TOXICOLOGICAL PROFILE FOR ETHION

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

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UPDATE STATEMENT

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

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FOREWORD

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

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

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

Each profile includes the following:

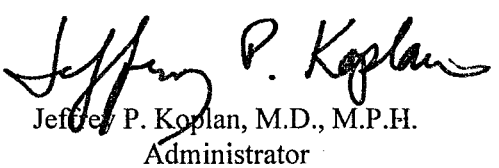
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

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

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

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

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



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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on October 21, 1999 (64 FR 56792). 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); and November 17, 1997 (62 FR 61332). 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: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), 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 Ethion Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to Ethion?
Section 2.7 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.8 Biomarkers of Exposure and Effect
Section 2.11 Methods for Reducing Toxic Effects

ATSDR Information Center

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

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

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

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

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

Other Agencies and Organizations

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

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

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

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: aoec@dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-228-6850 • FAX: 847-228-1856.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

PEER REVIEW

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

1. Dr. Robert Coppock, DABT, DABVT, P.O. Box 2031, Vegreville, Alberta T9C 1T2, Canada;

2. Dr. Frederick Oehme, Comparative Toxicology Laboratories, Kansas State University, Manhattan, Kansas, 66506; and

3. Dr. James Withey, 49 Wilton Crescent, Ottawa, Ontario K1S 2T6, Canada.

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

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

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

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1. PUBLIC HEALTH STATEMENT

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

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Ethion has been found in at least 9 of the 1,577 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which ethion is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

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

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

1.1 WHAT IS ETHION?

Ethion is a chemical used in agriculture as a pesticide. Ethion does not occur naturally in the environment but is manufactured by industry. Pure ethion is a clear-to-yellowish liquid with an unpleasant sulfur type of smell. Most of the ethion used in pest control is diluted with other liquids and used as a spray. It is also sometimes used as a liquid adsorbed on dust or granules. Ethion is sold under many trade names including Bladan®, Rodicide®, and Nialate®. The ethion

present at hazardous waste sites will most likely be in a liquid solution or adsorbed on solid granules.

Ethion is a member of a group of pesticides known as organophosphates. Diazinon and chlorpyrifos (Dursban®) are other members of this group.

In 1989, about one million pounds of ethion were used in the United States. In 1992, about 868,218 pounds of ethion were used in the United States in farming. The main use of ethion is for insect control on citrus trees. It is also used on cotton, fruit and nut trees, and a variety of vegetables. Ethion may also be used on lawns and turf grasses. Ethion is not used in the home for pest control.

You will find further information on the properties and uses of ethion in Chapters 3 and 4 of this profile.

1.2 WHAT HAPPENS TO ETHION WHEN IT ENTERS THE ENVIRONMENT?

Ethion enters the air, water, and soil during its manufacture and use. Wastes containing ethion that are generated during its manufacture and use are sometimes disposed of in landfills. Ethion can enter the environment from these landfills. Ethion also enters the environment from accidental spills during transport and leaks from storage containers.

Ethion evaporates only slightly into the air. Ethion that does evaporate can react with oxygen in the air. Ethion in air is estimated to break down in a day or two. These breakdown products are not believed to be harmful.

If ethion is spilled into a lake or river, a small portion will dissolve, but most of it will bind to particles in the water. Ethion can react with water and be broken down. In a test in an irrigation canal, one-half of the ethion broke down in 26 days. Laboratory experiments show that the less acidic the water is, the more rapidly ethion is broken down.

Ethion binds tightly to soil. This means it will not move through soil. Bacteria and other microorganisms (microscopic plants and animals) in the soil break down ethion. The breakdown in soil is less rapid than in air or water. Depending on the temperature and type of soil, it can take anywhere from 1 month to 1 year for half of the ethion in soil to break down.

Ethion does not seem to be stored or concentrated in the bodies of people or most animals. It is not known if ethion is stored or concentrated by plants or fish.

You will find further information about what happens to ethion in the environment in Chapter 5 of this profile.

1.3 HOW MIGHT I BE EXPOSED TO ETHION?

The general population may be exposed to very small amounts of ethion by eating or drinking. Ethion has been found only rarely in drinking water in the United States. Ethion has been found on raw foods (fruits, vegetables) at very low concentrations. These concentrations are usually far below the maximum limits established by the EPA.

People living near hazardous waste sites containing ethion or near its manufacturing, processing, or storage facilities could potentially be exposed. Because of the chemical properties of ethion, the most likely way a person would be exposed is by skin contact with soil contaminated by ethion.

You are most likely to be exposed to ethion if you are involved in manufacturing or using it. Chemical plant workers, transport workers, and pesticide applicators are the major occupational groups that might be exposed to ethion. People in these groups are mainly exposed by skin contact, but some exposure can also occur by breathing in air containing ethion.

You will find further information on the potential for exposure to ethion in Chapter 5.

1.4 HOW CAN ETHION ENTER AND LEAVE MY BODY?

Ethion can enter your body through your lungs if it is in the air you breathe. It can also enter your body through your stomach if it is in your drinking water or food. It can also enter through your skin. How much ethion enters your body depends on how long you are exposed and the amount to which you are exposed.

Once ethion enters your body, it goes into your bloodstream and is carried to all the organs in your body. Ethion is converted by an enzyme in your liver to its active form, called ethion monoxon. There are other enzymes in your liver and blood that rapidly break down both ethion and ethion monoxon. These breakdown products are less harmful than ethion. Most of these breakdown products quickly leave your body in the urine. Ethion and its breakdown products are not stored in your body.

You will find further information on how ethion enters and leaves your body in Chapter 2.

1.5 HOW CAN ETHION AFFECT MY HEALTH?

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

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

1. PUBLIC HEALTH STATEMENT

Ethion is a member of a group of chemicals called organophosphates. Some of these chemicals can kill insects and are widely used as insecticides. At higher doses than those used to kill insects, these chemicals can also be harmful to people. Ethion can chemically react with an important enzyme in your brain and nerves called acetylcholinesterase and stop it from working properly. When this happens, signals sent between your nerve cells and to your muscles are disrupted.

We do not know how much ethion is necessary to cause harmful effects in people. This is because few people have been exposed to enough ethion to cause symptoms of poisoning. If you have been poisoned by ethion, you will suddenly feel nauseated, anxious, and restless. You may also vomit, have tearing of the eyes, and heavy sweating. If this happens, you should seek medical attention immediately. Emergency rooms have drugs that stop the harmful effects of ethion. Further symptoms can include loss of bladder control, blurring or dimness of vision, muscle tremors, and labored breathing. Severe poisoning can result in coma, inability to breathe, and death.

Poisoning cases have occurred in people who accidentally drank ethion or who got it on their skin. If you use ethion in your work, it is extremely important that you follow all directions printed on the container.

People who have survived poisoning by ethion make a complete recovery, although this can sometimes take several months. Ethion poisoning does not appear to cause permanent damage to the nerves (a condition called "delayed neuropathy").

Volunteers who took capsules containing 0.15 milligrams ethion per kilogram of body weight (0.15 mg/kg) daily for 21 days showed no harmful effects. In studies where animals (rats and mice) have been fed ethion, about half the animals died when given approximately 100 mg/kg. Before the animals died, they showed signs of harmful effects to their nervous systems similar to those seen in human poisoning cases.

It is not known if exposure to ethion can affect fertility in people. Results of experiments done in animals that were fed ethion did not show any effect on fertility.

There is no evidence that exposure to ethion increases the risk of cancer in people. Rats and mice that were fed ethion for 2 years had the same rate of cancer as rats and mice that did not receive ethion. Ethion has not been classified for carcinogenicity by the Department of Health and Human Services (DHHS), the International Agency for Research on Cancer (IARC) or the EPA.

You will find further information on how ethion may affect your health in Chapter 2.

1.6 HOW CAN ETHION AFFECT CHILDREN?

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

Children playing on or near hazardous waste sites may be exposed to ethion in soil by skin contact, accidentally putting soil into their mouths, through hand to mouth activity, or eating dirt on purpose. They can also be exposed through food and drink. Since children have more fruit and fruit drinks in their diets, their exposure to ethion may be higher than for adults when you adjust for the difference in weight.

One case of ethion poisoning occurred in a 6-month-old boy. He had symptoms of harmful effects on his nervous system (muscle twitching, lack of coordination, pinpoint pupils, difficulty breathing). These symptoms are the same as those seen in adults and can be treated with drugs. It is not known if there are health effects in adults who were exposed as children. There is not enough information to tell if ethion is more harmful to young animals than adult animals.

We do not know whether children differ from adults in their susceptibility to health effects from ethion.

Newborn babies of pregnant animals that were exposed to very high doses of ethion showed a delayed development of the skeleton. Animals that were fed ethion at doses that did not cause symptoms of poisoning did not show significant effects on the health or development of their newborn babies. It is not known if ethion exposure to parents can affect development of the fetus in the womb or the newborn child.

Ethion and one of its metabolites (a substance created when something is changed in the body, soil, or water), ethion monoxon, can probably cross the placenta; however, no measurements have been made in people or animals. Ethion and ethion monoxon can appear in breast milk. Ethion appeared in goat milk after skin exposure in an animal experiment. Additional information about ethion in breast milk can be found in Chapters 2 and 5.

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

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

It may be possible to carry ethion from work on your clothing, skin, hair, tools, or other objects removed from the workplace. This might happen if you work as a pesticide applicator in agriculture, but no actual incidents where this has happened have been observed before. You might contaminate your car, home, or other locations outside work where children might be exposed to ethion. You should know about this possibility if you work with ethion.

Your occupational health and safety officer at work can and should tell you whether chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools, and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes. Material safety data sheets (MSDS) should be found at your place of work for many of the chemicals used there, as required by the Occupational Safety and Health

Administration (OSHA). MSDS information should include chemical names and hazardous ingredients, and important properties, such as fire and explosion information, potential health effects, how you get the chemical(s) in your body, how to handle the materials properly, and what to do in the case of emergencies. Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. OSHA or your state OSHA-approved occupational safety and health program can answer any further questions and help your employer identify and correct problems with hazardous substances. Your state OSHA-approved occupational safety and health program or OSHA will listen to your formal complaints about workplace health hazards and inspect your workplace when necessary. Employees have a right to safety and health on the job without fear of punishment.

If you buy over-the-counter pesticide products to apply yourself, be sure that the products are in unopened pesticide containers that are labeled and contain an EPA registration number. Carefully follow the instructions that are labeled on the pesticide container. In the case of ethion, it is not intended for indoor use except in greenhouses. The use of ethion is only permitted for use by proper personnel and it is illegal for the general public to use this compound at their residence. Pesticides and household chemicals should be stored out of reach of young children to prevent unintentional poisonings. Always store pesticides and household chemicals in their original labeled containers. Never store pesticides or household chemicals in containers children would find attractive to eat or drink from, such as old soda bottles.

Your children may be exposed to ethion if unqualified people apply pesticides around your home. In some cases, the improper use of pesticides banned for use in homes has turned homes into hazardous waste sites. Make sure that any person you hire is licensed and, if appropriate, certified to apply pesticides. Your state licenses each person qualified to apply pesticides using EPA standards and further certifies each person qualified to apply “restricted use” pesticides. Ask to see the license and certification. Also ask for the brand name of the pesticide, an MSDS, the name of the product's active ingredient(s), and the EPA registration number. Ask whether EPA has designated the pesticide “for restricted use” and what the approved uses are. If you feel sick after the use of ethion, consult your doctor or local poison control center.

Children can be exposed to pesticides by playing on a lawn too soon after a pesticide has been applied. Carefully read and follow the directions on the pesticide label about how long to wait before re-entering the treated area.

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

Two blood tests are available that can determine whether you have been exposed to significant amounts of ethion. These tests can be performed by any hospital or clinical laboratory. These tests measure the activity of two enzymes (called plasma cholinesterase and erythrocyte [red blood cell] acetylcholinesterase) that are affected by ethion. Ethion affects these enzymes at lower levels of exposure than are necessary to produce harmful effects. This means that if these enzymes have been affected, you will not necessarily have effects on your health. Many other insecticides also affect these enzymes. To determine whether you have been exposed specifically to ethion, a laboratory test must measure its breakdown products in your urine. Tests of this type are not routinely done in hospital laboratories, and your doctor will have to send a sample to a special laboratory. Both the blood and urine tests are most accurate if done within a few days of exposure. These tests cannot tell you if you have been exposed to ethion if the exposure took place more than 2–3 months before the test is done.

You will find further information on how you can be tested for exposure to ethion in Chapter 2.

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

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

Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

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

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

Regulations for maximum limits of ethion on food products, ranging from 0.1 to 14 parts per million (ppm), have been established by EPA.

NIOSH recommends that ethion concentrations in workplace air not exceed 0.4 milligrams per cubic meter (mg/m^3) for a 10-hour time-weighted average (TWA).

1.10 WHERE CAN I GET MORE INFORMATION?

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

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

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)
Fax: (404) 639-6359

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

* To order toxicological profiles, contact

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

2. HEALTH EFFECTS

2.1 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 ethion. 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.

2.2 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 (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

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

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

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

Ethion is a pesticide, and its use is regulated under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Virtually all of the toxicity information on ethion is from unpublished studies performed

by the manufacturer and submitted for review to the EPA. A few of these studies were unable to be retrieved by ATSDR. In these cases, NOAEL and LOAEL values were taken from study summaries in "Guidance for the Reregistration of Pesticide Products Containing Ethion as the Active Ingredient" (EPA 1989d) and are so cited in the text.

2.2.1 Inhalation Exposure

2.2.1.1 Death

Male and female rats (number and strain not specified) were exposed to technical ethion via inhalation and the LC_{50} (lethal concentration, 50% kill), was calculated. The acute inhalation LC_{50} was 2.31 mg/m^3 for male rats and 0.45 mg/m^3 for females (Feiser 1983 as cited in EPA 1989d).

No studies were located regarding the following effects in humans or animals after inhalation exposure to ethion:

2.2.1.2 Systemic Effects

2.2.1.3 Immunological and Lymphoreticular Effects

2.2.1.4 Neurological Effects

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals afer inhalation exposure to ethion.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to ethion.

Several acute lethality studies have demonstrated the high toxicity of ethion by the oral route. In a study reporting results for 98 (single dose) pesticides, (Gaines 1969) LD_{50} (lethal dose, 50% kill) values for ethion via gavage were 65 mg/kg for male and 27 mg/kg for female Sherman rats. The minimum survival time was 3 hours for males and 4 hours for females. The maximum time to death was 9 days for males and 6 days for females. The lowest dose to kill a rat was 50 mg/kg for males and 20 mg/kg for females. LD_1 (lethal dose, 1% kill) values were calculated at 27 mg/kg/males and 15 mg/kg for females. In a toxicokinetic study in Sprague-Dawley rats (Selim 1985a), two of seven males died after a gavage dose of 100 mg/kg; clinical signs of toxicity preceding death included salivation, tremors, diarrhea, and convulsions. Five of seven females died after receiving 25 mg/kg. Female rats appear to be more susceptible to ethion than males, but no explanations have been proposed.

Multiple oral exposures to ethion at lower doses in animals have generally not resulted in fatalities. For example, no deaths occurred in pregnant Charles River rats receiving up to 2.5 mg/kg/day ethion by gavage over gestation days (Gd) 6–15 (Hoberman et al. 1983a) or pregnant New Zealand rabbits receiving up to 9.6 mg/kg/day over Gd 6–18 (Hoberman et al. 1983b).

In an intermediate-duration exposure to ethion in feed to groups of albino rats (25/dose/sex), survival was similar after 96 days at doses of #9 mg/kg/day in males and 10 mg/kg/day in females (Keller and Paynter 1958). No deaths occurred in the parental generation (F_0) in a three-generation reproductive study in CD rats (Enloe and Salamon 1985). Exposure to ethion in feed was #1.25 mg/kg/day for 236–238 days. One of a group of four female Beagle dogs was sacrificed in a moribund condition after 90 days of exposure to ethion in feed at a dose of 8.25 mg/kg/day (Bailey 1988). Clinical signs included emesis, dehydration, and thin body mass. The other females in the group and the males exposed at #6.9 mg/kg/day survived.

In a 2-year feeding study in Sprague-Dawley rats and CF_1 mice (Morrow 1985a, 1985b), survival was similar between control and treated groups. Exposures in rats were #2 mg/kg/day (80/dose/sex) and #1.2 mg/kg/day in mice (10–50/dose/sex).

All reliable LD_{50} values and LOAELs for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.2 Systemic Effects

Most, if not all, of the systemic effects observed after oral exposure to ethion are the result of the neurological effects of this chemical (see Section 2.2.2.4).

The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. A 6-month-old boy who accidentally ingested 15.7 mg/kg ethion from a contaminated milk bottle presented with diaphragmatic respiration with shallow excursions and intercostal retraction (Comstock et al. 1967). Respiratory rate was 60/minute. Auscultation revealed generalized rales and rhonchi and inspiratory and expiratory wheezes. Symptoms appeared one hour following ingestion and were treated with atropine and Protopam® (pralidoxime). Approximately 5 hours after ingestion, respiratory arrest occurred and mechanical ventilation was necessary for the next 3 hours. Treatment with atropine and pralidoxime continued for 5 days until symptoms ceased. Follow-up examinations after 1 week, 1 month, and 1 year indicated that a complete recovery was made by this patient. The respiratory effects seen in this case are consistent with cholinergic overstimulation caused by ethion (see Section 2.2.2.4).

Histopathological examinations of respiratory tract tissues after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Cardiovascular Effects. Tachycardia was reported in a 6-month-old boy who accidentally ingested 15.7 mg/kg ethion (Comstock et al. 1967).

Blood pressure and pulse rate were measured in a group of 6 male volunteers (age range, 23–43 years) who were given ethion in corn oil solutions in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) via

Table 2-1. Levels of Significant Exposure to Ethion - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (Sherman)	once (GO)				50 M (lowest lethal dose; LD_{50} = 65 mg/kg)	Gaines 1969
						20 F (lowest lethal dose; LD_{50} = 27 mg/kg)	
2	Rat (Sprague-Dawley)	once (GO)				25 F (5 of 7 died)	Selim 1985a
						100 M (2 of 7 died)	
	Systemic						
3	Human	once (IN)	Resp			15.7 M (rales and rhonchi, wheezing, increased respirations)	Comstock et al. 1967
			Cardio			15.7 M (tachycardia)	
			Gastro		15.7 M (emesis, watery bowel movement, hyperactive bowels)		
			Renal		15.7 M (proteinuria, increased urinary WBC)		

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
4	Rabbit (New Zealand)	13 d Gd 6-18 1x/d (GO)	Renal	0.6 F	2.4 F (increased incidence of orange-colored urine)		Hoberman et al. 1983b
			Bd Wt		9.6 F		
	Neurological						
5	Human	once (IN)				15.7 M (muscular twitching, lack of coordination, flaccid paralysis and areflexia, excessive salivation, pinpoint pupils)	Comstock et al. 1967
6	Rat (Charles River)	10 d Gd 6-15 (GO)		0.6 F	2.5 F (hyperactivity in dams)		Hoberman et al. 1983a
7	Rat (Sprague-Dawley)	once (GO)		2		10 F (salivation, tremors, nose bleeding, urination, diarrhea and convulsions)	Selim 1985a
						100 M (salivation, tremors, nose bleeding, urination, diarrhea and convulsions)	
	Developmental						
8	Rat (Charles River)	10 d Gd 6-15 (GO)		0.6	2.5 (delayed ossification of the ischium and pubes)		Hoberman et al. 1983a

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
9	Rabbit (New Zealand)	13 d Gd 6-18 1x/d (GO)		2.4		9.6 (increased incidence of fused sterna centra)	Hoberman et al. 1983b
	INTERMEDIATE EXPOSURE						
	Systemic						
10	Human	21 + 21+ 21 + 3 d 3x/d (C)	Cardio	0.15 M			Palazzolo 1970
			Hemato	0.15 M			
			Musc/skel	0.15 M			
11	Rat (albino)	96 d ad lib (F)	Resp	10			Keller and Paynter 1958
			Cardio	10			
			Gastro	10			
			Hemato	10			
			Musc/skel	10			
			Hepatic	10			
			Renal	10			
			Endocr	10			
			Bd Wt	10			
12	Rat (albino)	30 d ad lib (F)	Bd Wt	10			Keller and Paynter 1958

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
13	Rat (Sprague-Dawley)	6 or 12 mo ad lib (F)	Resp	2			Morrow 1985a
			Cardio	2			
			Gastro	2			
			Hemato	2			
			Musc/skel	2			
			Hepatic	2			
			Renal	2			
			Endocr	2			
			Dermal	2			
			Ocular	2			
			Bd Wt	2			
14	Mouse (CF1)	6 mo ad lib (F)	Resp	1.2			Morrow 1985b
			Cardio	1.2			
			Gastro	1.2			
			Hemato	1.2			
			Musc/skel	1.2			
			Hepatic	1.2			
			Renal	1.2			
			Endocr	1.2			
			Bd Wt	1.2			
			Other	1.2			

