.1), and in both the absence of light and under natural sunlight illumination in Bordeaux, France during the months of February to July. The experimental details and results are summarized in Table 6-2. In general, increasing pH led to greater degradation due to the base-catalyzed hydrolysis reaction of guthion; however, both hydrolysis and biodegradation appear to be attenuated at low temperatures. Degradation of guthion was enhanced considerably when the solutions were exposed to natural sunlight. Similar experimental results were obtained by Medina et al. (1999), using filtered and unfiltered water from the Limon River in Venezuela. The half-life of guthion was 23.5 days in filtered river water that was maintained under dark conditions and 13.4 days in filtered

Table 6-2. Aqueous Degradation Rate of Guthion

		Half-life (days)		
	pH	6 °C	22 °C	Outdoor sunlight[a]
MQW	6.1	415	115	No data
River water	7.3	278	42	8
Filtered river water	7.3	506	35	No data
Seawater (salinity 25 g/L)	8.1	No degradation	26	11

[a]The temperatures under natural environmental conditions ranged from -2 to 25 °C.

MQW = ultrapure water from a Millipore apparatus

Source: Lartiges and Garrigues 1995

river water that was illuminated with natural sunlight. The half-life decreased to 6.1 days for nonfiltered river water exposed to sunlight during the course the experiments (Medina et al. 1999).

The effect of chlorinating drinking water and the consequence that this has on organophosphate pesticides has been addressed (EPA 2002). Chemical oxidation of the thiophosphate group leads to the formation of guthion oxygenated metabolites (oxons), which were shown to be more stable than the parent compound in chlorinated systems. In water samples amended with sodium hypochlorite to yield a total chlorine residue level of 2 mg/L, guthion at a nominal concentration of 0.5 μg/L was transformed to its oxon, with a half-life of approximately 2 hours. After 24 additional hours, only 10% degradation of the oxon was observed.

6.3.2.3 Sediment and Soil

Guthion undergoes biodegradation, photolysis, and hydrolysis in soils at varying rates depending upon the physical characteristics of the soil such as moisture, pH, and percentage of organic matter. Environmental conditions such as ambient temperature and amount of sunlight also affect the persistence of guthion. Since sunlight is rapidly attenuated as a function of soil depth and hydrolysis is only significant in moist alkaline soils, biodegradation is likely to be the major transformation pathway for guthion under ordinary environmental conditions. A soil photolysis half-life of 180 days was reported for guthion applied to a sandy loam soil (pH 5.1) during the month of January in Kansas City, Missouri (EPA 1999a). In a subsequent study, the estimated half-life was 66 days when guthion was applied to sterile sandy loam soil (pH 7) and exposed to natural sunlight (California EPA 2004). After correcting for nonphotolytic degradation, the estimated half-life was 241 days. No degradation products were identified in either of these two experiments.

The aerobic degradation of ^{14}C labeled guthion in a sandy loam soil was studied under laboratory conditions over the course of a 1-year incubation period (EPA 1999a). The time for 50% dissipation (DT_{50}) was 27 days and the DT_{90} of guthion in this soil was 146 days. Although it was observed that the degradation rate did not closely follow first-order kinetics, a nonlinear regression of the concentration versus time profile yielded an estimated half-life of 32 days (EPA 1999a). No single identified metabolite was found at >10% of the initially applied radioactivity; the oxygen analog of guthion peaked at 5.3% of the applied radioactivity 186 days after application. Four metabolites, mercaptomethyl benzazimide, hydroxymethyl benzazimide, benzazimide, and bismethyl benzazamide sulfide, were reported as a single metabolite, with a maximum of 12% of the applied amount observed at 120 days postapplication. Only

4.1% of residues were trapped as $^{14}CO_2$. The majority of the radioactivity (72%) was in unidentified soil-bound residues at the end of the experiment. Under anaerobic conditions, the estimated half-life of guthion in soil was calculated as 66 days (EPA 1999a).

Field dissipation studies using alfalfa fields in California indicated a fairly rapid rate of dissipation. Guthion applied at a rate of 3 pounds a.i./A in August to a Salinas silt loam (pH 6.9–8.0) located in Watsonville, California had a DT_{50} of 9 days (EPA 1999a). A similar experiment was conducted using an alfalfa field in Fresno, California during the month of May. The soil type in this field was characterized as a Hesperia fine sandy loam (pH 7.6–8.7). The DT_{50} was 2 days in this soil following a single application at 3 pounds a.i./A (EPA 1999a). Both of these fields are somewhat more alkaline than typical soils, which may account for the relatively rapid rate of degradation.

The DT_{50} of guthion in laboratory studies employing four different soils from Italy ranged from 4 to 20 days (Diaz Diaz et al. 1995). The shortest dissipation times were observed in alkaline soils that were high in organic matter. The soil properties and the experimental results of this study are summarized in Table 6-3.

When the initial guthion concentration in soil is very high (for example, in the case of an accidental spill), its persistence is expected to be much longer than when applied under general agricultural use conditions. Guthion, applied as an emulsifiable concentrate to plots of soil at initial levels of approximately 25,000–70,000 mg/kg (ppm), had DT_{50} values of up to 1 year, and measurable levels remained in the treated soil for up to 8 years (Staiff et al. 1975).

6.3.2.4 Other Media

Foliar wash off and foliar degradation are important environmental fate processes for guthion applied to plant surfaces. The presence of sensitizing agents in leaves and vegetation can result in enhanced photolysis, thus increasing the degradation rates of pesticides in sunlight (Floesser-Mueller and Schwack 2001). Foliar degradation half-lives on plants and leaves have been reported to range from 1.6 to 16.0 days for guthion (EPA 1999a). Louisiana sugarcane crops treated with guthion at an application rate of 0.82 kg/ha (3 times annually) had foliar dissipation half-lives of approximately 2–8 days (Granovsky et al. 1996).

Table 6-3. Soil Properties and Degradation Rate of Guthion in Four Italian Soils

Soil type	pH	Percent organic matter	Percent clay	Percent silt	Percent sand	DT_{50} (days)[a]
Sandy	7.70	0.7	12.8	8.7	76.8	20
Orchard	7.41	8.8	17.3	22.7	61.2	4
Agricultural	7.38	3.7	18.8	23.4	60.8	5
Volcanic	4.86	4.1	21.2	28.3	52.2	12

[a]DT_{50} is the time required for 50% dissipation of the initially applied amount of guthion.

Source: Diaz Diaz et al. 1995

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to guthion depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of guthion 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 guthion 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 and the presence/detection of guthion does not necessarily indicate an adverse biological effect. The analytical methods available for monitoring guthion in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Guthion has been infrequently detected in atmospheric samples collected throughout the United States. Weekly composite rainfall samples that were obtained in urban and agricultural regions of the Midwestern United States and along the Mississippi River indicated a low frequency of detection for guthion from April to September 1995 (Majewski et al. 2000). Guthion was not detected in any samples of rainfall from a background location (Eagle Harbor, Michigan) where it had no known use. Guthion was detected in approximately 10% of the rainfall samples collected in agricultural areas of Mississippi and in approximately 5% of the rainfall samples collected in an urban area (Jackson, Mississippi). Guthion was not detected in rainfall samples obtained in either agricultural or urban areas of Iowa, but was detected in approximately 1% of the rainfall samples collected in an agricultural location in Minnesota (Majewski et al. 2000). During the same collection period, guthion was identified, not quantified, in approximately 20% of the vapor-phase and particulate-phase air samples collected from Rolling Forks, Mississippi (agricultural location), but was not detected in air samples collected in Jackson, Mississippi (Coupe et al. 2000; Foreman et al. 2000).

Guthion was detected in 36% of the atmospheric samples obtained near locations in Kern and Glenn Counties, California where it was being used as an insecticide on almond crops (Baker et al. 1996). The 24-hour mean concentration was 0.035 $\mu g/m^3$ and the maximum concentration was 0.11 $\mu g/m^3$. The maximum concentration observed in the air at the application site was 1.6 $\mu g/m^3$ (Baker et al. 1996). During application of insecticides to an apple orchard in Massachusetts approximately 1 acre in size by airblast ground sprayers, guthion applied at 0.75 kg/ha was detected downwind of the spray zone (75 feet away) at a maximum concentration of 3.87 $\mu g/m^3$ (Clark et al. 1991). Within 2 hours, the atmospheric level was reduced to 0.031 $\mu g/m^3$ as deposition processes transported the insecticide to the ground.

6.4.2 Water

Guthion has moderate to low mobility in soils and therefore has limited potential to leach into groundwater. Biotic and abiotic degradation that occurs in soils may also limit the leaching potential of guthion. Guthion was only detected (detection limit 0.001 µg/L) in 4 out of 2,451 groundwater samples collected from 1992 to 1996 in 20 major hydrological basins across the United States (Kolpin et al. 2000). The maximum observed concentration in these four positive samples was 0.18 µg/L. Guthion was not detected in 94 shallow groundwater wells sampled in 1992 in the Midwestern United States (Kolpin et al. 1995). In a compilation of groundwater data from 1971 to 1991, the EPA initially reported that guthion was detected in 5 out of 30 wells sampled in the state of Virginia in 1987 at levels ranging from 0.04 to 2.87 µg/L (EPA 1992b). According to an environmental fate and exposure assessment for guthion, these values are incorrect (EPA 1999a). According to this risk assessment there were 16 detections of guthion obtained from 60 wells sampled in July and August of 1987 in Clarke and Frederick County in the Shenandoah Valley. However, guthion was not detected in 1,598 other wells sampled in California, Indiana, Georgia, Hawaii, Maine, New York, Oklahoma, Rhode Island, or Texas from 1983 to 1991 (EPA 1992b, 1999a). Guthion was not detected in 68 wells sampled in 12 counties of California from July 1, 1994 to June 30, 1995 (California EPA 1995).

Very little data exist for guthion in finished drinking water; however, limited monitoring data suggest that its occurrence is not widespread. In a cumulative risk assessment for organophosphate pesticides, the EPA Office of Pesticide Programs (OPP) performed a 2-year pilot reservoir monitoring study of raw and finished water data for 18 active organophosphate parent compounds and 13 transformation products (EPA 2002). Guthion was detected in 8 out of 321 raw water samples at a mean concentration of 0.077 µg/L and a maximum concentration of 0.144 µg/L. Guthion was detected in 5 out of 225 finished drinking water samples at a mean concentration of 0.059 µg/L and a maximum concentration of 0.114 µg/L. The main metabolite in chlorinated waters, gutoxon was detected in 1 out of 316 raw water samples at a concentration of 0.263 µg/L and in 4 out of 219 finished drinking water samples at a mean concentration of 0.18 µg/L and a maximum concentration of 0.26 µg/L (EPA 2002). Guthion or the oxon metabolite was only detected in drinking water samples collected from Missouri, New York, Oklahoma, and South Carolina. Guthion and its metabolite were not detected in raw or treated water samples obtained from California, Indiana, Louisiana, North Carolina, Ohio, Pennsylvania, South Dakota, or Texas (EPA 2002).

Due to spray drift, runoff, and erosion of treated soils, guthion is frequently detected in surface waters adjacent to farming areas where it has been applied as an insecticide. The U.S. Geological Survey maintains and operates The National Water Quality Assessment Program (NAWQA) database, which frequently updates groundwater and surface water monitoring data for various pesticides, including guthion, in >50 major river basins in the United States. Data from 1991, 1994, and 1997 indicated that guthion was detected in 1.31% of 1,800 water samples collected at 75 streams near agricultural locations in the United States. The maximum concentration of guthion in these streams was reported as 0.5 µg/L (USGS 2003).

Guthion was detected in 13 out of 142 surface water samples collected at four sites in the San Joaquin River Basin at a maximum concentration of 0.39 µg/L (Dubrovsky et al. 2000). Guthion levels at these sites tended to spike during the summer months, coinciding with the agricultural season and then decrease during the winter. For example, guthion levels in Orestimba Creek in the San Joaquin River Basin fluctuated between 0.1 and 0.2 µg/L from June to September 1992, and then decreased sharply from November 1992 to May 1993, before increasing to 0.4 µg/L in June 1993 (USGS 1999). Guthion was detected in 64 out of 98 surface water samples at a maximum concentration of 0.523 µg/L obtained from various sites in a heavy apple growing region along the Yakima River Basin, Washington during the period of May 1999 through January 2000 (USGS 2001). The study authors noted that concentrations of guthion exceeded its chronic-toxicity guideline for the protection of aquatic life in 50% of the samples. Monitoring data from the Washington State Department of Agriculture from April to October 2004, reported guthion levels of 0.013–0.042 µg/L (4 positive detections out of 31 samples) in the Sulphur Creek Wasteway near its confluence with the Yakima River (Burke et al. 2005). In addition, it was detected in 4 out of 45 samples obtained from Spring Creek near its confluence with the Yakima River at levels ranging from 0.014 to 0.023 µg/L (Burke et al. 2005). Sampling data from April to December 2003 in Sulphur Creek had 11 positive detections of guthion with a maximum concentration of 0.025 µg/L (Anderson et al. 2004). Guthion was detected in 0.5% of the surface water samples collected in two streams located in Oregon, at a maximum concentration of 0.171 µg/L (Hoffman et al. 2000). Guthion was detected in 12 out of 29 surface water samples obtained from a creek (Crab Creek Lateral) that feeds into Royal Lake, in Central Washington State during March 1993 to May 1994 sampling (Gruber and Munn 1998). The maximum observed concentration was 0.2 µg/L. It was reported that most of the flow of water into Crab Creek Lateral is the result of excess irrigation water that enters the canal from agricultural drains and groundwater discharges. An analysis of pesticide residues in U.S. groundwater and streams from 1992 to 2001 was recently summarized by analyzing data in the NAWQA database (USGS 2006a). Guthion exceeded benchmark levels (0.18 µg/L for acute fish toxicity,

0.36 µg/L for chronic fish toxicity, 0.08 µg/L for acute invertebrate toxicity, 0.16 µg/L for chronic invertebrate toxicity) for aquatic life in approximately 20% of the agricultural streams and 10% of the urban streams included in the sampling program (USGS 2006a). Guthion was detected in 11 water samples at a maximum concentration of 0.034 µg/L collected from four major irrigation return-flow drainage basins, in agricultural areas of Washington State from July 2002 through October 2004 (USGS 2006b).

The EPA Office of Water maintains the STOrage and RETrieval (STORET) database, which contains data for guthion in surface water throughout the United States. Information from this database is of limited value because it is difficult to determine the purpose and circumstances of the studies contained in the database. According to the studies included in STORET, only 15 out of 1,123 samples at 653 sites had detectable levels of guthion in the United States over a multi-year period (EPA 1999a). These data are summarized in Table 6-4. Data maintained in the STORET database for 2005–2006 did not include any positive detections of guthion in water samples (EPA 2006k).

6.4.3 Sediment and Soil

Guthion was detected at levels of <0.1 mg/kg in surface soils (upper 6 inches) of Marengo, Alabama (Albright et al. 1974). Soil samples collected from 48 homes of agricultural families in eastern Washington State had mean guthion levels of 60 µg/kg (range: not detected to 814 µg/kg), while soil samples collected from 11 homes of nonagricultural families had no detectable levels of guthion (detection limit 32 µg/kg) (Simcox et al. 1995). For the homes of the agricultural families, a positive correlation was observed between guthion levels in the soil and household dust, and the proximity to nearby apple orchards (Simcox et al. 1995). In a study of 49 randomly chosen agrichemical facilities located throughout the state of Illinois, guthion was detected in soil samples at 5 of the 10 sites that processed, used, or handled it (Krapac et al. 1995). The mean, median, and range of guthion concentrations in the soil samples at these five sites were reported as 148, 110, and 45–878 µg/kg, respectively.

Data maintained in the STORET database for 2005–2006 included seven detections of guthion in sediment samples obtained from Escambia County, Florida at concentrations ranging from 6.6 to 23 µg/kg (EPA 2006k).

Table 6-4. Guthion Levels in Surface Water from the STORET Database

Water body	Number of samples	Number of detects	Number of sites	Maximum concentration (µg/L)	Years
Canals	289	3	63	0.01	1974–1993
Estuaries	185	2	162	3	1969–1997
Lakes	406	1	242	0.01	1974–1996
Oceans	16	0	6	Not applicable	1980–1985
Reservoirs	91	9	57	0.01	1975–1995
Springs	136	0	123	Not applicable	1987–1996

Source: EPA 1999a

6.4.4 Other Environmental Media

Guthion has frequently been detected in foods in the United States, primarily in fruits and vegetables. In 2002, the EPA Office of Pesticides Programs published a cumulative risk assessment that evaluated the cumulative dietary risk due to the use of organophosphate pesticides on food crops (EPA 2002). In this assessment, residue monitoring data collected by the U.S. Department of Agriculture's Pesticide Data Program (USDA-PDP) supplemented with information from the FDA Center for Food Safety and Applied Nutrition (FDA/CFSAN) were analyzed. Residue data were collected on approximately 44 food commodities monitored by PDP between the years 1994 and 2000. The data pertaining to guthion are summarized in Table 6-5. In general, guthion was detected at levels below 1 ppm in most food items, although a single maximum occurrence of 1.9 ppm was reported for guthion in pears (EPA 2002). Data from the FDA Total Diet Study Market Basket Survey from 1991 to 2001 indicated that guthion was detected in 15 out of 320 food items in the surveys. It was most frequently detected in red apples (32 detections with a maximum concentration of 0.19 ppm) and pears (29 detections with a maximum concentration of 0.227 ppm), but was also detected in nonfruit or vegetable items including cheddar cheese and blueberry muffins (FDA 2003).

Over a 5-year period (1991–1995), guthion was detected in 295 out of 2,338 fruits and vegetables analyzed in a market basket survey in Canada (Ripley et al. 2000). Only two other pesticides (dithiocarbamate and captan) were detected more frequently in fruits and vegetables than guthion in this Canadian survey.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is primarily exposed to guthion through the ingestion of food items, although minor exposure may occur from inhalation of ambient air and ingestion of drinking water. Urinary metabolites that are reflective of exposure to guthion were measured as a part of the National Health and Nutrition Examination Surveys (NHANES) (CDC 2005). These dialkyl phosphate metabolites are not specific to guthion, but their detection indicates the possibility of exposure to guthion and several other organophosphate pesticides. Dialkyl phosphates may also be present in the environment from the degradation of these pesticides. Therefore, in addition to reflecting exposure to guthion or other organophosphate pesticides, the presence of the metabolites in a person's urine may also reflect exposure to the metabolite itself (CDC 2005). Six dialkyl phosphates were measured in the most recent NHANES and the results for the three compounds that are known metabolites of guthion, dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP), and dimethyl dithiophosphate (DMDTP) are reported in

Table 6-5. Guthion Residues in Various Foods from 1994 to 2000

Food item	Number analyzed	Number of detections	Average concentration (ppm)[a]	Maximum concentration (ppm)
Apple juice	1,554	81	$4.9x10^{-5}$	0.008
Apples	2,471	1,228	0.028	0.46
Apples (single serving)	377	220	0.022	0.77
Bananas	1,126	0	0	0
Broccoli	678	0	0	0
Cantaloupe	1,640	0	0	0
Carrots	2,072	0	0	0
Celery	176	0	0	0
Cherries	275	163	0.027	0.44
Corn Syrup	423	0	0	0
Cucumbers	1,467	0	0	0
Grape juice	1,379	0	0	0
Grapes	2,625	41	0.00119	0.47
Green beans (canned)	853	0	0	0
Green beans (fresh)	1,897	9	$1.2x10^{-4}$	0.051
Green beans (frozen)	729	3	$1.2x10^{-4}$	0.038
Lettuce	1,616	0	0	0
Milk	1,892	0	0	0
Nectarines	345	48	0.0049	0.2
Oats (bran)	45	0	0	0
Oats (rolled)	287	0	0	0
Orange juice	1,392	0	0	0
Oranges	2,636	2	$3.5x10^{-5}$	0.073
Peaches (canned)	754	1	$7.0x10^{-5}$	0.053
Peaches (fresh)	1,623	511	0.022	0.72
Peaches (single serving)	534	218	0.0214	0.65
Pears (canned)	737	0	0	0
Pears (fresh)	1,773	1,039	0.0503	1.9
Pears (single serving)	696	275	0.0318	0.87
Pineapples	104	0	0	0
Potatoes	1,770	0	0	0
Poultry (adipose tissue)	476	0	0	0
Poultry (liver)	479	0	0	0
Poultry (muscle)	145	0	0	0
Soybean grain	748	0	0	0
Spinach (canned)	863	0	0	0
Spinach (fresh)	1,639	4	$4.46x10^{-4}$	0.4
Spinach (frozen)	714	1	$1.8x10^{-5}$	0.013
Strawberries (fresh)	1,768	2	$1.52x10^{-4}$	0.2
Strawberries (frozen)	155	3	0.001781	0.2

Table 6-5. Guthion Residues in Various Foods from 1994 to 2000

Food item	Number analyzed	Number of detections	Average concentration (ppm)[a]	Maximum concentration (ppm)
Straw bell peppers	1,468	9	$1.9x10^{-4}$	0.11
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	0	0	0
Sweet potatoes	1,559	0	0	0
Tomatoes (canned)	737	5	$8.4x10^{-5}$	0.013
Tomatoes (fresh)	1,960	31	0.000748	0.71
Wheat	940	3	$7.0x10^{-5}$	0.022
Winter squash (fresh)	1,216	0	0	0
Winter squash (frozen)	470	0	0	0

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

Source: EPA 2002

Tables 6-6, 6-7, and 6-8. A general reduction in urinary levels of these metabolites has been observed from the 1999–2000 survey data with the levels from the 2001–2002 data.

The average daily dietary intake (AVDI) of guthion categorized by age and gender groups is shown in Table 6-9. These data were developed from the FDA Total Diet Study (TDS), which collects foods from several regional and metropolitan areas that are representative of the total diet of the U.S. population. These dietary intake values are lower than several toxicological benchmark values including the World Health Organization (WHO) Acceptable Daily Intake (ADI) of 5 μg/kg/day and the EPA Office of Pesticides Program's acute oral reference value of 3 μg/kg/day (EPA 1999b, 2001b; Fenske et al. 2000a).

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).

Similar to adults, children are primarily exposed to guthion through the ingestion of foods. The dietary AVDI of guthion has been reported as 0.069–0.083 μg/kg-body weight/day for 6–11-month-old infants and 0.022–0.031 μg/kg-body weight/day for 2-year-old toddlers (Gunderson 1988, 1995). No measurements have been made of guthion in amniotic fluid, meconium, cord blood, neonatal blood, or any other tissues that may indicate prenatal exposure. No data have been reported on the levels of guthion in breast milk. The metabolite DMP was detected in 1 out of 20 postpartum meconium samples obtained from newborn infants at the New York Presbyterian Hospital (Whyatt and Barr 2001). The metabolites DMTP and DMDTP were not detected. A study conducted in Rio Negro, Argentina analyzed the acetylcholinesterase activity in placenta tissue and plasma of 200 pregnant females (Souza et al. 2005). Guthion is a frequently used pesticide in this heavy apple and pear growing region. A correlation

Table 6-6. Selected Percentile Urine Concentrations (µg/L) of DMP in the U.S. Population from 1999 to 2002[a]

Group	Percentile				Sample size
	50th	75th	90th	95th	
Age 6 and older					
1999–2000	0.740	2.80	7.90	13.0	1,949
2001–2002	<LOD	3.25	8.22	13.4	2,519
6–11 Years					
1999–2000	1.00	4.40	10.0	21.0	471
2001–2002	0.970	5.03	12.2	18.2	576
12–19 Years					
1999–2000	0.650	3.80	9.90	22.0	664
2001–2002	0.670	4.27	9.27	14.6	822
20–59 Years					
1999–2000	0.680	2.60	6.50	9.70	814
2001–2002	<LOD	2.93	6.89	11.5	1,121
Males					
1999–2000	0.650	2.80	7.90	18.0	952
2001–2002	<LOD	3.40	8.22	12.6	1,187
Females					
1999–2000	0.780	2.80	7.60	10.0	997
2001–2002	<LOD	3.05	8.34	13.7	1,332
Mexican Americans					
1999–2000	1.00	3.80	9.50	15.0	672
2001–2002	0.660	3.22	9.38	14.4	678
Non-Hispanic blacks					
1999–2000	0.980	3.60	8.90	21.0	509
2001–2002	0.910	5.45	11.5	19.4	695
Non-Hispanic whites					
1999–2000	<LOD	2.90	7.90	10.0	595
2001–2002	<LOD	3.01	7.39	12.3	948

[a]The proportion of the results below the LOD was too high to calculate geomethric means for DMP.

DMP = dimethyl phosphate; LOD = limit of detection

Source: CDC 2005

Table 6-7. Geometric Mean and Selected Percentile Urine Concentrations (µg/L) of DMTP in the U.S. Population from 1999 to 2002

Group	Geometric mean	Percentile				Sample size
		50th	75th	90th	95th	
Age 6 and older						
1999–2000	1.82	2.70	10.0	38.0	46.0	1,948
2001–2002	[a]	0.450	4.02	16.2	32.6	2,518
6–11 Years						
1999–2000	2.72	4.10	20.0	40.0	62.0	471
2001–2002	[a]	1.44	8.33	28.2	45.7	575
12–19 Years						
1999–2000	2.53	3.60	16.0	37.0	69.0	664
2001–2002	[a]	1.03	4.83	20.8	33.9	822
20–59 Years						
1999–2000	1.59	2.20	9.10	38.0	38.0	813
2001–2002	[a]	<LOD	3.32	13.6	29.5	1,121
Males						
1999–2000	2.10	3.40	13.0	38.0	41.0	952
2001–2002	[a]	0.610	4.21	18.3	30.4	1,187
Females						
1999–2000	1.59	2.00	9.70	38.0	52.0	996
2001–2002	[a]	<LOD	3.76	15.9	34.3	1,331
Mexican Americans						
1999–2000	1.79	2.00	10.0	38.0	130	671
2001–2002	[a]	<LOD	3.74	15.1	35.2	678
Non-Hispanic blacks						
1999–2000	2.13	3.60	11.0	37.0	39.0	509
2001–2002	[a]	1.25	5.54	20.6	42.2	695
Non-Hispanic whites						
1999–2000	1.77	2.60	11.0	38.0	45.0	595
2001–2002	[a]	<LOD	3.99	17.0	32.6	947

[a]The proportion of the results below the LOD was too high to calculate a geometric mean.

DMTP = dimethyl thiophosphate; LOD = limit of detection

Source: CDC 2005

Table 6-8. Selected Percentile Urine Concentrations (µg/L) of DMDTP in the U.S. Population from 1999 to 2002[a]

Group	Percentile				Sample size
	50th	75th	90th	95th	
Age 6 and older					
1999–2000	<LOD	2.30	12.0	19.0	1,949
2001–2002	<LOD	0.890	0.49	4.95	2,518
6–11 Years					
1999–2000	0.730	4.30	16.0	32.0	471
2001–2002	<LOD	1.30	3.53	7.33	575
12–19 Years					
1999–2000	<LOD	2.20	12.0	19.0	664
2001–2002	<LOD	0.810	2.51	4.63	821
20–59 Years					
1999–2000	<LOD	2.10	10.0	16.0	814
2001–2002	<LOD	0.840	2.32	4.90	1,122
Males					
1999–2000	0.110	2.30	16.0	18.0	952
2001–2002	<LOD	0.840	2.40	5.13	1,187
Females					
1999–2000	<LOD	2.10	10.0	20.0	997
2001–2002	<LOD	0.950	2.52	5.10	1,331
Mexican Americans					
1999–2000	0.240	1.80	5.70	12.0	672
2001–2002	<LOD	0.960	2.66	4.47	678
Non-Hispanic blacks					
1999–2000	0.330	3.20	14.0	18.0	509
2001–2002	<LOD	0.750	2.11	4.38	695
Non-Hispanic whites					
1999–2000	<LOD	2.00	13.0	20.0	595
2001–2002	<LOD	0.940	2.49	5.74	947

[a]The proportion of the results below the LOD was too high to calculate geomethric means for DMDTP.

DMDTP = dimethyl dithiophosphate; LOD = limit of detection

Source: CDC 2005

Table 6-9. Dietary Average Daily Intake of Guthion (µg/kg/day)

	1982–1984[a]	1986–1991[b]
6–11 Months	0.0069	0.0083
2 Years	0.022	0.0311
14–16 Years (female)	0.0048	0.0061
14–16 Years (male)	0.0050	0.0073
25–30 Years (female)	0.0046	0.0061
25B30 Years (male)	0.0033	0.0044
60B65 Years (female)	0.0062	0.0079
60B65 Years (male)	0.0051	0.0064

[a]Gunderson 1988
[b]Gunderson 1995

between acetylcholinesterase activity in plasma and timing of pesticide applications was observed. An 18% reduction in maternal plasma acetylcholinesterase activity was observed during the pesticide application months of November–February as compared to samples collected in non-application months (March–October); however, a slight increase in activity was observed in placenta tissue during the pesticide application months.

Nondietary ingestion may be an important exposure pathway in agricultural areas, where guthion is used as an insecticide. The tendency of young children to ingest soil, either intentionally through pica or unintentionally through hand-to-mouth activity, is well documented. These behavioral traits can result in ingestion of guthion present in soil and dust. Young children often play on the ground or on carpets and this will increase the likelihood of dermal exposure and inhalation of contaminated particles from soil, household dust, and treated surfaces. The exposure of young children to organophosphate pesticides, including guthion, in an agricultural community in central Washington was studied by collecting spot urine and hand wipe samples from a group of 109 children aged 6 months to 6 years during the pesticide spraying months of May–July (Lu et al. 2000). Participants included 62 agricultural families (49 applicators and 13 farm workers) and 14 reference families in which no family member was employed in occupations requiring contact with pesticides, and the residence was located at least one quarter mile away from any pesticide treated orchard. There were 72, 19, and 18 children of pesticide applicators, farm workers, and reference families, respectively. The median urinary levels of the dimethyl metabolites DMTP and DMDTP were 0.05 μg/mL in the children of the agricultural families and 0.01 μg/mL in the children of reference families (Lu et al. 2000). Approximately 67% of the urine samples collected from the children of farm applicator and farm workers contained detectable levels of DMTP, while 53% of the urine samples collected from the children of reference families contained detectable levels. Wipes obtained from the hands of the children indicated that detectable levels of guthion were present in approximately 13% of the children's hands from agricultural families; while none of the children from the reference families had detectable levels of guthion in hand wipe samples. Additional exposure to guthion may also arise from the clothing or personal items of adults that are employed in pesticide application or other farm work. For instance, the mean guthion level on the surface of work boots in the agricultural families was 0.03 $\mu g/cm^2$ and the mean level on the steering wheel of the family vehicle was 0.001 $\mu g/cm^2$ (Lu et al. 2000). Guthion was not detected on personal clothing items or in the vehicles of the 14 reference families.

Urinary levels of dialkyl phosphates were monitored in children residing in agricultural communities in Washington State over a 21-month period (Koch et al. 2002). Although several pesticides are used in this

area, the authors reported that guthion is the most frequently applied insecticide in the agricultural region studied. The overall geometric mean urinary level of combined DMP, DMTP, and DMDTP was reported as 0.080 μmols/L for all samples collected over this 21-month period. The highest levels of dialkyl phosphates measured in the urine coincided with the orchard spraying season (geometric mean of 0.096 μmols/L), while the lowest levels were observed during the winter nonspraying months (geometric mean of 0.072 μmols/L). A similar study was conducted by measuring the combined levels of DMP, DMTP, and DMDTP in the urine of children from 218 farm workers households in agricultural communities of Washington State (Curl et al. 2002). DMP, DMTP, and DMDTP were identified in 19, 88, and 45%, respectively, of the 211 urine samples collected and the geometric mean concentration of the combined dialkyl phosphate metabolites was 0.09 μmols/L (Curl et al. 2002). Urine samples collected from 88 children in central Washington State indicated that DMTP was quantified more often in the urine of children of pesticide applicators when compared with reference children (Loewenherz et al. 1997). Detectable levels of DMTP were observed in 47% of the urine samples obtained from the children of pesticide applicators, compared to 27% for the reference group. The median DMTP concentration in the urine of the agricultural children was 0.021 μg/mL (0.15 μmols/L) compared to 0.005 μg/mL (0.035 μmols/L) for the reference children (Loewenherz et al. 1997).