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
15	Dog (Beagle)	90 d ad lib (F)	Resp	6.9 M 8.25 F			Bailey 1988
			Cardio	6.9 M 8.25 F			
			Gastro	6.9 M 8.25 F			
			Hemato	6.9 M 8.25 F			
			Musc/skel	6.9 M 8.25 F			
			Hepatic	6.9 M 8.25 F			
			Renal	6.9 M 8.25 F			
			Endocr	6.9 M 8.25 F			
			Dermal	6.9 M 8.25 F			
			Ocular	6.9 M 8.25 F			
			Bd Wt	6.9 M 8.25 F			
	Immunological/Lymphoreticular						
16	Rat (albino)	96 d ad lib (F)		10			Keller and Paynter 1958
17	Rat (Sprague-Dawley)	6 or 12 mo ad lib (F)		2			Morrow 1985a

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
18	Dog (Beagle)	90 d ad lib (F)		6.9 M 8.25 F			Bailey 1988
	Neurological						
19	Human	21 + 21+ 21 + 3 d 3x/d (C)		0.15 M			Palazzolo 1970
20	Rat (albino)	96 d ad lib (F)		1	3 F (42.4-48.6% erythrocyte AChE inhibition)	10 F (67.4-74.3% brain AChE inhibition; 100% erythrocyte AChE inhibition)	Keller and Paynter 1958
					3 M (45-55% erythrocyte AChE inhibition)	9 M (87-95% erythrocyte AChE inhibiton, 22-29% brain AChE inhibition)	
21	Rat (albino)	30 d ad lib (F)		0.3 F		3 F (70% brain AChE inhibition)	Keller and Paynter 1958
				3 M	9 M (34.1% brain AChE inhibition)		
22	Rat (Sprague-Dawley)	6 or 12 mo ad lib (F)		2			Morrow 1985a
23	Mouse (CF1)	6 mo ad lib (F)		1.2			Morrow 1985b

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
24	Dog (Beagle)	90 d ad lib (F)		0.06[b] M 0.71 F	0.71 M (23% brain AChE inhibition)	6.9 M (tremors, ataxia, emesis, miosis, 61-64% brain and 93-96% erythrocyte AChE inhibition) 8.25 F	Bailey 1988
	Reproductive						
25	Rat (albino)	96 d ad lib (F)		10			Keller and Paynter 1958
26	Rat (Sprague-Dawley)	6 or 12 mo ad lib (F)		2			Morrow 1985a
27	Mouse (CF1)	6 mo ad lib (F)		1.2			Morrow 1985b
28	Dog (Beagle)	90 d ad lib (F)		6.4 M 8.25 F			Bailey 1988

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	CHRONIC EXPOSURE						
	Systemic						
29	Rat (CD)	3 gen ad lib (F)	Resp	1.25			Enloe and Salamon 1985
			Cardio	1.25			
			Gastro	1.25			
			Musc/skel	1.25			
			Hepatic	1.25			
			Renal	1.25			
			Endocr	1.25			
			Dermal	1.25			
			Ocular	1.25			
			Bd Wt	1.25			
30	Rat (Sprague-Dawley)	18 or 24 mo ad lib (F)	Resp	2			Morrow 1985a
			Cardio	2			
			Gastro	2			
			Hemato	2			
			Musc/skel	2			
			Hepatic	2			
			Renal	2			
			Endocr	2			
			Dermal	2			
			Ocular	2			
			Bd Wt	2			

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
31	Mouse (CF1)	12, 18, or 24 mo ad lib (F)	Resp	1.2			Morrow 1985b
			Cardio	1.2			
			Gastro	1.2			
			Hemato	1.2			
			Musc/skel	1.2			
			Hepatic	1.2			
			Renal	1.2			
			Endocr	1.2			
			Bd Wt	1.2			
			Other	1.2			
Immunological/Lymphoreticular							
32	Rat (CD)	3 gen ad lib (F)		1.25			Enloe and Salamon 1985
33	Rat (Sprague-Dawley)	18 or 24 mo ad lib (F)		2			Morrow 1985a
Neurological							
34	Rat (CD)	3 gen ad lib (F)		1.25			Enloe and Salamon 1985
35	Rat (Sprague-Dawley)	18 or 24 mo ad lib (F)		2			Morrow 1985a

Table 2-1. Levels of Significant Exposure to Ethion - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
36	Mouse (CF1)	12, 18, or 24 mo ad lib (F)		1.2			Morrow 1985b
	Reproductive						
37	Rat (CD)	3 gen ad lib (F)		1.25			Enloe and Salamon 1985
38	Rat (Sprague-Dawley)	18 or 24 mo ad lib (F)		2			Morrow 1985a
39	Mouse (CF1)	12, 18, or 24 mo ad lib (F)		1.2			Morrow 1985b

Table 2-1. Levels of Significant Exposure to Ethion - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
40	Rat (CD)	3 gen ad lib (F)		1.25			Enloe and Salamon 1985

[a]The number corresponds to entries in Figure 2-1.

[b]Used to derive a minimal risk level of 0.002 mg/kg/day for acute and intermediate durations based on a no-observed-adverse-effect-level of 0.06 mg/kg/day for inhibition of erythrocyte acetylcholinesterase in dogs. Dose divided by an uncertainty factor of 10 for human variability and 3 for extrapolation of an animal study to humans. For the chronic duration, an additional modifying factor of 5 was applied to reflect uncertainties of possible non-cholinesterase actions over long periods of exposure, and to protect against possible susceptibility in children, resulting in a minimal risk level of 0.0004 mg/kg/day.

AChE = acetylcholinesterase; ad lib = ad libitum; Bd Wt = body weight; (c) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; (GO) = gavage in oil; gen = generation; Gd = gestation day; Hemato = hematological; IN = ingestion; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; WBC = white blood cells; wk = week(s); x = time(s); yr = year(s).

Figure 2-1. Levels of Significant Exposure to Ethion - Oral

Acute (≤14 days)

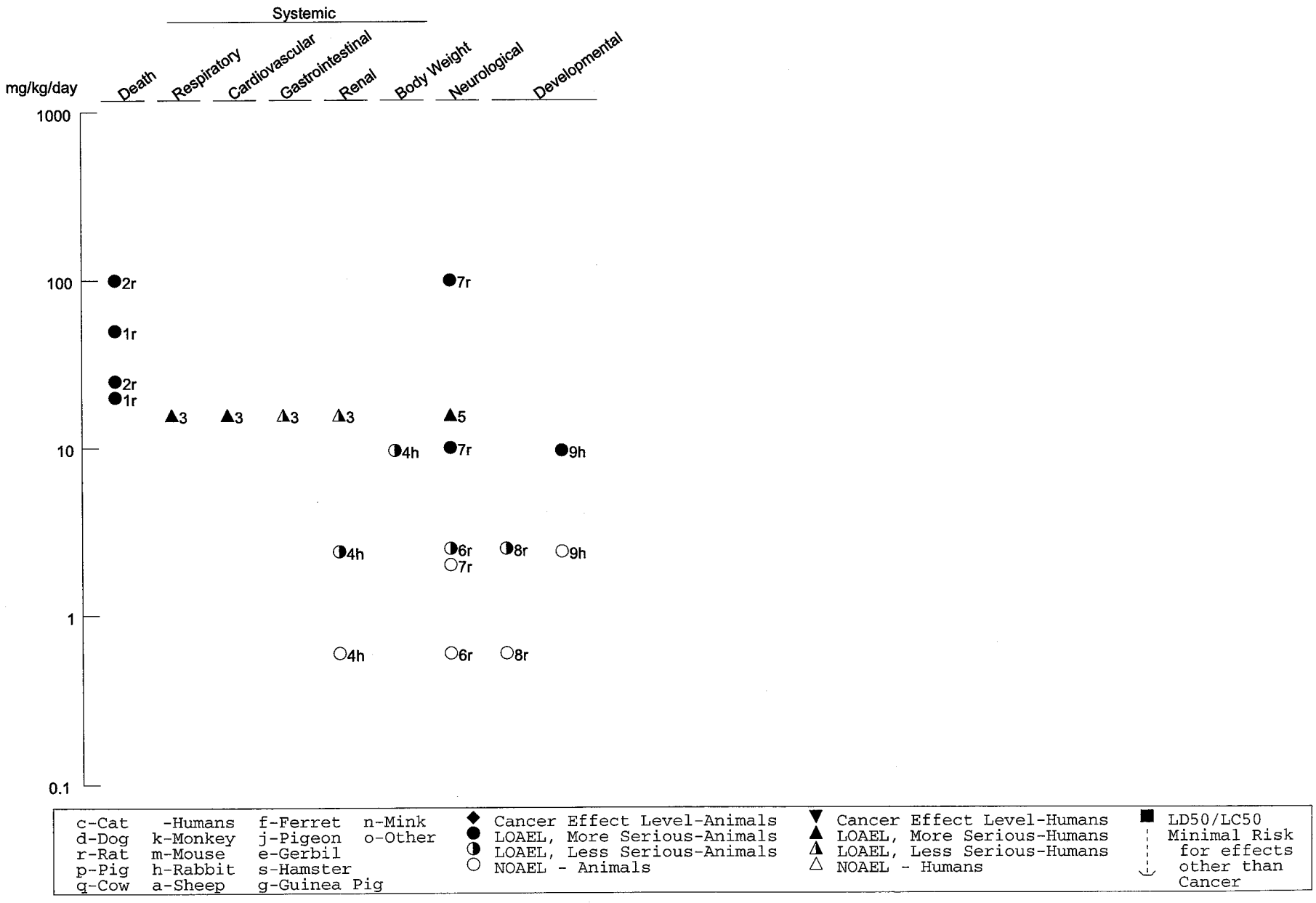


Figure 2-1. Levels of Significant Exposure to Ethion - Oral (Continued)

Intermediate (15-364 days)

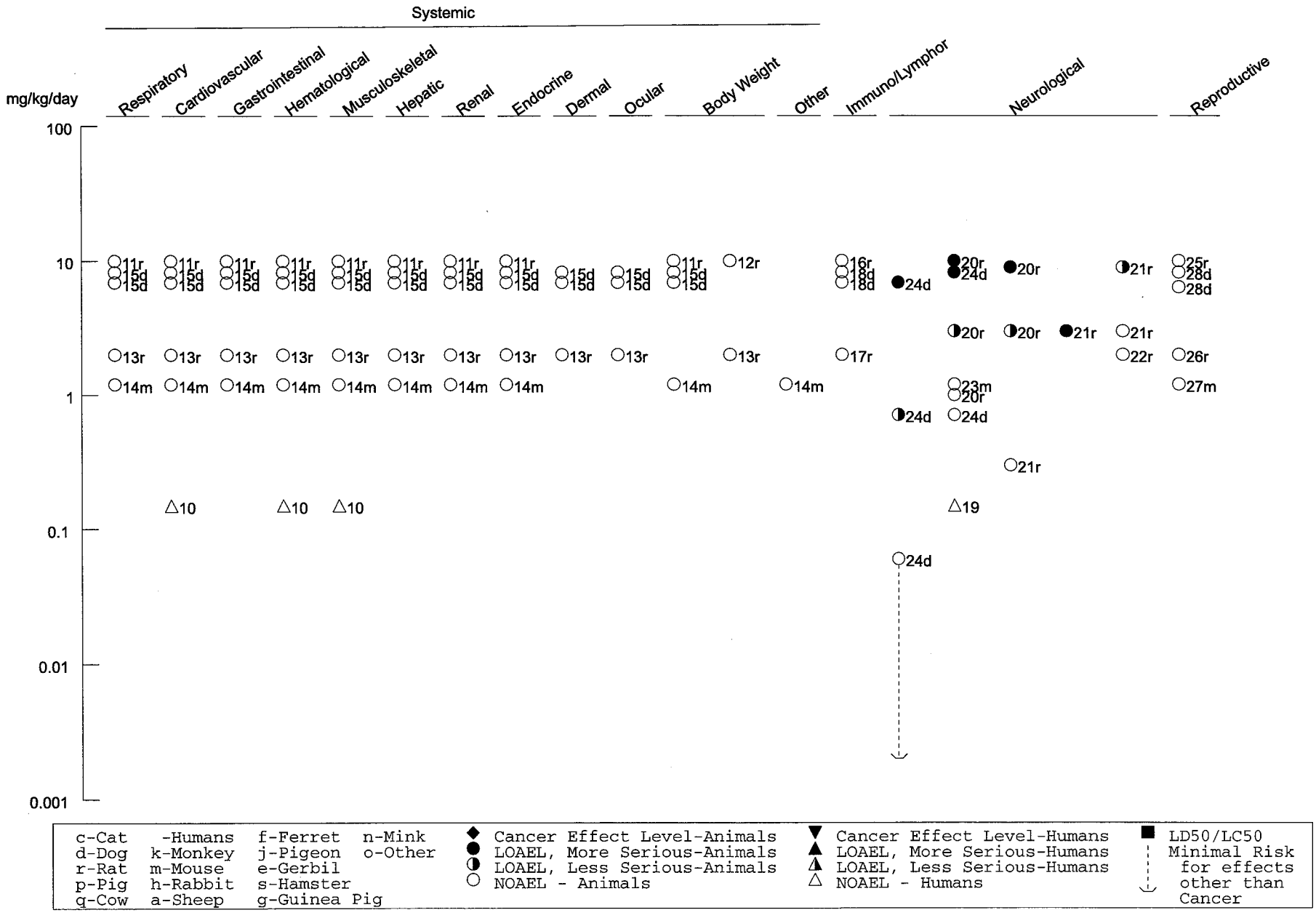
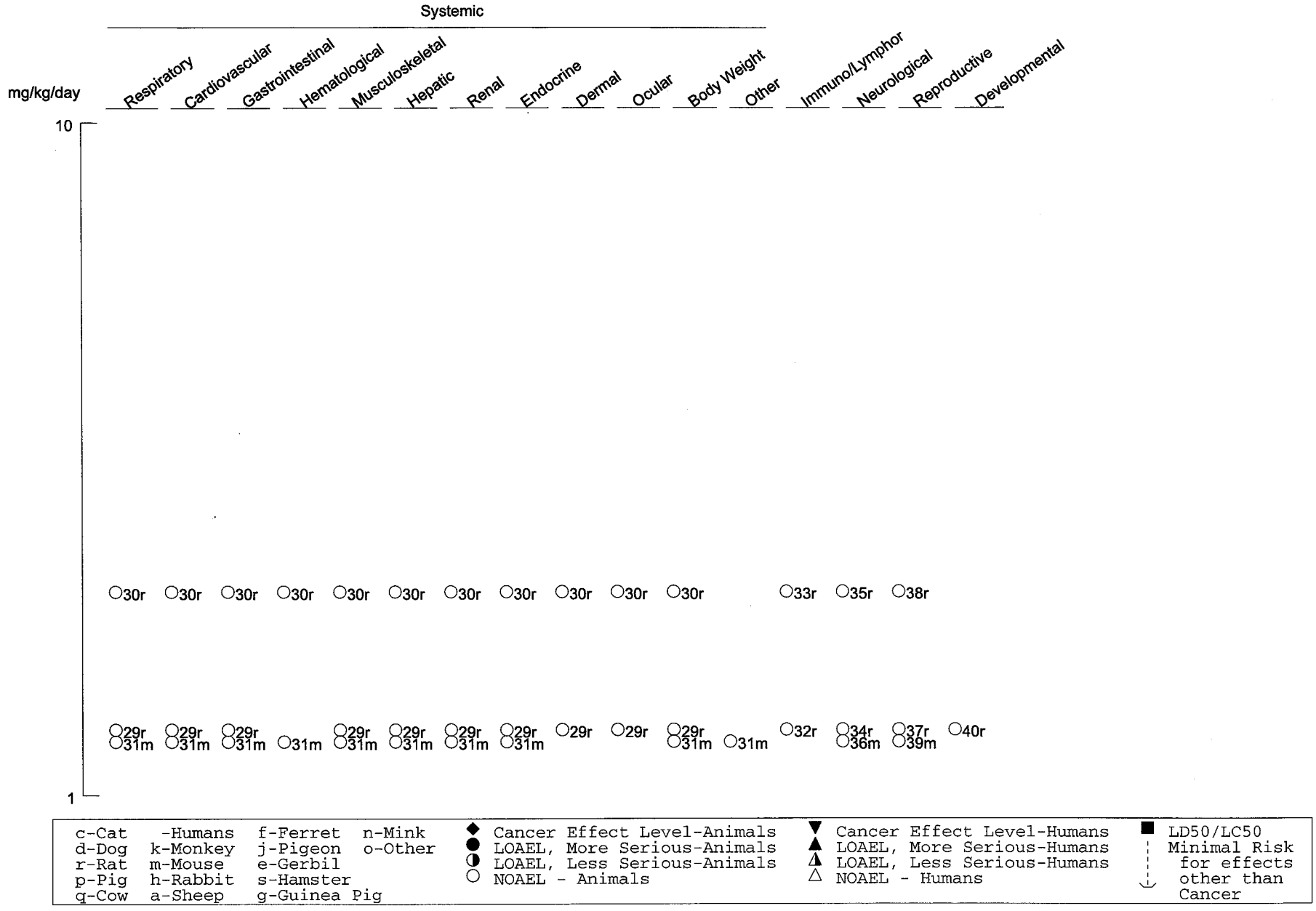


Figure 2-1. Levels of Significant Exposure to Ethion - Oral (Continued)

Chronic (≥365 days)



gelatin capsule (Palazzolo 1970). Doses were 0.05 mg/kg/day for 21 consecutive days, 0.075 mg/kg/day for the next 21 days, 0.10 mg/kg/day for the next 21 days, and 0.15 mg/kg/day for the next 3 days. Controls (n=4; age range, 22–40 years) received gelatin capsules containing corn oil. No differences were noted between the control and test groups or between individual pre-treatment, treatment, or post-treatment results for blood pressure or pulse rate.

Histopathological examinations of cardiovascular tissues (heart, aorta) after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Gastrointestinal Effects. Gastrointestinal effects reported in a 6-month-old boy who accidentally ingested 15.7 mg/kg ethion (Comstock et al. 1967) included frothy saliva 1 hour after ingestion and a watery bowel movement at 90 minutes. Bowel sounds were hyperactive and an episode of emesis occurred 5 hours after ingestion.

Diarrhea was reported in Sprague-Dawley rats exposed to ethion by gavage at 10 mg/kg in females and 100 mg/kg in males (Selim 1985a). Severe signs of neurotoxicity (convulsions) were also present. The gastrointestinal effects seen in both cases are consistent with cholinergic overstimulation of the gastrointestinal tract.

Histopathological examinations of gastrointestinal tract tissues after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Hematological Effects. Significant hematological effects have not been observed in two cases of human exposure to ethion. In a poisoning case of a 6-month-old boy who accidentally ingested 15.7 mg/kg ethion, hematocrit, hemoglobin level, and red blood cell (RBC) and platelet counts were

normal (Comstock et al. 1967). White blood cell (WBC) counts were initially slightly depressed but returned to normal after 1 day.

Similar results were seen for intermediate-duration oral exposure in a group of 6 male volunteers (age range, 23–43 years) who were given ethion in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) via gelatin capsule (Palazzolo 1970). Doses were 0.05 mg/kg/day for 21 consecutive days, 0.075 mg/kg/day for the next 21 days, 0.1 mg/kg/day for the next 21 days, and 0.15 mg/kg/day for the next 3 days. Controls (n=4; age range, 22–40 years) received gelatin capsules containing corn oil. Blood studies (hemoglobin concentration, hematocrit, RBC, and total and differential leukocyte counts) were performed on days -15 and -1 of the pretreatment period, at the end of each of the 4 treatment periods, and after a 19-day recovery period after dosing ended. No differences were noted between the control and test groups or between individual pre-treatment, treatment, or post-treatment results for any of the parameters.

Analysis of hematological parameters after oral exposure to ethion in animals has shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Musculoskeletal Effects. Oral exposure to ethion can result in muscle tremors and fasciculations. These effects are discussed in Section 2.2.2.4, Neurological Effects.

The effect of intermediate-duration oral exposure to ethion on muscle tone was assessed in a group of 6 male volunteers (age range, 23–43 years) who were given ethion in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) via gelatin capsule (Palazzolo 1970). Doses were 0.05 mg/kg/day for 21 consecutive days, 0.075 mg/kg/day for the next 21 days, 0.1 mg/kg/day for the next 21 days, and 0.15 mg/kg/day for the next 3 days. Controls (n=4; age range, 22–40 years) received gelatin capsules containing corn oil. Muscle tone was assessed at the beginning and end of each treatment period. No differences were noted between the control and test groups or between individual pre-treatment, treatment, or post-treatment results.

Histopathological examinations of musculoskeletal tissues (bone, skeletal muscle) after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to ethion.

Histopathological examinations of the liver after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Renal Effects. Proteinurea and increased urinary WBC counts were observed in a severely intoxicated 6-month-old boy who accidentally ingested 15.7 mg/kg ethion (Comstock et al. 1967).

An increased incidence of orange-colored urine was observed in pregnant New Zealand rabbits receiving ethion by gavage at 2.4, or 9.6 mg/kg/day during Gd 6–18 (Hoberman et al. 1983b). This effect was not observed at 0.6 mg/kg/day. Urinalysis was not performed.

Histopathological examinations of the kidney and bladder after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to ethion.

Histopathological examinations of endocrine tissues (pituitary, thyroid, parathyroid, thymus, adrenals) after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

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

Histopathological examinations of the skin after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Ocular Effects. Histopathological examinations of the eye after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to ethion.

An unspecified body weight decrease occurred in New Zealand rabbit does receiving 2.4 mg/kg/day ethion via gavage over Gd 6–18. No effect on body weight was seen at 0.6 mg/kg/day (Hoberman et al. 1983b). No effect was observed on body weight in male and female dogs receiving #0.71 mg/kg/day in the diet for 13 weeks (Bailey 1988).