Aggregate dose estimates for guthion and phosmet were calculated for children in an agricultural community in the state of Washington (Fenske et al. 2000a). These estimates were generated from the urinary metabolite concentrations of DMTP and DMDTP in 109 children up to 6 years of age residing in this community. Since guthion and phosmet were the organophosphates most often used in this area, it was assumed that the dialkyl phosphate metabolites measured in urine samples were due exclusively to these two pesticides. The mean (± standard deviation) creatinine adjusted dose for the children of agricultural families was 3.5 (±4.2) μg/kg/day during the 6–8-week spraying season (May—July), as compared to 2.0 (±3.1) μg/kg/day for reference children. The mean creatinine adjusted single day dose was 3.7 (±5.9) μg/kg/day for children of agricultural families as compared to 2.1±4.1 μg/kg/day for reference children (Fenske et al. 2000a). Although the large standard deviation suggests a high degree of variability, these estimated intakes are much larger than the FDA estimated dietary intakes of the general population (Gunderson 1988, 1995) and are of the same order of magnitude as the WHO ADI of 5 μg/kg/day.

These findings suggest that children in agricultural communities where guthion is used as an insecticide are potentially exposed more frequently and to higher levels than children in the general population through nondietary exposure pathways.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Pesticide applicators, farm workers, and people living in close proximity to agricultural areas such as apple and cherry orchards where guthion is frequently used are potentially exposed to higher levels of guthion than the general population. In addition to ingestion of contaminated foods, inhalation and dermal exposures to farm workers and their families are considerably higher than for the general population. Household dust and soil samples were collected from 59 residences in Washington State (Simcox et al. 1995). The households were classified as 26 farming, 22 farm workers, and 11 nonfarming families. The majority of agricultural families inhabited homes within 200 feet of an operating apple or pear orchard. The mean concentration of guthion in household dust of the 48 agricultural households was 1.870 μg/g (0.170–11.270 μg/g range), while the mean concentration in household dust of the nonagricultural homes was 0.330 μg/g (0.134–0.816 μg/g range) (Simcox et al. 1995). Household dust samples were collected from the homes of 96 farm workers and 24 apple growers in Oregon to assess potential exposure of migrant farm workers to organophosphate pesticides in this community (McCauley et al. 2001). Mean levels of guthion in dust samples were 1.45 μg/g in the homes of farm workers and 1.64 μg/g in the homes of growers. The mean guthion level in household dust samples collected from the homes of 62 agricultural families in central Washington State was 1.94 μg/g (Lu et al. 2000). The mean guthion level in household dust obtained from the homes of 14 reference families was 0.29 μg/g. This represents an approximate 7-fold greater guthion exposure level in the homes of agricultural workers as compared to nonagricultural families. Levels of guthion in household dust samples were also shown to be highest among residences closest to the pesticide-treated apple orchards (Lu et al. 2000). Guthion was detected in 133 out of 156 household dust samples and 165 out of 190 vehicle dust samples from agricultural workers in Washington State (Curl et al. 2002). The geometric mean concentration in house dust was reported as 0.53 μg/g (14.9 μg/g maximum level), while the geometric mean concentration of guthion in vehicle dust was reported as 0.75 μg/g (38.3 μg/g maximum level).

The urinary levels of DMP, DMTP, and DMDTP were measured in 11 workers engaged in thinning and picking practices in a peach orchard that had been sprayed 20 days prior with chlorpyrifos methyl and guthion (Aprea et al. 1994). The average level of the three metabolites in the urine of workers wearing different types of protective equipment in the peach orchard during work operations ranged from approximately 470 to 940 nmols/g creatinine, depending on the type of equipment used. A separate subject not wearing gloves or a mask during work operations had a mean urinary level of nearly 4,000 nmols/g creatinine for the three metabolites (Aprea et al. 1994). A control group of

99 nonoccupationally exposed persons had a mean urinary level of approximately 200 nmols/g creatine. The authors concluded that the main route of guthion absorption to the workers was from dermal exposure, but that respiratory exposure was also significant (Aprea et al. 1994).

Dermal absorption of guthion in humans and animals have been demonstrated in several studies. The amount of guthion absorbed through human skin was studied by applying 500–6,000 µg guthion to the forehead of volunteers and monitoring the level of DMTP excreted in urine over a 72-hour period (Franklin et al. 1986). The results of this pilot study are summarized in Table 6-10. The authors concluded that approximately 30–40% of the applied dose was absorbed in humans, as compared to nearly 100% in rats and rabbits (Franklin et al. 1986). This estimate is somewhat higher than other estimates from experimental data. As summarized in a risk characterization document developed by the California EPA, guthion was applied topically to the forearms of six volunteers in isopropyl alcohol at 2.6 and 9.2 µg/cm^2 or in an aqueous suspension of Guthion 25 WP at 4.7 µg/cm^2 for an exposure period of 8 hours (California EPA 2004). Blood samples were collected up to 5 days postapplication and urine and feces were collected for 13 days postapplication. The dermal absorption was measured as the sum of the radioactivity in the urine, feces, and tape stripping. The dermal absorption ranged from 21.5% for aqueous suspension of the wettable powder to 27.8% for the technical-grade material applied in isopropyl alcohol at the lower concentration. Another study summarized in this document estimated the dermal absorption of guthion in an acetone-based solution as 16% (California EPA 2004). Absorption of guthion applied to the skin of male rats continued following application with subsequent washing with water, and the amount of absorption was observed to be dose-dependent (Zendzian 2003).

In conclusion, agricultural workers and their families are likely to be exposed more frequently, and to higher levels of guthion than the general population if they are involved with procedures such as spraying, harvesting, or thinning of crops in which guthion has been applied as an insecticide. In addition to ingesting food items containing guthion, agricultural workers and their families may be subject to additional dermal and inhalation exposures from dusts, soils, and personal items such as clothing contaminated with guthion.

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 guthion is available. Where adequate information is not

Table 6-10. Excretion of DMTP Following the Dermal Application of Guthion to Volunteers

Dose (µg/person)	Cumulative DMTP total in urine (µg)			DMTP/guthion[a]
	24 hours	48 hours	72 hours	
500	54	76	85	17
1,000	96	130	152	15
2,000	56	90	119	6
4,000	154	267	404	10
6,000	153	284	323	5

[a]Cumulative amount of DMTP excreted divided by amount of guthion applied, multiplied by 100.

DMTP = dimethyl thiophosphate

Source: Franklin et al. 1986

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 guthion.

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

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of guthion are sufficiently well defined to allow assessments of the environmental fate of this compound to be made (Gawlik et al. 1998; Hansch et al. 1995; Suntio et al. 1988; Tomlin 2003). Some physical and chemical properties of guthion that are not relevant to environmental fate are lacking. Knowledge of these properties, such as flashpoint and flammability limits, would be useful for workers involved in the manufacture, use, or clean-up of guthion; however, no data need is identified at this time.

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 2005, became available in May of 2007. This database is updated yearly and should provide a list of industrial production facilities and emissions.

There are no data available regarding the production, import, or export volumes of guthion. Many of guthion's uses were cancelled by the EPA in 2001 and all remaining uses are scheduled to be cancelled by 2012. Incineration and alkaline hydrolysis are the two methods employed to dispose of guthion. No data need is identified at this time.

Environmental Fate. Sufficient data are available to characterize the environmental fate of guthion. When applied as an insecticide, guthion adsorbs strongly to soil surfaces and is degraded in the environment by a combination of biotic and abiotic reactions. It may enter nearby water bodies through spray drift, runoff, and erosion of treated soils where it is expected to partition to suspended solids and

sediment. Data are available regarding the rate of hydrolysis (EPA 1999a; Lartiges and Garrigues 1995), photolysis (EPA 1999a; Lartiges and Garrigues 1995), biodegradation (Diaz Diaz et al. 1995; EPA 1999a), foliar dissipation (Granovsky et al. 1996), and terrestrial field dissipation for guthion (EPA 1999a). The important transport and partitioning properties of guthion have also been studied including adsorption/desorption in soil (EPA 1999a; Gawlik et al. 1998) and runoff potential following its application (EPA 1999a). No data needs are identified at this time.

Bioavailability from Environmental Media. Guthion is absorbed following both oral and dermal exposures (Fakhr et al. 1996; Franklin et al. 1986). No experimental studies were located regarding the bioavailability of guthion from contaminated soil, water, and air; therefore, data are needed regarding the bioavailability of guthion from soil and other environmental media.

Food Chain Bioaccumulation. Data are needed regarding the food chain bioaccumulation of guthion. An estimated BCF value of 26 was calculated for guthion; however, experimentally determined BCF values in fathead minnows were significantly larger than this estimated value (Knuth et al. 2000). A lipid-corrected BCF value of approximately 3,000 was observed in minnows. When these lipid corrected BCF values were adjusted to whole-body BCF values, the data were more consistent with the estimated value. More experimental bioconcentration data on different species of fish along with depuration kinetics are required to assess this end point.

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

Monitoring data for guthion are available in air (Coupe et al. 2000; Foreman et al. 2000; Majewski et al. 2000), water (California EPA 1995; EPA 1992b, 1999a, 2002; Gruber and Munn 1998; Kolpin et al. 2000; USGS 2006a, 2006b), soil (Krapac et al. 1995; Simcox et al. 1995), and food (EPA 2002; FDA 2003; Ripley et al. 2000). Additional data are required regarding the levels of guthion in fish and animal tissues. Continued monitoring of guthion residues in foods and other environmental media, particularly in agricultural fields where it is extensively used or from hazardous waste sites, would be helpful for further assessing the potential for human exposure.

Exposure Levels in Humans. Direct monitoring data of guthion in humans is rare since its biological half-life is short. Metabolites such as DMP, DMTP, and DMDTP have been monitored in urine of individuals (Aprea et al. 1994; CDC 2005; Fenske et al. 2000a; Loewenherz et al. 1997; Lu et al. 2000). These metabolites are not specific to guthion, but indicate potential exposure to several organophosphate pesticides. Continued monitoring data, particularly chronic low-level exposure data for humans in the vicinity of agricultural locations where it is frequently used or hazardous waste sites, are necessary.

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

Exposures of Children. Similar to adults, exposure measurements for the guthion metabolites in children are available (CDC 2005; Fenske et al. 2000a; Koch et al. 2002; Loewenherz et al. 1997; Lu et al. 2000). Children in the general population are exposed to guthion primarily through the dietary ingestion of contaminated food items. A unique exposure pathway exists for children of agricultural families that reside near farms or orchards where guthion is used. Potential exposure to guthion from parents clothing, family automobiles, and personal items exists (Lu et al. 2000). Since guthion has also been detected in soil and dust samples in or around homes where it is used, common play activities on the ground or pica may result in exposure for these children. Continued monitoring data is necessary for assessing the need to conduct health studies on exposed children. In addition, a data need exists for the levels of guthion or metabolites in breast milk.

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 guthion 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

The Federal Research in Progress (FEDRIP 2006) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. Researchers at the University of California, Department of Entomology (R.I. Krieger, principal investigator) are studying the dermal transfer of guthion and other pesticides from treated turf and other environmental surfaces to children. Researchers at the Washington State University Food and Environmental Quality Laboratory are measuring the atmospheric deposition and spray drift characteristics of guthion applied to apple orchards in Washington State.

7. ANALYTICAL METHODS

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

The biological half-life of guthion ranges from approximately 24 to 36 hours in humans (California EPA 2004; Loewenherz et al. 1997). As a consequence, monitoring human tissue for the parent compound only provides information regarding recent exposure or acute intoxication. Exposure to guthion is often measured by monitoring for dialkyl phosphate metabolites such as dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP), and dimethyl dithiophosphate (DMDTP) in the urine (Koch et al. 2002) or measuring cholinesterase activity in plasma, red blood cells, and whole blood (Vasilic et al. 1987). These methods are not specific to guthion because these metabolites are produced from the breakdown of other organophosphate compounds as well. Therefore, monitoring for DMP, DMTP, and DMDTP provide information regarding the potential exposure to organophosphate pesticides in general.

Quantification of the metabolites DMP, DMTP, and DMDTP in urine samples is typically accomplished using gas chromatography (GC) with nitrogen phosphate detection (NPD) or with flame photometric detection (FPD). Sample preparation usually includes solid-phase extraction, azeotropic distillation, and derivatization with pentafluorobenzylbromide (PFBB) in order to convert the dialkyl phosphate acids to esters (Loewenherz et al. 1997). Recoveries are usually around 90% and detection limits for the metabolites are in the parts per billion (ppb) range (Koch et al. 2002; Loewenherz et al. 1997).

GC with NPD or electron capture detection (ECD) has been used to quantify levels of guthion and other pesticides in human serum and urine (Pitarch et al. 2001). Mass spectroscopy (MS) in ion selective mode is used to confirm peak identity of the suspected compounds. These analyses require either solid-phase

extraction (SPE) with a C_{18} cartridge or liquid-liquid microextraction (LLME) procedure prior to quantification. In general, recoveries in both urine and serum were high for guthion (≥96% depending upon the extraction procedure) and the detection limits are 1.7–6.0 µg/L for urine and 10 µg/L for serum (Pitarch et al. 2001). For human serum samples, the authors determined that the SPE extraction procedure was the preferred method since it was faster, less tedious, and avoided the formation of emulsions that were frequently encountered in the LLME procedure.

Organophosphates such as guthion cause toxic effects in humans primarily through the inhibition of acetylcholinesterase enzyme. Spectroscopic methods of measuring the depression of cholinesterase activity are based on the Ellman method (Ellman et al. 1961). Acetylthiocholine is hydrolyzed by acetylcholinesterase (AChE—also referred to as erythrocyte acetylcholinesterase or red blood cell [RBC] acetylcholinesterase) and plasma cholinesterase (PChE—also referred to as butrylcholinesterase, serum cholinesterase, or pseudocholinesterase), producing acetic acid and thiocholine. Thiocholine reacts with the Ellman reagent dithionitrobenzoic acid (DTNB) to produce the anion of 5-thio-2-nitrobenzoic acid, which forms a yellow color that is measured spectrophotometrically at 412 nm. The rate of color formation is proportional to the amount of either AChE or PChE. An adaptation of the Ellman assay is a microtiter assay method for AChE that has been developed by Doctor et al. (1987). The AChE samples to be assayed are added to microtiter plates and enzymatic hydrolysis is initiated by adding Ellman reaction mixture (DTNB). The hydrolysis reaction is terminated by the addition of an AChE inhibitor (1,5-bis(4-allyldimethylammoniumphenyl)-pentan-3-one dibromide. The absorbance of the microtiter is measured continuously at 405 nm.

An automated version of the Ellman assay has been implemented by the state of California to detect exposure to organophosphate pesticides in field workers (Knaack et al. 1978). Samples of whole blood and plasma are diluted with tris(hydroxymethyl)aminomethane (0.05 Molar) and sodium chloride (0.114 Molar) buffer adjusted to pH 7.7 with hydrogen chloride. The samples are centrifuged at 1,600 rpm for 4 minutes to separate red blood cells from plasma, which are then analyzed for esterase activity using a continuous flow Technicon Analyzer. Prediluted whole blood or plasma samples are passed through a 37 °C dry bath incubator for approximately 1 minute. The sample is then passed through a 12-inch dialyzer equipped with a Type C membrane and the released thiocholine is passed through a solution of DTNB. The thiocholine DTNB mixture is sent to a delay coil for color development prior to being passed through a 15x1.5 mm flow cell.