Body weight decreases accompanied by reduced food consumption have been observed in New Zealand rabbit does receiving 9.6 mg/kg/day ethion via gavage over Gd 6–18 (Hoberman et al. 1983b) and in male and female Beagle dogs receiving 6.9 and 8.25 mg/kg/day, respectively, in feed (Bailey 1988). In

other studies where doses were low enough that overt signs of cholinergic toxicity were not observed, body weight was unaffected (Keller and Paynter 1958; Morrow 1985a, 1985b).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological/lymphoreticular effects in humans after oral exposure to ethion.

Histopathological examinations of immunological/lymphoreticular tissues after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988).

2.2.2.4 Neurological Effects

Ethion exerts its toxic effects in humans and animals by inhibiting neural acetylcholinesterase. This enzyme, which is present at cholinergic synapses throughout the central and peripheral nervous systems, is responsible for hydrolyzing acetylcholine released from the pre-synaptic terminal. If this enzyme is inhibited, acetylcholine accumulates in the synapse, resulting in increased firing of the post-synaptic neuron or increased neuroeffector activity. The consequences of increased cholinergic activity in the parasympathetic autonomic nervous system (muscarinic receptors) can include increased salivation, lacrimation, perspiration, miosis, nausea, vomiting, diarrhea, excessive bronchial secretions, bradycardia, frequent micturition, and incontinence. The effects of increased neuroeffector activity on skeletal muscles (nicotinic receptors) can include muscle fasciculations, cramps, muscle weakness, and depolarization-type paralysis. Effects on cholinergic synapses in the central nervous system (predominantly muscarinic) can result in drowsiness, fatigue, mental confusion, headache, convulsions, and coma. These classical symptoms of organophosphate neurotoxicity increase in severity and rapidity of onset in a dose-dependent manner (Ecobichon 1991).

Acetylcholinesterase is also present in erythrocytes where it is referred to as erythrocyte acetylcholinesterase. Both forms of acetylcholinesterase are produced by the same gene (Taylor et al. 1993). In

in vitro assays, erythrocyte and neural acetylcholinesterase are inhibited to roughly the same extent by exposure to organophosphate compounds with insecticide activity (Hayes 1982). Measurement of erythrocyte acetylcholinesterase is used as a surrogate for the inhibition of neural acetylcholinesterase. A cholinesterase capable of hydrolyzing acetylcholine is also produced by the liver and circulates in the blood. This enzyme, called plasma cholinesterase, is also inhibited by ethion and other organophosphates and can be used as a marker for exposure. The endogenous substrate of this enzyme is unknown. Experiments in both humans and animals show that this enzyme is inhibited by ethion at lower levels of exposure than required to inhibit neural or erythrocyte acetylcholinesterase (Bailey 1988; Palazzolo 1970).

A case report of a 6-month-old boy who accidentally ingested 15.7 mg/kg ethion from a contaminated milk bottle illustrates the toxic neurological effects of ethion (Comstock et al. 1967). Symptoms appeared one hour following ingestion. The child awoke crying and choking on frothy saliva. He was unable to control his head and limbs and subsequently had a watery bowl movement, and became limp (depolarization-type paralysis). Occasional twitching movements of the hands and around the mouth were noted. Upon admission to the hospital, he was slightly cyanotic with a generalized flaccid paralysis and areflexia. Respiration was increased (60/min) as was heartbeat (200/min). Pupils were pinpoint and nonreactive to light, and eye movements were purposeless. Salivation was excessive but not copious. Respiration was diaphragmatic with shallow respiratory excursions and intercostal retraction. Generalized rales and rhonchi and inspiratory and expiratory wheezes were noted. The liver and spleen were palpable. Bowel sounds were hyperactive. There were no abnormal heart sounds. Treatment with atropine and pralidoxime was started immediately. Approximately 5 hours after ingestion, respiratory arrest occurred and mechanical ventilation was necessary for the next 3 hours. Laboratory and roentgenologic studies showed protein in the urine and increased WBC in the urine. Treatment with atropine and pralidoxime continued for 5 days until symptoms ceased. Follow-up examinations after 1 week, 1 month, and 1 year indicated that a complete recovery was made by this patient.

A study with male volunteers established oral levels of exposure to ethion that had no adverse effect in humans (Palazzolo 1970). Male volunteers (n=6; age range, 23–43 years) were given ethion in corn oil solutions in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) of 0.05, 0.075, 0.1, and 0.15 mg/kg/day via gelatin capsule. Controls (n=4; age range, 22–40 years) received gelatin capsules containing corn oil. Medical histories and baseline plasma cholinesterase and erythrocyte acetylcholinesterase activities were determined prior to the start of the study (days -15, -11, -8, -4, and -1). Blood samples were taken prior

to dose administration. Subjects received 0.05, 0.075, and 0.1 mg/kg/day for 3 weeks each. Cholinesterase determinations were conducted on days 1, 3, 7, 14, and 21 for these dose levels. Subjects received 0.15 mg/kg for 3 days and cholinesterase determinations were made on days 1 and 3. A 19-day recovery period followed, and cholinesterase determinations were made on days 7, 12, and 19. At the beginning and end of each treatment period, pupil size, light reflex, eye accommodation, muscle tone, knee jerk, tongue tremor, and finger tremor were measured.

No effect on erythrocyte acetylcholinesterase was observed at any time during the study. No effect on plasma cholinesterase were observed at the 0.05 mg/kg/day dose level. Statistically significant decreases from pretreatment values were observed for all plasma cholinesterase determinations during the 0.075, 0.1, and 0.15 mg/kg/day treatment periods. A 16% decrease in plasma cholinesterase activity was seen in the 0.075 mg/kg/day group. Decreases of 23 and 31% were seen at the 0.1 and 0.15 mg/kg/day levels. A partial recovery of plasma cholinesterase levels was seen after 7 days of recovery, and a complete recovery was seen after 12 days. No clinical signs of adverse neurological effects were observed.

Severe neurological effects have also been observed in rats after a single oral exposure to ethion. Male Sprague-Dawley rats receiving 100 mg/kg ethion in corn oil by gavage had cholinergic signs, including salivation, tremors, nose bleeding, urination, diarrhea, and convulsions (Selim 1985a). Female rats exhibited these same signs at a 10-fold lower dose (10 mg/kg). In another acute oral exposure to ethion, groups of pregnant Charles River rats (n=25) were administered ethion via gavage at doses of 0, 0.2, 0.6, and 2.5 mg/kg from Gd 6 to 15 (Hoberman et al. 1983a). An increased incidence of hyperactivity was observed in dams in the 2.5 mg/kg group. Incidence was 2/25 in control, 3/25 at 0.2 mg/kg/day, 1/26 at 0.6 mg/kg/day, and 11/25 at 2.5 mg/kg/day ($p<0.01$). No other statistically significant physical signs were observed.

No reports were located describing organophosphate-induced delayed neurotoxicity (OPIDN) in humans after oral exposure to ethion. This is a syndrome observed in humans and some animal models after recovery from the acute cholinergic effects of certain organophosphorus compounds, for example tri-o-cresyl phosphate (Ecobichon 1991). The characteristic signs are disturbances of gait and ataxia beginning 7–14 days after exposure, progressing to severe muscular weakness and paralysis. Histological analysis reveals a "dying-back" type degeneration of motor fibers. This condition can be produced in chickens and cats but not in other test species. In a test to determine the potential of ethion to cause delayed neurotoxicity, 4 groups of 10 chickens received a single gavage dose of 2,792 mg/kg

ethion in corn oil after protection from acute cholinergic effects with 10 mg/kg atropine given intramuscularly (Roberts et al. 1986). Preliminary experiments determined that this dose is equal to the LD_{50} for ethion in chickens with atropine prophylaxis. A positive control group received 500 mg/kg of the known delayed neurotoxic agent tri-o-cresyl phosphate in corn oil, the control group received vehicle only. As expected, acute cholinergic signs were observed (inability to stand or walk, unsteadiness, lethargy) in the treated groups including deaths in 14 of the 40 chickens dosed. However, after recovery from the acute effects, no clinical or histopathological signs of delayed neurotoxicity were observed in the ethion groups. These signs were observed in the tri-o-cresyl phosphate group.

In an intermediate-duration feeding study in albino rats (Keller and Paynter 1958) significant inhibition of cholinesterase activities was observed at and above ethion doses of 3 mg/kg/day. Plasma cholinesterase was most sensitive to inhibition, followed by erythrocyte and then brain acetylcholinesterase. For example, for males receiving 9 mg/kg/day in the diet for 93 days, brain acetylcholinesterase was inhibited 22%, erythrocyte acetylcholinesterase 87%, and plasma cholinesterase 100%. This study also examined recovery of blood cholinesterases by putting the rats on a normal diet for 14 days after the 93 day exposure to ethion. Plasma cholinesterase recovered completely over this period while erythrocyte acetylcholinesterase recovered 63%. The no-effect level in this study was 1 mg/kg/day. In longer-term experiments in animals, groups of Sprague-Dawley rats (n=80/sex/group) were fed diets resulting in ethion consumption of 0, 0.1, 0.2, and 2 mg/kg/day; no effect on erythrocyte acetylcholinesterase was observed at 6, 12, or 18 months (Morrow 1985a). Significant neurological effects were observed in dogs receiving higher doses of ethion (Bailey 1988). Groups of dogs (n=4/sex/group) received ethion in the diet for 90 days, the average consumed was 0, 0.01, 0.06, 0.71, and 6.9 mg/kg/day for males and 0, 0.012, 0.07, 0.71, and 8.25 mg/kg/day for females. Clinical signs included ataxia, emesis, miosis, and tremors in the highest-dose groups. Strong inhibition of both brain (61–64%) and erythrocyte acetylcholinesterase (93–94%) was observed in the highest-dose groups. A reduction of 23% in brain acetylcholinesterase was observed in males at 0.71 mg/kg/day and 64% at 6.9 mg/kg/day, no effect was seen at 0.06 and 0.01 mg/kg/day. Plasma cholinesterase activity was inhibited in all groups except the low-dose males and females and was dose-related. No compound-related histopathological changes were observed in nervous system tissues (brain [with medulla/pons, cerebellar cortex, and cerebral cortex], sciatic nerve, or spinal cord [cervical, thoracic, lumbar]). Based on the NOAEL of 0.06 mg/kg/day for inhibition of brain acetylcholinesterase observed in this study, an MRL of 0.002 mg/kg/day for oral exposure for the acute and intermediate durations was calculated, as

well as a chronic-duration MRL of 0.0004 mg/kg/day. More information on this MRL and how it was derived is located in footnote b of Table 2-1, in Section 2.5, and in Appendix A of this profile.

In chronic-duration experiments, a 3-generation reproduction study in albino rats that consumed ethion in feed at 0, 0.1, 0.2, and 1.25 mg/kg/day, showed that plasma cholinesterase was inhibited in F_1 and F_2 females in the high-dose group. No effect was observed on erythrocyte acetylcholinesterase in any group (Enloe and Salamon 1985). In 2-year carcinogenicity bioassay experiments, no effect on erythrocyte acetylcholinesterase was observed at daily exposures of #2 mg/kg/day in rats and #1.2 mg/kg/day in mice (Morrow 1985a, 1985b).

2.2.2.5 Reproductive Effects

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

In a 3-generation reproduction study, ethion was administered to F_0, F_1, and F_2 male (n=15) and female (n=30) rats in the diet at concentrations of 0, 0.1, 0.2, and 1.25 mg/kg/day. No effect on reproduction was observed (Enloe and Salamon 1985). Indices measured were: mating index (number of copulations/number of estrus cycles utilized), fertility index (number of pregnancies/number of copulations), gestation (number of parturitions/number of pregnancies), female fertility (number of pregnancies/number of females mated), and male fertility (number of sires/number of males mated).

Histopathological examinations of reproductive tissues after oral exposure to ethion in animals have shown no effect of treatment. Doses and durations include 96 days in male and female albino rats at #10 mg/kg/day in feed (Keller and Paynter 1958), 6–24 months in male and female Sprague-Dawley rats at #2 mg/kg/day (Morrow 1985a), 6–24 months in male and female CF_1 mice at #1.2 mg/kg/day (Morrow 1985b), and 13 weeks in male and female Beagle dogs at #8.25 mg/kg/day (Bailey 1988)

2.2.2.6 Developmental Effects

No studies regarding developmental effects in humans after oral exposure to ethion were located.

Three studies examining the effects of ethion on development in animals are available. Groups of pregnant Charles River rats (n=25) were administered ethion in a corn oil vehicle via gavage at doses of

0, 0.2, 0.6, and 2.5 mg/kg from Gd 6 to 15 (Hoberman et al. 1983a). Dams were observed and skeletal examinations were performed on the fetuses. Fetuses from the 2.5 mg/kg group had an increased incidence of delayed ossification of pubes. Groups of pregnant New Zealand rabbits (n=17) received ethion via gavage at doses of 0, 0.6, 2.4, and 9.6 mg/kg from Gd 6 to 18 (Hoberman et al. 1983b). Does were observed for clinical signs. Does in the 2.4 and 9.6 mg/kg/day groups had an increased incidence of orange-colored urine; however, this was not considered to be a toxic effect. Additionally, does in these groups had decreased body weights (not specified). Food consumption was also reduced in the 9.6 mg/kg/day females. Fetuses in the 9.6 mg/kg/day group had an increased incidence of fused sterna centra.

In a 3-generation reproduction study, ethion was administered to F_0, F_1, and F_2 male (n=15) and female (n=30) rats in the diet at concentrations of 0, 0.1, 0.2, and 1.25 mg/kg/day. No effect was observed on pup viability, survival, body weight, or structural development (Enloe and Salamon 1985).

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to ethion. Twenty-four hours after a single oral dose (2 mg/kg), ethion induced a small, but statistically significant, increase in the frequency of sister chromatid exchanges in white Leghorn chicks (Bhunya and Jena 1994). No other studies on the genotoxicity of ethion following oral exposure in animals were located.

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies regarding carcinogenicity in humans after oral exposure to ethion were located.

In 2-year carcinogenicity bioassays, groups of Sprague-Dawley rats (n=80/sex/group) receiving diets containing ethion at 0, 0.1, 0.2, and 2 mg/kg/day had similar tumor incidences (Morrow 1985a). Similar results were observed in CF_1 mice receiving 0, 0.113, 0.225, and 1.2 mg/kg/day (Morrow 1985b).

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans following dermal exposure to ethion.

In a study comparing LD_{50} values for 98 pesticides, including ethion, groups of 80 male and 60 female adult Sherman rats were dermally dosed with technical-grade ethion dissolved in xylene (Gaines 1969). The calculated LD_{50} value was 245 mg/kg for males and 62 mg/kg for females. The minimum survival time was 3 hours for males and 6 hours for females. The maximum time to death was 7 days for males and 3 days for females. The lowest dose to kill a rat was 150 mg/kg for males and 50 mg/kg for females. LD_1 values were calculated at 100 mg/kg for males and 34 mg/kg for females. The LD_{50} values for death in rats are shown in Table 2-2.

2.2.3.2 Systemic Effects

No studies were located regarding systemic effects in humans following dermal exposure to ethion. The only systemic effects reported in animals after dermal exposure to ethion are dermal effects in rabbits.

Dermal Effects. Groups of rabbits (n=6/sex/dose) received dermal applications of technical-grade ethion at doses of 0, 1, 3, 25, and 250 mg/kg for 21 days (Weiner 1985a as cited in EPA 1989d). An increased incidence of erythema and desquamation was observed at the application sites in both male and females of the 25 and 250 mg/kg group.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies regarding immunological and lymphoreticular effects in humans after dermal exposure to ethion were located.

Groups of guinea pigs (number and sex not specified) were dermally exposed to technical-grade ethion in a skin sensitization test (Freeman 1984 as cited in EPA 1989d). Ethion caused slight erythema which cleared within 48 hours. Ethion was determined not to be a skin sensitizer.

Table 2-2. Levels of Significant Exposure to Ethion - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
ACUTE EXPOSURE						
Death						
Rat (Sherman)	once				150 mg/kg M (lowest lethal dose; LD_{50} = 245 mg/kg) 50 mg/kg F (lowest lethal dose; LD_{50} = 62 mg/kg)	Gaines 1969

F = female; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level

2.2.3.4 Neurological Effects

No studies regarding neurological effects in humans after dermal exposure to ethion were located.

Inhibition of brain acetylcholinesterase was observed in rabbits after dermal exposure to ethion for 21 days at 1 mg/kg/day, (Weiner 1985a, 1985b as cited in EPA 1989d). The NOAEL in these studies was 0.8 mg/kg/day.

No studies were located regarding the following health effects after dermal exposure to ethion:

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

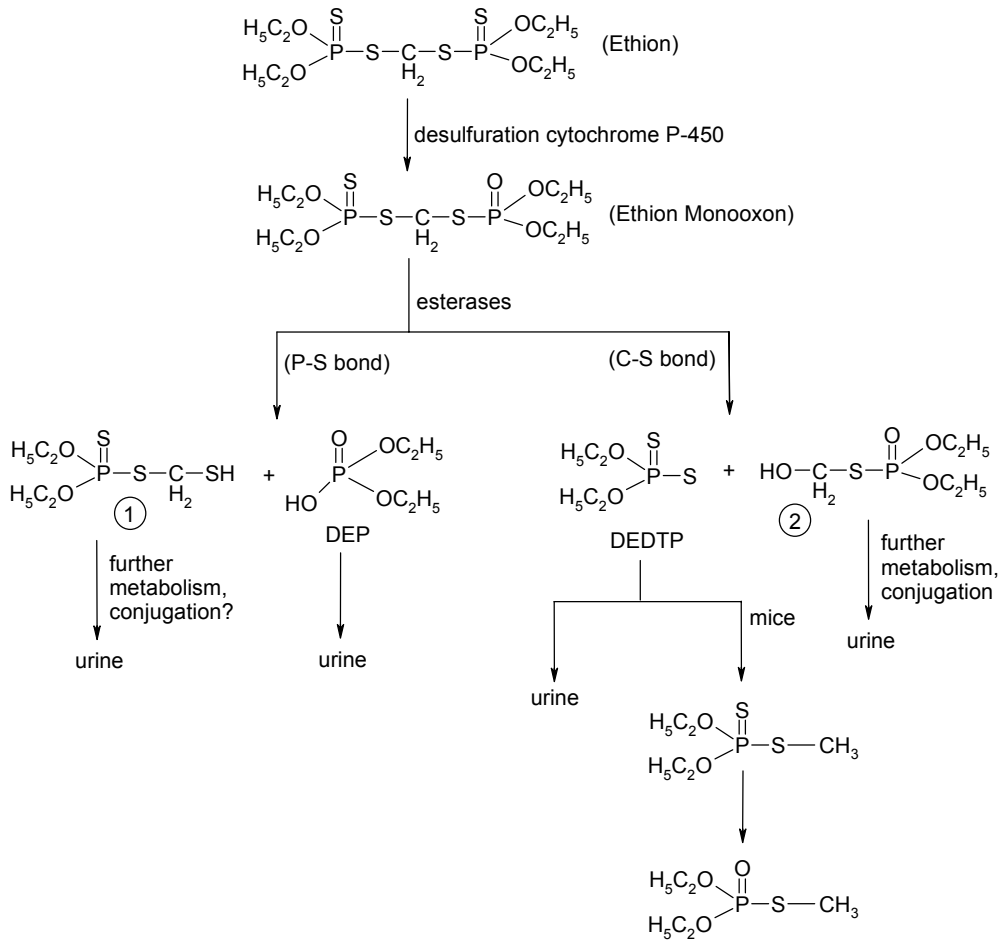
Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

2.3 TOXICOKINETICS

Ethion is a small (MW 384), lipid-soluble molecule that can be absorbed by passive diffusion through the lungs, gastrointestinal tract, or skin. Absorption appears to be rapid by the oral and dermal routes; the time course of absorption is inferred from the onset of clinical signs within 1 hour after accidental ingestion of ethion in a 6-month-old boy (Comstock et al. 1967) and deaths within 3–6 hours in dermally exposed Sherman rats (Gaines 1969). Ethion is desulfurated by cytochrome P-450 enzymes in the liver to its active form, ethion monoxon, which causes toxicity due to its potent inhibition of neural acetylcholin-esterase. Ethion and its oxon form can be detoxified by the action of esterases in the blood and liver, producing diethyl phosphate, diethyl thiophosphate, diethyl dithiophosphate, and other metabolites that have not been characterized. A proposed pathway for ethion metabolism is presented in Figure 2-2. Information on other aspects of toxicokinetics (distribution, metabolism, elimination/excretion) is limited by the nature of the studies available. Most toxicokinetic studies using ethion were designed to assess the persistence of ethion and its metabolites in meat or milk in the event that livestock were exposed to ethion-contaminated feed. Animals were exposed to [^{14}C-methylene]ethion and tissues harvested at

Figure 2-2. Proposed Mammalian Pathways of Ethion Biotransformation



Source: Mahajna et al. 1996; Nigg et al. 1993; Rao and McKinley 1969

DEP = diethylphosphate; DEDTP = diethyldithiophosphate
â O,O-diethyl-S-mercaptomethyldithiophosphate
ã O,O-diethyl-S-hydroxymethylphosphate

various times after exposure, and radioactivity was measured by liquid scintillation in ashed samples and expressed as ethion "equivalents." These experiments show that ethion and its metabolites are not stored in the body; however, since chemical characterization of the residues was not performed, no distinction can be made between the kinetics of the parent compound, active metabolite, and nontoxic metabolites.