Methods for analyzing guthion in biological samples are shown in Table 7-1.

Table 7-1. Analytical Methods for Determining Guthion and Various Metabolites in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human blood	Solid-phase extraction (SPE) with C_{18} cartridge followed by elution with MTBE	GC/NPD	10 µg/L	119–121	Pitarch et al. 2001
Human blood	Collection of blood samples, addition of 0.1 M phosphate buffer (pH=8.0) and DTNB	UV absorbance (at 410–412 nm)	No data	No data	Ellman et al. 1961
Urine	SPE with C_{18} cartridge followed by elution with MTBE	GC/NPD	1.7 µg/L	96–107	Pitarch et al. 2001
Urine	LLME using dichloromethane	GC/NPD	6.0 µg/L	98–109	Pitarch et al. 2001
Urine	Solid-phase extraction, followed by derivitization with PFBB	GC/FPD	7.4 µg/L (DMP) 1.1 µg/L (DMTP) 0.7 µg/L (DMDTP)	85–137	Koch et al. 2002
Urine	Solid-phase extraction, followed by derivitization with PFBB	GC/FPD	15 µg/L (DMTP) 13 µg/L(DMDTP)	47–116	Loewenherz et al. 1997

DMDTP = dimethyl dithiophosphate; DMP = dimethyl phosphate; DMTP = dimethyl thiophosphate; DTNB = dithionitrobenzoic acid (Ellman reagent); FPD = flame photometric detector; GC = gas chromatography; LLME = liquid-liquid microextraction; MTBE = methyl t-butyl ether; NPD = nitrogen phosphorous detector; PFBB = pentafluorobenzylbromide; SPE = solid-phase extraction; UV = ultraviolet

7.2 ENVIRONMENTAL SAMPLES

The detection and analysis of guthion in environmental samples is routinely accomplished by GC/NPD, GC/FPD and GC/MS techniques. Organophosphate pesticides such as guthion may also be detected by the electron capture detector; however, the GC/ECD is not as specific as the NPD or FPD (EPA 2000b). Like most organophosphate pesticides, guthion is subject to hydrolysis under alkaline conditions; therefore, care must be exercised during the extraction and storage process in order to avoid hydrolytic degradation. Aqueous extraction is usually performed at neutral pH with methylene chloride using separatory funnel techniques such as EPA Method 3510 (EPA 1996a). Solid samples may be extracted with hexane-acetone (1:1) or methylene chloride-acetone (1:1) using Method 3540 (Soxhlet extraction) (EPA 1996b), Method 3541 (automated Soxhlet extraction) (EPA 1994a), Method 3545 (pressurized fluid extraction) (EPA 1998a), Method 3546 (microwave extraction) (EPA 2000a), or other appropriate technique. Method 3550 (ultrasonic extraction) is not as rigorous as other extraction methods for soils/solids, and EPA has not yet validated this technique for organophosphate pesticides (EPA 1996c). Storage is maintained under dark conditions at 4 °C in order to minimize biotic and abiotic degradation. Extraction is usually performed within 7 days of sample collection and analysis should begin within 40 days of extraction. Cleanup procedures using Florisil, silica gel, size exclusion chromatography, or some other appropriate method is usually required to remove various contaminants found in environmental matrices. Detection limits in water and soil are 0.10 µg/L and 5 µg/kg, respectively, using EPA Method 8141B (GC/FPD) (EPA 2000b). Method 8270D is a GC/MS method used for the detection of guthion in groundwater and has a detection limit of 100 µg/L (EPA 1998b). Air samples can be analyzed for the presence of guthion by GC/FPD as described by NIOSH Method 5600 (NIOSH 1994). The detection limit for this method is approximately 0.0012 mg/m^3.

Several analytical methods have been published in the open literature that summarize the analysis of guthion in environmental samples including fruits/foods/juices (Danis et al. 2002; Kyriakidis et al. 2001; Sheridan and Meola 1999). Using GC coupled with flame thermionic detectors (FTD) or MS detectors, Danis et al. (2002) demonstrated guthion detection limits in the low µg/kg range for fresh and canned peaches. Recoveries in spiked samples were essentially 100% using an SPE method with nonporous carbon-based packing (Danis et al. 2002). GC with ion trap tandem MS/MS was used to detect guthion and other pesticides at the parts per billion (ppb) levels in fruits, vegetables, and milk (Sheridan and Meola 1999). GC/NPD was used to detect guthion in peach and orange juice (Kyriakidis et al. 2001). Household or vehicular dust samples are analyzed for the presence of guthion using solvent extraction

followed by size exclusion chromatography and analysis by GC/MS (Moate et al. 2002; Simcox et al. 1995).

Methods for analyzing guthion in environmental samples are shown in Table 7-2.

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 guthion 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 guthion.

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. The most specific biomarkers for exposure to guthion are the parent compound itself and metabolites in body fluids. However, because guthion is rapidly metabolized and eliminated (see Section 3.4), the parent compound may only be found in cases of acute exposure to considerable amounts of the pesticide (Pitarch et al. 2001). Although an analytical method has been described for determining the level of guthion in blood and urine (Pitarch et al. 2001), exposure is usually analyzed by measuring the level of urinary metabolites DMP, DMTP, and DMDTP. Methods exist that can measure background levels as well as levels at which biological effects might occur for these metabolites in urine by GC or GC/MS (Koch et al. 2002; Loewenherz et al. 1997). These three metabolites are not specific to guthion, and may be present due to exposure to other organophosphates. A biomarker of exposure specific to guthion is needed.

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection on sorbent filter with a sampling flow rate of 0.2–1.0 L/minute. Extraction with toluene/acetone (9:1)	GC/FPD	0.0012 mg/m^3	97	NIOSH 1994
Air	Collection with high volume sampler followed by extraction with ethyl acetate/hexane	GC/MS SIM	No data	76	Foreman et al. 2000
Water	Sepratory funnel extraction with methylene chloride at neutral pH	GC/FPD	0.10 µg/L	101–126	EPA 2000b (Method 8141)
Groundwater	Sepratory funnel extraction with methylene chloride at neutral pH	GC/MS	100 µg/L	No data	EPA 1998b (Method 8270)
Soil	Extraction with hexane-acetone (1:1) or methylene chloride-acetone (1:1), cleanup with Florisil, silica gel, size exclusion chromato-graphy, or sulfur	GC/FPD	5 µg/kg	87–156	EPA 2000b (Method 8141)
Soil	Extraction with acetone/ dichloromethane (1:1)	GC/FPD	10 µg/kg	No data	Gamon et al. 2003
Soil	Ultrasonic sonication with acetone. Separation with hexane and water followed by drying with anhydrous sodium sulfate	GC/MS SIM	32 µg/kg	90	Simcox et al. 1995
Dust	Sieve samples to remove debris followed by acetone extraction and cleanup with size exclusion chromatography	GC/MS	55 µg/kg	62–81 (house dust); 81.4–106 (vehicle dust)	Moate et al. 2002
Dust	Collection with high volume surface sampler, sieve samples through mesh to remove debris, followed by extraction with acetone	GC/MS SIM	40 µg/kg	77	Simcox et al. 1995
Sediment	Soxhlet extraction in hexane/acetone	GC/MS SIM	14 µg/kg	70–100	Villa S et al. 2003
Sediment	Soxhlet extraction in acetone/dichloromethane	GC/ECD	0.20 µg/kg	96	Knuth et al. 2000

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fruit (peaches)	Homogenization followed by extraction with acetonitrile/toluene (3:1)	GC/FTD; GC/MS	8 µg/kg (GC/FTD); 12 µg/kg (GC/MS)	100–105	Danis et al. 2002
Fruit, vegetables, milk	Homogenization followed by extraction with acetonitrile/ethanol (95:5)	GC/MS/MS	ppb range	No data	Sheridan and Meola 1999
Apples	Homogenization and extraction with acetone/hexane (5:1), followed by cleanup with gel permeation chromatography and Florisil	GC/MS	0.022 µg/kg	84	Rawn et al. 2006
Fruit juice	Extraction with ethyl acetate and sodium sulphate, followed by filtration with No. 1 Whatman filter paper	GC/NPD	0.004 mg/kg	87–110 (orange juice); 92–108 (peach juice)	Kyriakidis et al. 2001
Fish and macrophytes	Homogenized samples were extracted with acetone/dichloroethane	GC/FPD	0.20 µg/kg (fish); 0.22 µg/kg (macrophyte)	105 (fish); 86 (macro-phyte)	Knuth et al. 2000

ECD = electron capture detector; FPD = flame photometric detector; FTD = flame thermionic detector; GC = gas chromatography; MS = mass spectrometry; NPD = nitrogen phosphorous detector; SIM = selected ion monitoring

Effect. Guthion causes toxic effects in humans through the inhibition of acetylcholinesterase, thereby resulting in a buildup of acetylcholine at the neuromuscular junction and affecting neuromuscular transmission. Diagnosis of organophosphate poisoning, including guthion, can be made by the presence of characteristic clinical signs and measurements of serum (plasma) cholinesterase and RBC acetylcholinesterase activities. Enzyme inhibition, however, is not specific for organophosphates since exposure to carbamate insecticides also results in cholinesterase inhibition. Nonspecific cholinesterase (pseudocholinesterase, butyrylcholinesterase) is present in myelin, liver, and plasma, whereas acetylcholinesterase is present in the central and peripheral nervous systems and in RBC. A spectroscopic method exists which can measure the depression of cholinesterase activity (Ellman et al. 1961). Erythrocyte acetylcholinesterase or AChE and plasma butrylcholinesterase or PChE are both measured to diagnose exposure to organophosphates; however, it is believed that AChE is a more accurate test of synaptic acetylcholinesterase (Tafuri and Roberts 1987). The PChE measurement determines the pseudocholinesterase activity in the liver, which may be depressed by factors other than organophosphate exposure such as liver disease caused by cirrhosis or hepatitis. In addition, normal cholinesterase values vary widely in the human population, and a person with baseline activity near the upper limit of normal could be exposed to organophosphates and still have a reading within normal limits (Midtling et al. 1985; Tafuri and Roberts 1987). Thus, one data need is the development of markers specific to guthion, which enable early and reliable detection of systemic responses and health effects arising from such exposures.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining guthion levels in air (Foreman et al. 2000; NIOSH 1994), water (EPA 1998b, 2000b), soil (EPA 2000b; Gamon et al. 2003), sediment (Knuth et al. 2000; Villa et al. 2003), and various foods (Danis et al. 2002; Kyriakidis et al. 2001; Sheridan and Meola 1999) exist. These methods provide well-tested, reliable, and sensitive means for the analysis of guthion in environmental media. These methods are sensitive enough for measuring background levels and levels at which adverse health effects might occur. No additional analytical methods for determining low levels of guthion in environmental media are needed at this time.

7.3.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2006) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs pertinent to the analysis of guthion in biological or environmental samples. Researchers at the University of Maine Laboratory for Surface

Science and Technology Center are developing an organophosphate pesticide vapor sensor and testing the feasibility of using this sensor to detect residues of two pesticides (guthion and phosmet) on blueberries.

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8. REGULATIONS AND ADVISORIES

ATSDR has derived an acute-duration inhalation MRL of 0.02 mg/m^3 for guthion based on a NOAEL of 1.24 mg/m^3 for significant reductions in erythrocyte AChE activity in male rats exposed to guthion aerosols 6 hours/day, 5 days/week for 2 weeks (Kimmerle 1976). The MRL was derived by dividing the $NOAEL_{[HEC]}$ of 0.50 mg/m^3 by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability).

ATSDR has derived an intermediate-duration inhalation MRL of 0.01 mg/m^3 for guthion based on a NOAEL of 1.24 mg/m^3 for significant reductions in erythrocyte AChE activity in male and female rats exposed to guthion aerosols 6 hours/day, 5 days/week for 12 weeks (Kimmerle 1976). The MRL was derived by dividing the $NOAEL_{[HEC]}$ of 0.37 mg/m^3 by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability).

The intermediate-duration inhalation MRL of 0.01 mg/m^3 was adopted for use as the chronic-duration inhalation MRL.

ATSDR has derived an acute-duration oral MRL of 0.01 mg/kg/day for guthion. The MRL is based on a BMDL of 1.04 mg/kg/day for inhibition of erythrocyte AChE activity in pregnant rats administered guthion by gavage on gestation days 6–15 (Astroff and Young 1998) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ATSDR has derived an intermediate-duration oral MRL of 0.003 mg/kg/day for guthion. The MRL is based on a BMDL of 0.29 mg/kg/day for inhibition of erythrocyte AChE activity in dogs exposed to guthion in the diet for 26 weeks (Allen et al. 1990) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ATSDR has derived a chronic-duration oral MRL of 0.003 mg/kg/day for guthion. The MRL is based on a BMDL of 0.30 mg/kg/day for inhibition of erythrocyte AChE activity in dogs exposed to guthion in the diet for 52 weeks (Allen et al. 1990) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

EPA has not derived an inhalation reference concentration (RfC) or an oral reference dose (RfD) for guthion.

The EPA Office of Pesticide Programs calculated an acute oral reference value of 0.003 mg/kg/day based on a LOAEL of 1.0 mg/kg/day from an acute neurotoxicity study in rats in which inhibition of plasma ChE and erythrocyte and brain AChE activities were observed (EPA 2001b). The uncertainty factor used in this assessment was 300 (10 for interspecies extrapolation, 10 for intraspecies variation, and 3 for the use of a LOAEL).

The EPA Office of Pesticide Programs calculated a chronic oral reference value 0.00149 mg/kg/day based on a NOAEL of 0.149 mg/kg/day from a 1-year chronic toxicity study in dogs in which erythrocyte AChE inhibition was observed (EPA 2001b). The uncertainty factor used in this assessment was 100 (10 for interspecies variation and 10 for intraspecies variation).

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), tolerances for residues on raw agricultural commodities for guthion range from 0.2 to 5 ppm (EPA 2006i); see 40 CFR 180.154 for a complete listing of tolerances for residues and the corresponding raw agricultural commodities. EPA has further upheld these tolerances for residues in an order denying objections from the Natural Resource Defense Council (NRDC) to the issuance of these tolerances (EPA 2004b). Guthion is a pesticide classified for restricted use and is limited to use by or under the direct supervision of a certified applicator (EPA 2006e).

Guthion is currently registered for use on the following crops (EPA 1999a): almonds; apples/crabapples; blueberries, lowbush and highbush; Brussels sprouts; cherries, sweet and tart; nursery stock; parsley; pears; pistachios; and walnuts. On June 9, 2006, EPA proposed the cancellation of guthion usage for apples, blueberries, cherries, parsley, and pears by 2010 and a phase out of its uses on almonds, Brussels sprouts, pistachios, walnuts, and nursery stock by 2007 (EPA 2006l).