2.3.1 Absorption

No information is available for any route as to whether absorption of ethion is different between children and adults or between juvenile and adult animals.

2.3.1.1 Inhalation Exposure

Absorption of ethion after inhalation exposure can be inferred from lethality reported in rats in an LC_{50} test (Feiser 1983 as cited in EPA 1989d). Time to death is not available from this summary, so no inference can be drawn as to how rapidly the ethion was absorbed.

2.3.1.2 Oral Exposure

Rapid absorption of ethion by the oral route in humans can be inferred from the onset of clinical signs within 1 hour after accidental ingestion of ethion in a 6-month-old boy (Comstock et al. 1967). Gastrointestinal absorption of ethion appears to be $80% in the rat based on residue studies performed with [^{14}C-methylene]ethion (Selim 1985a). In these studies, 75–85% of the total label was excreted in urine and 4–8% in feces. This pattern was the same whether labeled ethion was administered as a single dose or as the last dose after 14 days of dosing with unlabeled ethion.

2.3.1.3 Dermal Exposure

Dermal absorption of ethion has been measured in humans (Feldman and Maibach 1974). Radiolabeled ethion ([^{14}C]-specific activity not reported) was applied to the ventral forearm of 6 male volunteers at a concentration of 4 µg/cm^2 in acetone. The authors stated that this was equivalent to a thin film of a 0.25% solution. The skin sites were not protected, and the subjects were asked not to wash the area for 24 hours. All urine was collected for 5 days in a total of 8 samples (0–4, 4–8, 8–12, 12–24 hours, and the 4 subsequent 24-hour periods). Radioactivity in the urine was determined by combustion and liquid

scintillation counting. Results were calculated as percentage of applied dose corrected for incomplete urinary excretion using results from a parallel experiment where labeled ethion was administered intravenously. Over 24 hours, 3.3% of the dose was absorbed as calculated from urinary excretion of radioactivity.

In a study in goats dermally exposed with one application of 100 mg/kg ethion over a 600–700 cm^2 area, ethion in the blood was measured for 14 days (Mosha et al. 1990b). Unchanged ethion appeared in blood throughout the study and the $t_{1/2}$ for absorption was calculated as 85 hours, indicating that dermally applied ethion stays in the epidermis and is absorbed for a prolonged period.

2.3.2 Distribution

No information is available for any route as to whether distribution of ethion is different between children and adults or between juvenile and adult animals. Similarly, no information is available on whether ethion or its metabolites cross the placenta. However, given the high lipophilicity of ethion and ethion monoxon, it is probable that placental transfer occurs.

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution of ethion after inhalation exposure in humans or animals.

2.3.2.2 Oral Exposure

No studies were located regarding distribution of ethion after oral exposure in humans.

Seven days after rats received a single gavage dose of radiolabeled ethion, less than 1% of the radiolabel was detected in the body (blood, brain, heart, pancreas, leg muscle, lungs, adipose, spleen, bone, skin, hair, kidney, liver, gonads [uterus and ovaries for females, testes, seminal vesicle, and prostate for males]) (Selim 1985a). Total residues ranged from 0.21 to 0.34% of the original dose for females; and 0.18–0.28% for males. Similar results were obtained in a study where the radioactive dose was given after 14 consecutive daily doses of unlabeled ethion (Selim 1985a).

In a study designed to assess the presence of ethion in milk after oral exposure, two lactating goats (40 kg, strain not stated) were orally administered [^{14}C-methylene]ethion by capsule twice daily for 7 consecutive days (Jobsis and Zeitlow 1985). Test animals were sacrificed 4 hours after the final dose and the animals dissected. Tissues (blood, adductor muscle, pectoral muscle, liver, heart, kidney, peritoneal fat, and renal fat) along with daily milk samples taken during the test period were assayed for residues by combustion and liquid scintillation counting. Total daily dose was 1.12 mg/kg/day. The authors stated that this was comparable to a dietary level of 45–70 ppm in feed. Highest residue levels (radioactivity as ethion equivalents) were in liver (13–14 ppm) and kidney (7–9 ppm). Levels in muscle and heart tissues were approximately 1 ppm, and levels in fat were approximately 0.2 ppm. Levels in milk were approximately 1.2 ppm.

Unchanged ethion (the monoxon was not measured) was detected in goat milk after oral (~1.4% of administered activity) exposure to ethion. Equilibrium dialysis indicated that ethion was >99% bound to plasma proteins (Mosha et al. 1990b). Radioactivity derived from labeled ethion was present in goat milk after oral exposure (Jobsis and Zeitlow 1985); however, the chemical identity of the radioactivity was not determined.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of ethion after dermal exposure in humans. One animal study (Mosha et al. 1990b) examined the levels of ethion in goat milk following dermal exposure, reporting 0.04–0.05% of the total dose to be found in the milk. No other animal studies on the distribution of ethion following dermal exposure were located.

2.3.2.4 Other Routes of Exposure

A study by Mosha (1990b) examined the distribution of [^{14}C-methylene]ethion following a single intravenous administration in male and female goats. All tissues examined (kidney, liver, muscle, fat, heart, lung, and brain) had ^{14}C levels similar to or higher than the corresponding concentration in plasma, with the highest concentrations found in liver, kidney, and fat. No differences in distribution between male and female goats were noted.

2.3.3 Metabolism

While the basic features of ethion metabolism are known, detailed information is lacking. Like other organothiophosphate insecticides (chlorpyrifos, parathion), ethion is converted via desulfuration in the liver by cytochrome P-450 enzymes to its active oxygen analogue, ethion monoxon (Rao and McKinley 1969) (see Figure 2-2). It is not known if ethion monoxon can then be desulfurated to ethion dioxon. Ethion monoxon is a potent inhibitor of cholinesterases and exerts toxicity by reacting with and inhibiting neural acetylcholinesterase. The breakdown of ethion and ethion monoxon has not been characterized but is presumed to be by esterases in the blood and liver. Cleavage of the monoxon at the P-S bond would result in diethyl phosphate and a transient intermediate (O,O-diethyl-S-mercaptomethyldithiophosphate). Cleavage can occur in humans at both the P-S bond and the S-C bond, based on the detection of diethyl phosphate (P-S cleavage of the monoxon), diethyl thiophosphate (P-S cleavage of ethion or S-C cleavage of the monoxon), and diethyl dithiophosphate (S-C cleavage of ethion) in the urine of pest control workers using ethion (Nigg et al. 1993). Relative amounts were not reported. Evidence in mice for cleavage at the S-C bond and subsequent methylation of the sulfur has also been presented (Mahajna et al. 1996). Further metabolism of the product(s) of the esterase reaction continues but how it happens is unknown. Elimination from the body is mainly through excretion of water-soluble metabolites in the urine. Conjugation may occur, this is inferred from experiments where [^{14}C-methylene]ethion was administered orally to rats and the radioactivity in urine analyzed (Selim 1985b). Samples were extracted with ethyl acetate; the aqueous and organic phases were analyzed by high-performance liquid chromatography (HPLC). More than 99% of the urine radioactivity was in the aqueous phase. Another sample was acidified (presumably to hydrolyze conjugates) and also extracted with ethyl acetate. Acidification converted about 30% of the radioactivity in the aqueous phase to an organosoluble form, which may indicate that some of the products of ethion metabolism are present in urine as conjugates. Four to six radiolabeled metabolites were detected by HPLC, none migrated with standards for ethion, ethion monoxon, or ethion dioxon. None of the metabolites were specifically identified.

No information is available for any route as to whether the metabolism of ethion is different between children and adults or between juvenile and adult animals.

2.3.4 Elimination and Excretion

No information is available for any route as to whether elimination and excretion of ethion is different between children and adults or between juvenile and adult animals.

2.3.4.1 Inhalation Exposure

No studies were located regarding elimination or excretion following inhalation exposure to ethion in humans or animals.

2.3.4.2 Oral Exposure

No studies were located regarding elimination or excretion following oral exposure to ethion in humans.

Ethion and its metabolites were readily excreted from male and female Sprague-Dawley rats exposed to single and multiple dosing regimens of [^{14}C-methylene]ethion (Selim 1985a). A majority of the administered dose (75–85%) was excreted in urine. Most of the elimination occurred within 24 hours of dosing. Elimination also occurred by feces (4–8%) and respiratory gases (CO_2) (3–4%). Following oral exposure to 10 mg/kg [^{14}C]ethion in goats, 64% was excreted in the urine, 14% in the feces, and 1.7% in the milk (total recovery was 80%) (Mosha et al. 1990b).

2.3.4.3 Dermal Exposure

Excretion in urine accounted for 3.3% (SD +1.1%) of the [^{14}C]ethion radioactivity applied to the skin of volunteers for 24 hours over the 5 days following application (Feldman and Maibach 1974). Diethyl phosphate, diethyl thiophosphate, and diethyl dithiophosphate were detected in the urine of pest control workers using ethion and the carbamate pesticide, benomyl (Nigg et al. 1993). Total ethion metabolites (benomyl does not contain phosphorus) ranged from 0.30 to 7.0 ppm/day in a group of six workers; metabolites were not detected in two control workers not directly engaged in spraying. Relative amounts of the metabolites were not reported. Exposure is presumed to be primarily dermal. Unchanged ethion (the monoxon was not measured) was detected in goat milk after dermal exposure to ethion (Mosha et al. 1990b). A total of 0.04–0.05% of the dose appeared in the milk.

2.3.4.4 Other Routes of Exposure

Mosha (1990b) reported that following a single intravenous exposure to 2 mg/kg of [^{14}C-methylene]ethion in goats, one third of the administered activity was excreted in the urine within the first 24 hours. Two weeks following administration, a total of 66% of the administered activity was excreted in the urine, with another 8% found in the feces, and 4% in the milk (total recovery for the study was 78%). The identities of the excreted compounds were not determined. After intravenous exposure of 2 mg/kg [^{14}C] ethion to goats in another study, the peak of ethion in milk was 1.2 ppm (Mosha 1991).

2.3.5 Physiologically based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

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

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

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

1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-3 shows a conceptualized representation of a PBPK model.

If PBPK models for ethion 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.

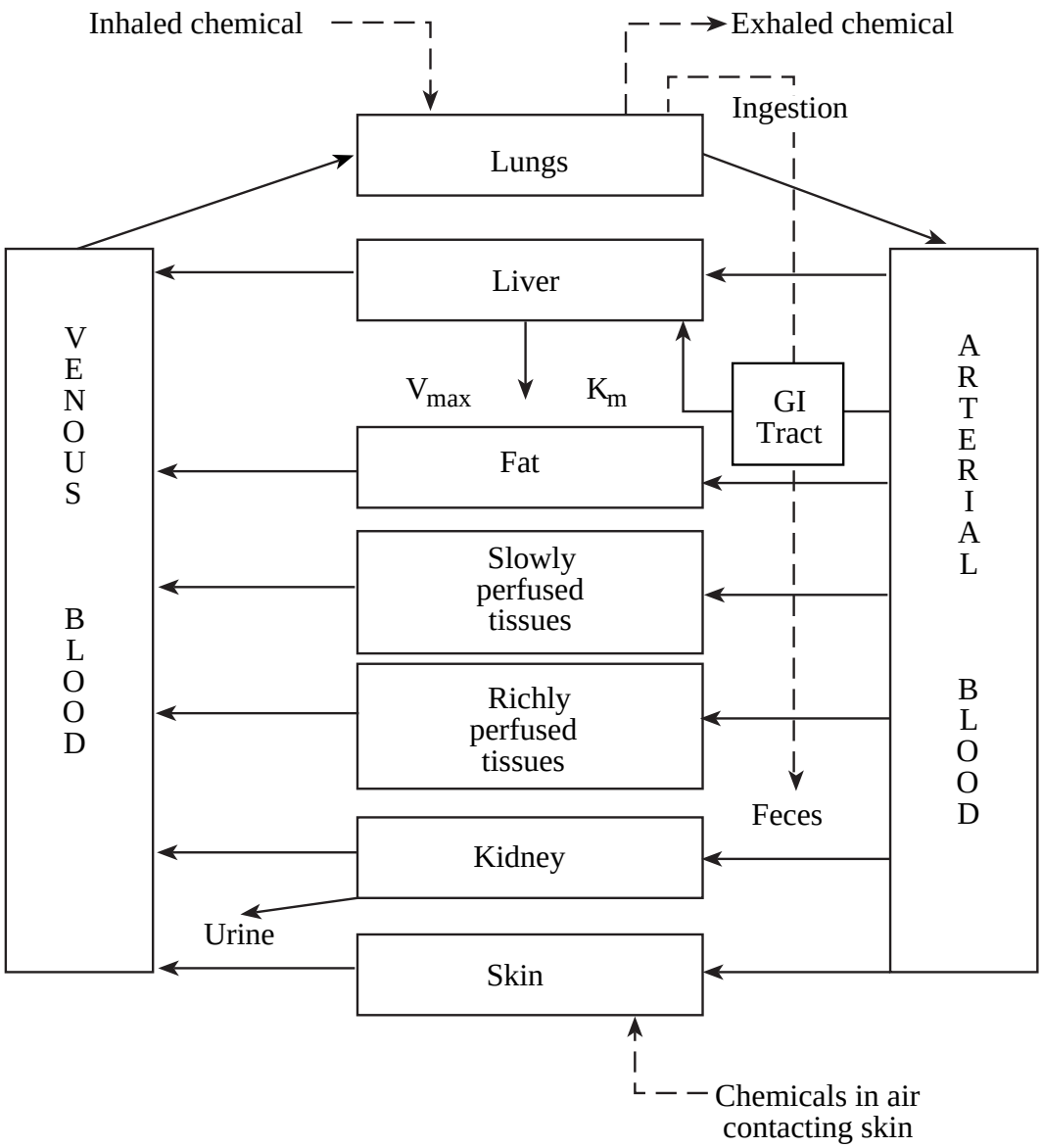
No PBPK models exist for ethion. Toxicokinetic information is insufficient for modeling.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

The pharmacokinetics of ethion have not been extensively studied. Ethion appears to be rapidly absorbed by the oral route. It is less well absorbed by the dermal route, but absorption may be prolonged as a consequence of using the epidermis as an intermediate storage depot (Feldman and Maibach 1974;

Figure 2-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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

Mosha et al. 1990b). Ethion is a small, lipophilic molecule and would be expected to be absorbed rapidly across cell membranes. Ethion is absorbed by passive diffusion from the gut, lungs, and skin to the blood. Ethion is desulfurated in the liver to its active metabolite, ethion monoxon. Some ethion monoxon and ethion can be inactivated by plasma cholinesterase or erythrocyte and neural acetylcholinesterase, but based on total esterase activity in the body, the liver is probably the major site of metabolism. The toxicity of a given dose of ethion depends on how rapidly neural acetylcholinesterase is inhibited; if this occurs before metabolic processes can reduce the blood level of ethion and ethion monoxon, significant toxicity will take place.

The reversibility of the reaction between ethion monoxon and neural acetylcholinesterase has not been studied. Based on studies with other diethyl organophosphates, it is probable that recovery of activity will depend on *de novo* synthesis of acetylcholinesterase rather than spontaneous reactivation (Ecobichon 1991).

2.4.2 Mechanisms of Toxicity

Ethion exerts its toxicity by inhibiting the neural acetylcholinesterase enzyme. Ethion is converted in the liver to ethion monoxon, a chemical form with an electrophilic phosphorus that is predisposed to nucleophilic attack. One potential nucleophile is the serine hydroxyl group located at the active site of acetylcholinesterase. The result of this reaction is a diethoxyphosphorylated acetylcholinesterase molecule. Over a time period of minutes to hours, a phenomenon known as “aging” can occur, whereby the diethoxyphosphorylated acetylcholinesterase molecule undergoes a spontaneous dealkylation, resulting in a monoethoxyphosphorylated acetylcholinesterase molecule, which is resistant to hydrolysis of the oxygen-phosphorus bond that would result in the regeneration of function of the enzyme. (The influence of the “aging” phenomenon on therapeutic interventions is discussed in section 2.11.3.) Neither the monoethoxyphosphorylated nor the diethoxyphosphorylated forms of acetylcholinesterase are capable of hydrolyzing acetylcholine. If this enzyme is inhibited, acetylcholine accumulates in the synapse and can interfere with neuron functioning. The parasympathomimetic consequences include lacrimation, perspiration, miosis, nausea, vomiting, diarrhea, excessive bronchial secretions, bradycardia, increased salivation, and increased urinary frequency and incontinence. Effects on motor nerve fibers in the skeletal muscles can include muscle fasciculations, cramps, muscle weakness, and flaccidity. Effects on cholinergic synapses in the central nervous system result in drowsiness, fatigue, mental confusion, headache, convulsions, and coma.

The nervous system can accept a certain amount of acetylcholinesterase inhibition without overt toxic effects. In humans and animals, toxic signs are generally not seen until at least 20% of this enzyme (erythrocyte acetylcholinesterase used as a marker) has been inhibited (Ecobichon 1991). In an animal study, brain acetylcholinesterase after a 2-year inhalation exposure to another organophosphate, dichlorvos, was inhibited more than 90% compared to control animals (Blair et al. 1976), yet signs of cholinergic overstimulation were not observed. With ethion and other organophosphate compounds, the best predictor of toxicity is not necessarily the actual percentage inhibition of acetylcholinesterase, but rather how rapidly this inhibition has occurred. Rapid inhibition does not give the nervous system time to adapt to acetylcholinesterase inhibition. This adaptation appears to involve desensitization and down-regulation of muscarinic receptors (Fitzgerald and Costa 1993).

There is no information available suggesting that the mechanism of toxicity of ethion is different between children and adults. Symptoms of toxicity in a 6-month-old boy poisoned by ethion (Comstock et al. 1967) were similar to those seen in adults acutely intoxicated by other organophosphates.

2.4.3 Animal-to-Human Extrapolations

Rats, dogs and goats all show clinical signs similar to those of humans after acute exposure to high doses of ethion. Information is insufficient to make any extrapolations from animal toxicokinetics to humans.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

Ethion is an organophosphorus insecticide that has been in use in the United States and elsewhere since the mid-1960s. Like other insecticides in this class, ethion is not only extremely toxic to insects, but also can be toxic to humans if high enough doses are received. The toxicity of ethion results from its inhibition of neural acetylcholinesterase. This enzyme is necessary to hydrolyze acetylcholine and terminate its action at synapses and ganglionic and neuromuscular junctions. The clinical signs of ethion toxicity are the result of overstimulation of the parasympathetic autonomic nervous system, somatic nerve fibers, and cholinergic pathways in the brain. After acute exposure to high concentrations of ethion by any route, signs such as lacrimation, perspiration, miosis, nausea, vomiting, diarrhea, bronchial secretion, dyspnea, increased salivation, and urinary frequency and incontinence can result from

overstimulation of the parasympathetic autonomic nervous system. The actions of ethion at neuromuscular junctions can result in muscle fasciculations (especially in fine facial muscles), cramps, muscle weakness, and paralysis. Ethion can also act in the central nervous system to produce drowsiness, fatigue, mental confusion, headache, convulsions, coma, and depression of respiratory centers in the brain.

There is limited information on the toxicity of ethion to humans. The potential hazards of this chemical were well known before it came into use because of experience with other organophosphorus compounds. Exposure to levels of ethion high enough to cause clinical symptoms of organophosphorus poisoning has been very rare in the United States. Clinical and biochemical signs of ethion toxicity in humans can be reproduced in animals. The metabolites of ethion are polar compounds that are excreted into the urine; thus, no potential for bioaccumulation exists. Laboratory studies in animals have not shown adverse reproductive or adverse developmental effects at doses that did not cause maternal toxicity. Ethion exposure has not been associated with organophosphate-induced delayed neurotoxicity (OPIDN) in humans and did not cause this condition in the preferred test species, the domestic hen.

Ethion has tested negative for mutagenicity in a number of *in vitro* test systems. Evaluation using *in vivo* test systems is limited to a single positive test for sister chromatid exchange in chickens (Bhunya and Jena 1994). Two-year oral exposure studies with ethion in rats and mice showed no evidence of carcinogenicity. Ethion has not been assessed for potential carcinogenicity in humans by the DHHS, the IARC, or the EPA.

The most likely population to be exposed to ethion is pesticide applicators. Exposure occurs during and/or after pesticide application. The National Institute of Occupational Safety and Health (NIOSH) recommends that ethion concentrations in workplace air not exceed 0.4 mg/m^3 for a 10-hour time-weighted average (TWA). Health effects could occur in workplaces if proper industrial hygiene and safety precautions are not followed. The exposure of the general population to ethion appears to be very low. Ethion has not been detected in drinking water in the United States and rarely detected in outdoor air (only at agricultural sites). Monitoring of the food supply by the U.S. Food and Drug Administration (FDA) and other government agencies has detected ethion, but levels are very rarely above tolerance levels set by the EPA. Thus, the risk of adverse health effects in the general population from ethion exposure appears to be negligible.

For people living near hazardous waste sites, the potential for adverse health effects would depend on the amount of ethion to which they were exposed. Ethion has been detected in at least 9 of the 1,577 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2000). However, the number of sites evaluated for ethion is not known. The most likely routes of exposure for people living near hazardous waste sites would be by breathing ethion-contaminated air, drinking ethion-contaminated water, or skin contact with ethion-contaminated soil. Monitoring of the air, drinking water, and soil levels of ethion at these sites is necessary to predict the possibility of adverse health effects.

Issues relevant to children are explicitly discussed in Sections 2.7, Children's Susceptibility, and 5.6, Exposures of Children.

Minimal Risk Levels for Ethion.

Inhalation MRLs.

No MRLs have been derived for inhalation exposure to ethion. No studies in humans on the effects of inhalation exposure to ethion were identified. The only animal study located (Fieser 1983 as cited in EPA 1989d) did not establish effect levels for neurological effects.

Oral MRLs.

- An MRL of 0.002 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to ethion. This MRL is also applicable to acute-duration (14 days or less) oral exposure to ethion.
- An MRL of 0.0004 mg/kg/day has been derived for chronic-duration (365 days or more) oral exposure to ethion.

These MRLs are based on a NOAEL of 0.06 mg/kg/day for brain acetylcholinesterase activity observed in dogs (Bailey 1988). To derive the intermediate-duration oral MRL, the NOAEL was adjusted by a factor of 30, 3 for extrapolation of an animal study to humans and 10 for human variability. The purpose of this study (Bailey 1988) was to evaluate the toxicity of ethion administered orally to dogs for 13 weeks.

Groups of Beagle dogs (n=4/sex/group, 20–28 weeks old) received ethion (purity 93.4%) in the diet at target concentrations of 0, 0.5, 2.5, 25, and 300 ppm for 90 days. Food was available for 2 hours a day, water was available *ad libitum.* The average amount of ethion consumed was 0, 0.01, 0.06, 0.71, and 6.9 mg/kg/day for males and 0, 0.012, 0.07, 0.71, and 8.25 mg/kg/day for females. All dogs were observed twice daily for mortality and moribundity. Animals were observed once daily for clinical signs. Body weights were recorded during acclimation and quarantine, on day 0 (one day prior to initiation and during week 13. Clinical pathology parameters were evaluated for all dogs prior to initiation of treatment (day -16) and during weeks 5, 9, and 13 and included cholinesterase activities (plasma, erythrocyte, brain), hematology, and clinical chemistry. All surviving animals were sacrificed following the 13-week treatment period. Histopathological examination of the following tissues was conducted: lesions, brain (with medulla/pons, cerebellar cortex, and cerebral cortex), gallbladder, pituitary, thyroid (parathyroid), thymus, lungs, trachea, heart, bone (femur), salivary glands (mandibular), bone marrow (sternum), kidneys, uterus adrenals, liver, spleen, pancreas, testes (with epididymides), ovaries, aorta, esophagus, stomach, duodenum, jejunum, ileum, colon, cecum, rectum, urinary bladder, mesenteric lymph node, sciatic nerve, spinal cord (cervical, thoracic, lumbar), skin, mammary gland, and eyes.

One female dog in the 8.25 mg/kg/day group was sacrificed on day 90 (1 day before schedule). Clinical signs exhibited by this animal prior to sacrifice included emesis, dehydration, and thin body mass. All other animals survived until terminal sacrifice. In the highest dose group (6.9 mg/kg/day for males, 8.25 mg/kg/day for females) clinical signs included miosis (all animals), emesis (all animals), dehydration (3 males, 2 females), salivation (2 males, 2 females), and tremors (3 males, 4 females). Animals in this group appeared to be in generally poor condition at the end of the study. Erythrocyte acetylcholinesterase was inhibited at weeks 5 (94% M, 96% F), 9 (95% M, 93% F), and 13 (94% M, 93% F) in the highest dose groups, but not in any of the other groups. Mean percent brain acetylcholinesterase activity inhibition at termination was 64% in males and 61% in females at the highest dose. Male brain acetylcholinesterase was inhibited 23% at 0.71 mg/kg/day but no inhibition of brain acetylcholinesterase occurred in females at this dose. Plasma cholinesterase inhibition was dose-related in both males and females. No significant differences in absolute organ weights were observed between treated and control animals. No compound-related Histopathological effects were observed in any organ, including brain, sciatic nerve and spinal cord. The NOAEL for inhibition of brain acetylcholinesterase is 0.06 mg/kg/day.

This study was chosen for MRL derivation because it identifies both a NOAEL and LOAELs for inhibition of neural acetylcholinesterase, the target for ethion toxicity in humans. A study in albino rats

fed ethion for 93 days established a NOAEL for brain acetylcholinesterase inhibition of 1 mg/kg/day (Keller and Paynter 1958), which is higher than that used to derive the MRL. Neither erythrocyte nor brain acetylcholinesterase activities were inhibited in rats (up to 2 mg/kg/day) or mice (up to 1.25 mg/kg/day) receiving ethion in the diet for 6 or 12 months (Morrow et al. 1985a, 1985b).

This MRL should be protective against adverse health effects in individuals potentially exposed to ethion at hazardous waste sites. A study in volunteers (Palazzolo 1970) has determined the sensitivity of humans to the effects of ethion on blood cholinesterase activities. A group of six male volunteers were given ethion in corn oil solutions in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) of 0.05, 0.075, 0.1, and 0.15 mg/kg/day via gelatin capsule. Subjects received 0.05, 0.075, and 0.1 mg/kg/day for 3 weeks each and then 0.15 mg/kg/day for 3 days. No adverse clinical signs (blood pressure, pulse rate, pupil size, light reflex, eye accommodation, chest sound, muscle tone, knee jerk, tongue tremor and finger tremor) or effects on erythrocyte acetylcholinesterase were observed at any time during the study. Absorption of ethion by the volunteers was confirmed by a decrease in plasma cholinesterase levels. While no effect on plasma cholinesterase was observed at the 0.05 mg/kg/day dose level, a 16% decrease was seen in the 0.075 mg/kg/day group. Decreases of 23 and 31% were seen in the 0.1 and 0.15 mg/kg/day groups.

To derive the intermediate oral MRL, the NOAEL of the Bailey (1988) study for inhibition of brain acetylcholinesterase was adjusted by a factor of 10 for human variability and a factor of 3 for extrapolation of an animal study to humans. A factor of 3 was used for extrapolation rather than the full uncertainty factor of 10 because the results of the Palazzolo (1970) study indicated that dogs appear to be at least as sensitive to the neurological effects of ethion as humans when exposed to comparable doses.

The MRL value of 0.002 mg/kg/day for intermediate-duration oral exposure to ethion was extended to acute oral exposure based on the toxicokinetics of ethion. Cholinesterase inhibition occurs quickly and there are no indications of progressive inhibition over time at a given dose in either the Palazzolo (1970) study in humans or the Bailey (1988) study in dogs. A similar lack of progression of inhibition was seen in 2-year studies in rats and mice where brain and erythrocyte acetylcholinesterase and plasma cholinesterase were measured at 6-month intervals (Morrow et al. 1985a, 1985b). The toxicity database indicates no change in ethion toxicity over time (i.e., toxicity is dependent on the dose, not the duration of exposure). Because the toxicological effects of ethion are due to a series of repeated acute exposures, it is proposed that the intermediate-duration oral MRL should be protective for the acute exposure

duration. For chronic duration, an additional modifying factor of 5 was applied to protect against possible long-term effects, seen in structurally-related cholinesterase inhibitors, which might be the result of mechanisms other than cholinesterase inhibition, and to protect against possible susceptibility in children. Application of this factor resulted in a chronic-duration oral MRL of 0.0004 mg/kg/day.

Death. No studies were located describing death in humans after exposure to ethion. However, without prompt medical attention, it is likely that a 6-month-old boy who ingested 15.7 mg/kg ethion from a contaminated milk bottle would have died (Comstock et al. 1967).

Animal studies show that ethion is highly toxic by the oral route; reported LD_{50} values in the rat range from 21 to 191 mg/kg. Deaths have also occurred by the inhalation and dermal route in animal studies. Reported LD_{50} values for dermal exposure in rats range from 62 to 838 mg/kg while inhalation LC_{50} values range from 0.45 to 2.31 mg/m^3 (Gaines 1969; Fieser 1983 as cited in EPA 1989d).

Systemic Effects. Ethion exerts its toxicity by inhibiting neural acetylcholinesterase in the central and peripheral nervous systems. Some of these effects occur in different organ systems but are ultimately the result of neurological effects. In animal studies where tissues have been examined histopathologically, ethion does not appear to have direct effects on organ systems.

Respiratory Effects. Respiratory effects have been reported in humans after oral exposure to ethion. A 6-month-old boy who accidentally ingested 15.7 mg/kg ethion from a contaminated milk bottle presented with diaphragmatic respiration with shallow excursions and intercostal retraction (Comstock et al. 1967). Respiratory rate was 60/minute. Auscultation revealed generalized rales and rhonchi and inspiratory and expiratory wheezes; all signs of increased secretions in the respiratory tract. Symptoms appeared one hour following ingestion and were treated with atropine and pralidoxime. Approximately 5 hours after ingestion respiratory arrest occurred and mechanical ventilation was necessary for the next 3 hours. It is not known if respiratory arrest was due to muscular paralysis. The respiratory effects seen in this case are consistent with cholinergic overstimulation caused by ethion.

Longer-term oral exposure at lower doses in animal experiments did not show effects on the respiratory system. Histopathological examination of the lungs and trachea revealed no treatment-related lesions several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Cardiovascular Effects. Tachycardia was reported in a 6-month-old boy who accidentally ingested 15.7 mg/kg ethion (Comstock et al. 1967).

Blood pressure and pulse rate were measured in a group of 6 male volunteers (age range, 23–43 years) who were given ethion in corn oil solutions in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) via gelatin capsule (Palazzolo 1970). Doses were 0.05 mg/kg/day for 21 consecutive days, 0.075 mg/kg/day for the next 21 days, 0.1 mg/kg/day for the next 21 days, and 0.15 mg/kg/day for the next 3 days. Controls (n=4; age range, 22–40 years) received gelatin capsules containing corn oil. No differences were noted between the control and test groups, or between individual pre-treatment, treatment, or post-treatment results for blood pressure or pulse rate.

Studies on the effects of ethion on electrical activity of the heart were not found in the literature. Histopathological examination of the heart and aorta revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Gastrointestinal Effects. Gastrointestinal effects reported in a 6-month-old boy who accidentally ingested 15.7 mg/kg ethion (Comstock et al. 1967) included frothy saliva 1 hour after ingestion and a watery bowel movement at 90 minutes. Bowel sounds were hyperactive and an episode of emesis occurred 5 hours after ingestion.

Diarrhea was reported in Sprague-Dawley rats exposed to ethion by gavage at 10 mg/kg in females and 100 mg/kg in males (Selim 1985a). Severe signs of neurotoxicity (convulsions) were also present. The gastrointestinal effects seen in both cases are consistent with cholinergic overstimulation of the gastrointestinal tract.

Histopathological examination of gastrointestinal tissues (esophagus, stomach, duodenum, jejunum, ileum, colon, cecum, rectum) revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Hematological Effects. Significant hematological effects have not been observed in two cases of human exposure to ethion. In a poisoning case of a 6-month-old boy who accidentally ingested 15.7 mg/kg

ethion, hematocrit, hemoglobin level, and RBC and platelet counts were normal (Comstock et al. 1967). WBC counts were initially slightly depressed but returned to normal after one day.

Similar results were seen for intermediate-duration oral exposure in a group of 6 male volunteers (age range, 23–43 years) who were given ethion in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) via gelatin capsule (Palazzolo 1970). Doses were 0.05 mg/kg/day for 21 consecutive days, 0.075 mg/kg/day for the next 21 days, 0.1 mg/kg/day for the next 21 days, and 0.15 mg/kg/day for the next 3 days. Controls (n=4; age range, 22–40 years) received gelatin capsules containing corn oil. Blood studies (hemoglobin concentration, hematocrit, RBC and total and differential leukocyte counts) were performed on days -15 and -1 of the pretreatment period, at the end of each of the 4 treatment periods, and after a 19-day recovery period after dosing ended. No differences were noted between the control and test groups, or between individual pre-treatment, treatment, or post-treatment results for any of the parameters.

Hematological parameters (leukocyte count, erythrocyte count, hemoglobin, corrected leukocyte count, hematocrit, platelet count, differential leukocyte count) were unaffected by treatment in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Musculoskeletal Effects. Oral exposure to ethion can result in muscle tremor and fasciculations. These effects are discussed under Neurological Effects.

The effect of oral exposure to ethion on muscle tone was assessed in a group of 6 male volunteers (age range, 23–43 years) who were given ethion in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) via gelatin capsule (Palazzolo 1970). Doses were 0.05 mg/kg/day for 21 consecutive days, 0.075 mg/kg/day for the next 21 days, 0.1 mg/kg/day for the next 21 days, and 0.15 mg/kg/day for the next 3 days. Controls (n=4; age range, 22–40 years) received gelatin capsules containing corn oil. Muscle tone was assessed at the beginning and end of each treatment period. No differences were noted between the control and test groups or between individual pre-treatment, treatment, or post-treatment results.

Histopathological examination of the bone and skeletal muscle revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to ethion.

Histopathological examination of the liver revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to ethion.

Histopathological examination of endocrine tissues (pituitary, thyroid, parathyroid, thymus and adrenals) revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Renal Effects. Proteinuria and increased urinary WBC counts were observed in a severely intoxicated 6-month-old boy who accidentally ingested 15.7 mg/kg ethion (Comstock et al. 1967).

An increased incidence of orange-colored urine was observed in pregnant New Zealand rabbits receiving 2, 4, or 9.6 mg/kg/day during Gd 6–18 (Hoberman et al. 1983b). This effect was not observed at 0.6 mg/kg/day. The urine was not examined by chemical analyses.

Histopathological examination of the urinary bladder and kidneys revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

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

Histopathological examination of the skin revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to ethion.

Histopathological examination of the eyes revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to ethion.

An unspecified body weight decrease occurred in New Zealand rabbit does receiving 2.4 mg/kg/day ethion via gavage over Gd 6–18. No effect on body weight was seen at 0.6 mg/kg/day (Hoberman et al. 1983b). No effect was observed on body weight in male and female dogs receiving #0.71 mg/kg/day in the diet for 13 weeks (Bailey 1988).

Body weight decreases accompanied by reduced food consumption have been observed in New Zealand rabbit dams receiving 9.6 mg/kg/day ethion via gavage over Gd 6–18 and in male and female Beagle dogs receiving 6 and 8.25 mg/kg/day, respectively, in feed (Bailey 1988).

Immunological and Lymphoreticular Effects. No studies were located regarding immunological/lymphoreticular effects in humans after exposure to ethion.

Histopathological examination of immunological/lymphoreticular tissues (mesenteric lymph node, thymus, bone marrow) revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Neurological Effects. Ethion exerts its toxic effects in humans and animals by inhibiting neural acetylcholinesterase. This enzyme is present at cholinergic synapses throughout the central and peripheral nervous systems and is responsible for hydrolyzing acetylcholine released from the pre-synaptic terminal. If this enzyme is inhibited, acetylcholine accumulates in the synapse, resulting in increased firing of the post-synaptic neuron or increased neuroeffector activity. The consequences of increased cholinergic activity in the parasympathetic autonomic nervous system (muscarinic receptors) can include increased salivation, lacrimation, perspiration, miosis, nausea, vomiting, diarrhea, excessive bronchial secretions, bradycardia, frequent micturition, and incontinence. The effects of increased neuroeffector activity on skeletal muscles (nicotinic receptors) can include muscle fasciculations, cramps, muscle weakness, and depolarization-type paralysis. Effects on cholinergic synapses in the

central nervous system (predominantly muscarinic) can result in drowsiness, fatigue, mental confusion, headache, convulsions, and coma. These classical symptoms of organophosphate neurotoxicity increase in severity and rapidity of onset in a dose-dependent manner (Ecobichon 1991).

Acetylcholinesterase is also present in erythrocytes where it is referred to as erythrocyte acetylcholinesterase. Both forms of acetylcholinesterase are produced by the same gene (Taylor et al. 1993). In *in vitro* assays, erythrocyte and neural acetylcholinesterase are inhibited to roughly the same extent by exposure to organophosphate compounds with insecticide activity (Hayes 1982). Measurement of erythrocyte acetylcholinesterase is used as a surrogate of the inhibition of neural acetylcholinesterase. A cholinesterase capable of hydrolyzing acetylcholine is also produced by the liver and circulates in the blood. This enzyme, called plasma cholinesterase, is also inhibited by ethion and other organophosphates and can be used as a marker for exposure. The endogenous substrate of this enzyme is unknown. Experiments in both humans and animals show that this enzyme is inhibited by ethion at lower levels of exposure than required to inhibit neural or erythrocyte acetylcholinesterase (Bailey 1988).

A case study of a 6-month-old boy who accidentally ingested 15.7 mg/kg ethion from a contaminated milk bottle illustrates the toxic neurological effects of ethion (Comstock et al. 1967). Symptoms appeared one hour following ingestion. The child awoke crying and choking on frothy saliva. He was unable to control his head and limbs and subsequently had a watery bowl movement and became limp. Occasional twitching movements of the hands and around the mouth were noted. Upon admission to the hospital, he was slightly cyanotic with a generalized flaccid paralysis and areflexia. Respiration was increased (60/minute) as was heartbeat (200/minute). Pupils were pinpoint and nonreactive to light, and eye movements were purposeless. Salivation was excessive but not copious. Respiration was diaphragmatic with shallow respiratory excursions and intercostal retraction. Generalized rales and rhonchi and inspiratory and expiratory wheezes were noted. The liver and spleen were palpable. Bowel sounds were hyperactive. There were no abnormal heart sounds. Treatment with atropine and pralidoxime was started immediately. Approximately 5 hours after ingestion, respiratory arrest occurred and mechanical ventilation was necessary for the next 3 hours. Laboratory and roentgenologic studies showed protein in the urine and increased WBC in the urine. Serum WBC count was decreased and treated with atropine and pralidoxime. Treatment with atropine and pralidoxime continued for 5 days until symptoms ceased. Follow-up examinations after 1 week, 1 month, and 1 year indicated that a complete recovery was made by this patient.

2. HEALTH EFFECTS

A study with male volunteers established oral levels of exposure to ethion that had no adverse effect in humans (Palazzolo 1970). Male volunteers (n=6; age range, 23-43 years) were given ethion in corn oil solutions in three divided doses (9:00 a.m., noon, and 5:00 p.m.) of 0.05, 0.075, 0.1, and 0.15 mg/kg/day via gelatin capsule. Controls (n=4; age range, 22-40 years) received gelatin capsules containing corn oil. Medical histories and baseline plasma cholinesterase and erythrocyte acetylcholinesterase activities were determined prior to the start of the study (days -15, -11, -8, -4, and -1). Blood samples were taken prior to dose administration. Subjects received 0.05, 0.075, and 0.1 mg/kg/d for 3 weeks each. Cholinesterase determinations were conducted on days 1, 3, 7, 14, and 21 for these dose groups. Subjects received 0.15 mg/kg for 3 days and cholinesterase determinations were made on days 1 and 3. A 19-day recovery period followed, and cholinesterase determinations were made on days 7, 12, and 19. At the beginning and end of each treatment period, pupil size, light reflex, eye accommodation, muscle tone, knee jerk, tongue tremor, and finger tremor were measured.

No effect on erythrocyte acetylcholinesterase was observed at any time during the human exposure study. No effect on plasma cholinesterase were observed at the 0.05 mg/kg/day dose level. Statistically significant decreases from pretreatment values were observed for all plasma cholinesterase determination periods during the 0.075, 0.1, and 0.15 mg/kg/day treatment periods. A significant 16% decrease in plasma cholinesterase activity was seen in the 0.075 mg/kg/day group. When compared to pretreatment values, decreases of 23 and 31% were seen in the 0.1 and 0.15 mg/kg/day groups, respectively. A partial recovery of plasma cholinesterase levels were seen after 7 days of recovery, while a complete recovery was seen after 12 days. No clinical signs of adverse neurological effects were observed.

Severe neurological effects have also been observed in rats after a single oral exposure to ethion. Male Sprague-Dawley rats receiving 100 mg/kg ethion by gavage had cholinergic signs including salivation, tremors, nose bleeding, urination, diarrhea, and convulsions (Selim 1985a). Female rats exhibited these same signs at a 10-fold lower dose (10 mg/kg). In another acute oral exposure to ethion, groups of pregnant Sprague-Dawley rats (n=25) were administered ethion via gavage at doses of 0,0.2,0.6, and 2.5 mg/kg from Gd 6 to 15 (Hoberman et al. 1983a). An increased incidence of hyperactivity was observed in dams in the 2.5 mg/kg group. In a test of ethion in chickens for potential to cause delayed neurotoxicity, an oral dose of 2,792 mg/kg caused neither clinical or histopathological signs of this condition (Roberts et al. 1986).