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

Table 8-1. Regulations and Guidelines Applicable to Guthion

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2007
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines	No data	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)[a,b,c]	0.2 mg/m^3	ACGIH 2007
EPA	AEGL	No data	EPA 2006a
	Hazardous air pollutant	No data	EPA 2006c 42 USC 7412
NIOSH	REL (10-hour TWA)[d]	0.2 mg/m^3	NIOSH 2005
	IDLH	10 mg/m^3	
OSHA	PEL (8-hour TWA) for general industry[e]	0.2 mg/m^3	OSHA 2005c 29 CFR 1910.1000
	PEL (8-hour TWA) for construction industry[e]	0.2 mg/m^3	OSHA 2005b 29 CFR 1926.55, Appendix A
	PEL (8-hour TWA) for shipyard industry[e]	0.2 mg/m^3	OSHA 2005a 29 CFR 1915.1000
b. Water			
DOT	Marine pollutant	Yes	DOT 2005 49 CFR 172.101, Appendix B
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2006b 40 CFR 116.4
	Drinking water standards and health advisories	No data	EPA 2006m
	National primary drinking water standards	No data	EPA 2003
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	1 pound	EPA 2006f 40 CFR 117.3
	Water quality criteria for nonpriority pollutants		EPA 2006d
	Fresh water (CCC)	0.01 µg/L	
	Salt water (CCC)	0.01 µg/L	
c. Food			
EPA	Tolerances for residues (see 40 CFR 180.154 for a complete listing of tolerances for residues on raw agricultural commodities)	Range: 0.2–5 ppm	EPA 2006i 40 CFR 180.154

Table 8-1. Regulations and Guidelines Applicable to Guthion

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
FDA	Order denying objections to issuance of tolerance	Yes	EPA 2004b 69 FR 30042
	Bottled drinking water	No data	FDA 2005 21 CFR 165.110
d. Other			
ACGIH	Carcinogenicity classification	A4[f]	ACGIH 2007
	Biological exposure indices (for acetyl-cholinesterase inhibiting pesticides)		
	Cholinesterase activity in red blood cells (sampling time is discretionary)	70% of individual's baseline	
EPA	Carcinogenicity classification	No data	
	RfC	No data	
	RfD	No data	
	Pesticide classified for restricted use[g]	All liquids with a concentration >13.5%	EPA 2006e 40 CFR 152.175
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	Yes	EPA 2006g 40 CFR 302.4
	Reportable quantity	1 pound	
	Extremely hazardous substances and their threshold planning quantities	10/10,000 pounds	EPA 2006h 40 CFR 355, Appendix A
DHHS	Carcinogenicity classification	No data	NTP 2004

[a]Inhalable fraction and vapor
[b]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors, liquids, and solids.
[c]Sensitization: refers to the potential for an agent to produce sensitization, as confirmed by human or animal data.
[d]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.
[e]Skin designation
[f]A4: not classifiable as a human carcinogen
[g]Pesticide classified as restricted use: limited to use by or under the direct supervision of a certified applicator for agricultural crop uses. Criteria influencing restriction includes inhalation hazard to humans.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Level; CCC = Criterion Continuous Concentration; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DHHS = Department of Health and Human Services; DOT = Department of Transportation; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

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

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

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

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

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by 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 Environmental Medicine, 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 Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Guthion
CAS Numbers: 86-50-0
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 3
Species: Rat

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

Reference: Kimmerle G. 1976. Subchronic inhalation toxicity of azinphos-methyl in rats. Arch Toxicol 35:83-89.

Experimental design: In this study (Kimmerle 1976), groups of 10 male and 10 female SPF Wistar rats were exposed to aerosolized guthion at 0.195, 1.24, or 4.72 mg/m^3, 6 hours/day, 5 days/week for 12 weeks. Guthion aerosols were generated by first dissolving technical-grade guthion in a 1:1 solution of ethanol/polypropylene glycol. Ninety-seven percent of the droplets had a diameter of 1±0.5 µm. The animals were inspected daily and weighed weekly. Erythrocyte AChE and plasma ChE activities were determined after 2, 4, 6, 8, 10, and 12 weeks and determinations of hematology, serum glutamic-oxalacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), alkaline phosphatase, urea, creatinine, and bilirubin were conducted after 12 weeks of exposure. At study termination, animals were sacrificed for gross examination. The thyroid, thymus, heart, lungs, liver, spleen, kidneys, adrenals, and gonads were weighed and examined histologically and brain AChE activity was determined.

Effect noted in study and corresponding doses: There were no significant changes in appearance or behavior of male or female rats. Male rats in the 4.72 mg/m^3 group showed a 20% reduction in body weight gain during the 12-week exposure period. Although body weight was not reported on week 2, on week 4, body weight gain in male rats in the 4.72 mg/m^3 group was 60% that in control animals. After 2 weeks of exposure, erythrocyte AChE activity was reduced by 25 and 18% in male and female rats, respectively, in the 4.72 mg/m^3 group, but not at lower concentrations. There were no biologically significant reductions in plasma ChE activity at any of the doses tested.

Dose and end point used for MRL derivation: The MRL is based on a NOAEL of 1.24 mg/m^3 and a LOAEL of 4.72 mg/m^3 for decreased erythrocyte AChE activity after 2 weeks of exposure.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[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: As per MRL guidance from ATSDR, a 5–7-day duration adjustment is not conducted for acute inhalation

exposures. Thus, the NOAEL of 1.24 mg/m^3 was adjusted for intermittent exposure ($NOAEL_{[ADJ]}$) as follows:

$NOAEL_{[ADJ]}$ = 1.24 mg/m^3 x 6 hours/24 hours
$NOAEL_{[ADJ]}$ = 0.31 mg/m^3

The human equivalent concentration (HEC) of the $NOAEL_{[ADJ]}$ was calculated using the equations below. The $RDDR_{[ER]}$ is the regionally deposited dose ratio for the extrarespiratory effects. It is calculated using EPA's software (version 2.3) for calculating RDDRs (EPA 1994b) and particle size and body weight data from Kimmerle (1976). A presentation of the equations and assumptions used to calculate the RDDR can be found in EPA (1994b).

$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RDDR_{[ER]}$
$NOAEL_{[HEC]}$ = 0.31 mg/m^3 x 1.626
$NOAEL_{[HEC]}$ = 0.50 mg/m^3

An $RDDR_{ER}$ of 1.626 was estimated using the default parameters and body weight data presented in Table A-1.

Table A-1. Default Parameters Used in the Derivation of $RDDR_{ER}$

Parameter	Humans	Rats
Body weight (kg)	70.00	0.182[a]
Minute volume (L)	13.80	0.139
ET area (cm^2)[b]	200.00	15.00
TB area (cm^2)[c]	3,200.00	22.50
PU area (m^2)[d]	54.00	0.34

[a]2-week body weight value estimated from Kimmerle (1976)
[b]Extrathoracic respiratory tract region
[c]Tracheobronchial respiratory tract region
[d]Pulmonary respiratory tract region

$RDDR_{ER}$ = regionally deposited dose ratio for the extrarespiratory effects

Based on the information provided by Kimmerle (1976) it was assumed that the sizes of the aerosol particles were log-normally distributed in a manner such that 1.5% of these were <0.5 µm and 1.5% were >1.5 µm. Based on these assumptions, a geometric mean and geometric standard deviation of 0.9 and 0.23 µm, respectively, were calculated. These values were used to calculate a Mass Median Aerodynamic Diameter (MMAD) of 0.88 µm using the recommended equation in Table H-2 (shown below) of the guidance document Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b).

$$MMAD = CMAD\ e(3[\ln \text{variance}]^2)$$

No conversion is required for the geometric standard deviation and the geometric standard deviation of 0.23 was used. CMAD is the count median aerodynamic diameter (0.9 µm).

The $NOAEL_{[HEC]}$ of 0.50 mg/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability), resulting in an acute-

duration inhalation MRL of 0.02 mg/m^3. Application of the benchmark dose methodology to the data from Kimmerle (1976) was considered, but the data were presented as means without standard errors or standard deviations. Without these measures, the benchmark dose methodology could not be applied.

Was a conversion used from intermittent to continuous exposure? Yes, animals were exposed 6 hours/day, 5 days/week.

$NOAEL_{[ADJ]}$ = 1.24 mg/m^3 x 6 hours/24 hours
$NOAEL_{[ADJ]}$ = 0.31 mg/m^3

Other additional studies or pertinent information that lend support to this MRL: EPA (1978a) reported a 41% (range 27–59%) reduction in blood ChE activity in rats exposed to guthion aerosols (39 mg/m^3) for 1 hour. The consistent observation of reduced ChE activity in the two available inhalation studies is in agreement with the observations made in a number of studies with guthion administered orally to rats and dogs during acute (Astroff and Young 1998; Pasquet et al. 1976), intermediate (Holzum 1990; Sheets et al. 1997), and chronic (Allen et al. 1990; Schmidt and Chevalier 1984) exposures.

Agency Contacts (Chemical Managers): Nickolette Roney, Selene Chou, Yee-Wan Stevens

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Guthion
CAS Numbers: 86-50-0
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 7
Species: Rat

Minimal Risk Level: 0.01 [ ] mg/kg/day [ ] ppm [X] mg/m^3

Reference: Kimmerle G. 1976. Subchronic inhalation toxicity of azinphos-methyl in rats. Arch Toxicol 35:83-89.

Experimental design: In this study (Kimmerle 1976), groups of 10 male and 10 female SPF Wistar rats were exposed to aerosolized guthion at 0.195, 1.24, or 4.72 mg/m^3, 6 hours/day, 5 days/week for 12 weeks. Guthion aerosols were generated by first dissolving technical-grade guthion in a 1:1 solution of ethanol/polypropylene glycol. Ninety-seven percent of the droplets had a diameter of 1±0.5 µm (Kimmerle 1976). The animals were inspected daily and weighed weekly. Erythrocyte AChE and plasma ChE activities were determined after 2, 4, 6, 8, 10, and 12 weeks and determinations of hematology, SGOT, SGPT, alkaline phosphatase, urea, creatinine, and bilirubin were conducted after 12 weeks of exposure. At study termination, animals were sacrificed for gross examination. The thyroid, thymus, heart, lungs, liver, spleen, kidneys, adrenals, and gonads were weighed and examined histologically and brain AChE activity was determined.

Effect noted in study and corresponding doses: There were no significant changes in appearance or behavior of male or female rats. Male rats in the 4.72 mg/m^3 group showed a 20% reduction in body weight gain during the 12-week exposure period. No effects were detected in the examined hematological and serum clinical chemistry parameters. There were no observed differences in absolute or relative organ weights or morphological alterations in organs or tissues in any of the rats. From week 4 to week 12, erythrocyte AChE activity was reduced by 29–48% in male and 26–39% in female rats in the 4.72 mg/m^3 group. There were no additional reductions in erythrocyte AChE activity beyond week 4. Reductions in erythrocyte AChE activity in rats exposed to guthion doses <4.72 mg/m^3 were 17% or less and are not considered an adverse effect. The investigator noted that brain ChE activity was not reduced at any of the concentrations tested, but no data were shown.

Dose and end point used for MRL derivation: The MRL is based on a NOAEL of 1.24 mg/m^3 and LOAEL of 4.72 mg/m^3 for decreased erythrocyte AChE activity.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[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: The NOAEL of 1.24 mg/m^3 was adjusted for intermittent exposure (NOAEL[ADJ]) as follows:

$NOAEL_{[ADJ]}$ = 1.24 mg/m^3 x 6 hours/24 hours x 5 days/7 days
$NOAEL_{[ADJ]}$ = 0.22 mg/m^3

The human equivalent concentration (HEC) of the $NOAEL_{[ADJ]}$ was calculated using the equations below. The $RDDR_{[ER]}$ is the regionally deposited dose ratio for the extrarespiratory effects. It is calculated using EPA's software (version 2.3) for calculating RDDRs (EPA 1994b) and particle size and body weight data from Kimmerle (1976). A presentation of the equations and assumptions used to calculate the RDDR can be found in EPA (1994b).

$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RDDR_{[ER]}$
$NOAEL_{[HEC]}$ = 0.22 mg/m^3 x 1.695
$NOAEL_{[HEC]}$ = 0.37 mg/m^3

An $RDDR_{ER}$ of 1.695 was estimated using the default parameters and body weight data presented in Table A-2.

Table A-2. Default Parameters Used in the Derivation of $RDDR_{ER}$

Parameter	Humans	Rats
Body weight (kg)	70.00	0.253[a]
Minute volume (L)	13.80	0.182
ET area (cm^2)[b]	200.00	15.00
TB area (cm^2)[c]	3,200.00	22.50
PU area (m^2)[d]	54.00	0.34

[a]12-week body weight value from Kimmerle (1976)
[b]Extrathoracic respiratory tract region
[c]Tracheobronchial respiratory tract region
[d]Pulmonary respiratory tract region

$RDDR_{ER}$ = regionally deposited dose ratio for the extrarespiratory effects

Based on the information provided by Kimmerle (1976), it was assumed that the sizes of the aerosol particles were log-normally distributed in a manner such that 1.5% of these were <0.5 µm and 1.5% were >1.5 µm. Based on these assumptions, a geometric mean and geometric standard deviation of 0.9 and 0.23 µm, respectively, were calculated. These values were used to calculate a MMAD of 0.88 µm using the recommended equation in Table H-2 of the guidance document Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b).

$$MMAD = CMAD\ e(3[\ln \text{variance}]^2)$$

No conversion is required for the geometric standard deviation and the geometric standard deviation of 0.23 was used. CMAD is the count median aerodynamic diameter (0.9 µm).

The $NOAEL_{[HEC]}$ of 0.37 mg/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability), resulting in an intermediate-duration inhalation MRL of 0.01 mg/m^3. Application of the benchmark dose methodology

to the data from Kimmerle (1976) was considered, but the data were presented as means without standard errors or standard deviations. Without these measures, the benchmark dose methodology could not be applied.

Was a conversion used from intermittent to continuous exposure? Yes, animals were exposed 6 hours/day, 5 days/week.

$NOAEL_{[ADJ]}$ = 1.24 mg/m^3 x 6 hours/24 hours x 5 days/7 days
$NOAEL_{[ADJ]}$ = 0.22 mg/m^3

Other additional studies or pertinent information that lend support to this MRL: EPA (1978a) reported a 41% (range 27–59%) reduction in blood ChE activity in rats exposed to guthion aerosols (39 mg/m^3) for 1 hour. The consistent observation of reduced ChE activity in the two available inhalation studies is in agreement with the observations made in a number of studies with guthion administered orally to rats and dogs during acute (Astroff and Young 1998; Pasquet et al. 1976), intermediate (Holzum 1990; Sheets et al. 1997), and chronic (Allen et al. 1990; Schmidt and Chevalier 1984) exposures.

Agency Contacts (Chemical Managers): Nickolette Roney, Selene Chou, Yee-Wan Stevens

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Guthion
CAS Numbers: 86-50-0
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 7
Species: Rat

Minimal Risk Level: 0.01 [ ] mg/kg/day [ ] ppm [X] mg/m^3

Reference: Kimmerle G. 1976. Subchronic inhalation toxicity of azinphos-methyl in rats. Arch Toxicol 35:83-89.

Experimental design: In this study (Kimmerle 1976), groups of 10 male and 10 female SPF Wistar rats were exposed to aerosolized guthion at 0.195, 1.24, or 4.72 mg/m^3, 6 hours/day, 5 days/week for 12 weeks. Guthion aerosols were generated by first dissolving technical-grade guthion in a 1:1 solution of ethanol/polypropylene glycol. Ninety-seven percent of the droplets had a diameter of 1±0.5 µm (Kimmerle 1976). The animals were inspected daily and weighed weekly. Erythrocyte AChE and plasma ChE activities were determined after 2, 4, 6, 8, 10, and 12 weeks and determinations of hematology, SGOT, SGPT, alkaline phosphatase, urea, creatinine, and bilirubin were conducted after 12 weeks of exposure. At study termination, animals were sacrificed for gross examination. The thyroid, thymus, heart, lungs, liver, spleen, kidneys, adrenals, and gonads were weighed and examined histologically and brain AChE activity was determined.

Effect noted in study and corresponding doses: There were no significant changes in appearance or behavior of male or female rats. Male rats in the 4.72 mg/m^3 group showed a 20% reduction in body weight gain during the 12-week exposure period. No effects were detected in the examined hematological and serum clinical chemistry parameters. There were no observed differences in absolute or relative organ weights or morphological alterations in organs or tissues in any of the rats. From week 4 to week 12, erythrocyte AChE activity was reduced by 29–48% in male and 26–39% in female rats in the 4.72 mg/m^3 group. Reductions in erythrocyte AChE activity in rats exposed to guthion doses <4.72 mg/m^3 were 17% or less and are not considered an adverse effect. The investigator noted that brain AChE activity was not reduced at any of the concentrations tested, but no data were shown.