In longer-term experiments in animals, groups of Sprague-Dawley rats (n=80/sex/group) fed diets resulting in ethion consumption of 0, 0.1, 0.2, and 2 mg/kg/day, no effect on erythrocyte acetylcholinesterase was observed at 6, 12, or 18 months (Morrow 1985a). Significant neurological effects were observed in dogs receiving higher doses of ethion (Bailey 1988). Groups of dogs (n=4/sex/group) received ethion in the diet for 90 days, the average consumed was 0, 0.01, 0.06, 0.71, and 6.9 mg/kg/day for males and 0, 0.012, 0.07, 0.71, and 8.25 mg/kg/day for females. Clinical signs included ataxia, emesis, miosis, and tremors in the high-dose groups. Ethion inhibited brain and erythrocyte acetylcholinesterase activity in a dose-related manner. A reduction of 23% in brain acetylcholinesterase was observed in males at 0.71 mg/kg/day and 64% at 6.9 mg/kg/day; no effect was seen at 0.07 and 0.012 mg/kg/day. Plasma cholinesterase activity was inhibited in all groups except the low-dose males and females and was dose-related. No compound-related histopathological changes were observed in nervous system tissues (brain [with medulla/pons, cerebellar cortex, and cerebral cortex], sciatic nerve, spinal cord [cervical, thoracic, lumbar]).

In chronic-duration experiments, a 3-generation reproduction study in albino rats that consumed ethion in feed at 0, 0.1, 0.2, and 1.25 mg/kg/day, showed that plasma cholinesterase was inhibited in F_1 and F_2 females in the high-dose group. No effect was observed on erythrocyte acetylcholinesterase in any group (Enloe and Salamon 1985). In 2-year carcinogenicity bioassay experiments, no effect on erythrocyte acetylcholinesterase was observed at daily exposures of #2 mg/kg/day in rats and 1.12 mg/kg/day in mice (Morrow 1985a, 1985b).

Inhibition of brain acetylcholinesterase was observed in rabbits after dermal exposure to ethion for 21 days at 1 mg/kg/day, (Weiner 1985a, 1985b as cited in EPA 1989d). The NOAEL in these studies was 0.8 mg/kg/day.

Histopathological examination of nervous system tissues (brain, spinal cord, peripheral nerve) showed no treatment-related effects in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Reproductive Effects. In a 3-generation reproduction study, ethion was administered to F_0, F_1, and F_2 male (n=15) and female (n=30) rats in the diet at concentrations of 0, 0.1, 0.2, and 1.25 mg/kg/day. No effect on reproduction was observed (Enloe and Salamon 1985). Indices measured were: mating index (number of copulations/number of estrus cycles utilized), fertility index (number of

pregnancies/number of copulations), gestation (number of parturitions/number of pregnancies), female fertility (number of pregnancies/number of females mated), and male fertility (number of sires/number of males mated).

Histopathological examination of reproductive tissues (uterus, ovaries, testes) revealed no treatment-related lesions in several animal studies where exposure was via the oral route (Bailey 1988; Keller and Paynter 1958; Morrow et al. 1985a, 1985b).

Developmental Effects. Three studies examining the effects of ethion on development are available. Groups of pregnant Sprague-Dawley rats (n=25) were administered ethion via gavage at doses of 0, 0.2, 0.6, and 2.5 mg/kg from Gd 6 to 15 (Hoberman et al. 1983a). Dams were observed and skeletal examinations were performed on the fetuses. Fetuses from the 2.5 mg/kg group had an increased incidence of delayed ossification of pubes. Groups of pregnant New Zealand rabbits (n=17) received ethion via gavage at doses of 0, 0.6, 2.4, and 9.6 mg/kg from Gd 6 to 18 (Hoberman et al. 1983b). Does were observed for clinical signs. Maternal toxicity was noted, does in the 2.4 and 9.6 mg/kg/day groups had an increased incidence of orange-colored urine and decreased body weights (not specified). Food consumption was also reduced in the 9.6 mg/kg/day females. Fetuses in the 9.6 mg/kg/day group had an increased incidence of fused sterna centra. In a 3-generation reproduction study, ethion was administered to F_0, F_1, and F_2 male (n=15) and female (n=30) rats in the diet at concentrations of 0, 0.1, 0.2, and 1.25 mg/kg/day. No effect was observed on pup viability, survival, body weight, or structural development (Enloe and Salamon 1985).

Genotoxic Effects. Ethion has shown no evidence of genotoxicity in several *in vitro* tests (see Table 2-3). Ethion was negative in tests for point mutations (Kada et al. 1974; Waters et al. 1980), DNA repair (Shirasu et al. 1976; Waters et al. 1980), recombination (Waters et al. 1980), sister chromatid exchange (Sobti et al. 1982), and unscheduled DNA synthesis (Waters et al. 1980). An increase in the frequency of sister chromatid exchanges was observed in white Leghorn chicks following a single oral (2 mg/kg) or intraperitoneal (20 mg/kg) dose of ethion (Bhunya and Jena 1994). No other *in vivo* tests of ethion genotoxicity were located.

Cancer. In 2-year carcinogenicity bioassays, groups of Sprague-Dawley rats (n=80/sex/group) receiving diets containing ethion at concentrations of 0, 0.1, 0.2, and 2 mg/kg/day had similar tumor incidences (Morrow 1985a). Similar results were observed in mice receiving 0, 0.113, 0.225, and

Table 2-3. Genotoxicity of Ethion *In Vitro*

System	End points	Results		References
		With activation	Without activation	
Prokaryotes:				
S. typhimurium (Strains TA 98, TA 100, TA 1535, TA 1537, TA 1538)	Point mutation	All negative	All negative	EPA 1989a,b,c,d; Haworth 1984
S. typhimurium (Strains TA 1535, TA 1536, TA 1537, TA 1538)	Point mutation	No data	All negative	Kada et al. 1974
S. typhimurium (Strains TA 100, TA 1535, TA 1537, TA 1538)	Point mutation	All negative	All negative	Waters et al. 1980
E. coli (Strain WP2 (urvA$^-$))	Point mutation	All negative	All negative	Waters et al. 1980
E. coli (Strains W3110, P3478)	DNA repair	No data	All negative	Waters et al. 1980
B. subtilis (Strains H17 , M45)	DNA repair	No data	All negative	Waters et al. 1980
B. subtilis (Strains H17, M45)	DNA repair	No data	All negative	Shirasu et al. 1976
S. cerevisiae (Strain D3)	Recombination	Negative	Negative	Waters et al. 1980
Eukaryotes				
Human lymphoid cells (LAZ-007)	Sister chromatid exchange	No data	Negative	Sobti et al. 1982
Human fetal lung fibroblasts (WI-38)	Unscheduled DNA synthesis	No data	Negative	Waters et al. 1980

1.2 mg/kg/day (Morrow 1985b). Ethion has not been classified for carcinogenicity by DHHS, IARC or EPA.

2.6 ENDOCRINE DISRUPTION

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

No studies were located regarding endocrine disruption in humans or animals after exposure to ethion. No *in vitro* studies were located regarding endocrine disruption by ethion.

2.7 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 5.6 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).

The toxicological database for the effects of ethion on humans is sparse. Ethion is not used in the home, and no toxicological studies on individuals likely to have significant exposure (formulators and applicators) are available in the literature. One well documented case report of a poisoning incident in an infant has been published (Comstock et al. 1967). The only other human study located at this time is an unpublished study that established no-effect levels for oral exposure to ethion in adult males (Palazzolo 1970).

The effects of ethion have not been thoroughly studied in children, but they would likely experience the same health effects seen in adults exposed to ethion. Effects observed in an infant accidentally poisoned by ethion (Comstock et al. 1967) were similar in onset, severity, and duration to those seen in adults poisoned by other organophosphate insecticides (Ecobichon 1991). Symptoms observed in the infant (muscular twitching, lack of coordination, flaccid paralysis and areflexia, excessive salivation, pinpoint pupils, watery bowel movement, proteinurea, increased urinary white cell count, emesis, tachycardia) are classic symptoms of organophosphate poisoning in adults. Five days of treatment with atropine and pralidoxime were necessary before recovery; this is comparable to clinical courses seen in poisoned adults. Recovery appeared to be complete at a 1-year follow-up; this is also the case in adults (assuming that the organophosphate does not cause delayed neurotoxicity). These same effects are seen in animal studies. In the only animal study that directly compared weanling and adult animals (Brodeur and DuBois 1963), the LD_{50} for weanling male Holtzman rats after intraperitoneal injection was 100 mg/kg (95% confidence limits 92–109). For adult male Holtzman rats, the LD_{50} was 128 mg/kg (95% confidence limits 110–149). This indicates that weanlings may be slightly more susceptible to the lethal effects of ethion.

Specific information on whether children differ from adults in their susceptibility to the effects of ethion is not available. Animal studies do not provide any further information. Two areas of concern for exposure of children to ethion and other organophosphates have been identified. First, the target tissue for ethion is the peripheral and central nervous system. The central nervous system continues to develop after birth and it is not known if, or at what point, neural acetylcholinesterase inhibition can affect this process and result in permanent effects. It is possible that effects could occur with inhibition levels that

cause no clinical effects. Secondly, infants and children receive approximately 2–3 times more ethion in their diets per unit body weight than adults due to higher consumption of fruits and fruit drinks (See Chapter 5).

Ethion has not caused teratogenic effects in animal models (rats, rabbits), although some skeletal abnormalities have been reported (delayed ossification, fused sterna centra). These effects occurred at maternally toxic doses (Hoberman et al. 1983a, 1983b). Observation of the offspring after birth to maturity was not performed. No developmental effects were observed in progeny in a 3-generation rat reproduction study (Enloe and Salamon 1985). Ethion has not been tested in *in vitro* developmental systems.

The pharmacokinetics of ethion are not well understood in animal models, and no information is available on human adults or children. Studies in animals are limited by the fact that chemical characterization of radiolabeled ethion and its metabolic products in tissues was not performed. Ethion and its active metabolite ethion monoxon are highly lipophilic molecules so there should be no significant barrier to crossing the placenta. No studies have been done in animal models to confirm whether this occurs. Similarly, passage into breast milk is also possible. This has been examined in animal models. Radioactivity derived from labeled ethion was present in goat milk after oral exposure (Jobsis and Zeitlow 1985); however, the chemical identity of the radioactivity was not determined. Unchanged ethion (the monoxon was not measured) was detected in goat milk after oral (1.4% of administered activity) and dermal (0.04–0.05% of administered activity) exposure to ethion (Mosha et al. 1990b).

The toxicity of ethion is determined by two biotransformations, a desulfuration by a cytochrome P-450 enzyme yielding the active metabolite ethion monoxon and detoxication by an ester cleavage catalyzed by an esterase. Some, but not all, P-450 isozymes are regulated differently during development than during adulthood (Leeder and Kearns 1997); without knowing the specific isozymes involved in ethion metabolism it is impossible to predict whether its metabolism would vary developmentally. Comparisons of juvenile and adult animal toxicokinetics have not been made. There are no PBPK models for ethion available for children, adults, or animal models. The toxicokinetic database is insufficient for modeling purposes.

There is no evidence that the mechanism of ethion toxicity is different between children and adults. The symptoms of severe neural acetylcholinesterase inhibition observed in a 6-month-old infant were similar to those seen in adult poisonings with other organophosphate insecticides. The acetylcholinesterase molecule is believed to be the same at all stages of development (there is no evidence for a "fetal" acetylcholinesterase).

The biomarkers of exposure and effect (plasma cholinesterase and erythrocyte acetylcholinesterase in blood) are similar between adults and children. However, less is known about how much inhibition of these enzymes is associated with health effects in children than in adults. Information is not available for infants and children on the relationship between dietary intake and the activity of blood cholinesterases.

Interactions of ethion with other chemicals have not been reported in children or adults. There is not enough information from animal studies to determine if juvenile animals have unique interactions. As with adults, it is reasonable to expect interactions with compounds that inhibit acetylcholinesterases.

Methods for reducing the toxic effects of ethion in children are similar to those used in adults. Doses of the antidotes atropine and pralidoxime, adjusted for body weight, have been shown to be effective treatment for acute poisoning (Comstock et al. 1967).

There is no information on whether parental exposure to ethion can cause transgenerational effects in children. No effects were noted in a 3-generation rat reproduction study (Enloe and Salamon 1985). Ethion has tested negative for genotoxicity in a number of *in vitro* tests.

2.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC

1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to ethion are discussed in Section 2.8.1.

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 are discussed in Section 2.8.2.

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 2.10, Populations That Are Unusually Susceptible.

2.8.1 Biomarkers Used to Identify or Quantify Exposure to Ethion

Ethion at high doses will cause clinical symptoms of organophosphate toxicity, such as miosis, tremor, increased salivation, lacrimation, and respiratory distress. If these symptoms occur together and the individual has recently been in contact with pesticides containing ethion, it is highly likely that exposure to ethion has occurred.

Exposure to ethion can also be confirmed by blood tests; however, these tests are not specific for ethion. Ethion can inhibit the activity of two enzymes in the blood, plasma cholinesterase and erythrocyte acetylcholinesterase. Plasma cholinesterase is more sensitive to inhibition by ethion than erythrocyte acetylcholinesterase in both humans and animals. Plasma cholinesterase activity recovers more rapidly from inhibition than erythrocyte acetylcholinesterase because of the higher turnover rate of plasma cholinesterase proteins compared to erythrocytes. Exposures that occurred two weeks or more before testing probably would not be reflected in an inhibition of plasma cholinesterase. Because of the human variability in activity of these enzymes, follow-up determinations showing a rise back to a constant activity are more reliable evidence than a single determination that exposure has taken place. Many other organophosphate and carbamate insecticides can cause inhibition of blood cholinesterases.

Ethion has been detected in saliva of pest control applicators (Nigg et al. 1993). Diethyl phosphate metabolites of ethion were also detected in the workers' urine. The correlation between urinary metabolites and saliva ethion was 0.55, indicating that saliva ethion was not a good predictor of absorbed ethion. The authors stated that mouth contamination may have influenced the results. Further development of this method may result in a specific biomarker of exposure for ethion.

2.8.2 Biomarkers Used to Characterize Effects Caused by Ethion

The toxic effects of ethion are caused by its inhibition of neural acetylcholinesterase in the peripheral and central nervous systems. This inhibition is reflected by the level of depression of erythrocyte acetylcholinesterase activity in the blood.

The nervous system can accept a certain amount of acetylcholinesterase inhibition without overt toxic effects. In humans and animals, toxic signs are generally not seen until at least 20% of this enzyme (measured as erythrocyte acetylcholinesterase) has been inhibited (Ecobichon 1991). Adaptation can also occur. In an animal study, brain acetylcholinesterase was inhibited 90% after a 2-year inhalation exposure to the organophosphate dichlorvos (Blair et al. 1976), yet no symptoms of cholinergic overstimulation were observed. With ethion and other organophosphate compounds, the best predictor of toxicity is not necessarily the actual percentage of inhibition of acetylcholinesterase, but rather how rapidly this inhibition has occurred. Rapid inhibition does not give the nervous system time to physiologically adapt to acetylcholinesterase inhibition. This adaptation appears to involve desensitization and down-regulation of muscarinic receptors (Fitzgerald and Costa 1993).

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.9 INTERACTIONS WITH OTHER CHEMICALS

Reports on specific interactions of ethion with other chemicals are limited. Ethion administered orally at 25 mg/kg in rats did not increase the lethality of 53.5 mg/kg of the organophosphate bromophos-ethyl (Muacevic 1973). Several of the other organophosphates tested (parathion, chlorfenvinphos) increased the toxicity of bromophos-ethyl in this study. Pretreatment with phenobarbital to induce cytochrome P-450 enzymes significantly reduced the lethality of ethion in Holtzman rats after intraperitoneal injection (LD_{50} without pretreatment, 25.9 mg/kg; with phenobarbital pretreatment, 302.6 mg/kg). However, lethality in CF_1 mice in the same study was unaffected by pretreatment with phenobarbital (DuBois and Kinoshita 1968).

The major interaction of concern for ethion would be with chemicals that have the same mechanism of action (i.e., organophosphate and carbamate pesticides). Simultaneous exposure to ethion and one of these chemicals could possibly have an additive effect on inhibition of neural acetylcholinesterase.

Whether a toxic interaction would occur with a particular chemical depends on how it affects the toxicokinetics of ethion. The toxicity of a given dose of ethion could conceivably be potentiated by interactions with chemicals that interfere with its detoxication; however, no such interactions have been reported. This effect has occurred with other organophosphates, e.g., the potentiation of malathion by the carboxylesterase inhibitor EPN (ethyl *p*-nitrophenyl benzenethiophosphonate) in rats and dogs (Frawley et al. 1957). Some chemicals can induce the synthesis of cytochrome P-450 enzymes (polysubstrate mixed function oxidases) in the liver (e.g., organochlorines). Whether this would increase or decrease the toxicity of ethion in humans is not known. While mixed function oxidases are responsible for the activation of ethion (via desulfuration), it is not known if they play any role in detoxication since specific metabolic pathways are unknown. For the same reason, interactions of ethion with inhibitors of mixed function oxidases cannot be predicted. These effects are species specific; induction decreased the lethality of ethion in rats but had no effect in mice (DuBois and Kinoshita 1968).

2.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to ethion than will most persons exposed to the same level of ethion 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 ethion, or compromised function of organs affected by ethion. Populations who are at greater risk due to their unusually high exposure to ethion are discussed in Section 5.7, Populations With Potentially High Exposures.

Individuals with impaired respiratory function or diseases of the central or peripheral nervous systems may be more susceptible to the effects of ethion since these sites are the main targets for toxicity. People with impaired esterase production would be unusually susceptible to ethion exposure because of a reduced ability to metabolize ethion absorbed by the body. This population would include people suffering from liver diseases (hepatitis, cirrhosis). Pregnant women have lower levels of plasma cholinesterase and are more susceptible to agents such as succinylcholine, which is metabolized by this enzyme. Ethion can bind stoichiometrically to this enzyme and inhibit its activity, so pregnant women are at least hypothetically more susceptible to ethion exposure than other populations. A similar effect could be expected in individuals with inherited abnormally low plasma cholinesterase levels. Individuals may not know if they have decreased plasma cholinesterase and other esterases and, therefore, may not know that they are more susceptible to the effects of ethion.

2.11 METHODS FOR REDUCING TOXIC EFFECTS

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

"Cholinesterase inhibitor pesticides" in *Handbook of Poisoning*, 1987, Appleton and Lange, Norwalk, CT; R.H. Dreisbach and Robertson, WO

"Organophosphates and other insecticides" in *Clinical Management of Poisoning and Drug Overdose*, 2nd edition, 1990, W.B. Saunders, Philadelphia; L.M. Haddad and J.F. Winchester, eds.

"Insecticides: Organophosphates and carbamates" in *Goldfrank's Toxicologic Emergencies*, 5th ed., 1994, Norwalk; C.K. Aaron and M.A. Howland.

2.11.1 Reducing Peak Absorption Following Exposure

If exposure has occurred by the oral route, gastric lavage would reduce peak absorption if the treatment is given shortly after exposure. Treatment with activated charcoal would probably also be effective. If exposure has occurred by the dermal route, rinsing the exposed skin with large amounts of flowing water and soap would greatly reduce exposure.

2.11.2 Reducing Body Burden

Because ethion does not accumulate in the body and appears to be rapidly metabolized, specific efforts to reduce the body burden would not appear to be necessary.

2.11.3 Interfering with the Mechanism of Action for Toxic Effects

Ethion has the same mechanism of action as other organophosphorus insecticides. Poisonings with these types of chemicals are common enough that specific and effective medical interventions have been developed. The life-threatening effects of ethion poisoning are related to its effects on the respiratory system (respiratory depression, bronchospasm, increased bronchial secretions, pulmonary edema, muscular weakness). If these symptoms are present, artificial respiration and suctioning are performed via an endotracheal tube. Atropine is used to counteract the muscarinic effects of ethion, with care being taken that symptoms of atropine overdose do not occur (dry mouth, dilatation of the pupils).

Pralidoxime (2-PAM or Protopam), a cholinesterase reactivator, can be used as an antidote for organophosphate poisoning, and is typically given in conjunction with atropine. Enzyme reactivation, accomplished by hydrolysis of the oxygen-phosphorus bond, occurs most markedly at the neuromuscular junction, restoring skeletal muscle response and, importantly, normalizing diaphragm excursion and respiratory effort. Pralidoxime must be administered as rapidly after organophosphate exposure as possible, as its efficacy is inhibited by the “aging” phenomenon. The “aging” involves a chemical

change in the organophosphate-enzyme complex and occurs within minutes to hours (see Section 2.4.2 for more details). The resulting compound, a monoethoxyphosphorylated acetycholinesterase molecule, is very stable and resistant to the effects of pralidoxime.

2.12 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 ethion 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 ethion.

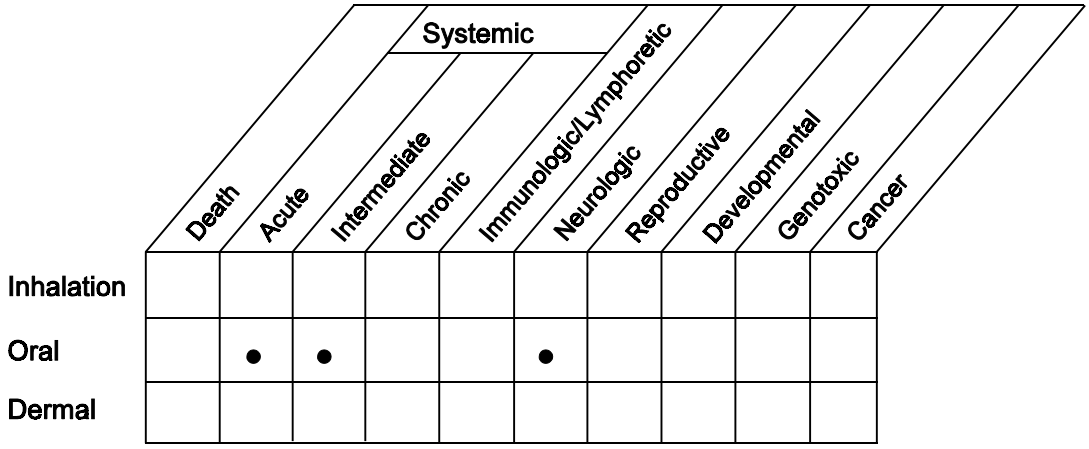
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

2.12.1 Existing Information on Health Effects of Ethion

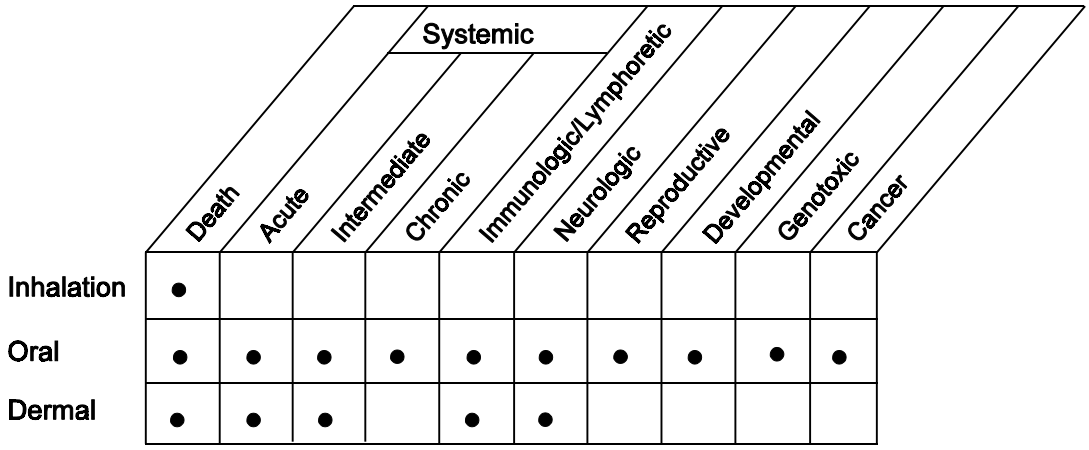
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of ethion. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As shown in Figure 2-4, information on health effects of ethion in humans is limited to systemic and neurological effects. A case report of a poisoning incident (Comstock et al. 1967) and an unpublished

Figure 2-4. Existing Information on Health Effects of Ethion



Human



Animal

● Existing Studies

intermediate-duration oral exposure study in volunteers (Palazzolo 1970) are available. No studies describing health effects in humans after inhalation or dermal exposure for any duration or chronic-duration oral exposure were located.

Information on health effects in animals after exposure to ethion is far more extensive (see Figure 2-4). However, almost all of these studies were performed to satisfy EPA pesticide registration requirements and have not been published in the open literature.

2.12.2 Identification of Data Needs

Acute-Duration Exposure. Populations in the vicinity of hazardous waste sites may be exposed to ethion for brief periods. Exposure would most likely occur by contact with contaminated soil, but drinking contaminated water is also possible. The central and peripheral nervous systems are the major target organs for ethion toxicity by the oral and dermal routes. The specific target of ethion is the enzyme that catalyzes the hydrolysis of the neurotransmitter acetylcholine, neural acetylcholinesterase. High doses of ethion can be extremely toxic by the oral route as demonstrated by a case report of a 6-month-old boy where a single oral dose of 15.7 mg/kg would have been fatal without aggressive medical intervention (Comstock et al. 1967). Threshold doses for clinical effects and/or cholinesterase/acetylcholinesterase inhibition after oral exposure to ethion are available for several species including humans, rats, mice, dogs and rabbits. Threshold doses for acetylcholinesterase inhibition after dermal exposure in the rabbit are also available (Weiner 1985a, 1985b cited in EPA 1989d).

The intermediate-duration oral MRL of 0.002 mg/kg/day derived for ethion based on a NOAEL of 0.06 mg/kg/day for inhibition of brain acetylcholinesterase in Beagle dogs (Bailey 1988) is applicable to acute-duration exposures as well. The acute-duration oral toxicity of ethion is well understood, and no further studies appear necessary. Inhalation exposure at hazardous waste sites to levels that produce detectable toxic effects is unlikely. Since the most likely route of exposure to ethion at hazardous waste sites is dermal contact with contaminated soil, a study that establishes a threshold value for acetylcholinesterase inhibition in a second species may be useful for risk assessment.

Intermediate-Duration Exposure. An intermediate-duration oral MRL of 0.002 mg/kg/day was derived for ethion based on a NOAEL of 0.06 mg/kg/day for inhibition of brain acetylcholinesterase in

dogs (Bailey 1988). A well conducted study in humans is available on the effects of intermediate-duration oral exposure to ethion (Palazzolo 1970). Results in animal studies indicate that the toxic effects of intermediate-duration exposure to ethion are similar to those for the acute-duration by both the oral and dermal routes. No further intermediate-duration studies in animals would appear to be necessary.

Chronic-Duration Exposure and Cancer. There is limited information regarding the potential toxic effects of chronic, low-level exposure to ethion. A chronic-duration oral MRL of 0.0004 mg/kg/day was derived for ethion based on a NOAEL of 0.06 mg/kg/day for inhibition of brain acetylcholinesterase in Beagle dogs in an intermediate-duration study (Bailey 1988). A chronic-duration (2-year) oral study has been done in rats and mice and produced no evidence of carcinogenicity by this route (Morrow 1985a, 1985b). No neurological or systemic effects were found at the doses (1.12–2 mg/kg/day) used in this study. Chronic-duration exposure is the most likely type of exposure that would be experienced by people living near hazardous waste sites containing ethion. This exposure is most likely to be by dermal contact with contaminated soil, although drinking contaminated water or soil ingestion by children could cause oral exposure. Exposure to ethion contaminated dust is not likely to cause intoxication.

Genotoxicity. Ethion has been tested for genotoxicity in several *in vitro* test systems and has tested uniformly negative both with and without metabolic activation. A single *in vivo* study in chickens showed an increase in sister chromatid exchanges following oral ethion exposure (Bhunya and Jena 1994). Further *in vivo* tests in rats or mice are needed to confirm these results.

Reproductive Toxicity. No information on reproductive toxicity in humans after ethion exposure is available. Ethion did not cause reproductive toxicity by the oral route in a 3-generation study in rats or histopathological evidence for damage to reproductive tissues in intermediate- or chronic-duration studies. Ethion is not known to be an endocrine disruptor. Further studies on reproduction in animals after exposure to ethion would not appear to be necessary.

Developmental Toxicity. No information on developmental toxicity in humans after ethion exposure is available. Ethion did not cause teratogenicity in rats or rabbits, although skeletal abnormalities were seen at maternally toxic doses. Additional animal studies in which neurobehavioral, immunological, and reproductive end points are assessed up through sexual maturity following pre- and postnatal exposure may be helpful to determine if developmental effects become apparent after birth.

Immunotoxicity. Ethion has tested negative in a skin sensitization study in guinea pigs. No reports of allergic contact dermatitis after exposure to ethion in humans were located. It appears that further immunotoxicity studies are not necessary.

Neurotoxicity. The neurotoxicity of ethion via acetylcholinesterase inhibition is understood. A no effect level is available for humans and threshold doses for acetylcholinesterase inhibition have been established for several species. A delayed neurotoxicity test was negative in chickens for ethion. Additional animal studies do not seem to be warranted at this time.

Epidemiological and Human Dosimetry Studies. Epidemiological/occupational studies would be useful for adequately assessing risk of exposure to ethion. At the present time, very few people are exposed to ethion outside occupational groups. The major group potentially exposed, pest control workers, generally use several different pesticides, and it may be difficult to identify a group exposed primarily to ethion. However, well designed epidemiological studies of exposed workers that examine the effects of ethion on the nervous system would be useful for establishing cause/effect relationships.

Biomarkers of Exposure and Effect.

Exposure. Reliable biomarkers for exposure to ethion already exist (plasma cholinesterase, erythrocyte acetylcholinesterase, and clinical symptoms of neurotoxicity). However, reliable methods to distinguish ethion intoxication from that caused by other organophosphorus compounds do not exist.

Effect. Reliable biomarkers for the effect of ethion exist (cholinergic symptoms of neurotoxicity and erythrocyte acetylcholinesterase).

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics of ethion are not well understood. Two major data needs were identified. Studies should be done where ethion and ethion monoxon are measured in tissues rather than radioactivity derived from labeled ethion. The metabolites of ethion (besides diethyl phosphate) have not been identified beyond their solvent extraction behavior. Without this information, the potential toxicity of metabolites cannot be assessed.

Comparative Toxicokinetics. No data needs have been identified for comparative toxicokinetics.

Methods for Reducing Toxic Effects. Further studies on retarding gastrointestinal absorption of ethion and the effectiveness of absorbents would be useful in the treatment of poisoning. No methods exist for increasing the excretion of ethion and the active metabolite ethion monoxon. The medical management of the toxic effects of ethion (respiratory support, atropine treatment, reactivation of neural acetylcholinesterase with oximes) is similar to that for poisoning by other organophosphate insecticides. Any improvements in the management of organophosphate poisoning would apply to ethion.

Children's Susceptibility There are no populations of children identified that are specifically exposed to ethion. Poisonings of children by this chemical appear to be exceedingly rare since only one case report could be found in the literature (Comstock et al. 1967). The clinical course for this 6-month-old was very similar to that seen in adults poisoned by other organophosphate insecticides, and his recovery appeared to be complete as late as one year post-exposure. In future incidents of ethion poisoning of children and adults, better estimates should be made of exposure level, exposure route, and metabolite levels relative to the observed symptoms of toxicity. The only animal study comparing effects of ethion between juveniles and adults showed marginally greater toxicity (lower LD_{50}) in juvenile rats after intraperitoneal injection (Brodeur and DuBois 1963). Additional animal studies examining nonlethal end points in juvenile and adult animals following ethion exposure are needed. In particular, studies examining the dermal and oral routes of exposure would be the most useful.

It is conceivable that children, particularly very young children, may be more susceptible to the effects of ethion than adults, due to suspected differences in metabolic activities. However, comparative metabolic data for ethion in children and adults is lacking, specifically data regarding cytochrome P450 and esterase activities. Data are also lacking as to whether there are differences in absorption, distribution, or excretion of ethion between children and adults. Additional animal pharmacokinetic and metabolic studies comparing fetal, juvenile and adult animals, preferably supplemented with studies utilizing human tissues where appropriate, will be needed to clarify these issues. Biomarkers of exposure need to be further studied in order to better estimate human exposure at all age levels following acute or chronic exposure to ethion. Also, developmental studies in animals are needed to quantitatively measure placental transfer of ethion and its metabolites and to determine whether ethion and its metabolites can be metabolized by placental tissue.

Child health data needs relating to exposure are discussed in Section 5.8.1 Identification of Data Needs: Exposures of Children.

2.12.3 Ongoing Studies

No ongoing studies on ethion were located.

3. CHEMICAL AND PHYSICAL INFORMATION

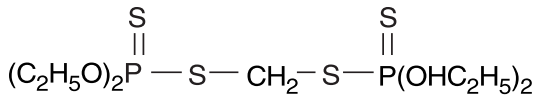
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of ethion is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of ethion is located in Table 3-2.

Table 3-1. Chemical Identity of Ethion

Characteristic	Information	Reference
Chemical name	Ethion	HSDB 1998
Synonym(s)	Phosphorodithioic acid; S,S'-methylene O,O,O',O'-tetraethyl ester; ethyl methylene phosphorodithioate; O,O,O',O'-tetraethyl S,S'-methylenediphosphorodithioate; bis[-(diethoxyphosphinothioyl)mercapto]methane	Merck 1989
Registered trade name(s)	NIA1240, Ethanox, Nialate, RP8167, Rodocide, and others	HSDB 1998
Chemical formula	$C_9H_{22}O_4P_2S_4$	Merck 1989
Chemical structure		
Identification numbers:		
CAS Registry	563-12-2	HSDB 1998
NIOSH RTECS	TE455000	HSDB 1998
EPA Hazardous Waste	7800010	HSDB 1998
OHM/TADS/DOT/UN/NA/IMCO	IMO 6.1; UN 3018; NA 2783	HSDB 1998
HSDB	399	HSDB 1998
NCI	No data	

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

Table 3-2. Physical and Chemical Properties of Ethion

Property	Information	Reference
Molecular weight	384.48	Merck 1989
Color	White/colorless to amber	Tomlin 1994
Physical state	Liquid	Tomlin 1994
Melting point	-12 to -13	Merck 1989
Boiling point	164–165 at 0.3 mm Hg	EPA 1989b
Density at 19 EC	1.220 at 20 EC	Merck 1989
Odor	Odorless in pure form; technical product has a disagreeable odor	HSDB 1998
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Fresh water at 25 EC	0.6 mg/L	Sharom et al. 1980a
Salt water at 25 EC	No data	
Organic solvent(s)	Xylene, chloroform, acetone, kerosene plus 1% methyl ethyl ketone, benzene	Merck 1989
	Most organic solvents	HSDB 1998
Partition coefficients:		
Log K_{ow}	5.073	Bowman and Sans 1983
Log K_{oc}	4.189 (average in four soils) 3.810 (organic soil) 3.936 (beverly sandy loam) 4.004 (plainsfield sand)	HSDB 1998 Sharom et al.1980b
Vapor pressure at 20 EC	1.5×10^{-6} mm Hg	EPA 1989b; Merck 1989
Henry's law constant: at 25 EC	6.9×10^{-7} atm m^3/mole	HSDB 1998

Table 3-2. Physical and Chemical Properties of Ethion *(continued)*

Property	Information	Reference
Hydrolysis half-life		
30 EC (sterile water)	pH 4 & 7 146 days pH 8 62 days pH 10 1 day	Dierberg and Pfeuffer 1983
30 EC (non-sterile drainage water)	26 days	
25 EC (Water with 1% ethanol)	pH 4.5 99 weeks pH 5 63 weeks pH 6 58 weeks pH 7 25 weeks pH 8 8.4 weeks	Chapman and Cole 1982
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits at 25 EC	May burn but does not ignite readily	HSDB 1998
Reactivity	Hydrolyzed by acids and alkalies	Tomlin 1994
	Emits toxic oxides of sulfur and phosphorous (T$150 EC)	Sax 1984
	Slowly oxidized in air	Tomlin 1994
Conversion factors (25 EC)	1 ppm = 15.7 mg/m^3 1 mg/m^3 = 0.064 ppm	Calculated
Explosive limits	Tends to decompose with violence above 150 EC	HSDB 1998

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

4.1 PRODUCTION

Ethion is the FMC Corporation trademark name for the active ingredient O,O,O',O'-tetraethyl S,S'-methylene bis (phosphorodithioate) (SRI 1997; Tomlin 1994). This insecticide is produced commercially by reacting dibromomethane with O,O-diethyl hydrogen phosphorodithioate in ethanol under controlled pH conditions (HSDB 1998). The FMC Corporation, the only U.S. manufacturer of this chemical, produces ethion at its Agricultural Chemical Group in Baltimore, Maryland (SRI 1991, 1992, 1993, 1995, 1996, 1997).

Ethion production in the United States for 1972 was estimated to be 1.36 million kg (2.97 million pounds) (HSDB 1998). No more recent production estimates for ethion were located. As with many toxic chemicals, especially those whose production or use involves proprietary information, quantitative estimates of production are virtually impossible to obtain (Bason and Colborn 1992).

No current information is available from the Toxics Release Inventory (TRI) database on facilities that manufacture or process ethion, the intended use, or the range of maximum amounts of ethion that are stored on-site because ethion is not one of the chemicals that facilities were required to report (EPA 1995e).

4.2 IMPORT/EXPORT

No historic or recent estimates are available on the volume of ethion imported into the United States (HSDB 1998). No information was located on either past or current volumes of ethion exported from the United States. Data on past and/or current import and export volumes are not adequate to assess trends in import and export volumes of this pesticide. While the import and export volume for pesticides as a group are often available, the data are not typically broken down by individual pesticide (Bason and Colborn 1992).

4.3 USE

Ethion is an organothiophosphate member of the organophosphate pesticide family that was first registered for use in the United States in 1965 (EPA 1989b, 1989d). This pesticide was first developed as a nonsystemic insecticide and acaricide for use on fruit trees, including citrus fruits (grapefruit, lemons, limes, oranges, tangelos, and tangerines), other fruit trees (apples, apricots, cherries, nectarines, peaches, pears, plums, and prunes), nut trees (almonds, chestnut, filberts, pecans, and particularly walnuts), fiber crops (cotton), and seed and forage crops (alfalfa, corn, and sorghum). as well as a wide variety of fruits and vegetables (beans, cucumbers, eggplants, grapes, melons, onions, peanuts, peppers, pimentos, summer squash, strawberries, and tomatoes) (EPA 1989b, 1989d). Ethion is used in conjunction with petroleum oils on dormant trees to kill eggs and scale insects (HSDB 1998). It is also used for control of aphids, spider mites, scale insects, thrips, lepidopterous larvae, leafhoppers, maggots, suckers, and soil-dwelling insects on a wide variety of food, fiber, and ornamental crops, including grapes, fruits, vegetables, and nuts (Farm Chemicals Handbook 1993; Tomlin 1997). Other uses include applications as a topically applied pesticide agent on livestock to control biting flies and other insects or skin parasites, such as ticks (EPA 1989b, 1989d).

With the steady elimination of older organochlorine pesticides from the market, the use of ethion and other organophosphates has replaced many of the functions once filled by organochlorine pesticides (Mosha et al. 1990a, 1990b, 1991). In addition to its registered applications in agriculture, ethion is also used in terrestrial nonfood crops (Bermuda grass, junipers, ornamental evergreens, pine trees, lawns, ornamental turf, and ornamental plants), in greenhouse nonfood crops including ornamental plants, and in domestic outdoor uses associated with domestic dwellings and lawns (EPA 1989b, 1989d; Farm Chemicals Handbook 1993). The methods of application for ethion include: ground and aerial foliar applications, furrow treatments by ground equipment, and seed treatments (EPA 1989b, 1989d). Several different types of ethion formulations are produced including: an emulsifiable solution (500 g/L), wettable powders (25%), dusts (2, 3, and 4%), emulsifiable concentrates (4 and 8 lbs/gal), granules (5 and 10%), and seed treatments (EPA 1989b; 1989d; Farm Chemicals Handbook 1993; Tomlin 1997).

Estimated ethion use in the United States was 0.32 million kg (0.70 million pounds) in 1974 (HSDB 1998). Estimated ethion use in the United States increased slightly to 1.255 million pounds (0.570 million kg) of the active ingredient in the early 1980s (Gianessi 1986). This volume appears to have remained steady through the late 1980s as EPA (1989d) estimated that between 1.2 and 1.5 million

pounds (0.55–0.68 million kg) of active ingredient of ethion were used in the United States annually. By 1992, the estimated annual use of ethion by agriculture was 868,218 pounds (USGS 1992). No more recent information on ethion use was located in the literature.

With respect to its use application in 1974, 70% of the ethion applied was used as an insecticide and acaricide on citrus fruit and 30% was used on other fruit and nut crops and cotton (HSDB 1998). In a study of use application, EPA (1989d) estimated that from 86 to 89% of the ethion used in the United States was applied to citrus crops, and the remaining 11–14% was applied to cotton, a variety of fruit and nut trees, and vegetables. No more recent information on use applications for this pesticide was located.

4.4 DISPOSAL

Ethion is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1995a, 1995b). Disposal of wastes containing ethion is controlled by a number of federal regulations (see Chapter 7).

There are two primary recommendable methods for the disposal of ethion and ethion-containing wastes including hydrolysis with subsequent disposal in a landfill and incineration by a variety of methods in a unit with effluent scrubbing (EPA 1981; IRPTC 1985). Ethion undergoes rapid chemical hydrolysis under alkaline (>pH 8) conditions (Dierberg and Pfeuffer 1983; IRPTC 1985). IRPTC (1985) recommends that ethion or ethion-containing wastes be mixed with excess calcium oxide or sodium hydroxide and sand or other adsorbent in a pit or trench at least 0.5 m deep in a clay soil. Sodium hydroxide (or sodium carbonate) can also be added to the mixture to help speed the reactions when calcium oxide is used as the primary alkali agent. The amount of calcium oxide or sodium hydroxide used depends on the amount of pesticide to be disposed of and, to some extent, the concentration of active ingredient in the pesticide, and the actual chemical nature of the active ingredient. A practical guideline, in the absence of specific directions, is to use an approximate volume or weight of alkali from 50 to 100% that of the pesticide. For dilute formulations, such as a 1% solution or dust formulations of ethion, the amount of calcium oxide or sodium hydroxide can be reduced by one-half. For very concentrated ethion formulations (over 80% active ingredient), the amount of calcium oxide or sodium hydroxide can be doubled, but the concentrate should be mixed first with water (or soapy water) before reaction with the alkali. For safety, a preliminary test should be conducted in which very small amounts

of ethion and alkali are mixed to ensure that the mixture does not react too vigorously. For added safety, sizable quantities of ethion can be disposed of in several smaller batches, rather than all at once (IRPTC 1985).