Dose and end point used for MRL derivation: The MRL is based on a NOAEL of 1.24 mg/m^3 and LOAEL of 4.72 mg/m^3 for decreased erythrocyte AChE activity.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 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: The NOAEL of 1.24 mg/m^3 was adjusted for intermittent exposure (NOAEL[ADJ]) as follows:

$NOAEL_{[ADJ]}$ = 1.24 mg/m^3 x 6 hours/24 hours x 5 days/7 days
$NOAEL_{[ADJ]}$ = 0.22 mg/m^3

The human equivalent concentration (HEC) of the $NOAEL_{[ADJ]}$ was calculated using the equations below. The $RDDR_{[ER]}$ is the regionally deposited dose ratio for the extrarespiratory effects. It is calculated using EPA's software (version 2.3) for calculating RDDRs (EPA 1994b) and particle size and body weight data from Kimmerle (1976).

$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RDDR_{[ER]}$
$NOAEL_{[HEC]}$ = 0.22 mg/m^3 x 1.695
$NOAEL_{[HEC]}$ = 0.37 mg/m^3

An $RDDR_{ER}$ of 1.695 was estimated using the default parameters and body weight data presented in Table A-3.

Table A-3. Default Parameters Used in the Derivation of $RDDR_{ER}$

Parameter	Humans	Rats
Body weight (kg)	70.00	0.253[a]
Minute volume (L)	13.80	0.182
ET area (cm^2)[b]	200.00	15.00
TB area (cm^2)[c]	3,200.00	22.50
PU area (m^2)[d]	54.00	0.34

[a]12-week body weight value from Kimmerle (1976)
[b]Extrathoracic respiratory tract region
[c]Tracheobronchial respiratory tract region
[d]Pulmonary respiratory tract region

$RDDR_{ER}$ = regionally deposited dose ratio for the extrarespiratory effects

Based on the information provided by Kimmerle (1976), it was assumed that the sizes of the aerosol particles were log-normally distributed in a manner such that 1.5% of these were <0.5 µm and 1.5% were >1.5 µm. Based on these assumptions, a geometric mean and geometric standard deviation of 0.9 and 0.23 µm, respectively, were calculated. These values were used to calculate a MMAD of 0.88 µm using the recommended equation in Table H-2 of the guidance document Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b).

$$MMAD = CMAD\ e(3[\ln \text{variance}]^2)$$

No conversion is required for the geometric standard deviation and the geometric standard deviation of 0.23 was used. CMAD is the count median aerodynamic diameter (0.9 µm).

The $NOAEL_{[HEC]}$ of 0.37 mg/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability), resulting in an intermediate-duration inhalation MRL of 0.01 mg/m^3. Application of the benchmark dose methodology to the data from Kimmerle (1976) was considered, but the data were presented as means without standard

errors or standard deviations. Without these measures, the benchmark dose methodology could not be applied.

Was a conversion used from intermittent to continuous exposure? Yes, animals were exposed 6 hours/day, 5 days/week.

$NOAEL_{[ADJ]}$ = 1.24 mg/m^3 x 6 hours/24 hours x 5 days/7 days
$NOAEL_{[ADJ]}$ = 0.22 mg/m^3

Other additional studies or pertinent information that lend support to this MRL: No studies were located that allowed the derivation of a chronic-duration inhalation MRL. However, the available acute- and intermediate-duration inhalation studies and the acute-, intermediate-, and chronic-duration oral exposure studies support adopting the intermediate-duration MRL for chronic-duration exposures. Erythrocyte AChE activity was reduced by 29–48% in male rats and 26–39% in female rats exposed to guthion aerosols at 4.72 mg/m^3 for 4–12 weeks without evident biologically significant changes in activity within the observation period (Kimmerle 1976). Intermediate- and chronic-duration oral exposures to 0.69–0.78 mg/kg/day in dogs (Allen et al. 1990) and 0.75–0.96 mg/kg/day in rats (Schmidt and Chevalier 1984) demonstrated biologically significant reductions in erythrocyte AChE activity that did not increase in severity with increasing exposure duration for up to 2 years (Allen et al. 1990; Schmidt and Chevalier 1984). Thus, a chronic-duration inhalation MRL of 0.01 mg/m^3 is adopted from the intermediate-duration inhalation MRL and supported by the intermediate- and chronic-duration oral exposure studies in dogs and rats, which suggest that there are no duration-dependent increases in the severity of the inhibition of erythrocyte AChE activity.

Agency Contacts (Chemical Managers): Nickolette Roney, Selene Chou, Yee-Wan Stevens

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Guthion
CAS Numbers: 86-50-0
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 11
Species: Rats

Minimal Risk Level: 0.01 [X] mg/kg/day [ ] ppm

Reference: Astroff AB, Young AD. 1998. The relationship between maternal and fetal effects following maternal organophosphate exposure during gestation in the rat. Toxicol Ind Health 14(6):869-889.

Experimental design: Pregnant Sprague-Dawley rats were administered guthion (87.7% a.i.) at 0.5, 1.0, or 2.0 mg/kg/day by gavage on gestation days 6–15 (Astroff and Young 1998). Erythrocyte AChE was determined on gestation days 16 and 20 and brain AChE activity was determined on day 20. Inseminated females were examined daily for clinical signs. Dam body weight was determined on gestation days 0, 6, 8, 10, 12, 15, and 20. Food consumption was also determined periodically. Two groups of dams were used to establish maternal plasma ChE and erythrocyte and brain AChE activities on gestation days 16 and 20. Gross pathological examination of dams was conducted. Several reproductive and developmental end points, including early or late resorptions, implantation losses, and fetal survival, growth, and malformations were evaluated.

Effect noted in study and corresponding doses: A >80% reduction in erythrocyte AChE activity was observed 24 hours after the last 2.0 mg/kg/day dose. A 40% reduction in brain AChE activity was also observed in dams in the 2.0 mg/kg/day group. Maternal plasma ChE activity in the 2.0 mg/kg/day group was approximately 30% lower than in controls on gestation day 16, but the effect was not statistically significant. On gestation day 20, maternal brain AChE activity remained 27% lower than control values, but erythrocyte AChE and plasma ChE activities were not significantly different from those of control animals. In spite of the magnitude of the AChE and ChE activity reductions, there were no adverse clinical signs observed in the treated dams. There were no statistically or biologically significant reductions in brain or erythrocyte AChE or plasma ChE activities in rats administered 0.5 or 1 mg/kg/day.

Dose and end point used for MRL derivation: The MRL is based on a BMDL of 1.04 mg/kg/day for inhibition of erythrocyte AChE activity.

[ ] NOAEL [ ] LOAEL [X] BMDL

In order to derive a point of departure to calculate an acute-duration oral MRL, a benchmark dose approach was applied to the changes in erythrocyte AChE activity observed in female rats exposed to guthion by gavage during gestation. Benchmark doses (BMDs) and the lower bound of the 95% confidence limits of the benchmark doses (BMDLs) were calculated using the EPA Benchmark Dose Software (BMDS version 1.3.2) as described below. The BMDs and BMDLs are estimates of the doses associated with a 20% change in erythrocyte AChE activity.

The simplest continuous variable model (a linear model) did not provide an adequate fit to the erythrocyte AChE activity data. Thus, four continuous variable models were fit to the erythrocyte AChE activity data presented in Table A-4. Results of the modeling are presented in Table A-5.

Table A-4. Erythrocyte Cholinesterase Activity in Female Rats Administered Guthion

Guthion dose (mg/kg/day)	Number of animals tested	Erythrocyte AChE activity (IU/mL)	Standard deviation	Percent inhibition
0	24	0.36	0.10	–
0.5	19	0.32	0.06	11
1.0	27	0.32	0.09	11
2.0	26	0.07	0.03	81

Source: Astroff and Young 1998

Table A-5. Model Predictions for Changes in Erythrocyte Cholinesterase Activity in Female Rats

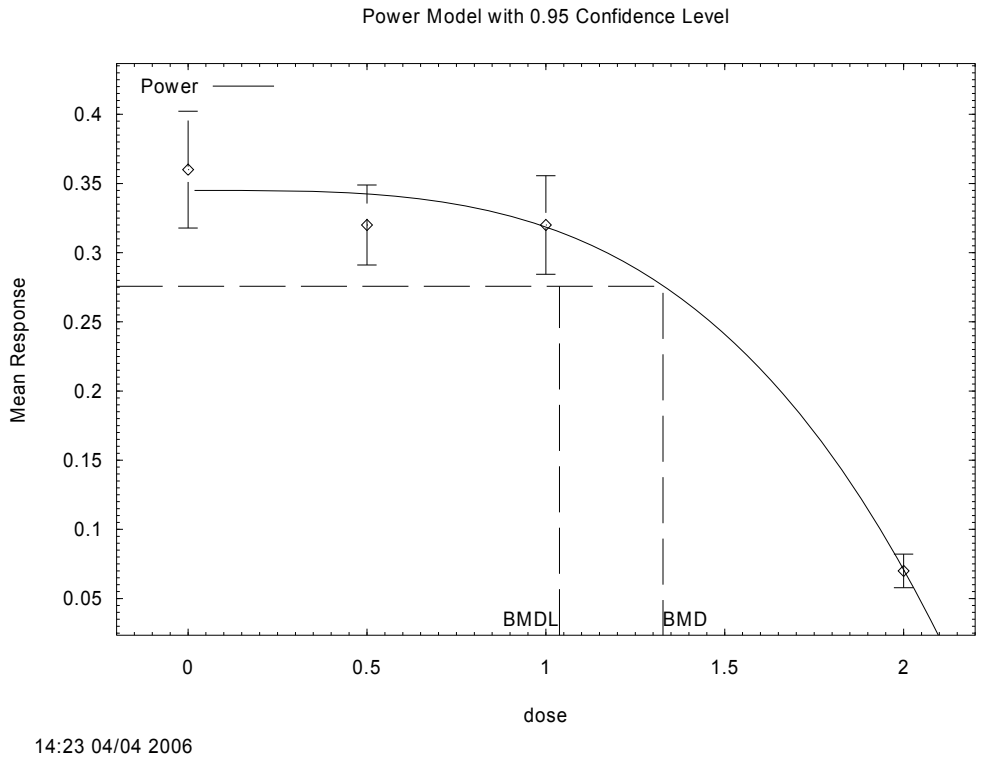
Model	Variance p-value[a]	X^2 test statistic for means	df	p-Value for the means[a]	AIC	BMD (mg/kg/day)	BMDL (mg/kg/day)
Linear[b]	<0.0001	29.9864	2	<0.0001	-369.520477	–	–
Linear[c]	0.1257	34.808	2	<0.0001	-390.935378	–	–
2-degree polynomial[d]	0.1257	5.50139	1	0.019	-418.242024	–	–
Power[c,e]	0.1257	3.42361	1	0.06427	-420.319802	1.32753	1.03839
Hill[f]	0.1257	3.42499	0	NA	-418.318425	–	–

[a]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Best-fitting model
[d]The lowest degree polynomial providing an adequate fit is reported
[e]Restrict power >=1
[f]Restrict n>1

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; df = degree of freedom; NA = not available (BMD software could not generate a model output); p = p-value from the chi-squared test

An adequate fit to the data for changes in erythrocyte AChE activity (as assessed by chi-square residuals and log-likelihood ratio fit tests in the BMDS) was obtained only with the power model with nonconstant variance assumed. A limitation of this data set is the large difference in maternal erythrocyte AChE activity between the NOAEL and the next, higher dose; relative to controls, maternal erythrocyte AChE activity was 11% lower in the 1 mg/kg/day group and 81% lower in the 2 mg/kg/day group. Statistical tests indicated that variances were not constant across exposure groups. The power model with non-homogeneous variance (i.e., variance as a power function of dose) provided an improved fit to the data as assessed with Akaike's Information Criteria (AIC) (Table A-5). The BMD and BMDL predicted from the power model are 1.33 and 1.04 mg/kg/day, respectively (Table A-5 and Figure A-1).

Figure A-1. Model Predictions for Changes in Erythrocyte Cholinesterase Activity in Female Rats



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? 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: Pasquet et al. (1976) observed reductions in erythrocyte and brain AChE activity in rats after single oral doses of guthion at 2, 6, or 18 mg/kg. Plasma ChE activity was reduced by ≥20% at >2 mg/kg, while brain AChE activity was reduced by ≥20% at doses ≥2 mg/kg/day. The results of the BMD approach is supported by the observation that application of a NOAEL approach (NOAEL ÷ 100 [uncertainty factor] would result in an MRL equal to the BMDL ÷ 100 [uncertainty factor].

Agency Contacts (Chemical Managers): Nickolette Roney, Selene Chou, Yee-Wan Stevens

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Guthion
CAS Numbers: 86-50-0
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 40
Species: Dog

Minimal Risk Level: 0.003 [X] mg/kg/day [ ] ppm

Reference: Allen TR, Janiak T, Frei T, et al. 1990. 52-Week oral toxicity (feeding) study with azinphos-methyl (E 1582) in the dog. Mobay Corporation. Submitted to the U.S. Environmental Protection Agency. MRID41804801.

Experimental design: Technical-grade guthion (91.9% a.i.) was administered to beagle dogs (four dogs/sex/group) in the food at 5.0, 25.0, and 125.0 ppm for up to 52 weeks. The guthion concentrations are equivalent to 0.15, 0.69, and 3.8 mg/kg/day, respectively, in male dogs, and 0.16, 0.78, and 4.3 mg/kg/day, respectively, in female dogs (Allen et al. 1990). The observations made at ≤26 weeks were used to derive the intermediate-duration MRL. Daily observations for clinical signs were conducted; body weight was determined weekly and food consumption was monitored daily. Hearing and ophthalmoscopic evaluations were conducted after 13, 26, and 52 weeks; hematological, clinical chemistry, and urinary chemistry parameters were determined on weeks 4, 13, 26, and 52; plasma ChE and erythrocyte AChE activities were determined on weeks 4, 13, and 26.

Effect noted in study and corresponding doses: Reductions of ≥20% in erythrocyte AChE activity were observed after 4, 13, and 26 weeks in male and female dogs administered guthion in food for up to 52 weeks (Allen et al. 1990). Dose-related reductions in erythrocyte AChE activity were evident at the week 4 sampling time. Erythrocyte AChE activity was further reduced from week 4 to week 13 but remained relatively constant from week 13 to 26 (Allen et al. 1990). Statistically nonsignificant reductions in erythrocyte AChE activity during the 26-week period were ≤8% in males at 0.15 mg/kg/day and 11–21% in females at 0.16 mg/kg/day. Reductions in erythrocyte AChE activity were 22–40% in males at 0.69 mg/kg/day and 20–43% in females at 0.78 mg/kg/day. Reductions in erythrocyte AChE activity from weeks 4 to 26 were 66–88% in males (3.8 mg/kg/day) and 86–92% in females (4.3 mg/kg/day). The relatively constant levels of erythrocyte AChE activity from weeks 4 to 26 suggest that the effects of guthion on AChE activity occur early and remain relatively steady during exposure. Male and female dogs administered 3.8 and 4.3 mg/kg/day, respectively, suffered from an increased incidence of mucoid diarrhea and occasional emesis. The same signs but with a greater severity were observed in male dogs at 0.69 mg/kg/day. These signs were believed to be related to guthion treatment. Terminal body weights were reduced by 12–16% in male and female dogs administered 3.8 and 4.3 mg/kg/day, respectively, although there was no difference in food consumption among treated and control animals. There were no treatment-related hematological effects or changes in urinalysis parameters. Findings were negative in hearing and ophthalmoscopic tests on weeks 13 and 26 and there was no treatment-related increase in mortality in any dose group (Allen et al. 1990). Clinical chemistry tests showed that albumin and albumin/globulin values were significantly reduced in males by 13 and 20%, respectively, in the 3.8 mg/kg/day group.

Dose and end point used for MRL derivation: The MRL is based on a BMDL of 0.29 mg/kg/day for inhibition of erythrocyte AChE activity in female dogs after 26 weeks.

[ ] NOAEL [ ] LOAEL [X] BMDL

In order to derive a point of departure to calculate an intermediate-duration oral MRL, a benchmark dose approach was applied to the changes in erythrocyte AChE activity observed in male and female dogs exposed to guthion in the diet for 26 weeks (Allen et al. 1990). It is recognized that the small number of animals per dose group (4 dogs/group) limits the characterization of variability in the response to guthion. Benchmark doses (BMDs) and the lower bound of the 95% confidence limits of the benchmark doses (BMDLs) were calculated using the EPA Benchmark Dose Software (BMDS version 1.3.2) as described below. The BMDs and BMDLs are estimates of the doses associated with a 20% change in erythrocyte AChE activity. The simplest continuous variable model (a linear model) was fit to the erythrocyte AChE activity data presented in Table A-6.

Table A-6. Erythrocyte Cholinesterase Activity (µmol/mL/minute) in Beagle Dogs Administered Guthion in the Diet for 26 Weeks (Four Dogs/Sex/Dose Group)

Dose (mg/kg/day)	Mean (standard deviation)	Percent reduction
Males		
0	2.57 (0.29)	–
0.15	2.37 (0.83)	8
0.69	1.75 (0.21)	32
3.8	0.32 (0.13)	88[a]
Females		
0	3.27 (0.38)	–
0.16	2.57 (0.63)	21
0.78	2.03 (0.53)	37[a]
4.3	0.28 (0.11)	91[a]

[a]Statistically significant reduction

Source: Allen et al. 1990

A nonhomogeneous variance linear model provided an adequate fit to the erythrocyte AChE activity data for female but not male dogs after 26–week and it was concluded that the male data at 26 weeks were not suitable for BMD modeling. For the 26-week data in female dogs, the best-fitting linear model predicted a BMD of 0.96 mg/kg/day and a BMDL of 0.93 mg/kg/day. However, this BMDL for a 20% reduction in erythrocyte AChE activity in dogs is higher than the observed LOAELs of 0.69 and 0.78 mg/kg/day in male and female dogs, respectively (Allen et al. 1990). At these LOAELs, reductions in erythrocyte AChE activity in the range of 32–37% were observed after 26 weeks. Thus, the linear model appears to underpredict the response of erythrocyte AChE activity to guthion in female dogs after 26 weeks. Reexamination of the data plots suggests that the experimental data at the high dose might be a high-leverage point, which exerts a high degree of influence on the model results. The plot of the erythrocyte AChE activity in female dogs after 26 weeks is presented in Figure A-2. Given that for the derivation of an MRL the most pertinent part of the dose-response curve is that which lies at the lower doses, the high-dose data point was removed from the dataset and the model fitting was conducted as described before. A nonhomogeneous variance linear model provided an adequate fit to the erythrocyte AChE activity data for females at week 26 when the high dose was removed from the data set. None of the other continuous

models available in the BMD software provided an adequate fit to the data. Results of the BMD linear modeling of the low-dose region of the dose-response curve are presented in Table A-7 and a plot of the 26-week data in females with the high-dose excluded is presented in Figure A-3.

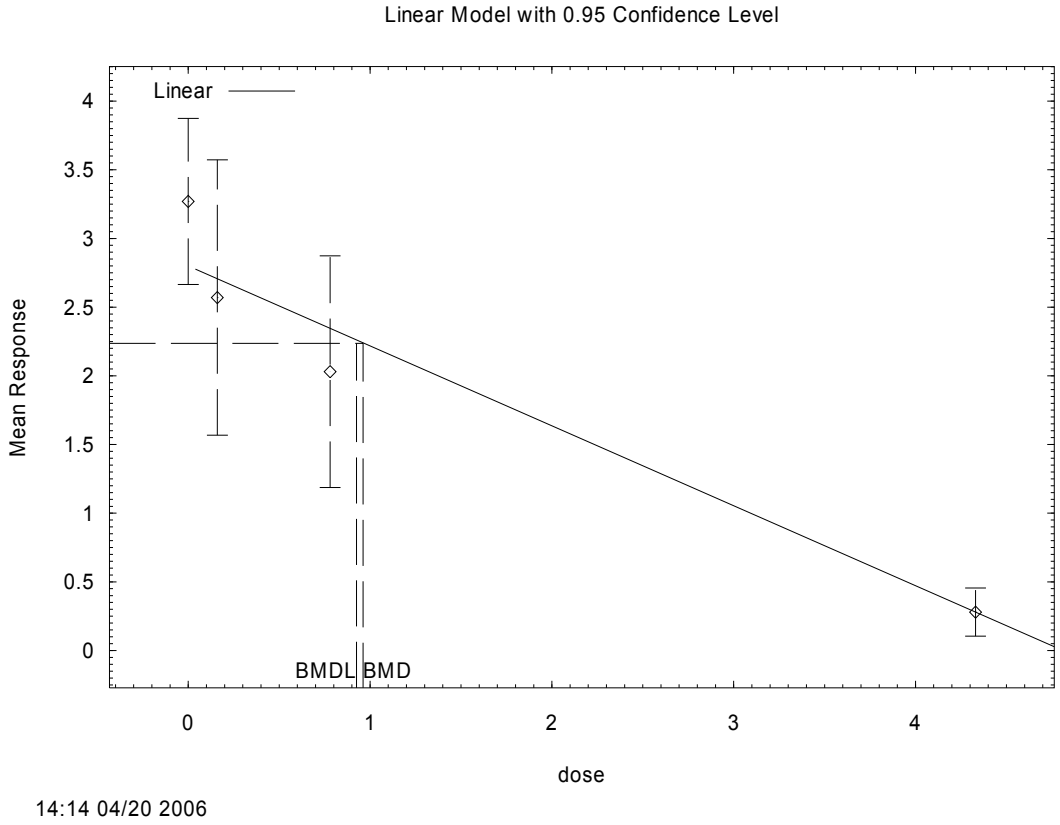
Table A-7. Model Predictions for Erythrocyte AChE Activity in Female Beagle Dogs Exposed to Guthion in the Diet for 26 Weeks

Model	Variance p-value[a]	X^2 test statistic for means	df	p-value for the means[a]	AIC	BMD (mg/kg/day)	BMDL (mg/kg/day)
Linear[b,c,d] (high dose excluded)	0.43	2.47	1	0.12	3.12	0.44	0.29

[a]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Best-fitting model
[d]Restriction = nonpositive

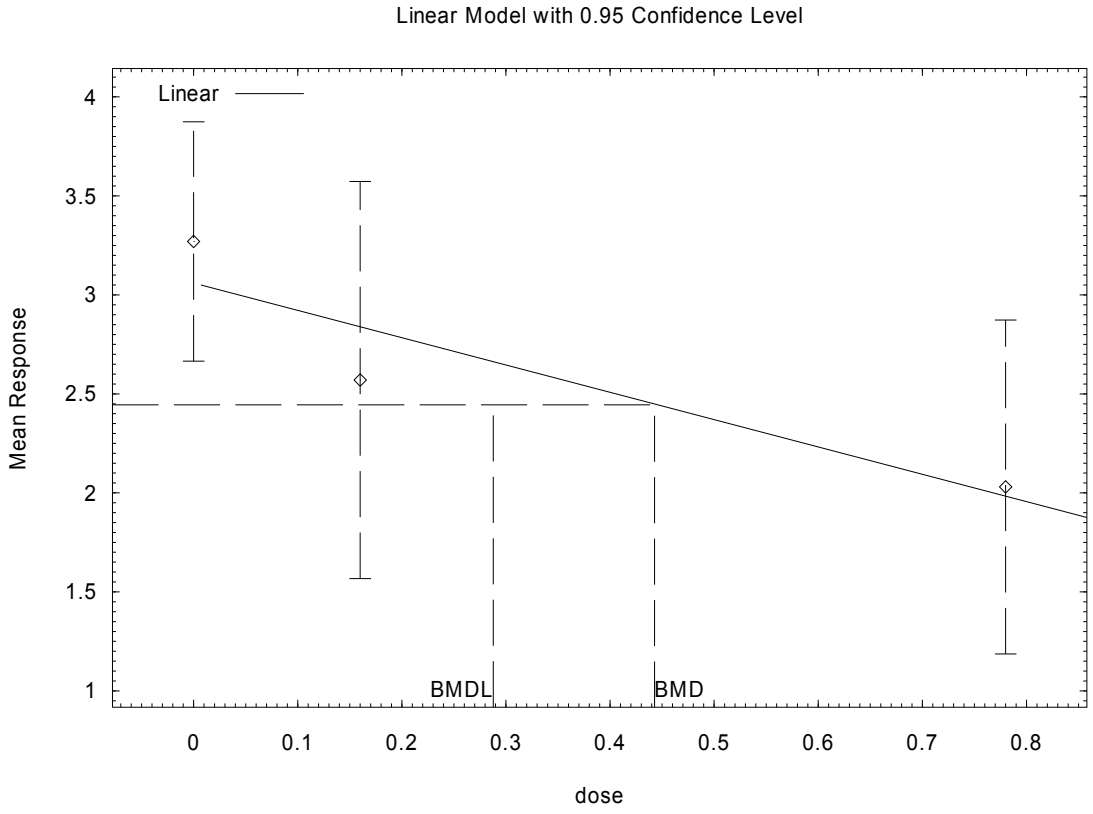
AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; df = degree of freedom; *p* = *p* value from the Chi-squared test

Figure A-2. Erythrocyte AChE Activity in Female Beagle Dogs Exposed to Guthion in the Diet for 26 Weeks*(Complete Dataset)



*BMDs and BMDLs are associated with a 20% change from the controls, and are in units of mg/kg/day.

Figure A-3. Erythrocyte AChE Activity in Female Beagle Dogs Exposed to Guthion in the Diet for 26 Weeks* (High-dose Group Excluded)



*BMDs and BMDLs indicated are associated with a change of 20% change from the control, and are in units of mg/kg/day

A BMDL of 0.29 mg/kg/day was obtained by analysis of the low-dose region of the dose-response curve for dogs exposed for 26 weeks.

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? No.

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

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

Other additional studies or pertinent information that lend support to this MRL: Inhibition of erythrocyte AChE activity was the most sensitive end point in a study with male and female rats administered technical-grade guthion in the feed for 13 weeks (Sheets et al. 1997). Brain and erythrocyte AChE activities were significantly inhibited in rats administered ≥0.91 mg/kg/day. The results obtained using the BMD approach are supported by those obtained using the NOAEL approach.

Agency Contacts (Chemical Managers): Nickolette Roney, Selene Chou, Yee-Wan Stevens

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Guthion
CAS Numbers: 86-50-0
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 63
Species: Dog

Minimal Risk Level: 0.003 [X] mg/kg/day [ ] ppm

Reference: Allen TR, Janiak T, Frei T, et al. 1990. 52-Week oral toxicity (feeding) study with azinphos-methyl (E 1582) in the dog. Mobay Corporation. Submitted to the U.S. Environmental Protection Agency. MRID41804801.

Experimental design: Technical-grade guthion (91.9% a.i.) was administered to beagle dogs (four dogs/sex/group) in the food at 5.0, 25.0, 125.0 ppm for up to 52 weeks. The guthion concentrations are equivalent to 0.15, 0.69, and 3.8 mg/kg/day, respectively, in male dogs, and 0.16, 0.78, and 4.3 mg/kg/day, respectively, in female dogs (Allen et al. 1990). Daily observations for clinical signs were conducted; body weight was determined weekly and food consumption was monitored daily. Hearing and ophthalmoscopic evaluations were conducted after 13, 26, and 52 weeks; hematological, clinical chemistry, and urinary chemistry parameters were determined on weeks 4, 13, 26, and 52; plasma ChE and erythrocyte AChE activities were determined prior to treatment and on weeks 4, 13, 26, and 52; brain AChE activity was determined on week 52. Terminal body weight and organ weights were determined and macroscopic and histopathological evaluations of organs were conducted.

Effect noted in study and corresponding doses: Dose-related reductions in erythrocyte AChE activity were evident in male and female dogs on week 52. A statistically nonsignificant reduction of 15% in erythrocyte AChE activity was observed in females at 0.16 mg/kg/day on week 52, but there was no effect in males. On week 52, reductions in erythrocyte AChE activity in males at 0.69 and 3.8 mg/kg/day were 27 and 86%, respectively. Females in the 0.78 and 4.3 mg/kg/day groups showed 35 and 86% reductions, respectively, in erythrocyte AChE activity. Brain AChE activity on week 52 in the 3.8 and 4.3 mg/kg/day groups was reduced by 27 and 20% in males and females, respectively. Reductions in brain AChE activity were 1 and 10% in female and male dogs receiving administered 0.78 and 0.69 mg/kg/day, respectively. No effect on brain AChE activity was observed in males administered 0.15 mg/kg/day or females administered 0.16 mg/kg/day. Plasma ChE activity was reduced by 53% in males and females administered 3.8 and 4.3 mg/kg/day, respectively. No statistically significant reductions in plasma ChE activity were observed in male or female dogs administered ≤0.69 or ≤0.78 mg/kg/day, respectively. Terminal body weights were reduced by 12% in males in the 3.8 mg/kg/day group and by 16% in females in the 4.3 mg/kg/day group, although there was no difference in food consumption among treated and control animals. There were no treatment-related hematological effects or changes in urinalysis parameters. Findings were negative in hearing and ophthalmoscopic tests conducted at study termination and there was no treatment-related increase in mortality in any dose group. There were no changes in absolute or relative organ weights in females at the doses tested. Absolute and relative spleen weights in were reduced in males in a dose-related manner with significant reductions in relative spleen weight at ≥0.69 mg/kg/day; however, congestion of the spleen and increased absolute spleen weight were observed in 4/4 male dogs in the control group. A 7–17% decrease in albumin and albumin/globulin values were observed on week 52 in males in the 3.8 mg/kg/day group. A 39 and 15% increase in P450 activity was observed in male dogs at 3.8 mg/kg/day and in female dogs at

4.3 mg/kg/day, respectively. A 34 and 30% increase in N-demethylase activity was observed in male dogs at 3.8 and in female dogs at 4.3 mg/kg/day, respectively. Other effects were restricted to the high dose groups (Allen et al. 1990).

Dose and end point used for MRL derivation: The MRL is based on a BMDL of 0.30 mg/kg/day for inhibition of erythrocyte AChE activity in male dogs after 52 weeks.

[ ] NOAEL [ ] LOAEL [X] BMDL

In order to derive a point of departure to calculate a chronic-duration oral MRL a benchmark dose approach was applied to the changes in erythrocyte AChE activity observed in male and female dogs exposed to guthion in the diet for 52 weeks (Allen et al. 1990). It is recognized that the small number of animals per dose group (4 dogs/group) limits the characterization of variability in the response to guthion. Benchmark doses (BMDs) and the lower bound of the 95% confidence limits of the benchmark doses (BMDLs) were calculated using the EPA Benchmark Dose Software (BMDS version 1.3.2) as described below. The BMDs and BMDLs are estimates of the doses associated with a 20% change in erythrocyte AChE activity. The simplest continuous variable model (a linear model) was fit to the erythrocyte AChE activity data presented in Table A-8.

Table A-8. Erythrocyte Cholinesterase Activity (µmol/mL/minute) in Beagle Dogs Administered Guthion in the Diet for 52 Weeks (Four Dogs/Sex/Dose Group)

Dose (mg/kg/day)	Mean (standard deviation)	Percent reduction
Males		
0	2.87 (0.36)	–
0.15	3.01 (0.84)	0
0.69	2.10 (0.45)	27
3.8	0.41 (0.15)	86[a]
Females		
0	3.36 (1.72)	–
0.16	2.87 (0.73)	15
0.78	2.20 (0.5)	35[a]
4.3	0.47 (0.16)	86[a]

[a]Statistically significant reduction

Source: Allen et al. 1990

The linear model under the assumption of constant variance did not provide an adequate fit for either the male or female erythrocyte AChE activity data at 52 weeks; however, a nonhomogeneous variance linear model provided an adequate fit to the erythrocyte AChE activity data for males and females at week 52. Therefore, the linear model with the assumption of nonhomogenous variance was chosen for estimating the BMDs and BMDLs for the males and females at week 52. The selected model predicted a BMD in the range of 0.90–1.0 mg/kg/day and a BMDL in the range of 0.85–0.97 mg/kg/day. However, these BMDLs for a 20% reduction in erythrocyte AChE activity in dogs are higher than the observed LOAELs of 0.69 and 0.78 mg/kg/day in male and female dogs, respectively (Allen et al. 1990). At these LOAELs, reductions in erythrocyte AChE activity in the range of 27–35% were observed after 52 weeks. Thus, the linear model appears to underpredict the response of erythrocyte AChE activity to guthion in dogs after

52 weeks. Reexamination of the data plots suggests that the experimental data at the high dose might be a high-leverage point which exerts a high degree of influence on the model results. The plots of the erythrocyte AChE activity in male and female dogs after 52 weeks are presented in Figures A-4(A) and A-5(A), respectively. Given that for the derivation of an MRL the most pertinent part of the dose-response curve is that which lies at the lower doses the high-dose data point was removed from the dataset and the model fitting was conducted as described before. A linear model with an assumption of homogenous variance provided an adequate fit to the 52-week data with dogs when the high-dose data were removed. The other continuous models in the software were also applied to the data, but did not provide adequate fits. Results of the BMD linear modeling of the low-dose region of the dose-response curve are presented in Table A-9. Plots of the 52-week data in males and females with the high-dose excluded are presented in Figures A-4(B) and A-5(B), respectively.

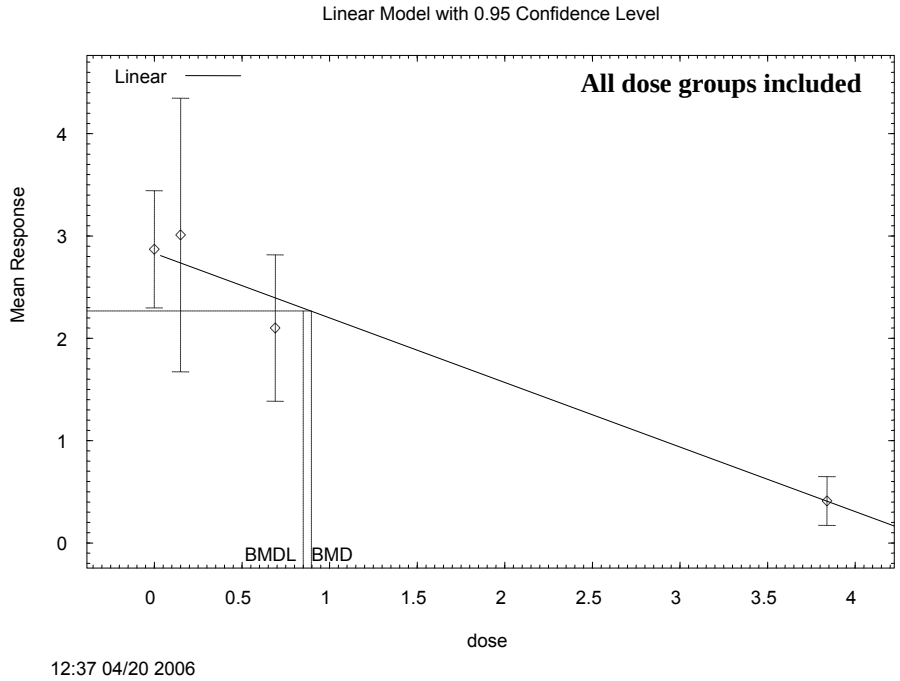
Table A-9. Model Predictions for Erythrocyte AChE Activity in Beagle Dogs Exposed to Guthion in the Diet for 52 Weeks

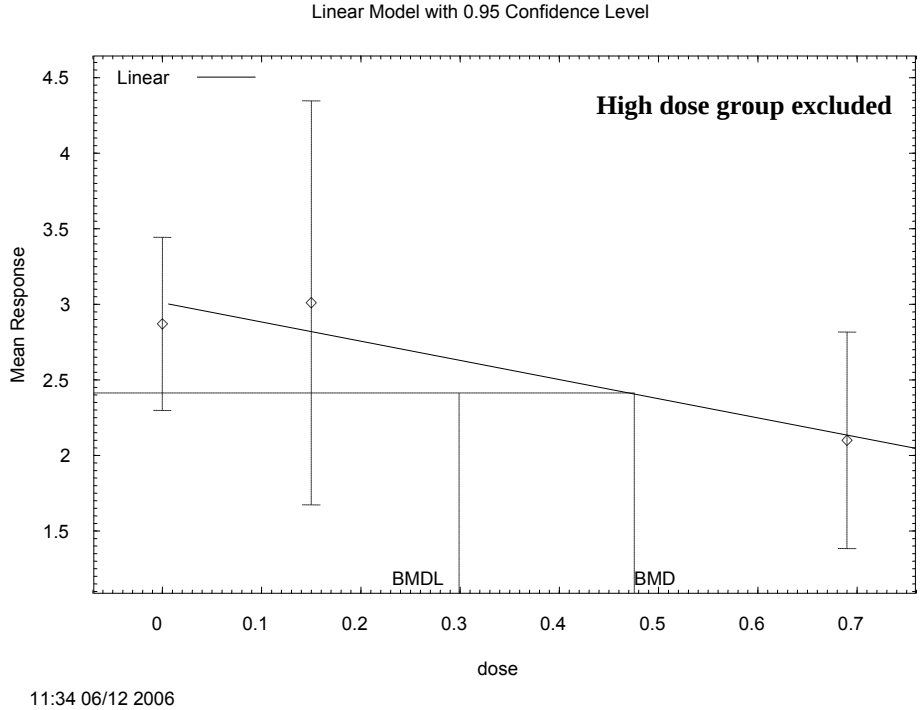
Model	Variance p-value[a]	X^2 test statistic for means	df	p-value for the means[a]	AIC	BMD (mg/kg/day)	BMDL (mg/kg/day)
Male							
Linear[b,c] (high dose dropped)	0.20	0.85	1	0.36	0.66	0.48	0.30
Female							
Linear[b,c] (high dose dropped)	0.55	1.5	1	0.23	14.5	0.50	0.32

[a]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Restriction = nonpositive

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; df = degree of freedom; p = p value from the Chi-squared test

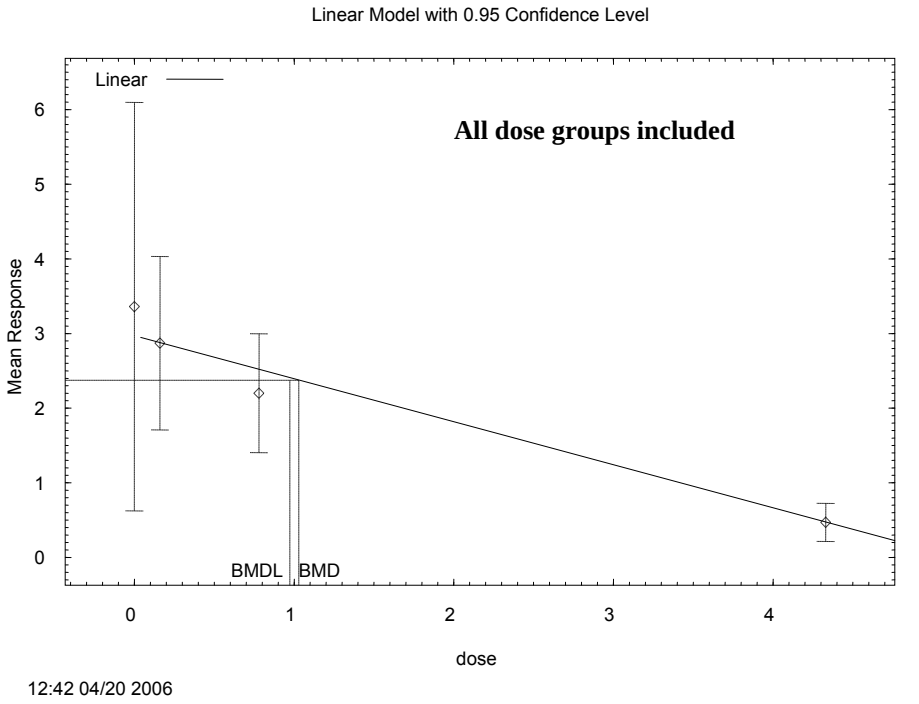
Figure A-4. Erythrocyte AChE Activity in Male Beagle Dogs Exposed to Guthion in the Diet for 52 Weeks*

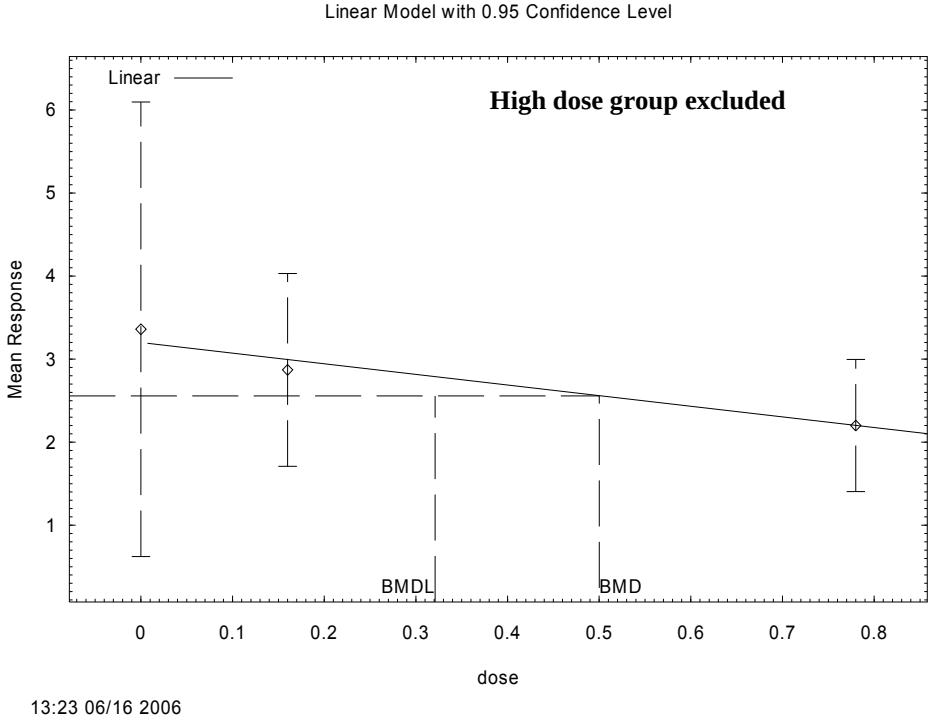




*BMDs and BMDLs are associated with a 20% change from the controls, and are in units of mg/kg/day.

Figure A-5. Erythrocyte AChE Activity in Female Beagle Dogs Exposed to Guthion in the Diet for 52 Weeks*





*BMDs and BMDLs are associated with a 20% change from controls, and are in units of mg/kg/day.

BMDLs of in the range of 0.30–0.32 mg/kg/day were obtained by analysis of the low-dose region only of the dose-response curve for dogs exposed for 52 weeks. The lowest BMDL (0.30 mg/kg/day) was selected as the point of departure. Applying an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to the BMDL yields a chronic-duration oral MRL of 0.003 mg/kg/day.

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? No.

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

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

Other additional studies or pertinent information that lend support to this MRL: Inhibition of erythrocyte AChE activity also was the most sensitive effect in a 2-year study with rats administered guthion in the diet at 0.25–2.3 mg/kg/day in males and 0.31–3.11 mg/kg/day in females (Schmidt and Chevalier 1984). These studies support selection of the effect on erythrocyte AChE activity as the critical end point for chronic oral exposure to azinphos-methyl. The 52-week study in dogs (Allen et al. 1990) was selected to derive the chronic-duration oral MRL because, at similar doses (0.69–0.78 mg/kg/day in dogs after 52 weeks and 0.75–0.96 mg/kg/day in rats after 2 years), there was a more marked reduction in erythrocyte AChE in dogs (20–43%) than in rats (10–22%).

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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

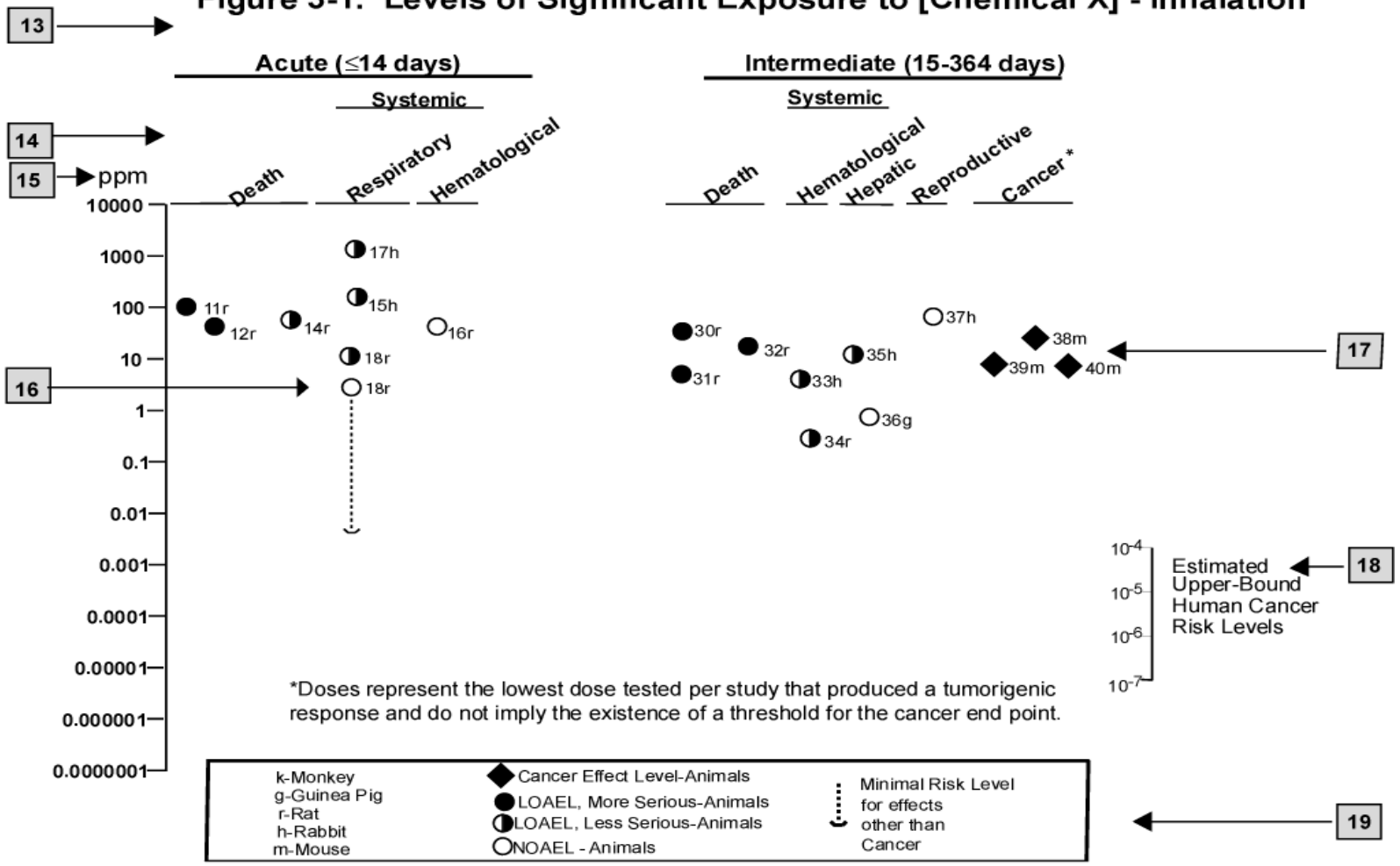
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → 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 $5x10^{-3}$ 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	benchmark dose
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/IMCO	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