For ultimate disposal, large amounts of ethion residuals can be incinerated in a unit with effluent gas scrubbing (IRPTC 1985) or by fluidized bed, rotary kiln, or liquid injection incineration (EPA 1981). Ethion is a potential candidate for fluidized bed incineration at a temperature range of 450–980 EC and residence times of seconds for liquids and gases and longer for solids. Ethion is also a potential candidate for rotary kiln incineration at a temperature range of 820–1,600 EC and residence times of seconds for liquids and gases and hours for solids. Ethion is also a potential candidate for liquid injection incineration at a temperature range of 650 to 1,600 EC and a residence time of 0.1–2 seconds (EPA 1981).

Currently, empty pesticide containers should be triple-rinsed with water and then transferred to a proper hazardous waste disposal facility. On February 11, 1994, the EPA proposed container design requirements for nonrefillable and refillable pesticide containers. This Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) authorized action also includes standards on pesticide removal from containers before disposal, standards for containment of bulk pesticide containers, and procedures for container refilling operations (EPA 1994). No information was located on past or current volumes of ethion or ethion-contaminated wastes disposed of by any of the disposal method described. Facilities involved in the production or processing of ethion are not required to report the amount of ethion wastes disposed of by any disposal method (EPA 1995e).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Ethion is released to the environment solely by human activities. Atmospheric emissions result from volatilization of the chemical during manufacturing and formulation, from soil and vegetation resulting from its use as an insecticide and acaricide or from drift during pesticide application or careless mixing and cleanup procedures during or after application. Ethion can be released to surface waters directly by point source dischargers, from drift during pesticide applications, and by nonpoint source runoff from agricultural and urban areas. Ethion is released to soils directly by pesticide application to the soil, from dripping off sprayed vegetation, when used as a seed treatment, and from careless mixing and cleanup procedures during and after application. No current information is available on total environmental releases of ethion from production and processing facilities to air, water, and soil because these facilities are not required to report releases to the Toxics Release Inventory (TRI) (EPA 1995e).

Although ethion is found in most environmental compartments, the compound shows a pronounced tendency to partition to soil and sediment. By using an equation for estimating the bioconcentration factor (BCF) of a chemical derived from its physical and chemical properties, it was determined that ethion has the potential to bioaccumulate in aquatic organisms (Kenaga 1980). However, no experimentally measured BCF values for ethion were located for fish, shellfish, or other aquatic organisms. The half-life of ethion in three tropical soils ranged from 9–15.5 days (Mithyantha and Agnihothrodu 1984), while in temperate sandy loam and organic soils of Ontario, Canada, the half-life values ranged from 7 to 8 weeks (49–56 days) (Miles et al. 1979). Given adequate time, ethion will be degraded by physical, chemical, and biological processes, however, the parent compound can persist at low concentrations from one growing season to the next (25% carryover), and these concentrations can build up slowly in the soil over several growing seasons (Chapman et al. 1984; Miles et al. 1978).

If released to the atmosphere, ethion can exist in both the vapor-phase and adsorbed-phase, although the adsorbed-phase will predominate (Eisenreich et al. 1981). In the vapor-phase, ethion will react with photochemically produced hydroxyl radicals at an estimated half-life (first-order kinetics) of 40.13 minutes (Meylan and Howard 1993; SRC 1995). Ethion in the adsorbed-phase will be subject to washout from the atmosphere by wet and dry deposition.

Ethion released to surface waters is subject to hydrolysis, volatilization, photolysis, and biodegradation. Volatilization, photolysis, and biodegradation are minor degradation processes that can remove small amounts of ethion in water. Hydrolysis, however, appears to be the most important mechanism for degradation, particularly in high alkaline conditions (pH >9) in water. Ethion is susceptible to very slow hydrolysis in water with half-lives ranging from 63 to 8.4 weeks at pH values ranging from 5 to 8. Hydrolysis becomes relatively rapid at alkaline pHs (pH 9 and above), resulting in half-life values of 1 day (Dierberg and Pfeuffer 1983). If released to water, this pesticide has the potential to bioaccumulate, assuming that rapid degradation of the compound by hydrolysis does not occur. Ethion has been detected only rarely in both surface water and groundwater monitoring studies typically at concentrations below 0.5 ppb.

If released to soils and sediments, microbial degradation of ethion is the most important process for the removal of the compound based on degradation studies with sterile versus nonsterile soils. The half-life of ethion in sterile sandy soil loam and organic soil was found to be greater than 24 weeks, while the half-life in these same nonsterile soils was 7–8 weeks (Miles et al. 1979). This suggests that microbial degradation is an important fate process. Ethion is generally only slightly mobile in some sandy soils with a low organic matter content (<3%). However, based on the compound's measured K_{oc} value in soils with moderate-to-high levels of organic matter, ethion is relatively immobile and does not leach into groundwater.

Although some historic information is available from large scale environmental monitoring efforts conducted in the 1970s, and 1980s (Carey et al. 1978; Cohen 1986; Gilliom 1985), recent monitoring efforts under national or regional programs have not analyzed for ethion in air, water, soil, sediment, or fish. This makes it difficult to provide current quantitative estimates on the fate, transport, and bioaccumulation of ethion in various environmental compartments. No information was located on measurement of ethion or of its oxons in the atmosphere. In addition, no information was located on ethion concentrations in air samples from rural or urban areas or in ambient indoor air. Ethion was detected in indoor air at a pesticide production facility, but not a pesticide storage area (Lewis and Lee 1976). This pesticide has been detected rarely in surface water and in groundwater, but little quantitative information is available. It has also been detected in soil and sediment in areas where it is extensively used in agriculture typically at concentrations less than 8 ppm (Miles and Harris 1978a). Current information is lacking on the total amount of ethion released to the environment and on the amount of ethion that partitions into each environmental compartment.

The best-documented concern over ethion relates to acute exposures of humans during or immediately following pesticide applications. This concern is warranted, since ethion is used for some applications in urban areas (lawns and gardens) that increase the possibilities of general population exposure. Ethion and its major oxygen analog, ethion monoxon, have significant acute toxicity to humans. The predominant exposure pathway for the general population appears to be via consumption of small amounts of the chemical in ethion-contaminated food, particularly fruits and root vegetables, and via inhalation both during or immediately following application in agricultural areas where this pesticide is extensively used (e.g., citrus crops). Relative to inhalation, oral exposure probably accounts for a major portion of the exposure of the general population.

In addition to small quantities of ethion that are ingested via ethion-contaminated food, infants and young children may be at increased risk via oral exposure if they put unwashed fingers, toys or other objects, or soil contaminated with ethion in their mouths. Children may also receive dermal exposure if they come in contact with freshly treated vegetation or soil around domestic structures, or if they unknowingly enter ethion-treated agricultural areas before appropriate reentry intervals have elapsed. Children living in households of farmers or agricultural workers that apply ethion or work in fields or orchards treated with ethion may be indirectly exposed if they come in contact with shoes and other contaminated clothing of their parents, or if these clothing articles are not separately washed and stored from other domestic laundry.

Occupational exposure may occur through inhalation and dermal exposure routes associated with the manufacture, formulation, and application of ethion. The magnitude of exposure is greatest for those individuals occupationally exposed to ethion, particularly those involved in production and manufacturing of ethion, those involved in its mixing and application for agricultural and commercial uses, and those workers involved in its disposal at hazardous waste sites. It should be noted that the amount of ethion detected by chemical analysis is not necessarily the amount that is bioavailable.

Ethion has been identified in at least 9 of the 1,577 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2000). However, the number of sites evaluated for ethion is not known. The frequency of these sites can be seen in Figure 5-1.

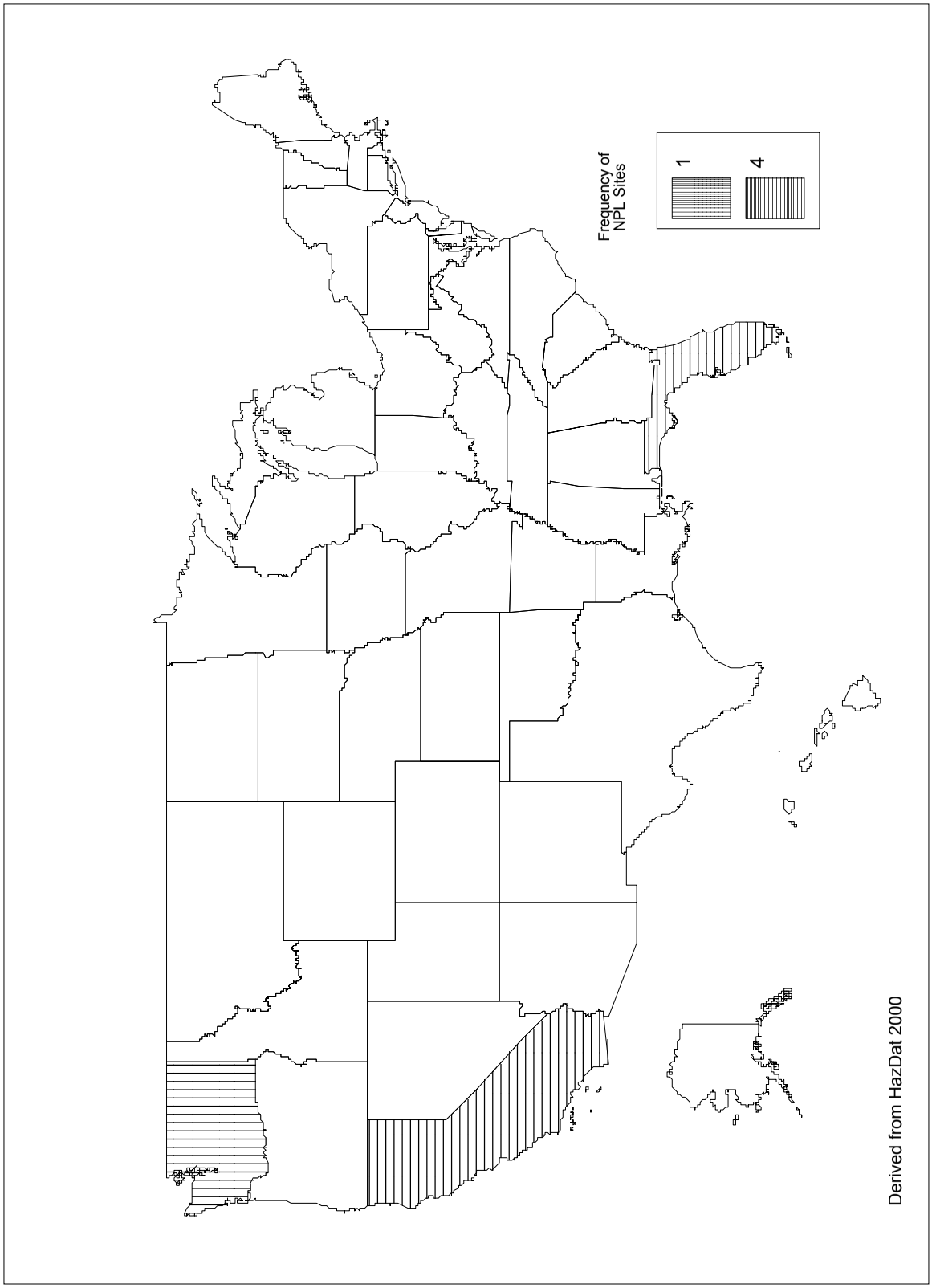


Figure 5-1. Frequency of NPL Sites with Ethion Contamination

5.2 RELEASES TO THE ENVIRONMENT

The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list. Facilities involved in the production or processing of ethion are not required to report the amount of releases of ethion to various environmental matrices (EPA 1995e, 1995f).

Ethion has been identified in a variety of environmental media (air, surface water, groundwater, soil, and sediment) collected at 9 of the 1,577 EPA National Priorities (NPL) hazardous waste sites (HazDat 2000).

5.2.1 Air

Ethion is released into the atmosphere solely by human activities associated with its production and use as a insecticide and acaricide. These releases include releases to ambient air from production and packaging facilities or agricultural applications. It appears that ethion, once field-applied, can undergo volatilization to the atmosphere. However, based on the vapor pressure for ethion (see Table 3-2), this appears to be a relatively minor fate process (Eisenreich et al. 1981; Thomas 1990).

There is no information on releases of ethion to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported to the TRI Database (EPA 1995e). Ethion was detected in indoor air at a formulation plant in south Florida in 1974 at 4 $\mu g/m^3$ (Lewis and Lee 1976). By contrast, ethion was not detected in indoor air of a storage shed where ethion was stored in sealed containers.

Ethion has been identified in 1 outdoor air sample collected from 9 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2000). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

5.2.2 Water

Ethion can reach surface waters directly from point source discharges associated with its production and from nonpoint source inputs introduced from agricultural applications associated with spray drift or careless applications near water (Braun and Frank 1980; Frank et al. 1982; Miles and Harris 1978a, 1978b). Frank et al. (1982) found evidence in a study of 11 agricultural watersheds in the Canadian Great Lakes Basin from 1975 to 1977 that residues of ethion and other pesticides could reach surface waters from deposition close to or directly into stream water during the process of drawing water, mixing the pesticide, spraying, or by cleaning pesticide spraying equipment and by seepage from discarded containers in or around the spray site. In addition, heavy rainfall within a few days of a field application often led to the runoff of the pesticide and deposition in streams. In the Frank et al. (1982) study, ethion was only rarely (0.4% of the samples) found in surface waters during the 1975–1976 study and was not detected during the 1976–1977 study. Ethion was typically found in surface waters samples immediately after application. The oxons of ethion were not detected in any surface water samples. These authors estimated that ethion unit-area loadings (losses) to streams draining these watersheds totaled 10 mg/hectare (ha) with the mean and maximum unit-area loading in 1975–1976 of 0.1 and 0.6 mg/ha, respectively, and the mean and maximum in 1976–1977 of 0.0 and 0.0 mg/ha, respectively. For ethion, all spray-season losses of ethion were attributed to spills, drift, or direct application in surface waters rather than to runoff events. The overall mean concentration of ethion in water collected from these watersheds was <0.01 ppb (minimum [not detected] to maximum [0.4 ppb]) for 1975–1976, and the overall mean was not detected (minimum [not detected] to maximum [not detected]) for 1976–1977. In a study of the Holland Marsh drainage basin in Ontario, Canada, Miles and Harris (1978a) reported that the rate of ethion transfer was highest in the spring during maximum runoff periods.

In another study in the Great Lakes region, ethion was qualitatively identified in tributary stream feeding into Lake Ontario, Lake St. Clair, and Lake Huron (Great Lakes Water Quality Board 1983). Gilliom (1985) also reported that as part of the U.S. Geological Survey (USGS) and EPA Pesticide Monitoring Network conducted between 1975 and 1980, ethion was monitored in surface water at 174 stations nationwide, but was detected at only 0.6% of the stations sampled (detection limit=0.25 ppb).

Based on its K_{oc} value (see Table 3-2), ethion is moderately to highly immobile in soils under most typical soil conditions and is not likely to migrate through the soil and contaminate groundwater (Swann et al. 1983). Although detected only rarely, ethion has been found in some groundwater wells in

agricultural areas in the United States (Cohen 1986). However, no quantitative information on groundwater concentrations were located for the United States. It has not been possible to obtain quantifiable estimates of ethion loadings to groundwater.

There is no information on releases of ethion to surface water from manufacturing and processing facilities because ethion releases are not required to be reported to the TRI Database (EPA 1995e).

Ethion has been identified in 1 surface water and 4 groundwater samples collected from 9 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2000).

The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

5.2.3 Soil

Ethion is released into soils primarily from its registered uses on various agricultural crops, as an acaricide in veterinary applications against various sucking insects of domestic stock, and as a seed treatment, or via spills directly to soils associated with the process of mixing the pesticide, spraying, or by cleaning pesticide spraying equipment and by seepage from discarded containers in or around the spray site. Because of its affinity for binding to organic matter, soils are the ultimate repository for the majority of ethion applications.

In agricultural areas, ethion may also be transferred to aquatic sediments through drift or spillage or via improper disposal of the chemical after application (Frank et al. 1982; Miles and Harris 1978b; Miles et al. 1978). Miles and Harris (1978b) reported that ethion residues in bed sediments from the Holland Marsh agricultural drainage system, an area where ethion was extensively used, ranged from 0.043–0.073 ppm. Since ethion undergoes various chemical and biological degradation reactions in the course of time ranging from days to months, these loadings to soils and sediments typically are a temporary phenomena (Dierberg and Pfeuffer 1983; Miles et al. 1979); however, carryover from one year to the next can result in a build-up of ethion residues under some field conditions (Chapman et al. 1984; Miles et al. 1978). The lack of environmental data makes it difficult to estimate the actual build-up of ethion in basins that receive drainage waters from ethion-treated agricultural lands.

There is no information on releases of ethion to soil from manufacturing and processing facilities because these releases are not required to be reported to the TRI Database (EPA 1995e).
Ethion has been identified in 8 soil and 2 sediment samples collected from 9 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2000).

The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

5.3 ENVIRONMENTAL FATE

Ethion can move into various environmental compartments (air, surface water, groundwater, soil, sediment, and biological organisms). For this chemical, the primary environmental reservoir or sink is soil and sediment. The compound is retained in soil for moderate periods of time, depending on soil temperature and the amount of organic matter content in the soil. Ethion can potentially bioaccumulate in aquatic food chains, although little quantitative information on concentrations in edible fish and shellfish was located.

5.3.1 Transport and Partitioning

Based on its vapor pressure (see Table 3-2), if ethion is released to the atmosphere, it will be expected to exist both in the vapor-phase and particulate phase, although the particulate phase will predominate (Kenaga 1980; Eisenreich et al. 1981). Ethion in the adsorbed particulate form will be subject to washout from the atmosphere by both wet and dry deposition. In the atmosphere, the kinetic motion of the pesticide molecules as well as air currents will cause their distribution (Haque and Freed 1974). The molecules will distribute vertically with the heavier molecules having the highest concentration at the bottom and the lighter molecules at the top. Vapor-phase ethion is heavier than air and will consequently concentrate on the bottom. The vapor pressure of a chemical can give a good estimate of air transport as long as the chemical is in the free state or is evaporating from an inert surface (Haque and Freed 1974). When the chemical is bound to a soil surface, the vapor pressure cannot be used to accurately predict vapor transport. The vapor pressure of ethion will be greatly attenuated by its strong sorption to soil surfaces (Sharom et al. 1980a; Swann et al. 1983). Therefore, ethion is not expected to exist in the vapor-phase at an appreciable level above soil surfaces.

Ethion released to water from both point and nonpoint sources may be emitted to the atmosphere by volatilization, sorbed to soils and sediments, or accumulated in aquatic organisms. Evaporation may not be significant based upon the Henry's law constant (see Table 3-2), and volatilization of ethion is not likely to be an important transport process (Racke 1992; Thomas 1990). Ethion released to water also may be adsorbed significantly by soils and sediments based on its K_{oc} values measured in soil (Sharom et al. 1980a; Swann et al. 1983). These authors reported that after 10 successive washes with distilled water, 13.9% of the ethion had leached from sandy soil, while only 1.2% had leached after 10 successive washes from organic soil. Because this pesticide is significantly adsorbed by soils with high organic content, leaching into groundwater is unlikely to occur to any significant extent except in soils with relatively low organic content (Miles et al. 1979).

Using the method of Kenaga (1980) to estimate the BCF value of ethion based on the compound's physical-chemical properties, ethion was found to have the potential to significantly bioaccumulate in aquatic organisms. The estimated BCF for ethion ranged from 418 to 1,300, based on water solubility data and the K_{oc} value, respectively. The BCF value estimated from the log K_{oc} suggests that bioconcentration can be potentially significant for this compound. However, there were no experimentally measured BCF values located in the scientific literature to verify that bioaccumulation occurs in any fish, shellfish, or other aquatic organism. Despite the high lipid solubility of ethion, distribution studies in rats (Selim 1985a), goats (Mosha 1991), and chickens (Mosha et al. 1990a) have shown no preferential distribution to adipose tissue. The high lability of ethion to esterases in the blood and liver may explain these findings.

Ethion and its metabolites have not been widely monitored in aquatic species such as fish and shellfish. Since ethion and its metabolite ethion monoxon are toxic, a measure of caution may still be in order in cases where there is reason to believe edible fish or shellfish have had recent exposure to ethion. This is partially the basis for the EPA recommendation that states consider routine monitoring for ethion in edible fish and shellfish species as part of their state toxics monitoring programs, particularly in those watersheds where extensive use of ethion is identified (EPA 1995g).

Ethion released in soil from its registered uses partitions slightly to the atmosphere through volatilization, slightly to surface water via runoff, and only slightly to groundwater as a result of leaching. According to Kenaga (1980), chemical compounds with a K_{oc} of <100 are considered moderately to highly mobile; ethion with a K_{oc} value of 15,435, therefore, would be considered almost immobile. Additional

parameters influencing the leaching potential of this chemical include the soil type (e.g., clay, organic matter, or sand), the amount of rainfall, the depth of the groundwater, and the extent of degradation. In laboratory tests of sand and organic soil, Sharom et al. (1980b) found that (after 5 successive 200 mL rinses with distilled water) 0.00, 0.4, 0.6, 1.0, and 1.5% of ethion leached from sand, respectively, and a total of only 13.9% of ethion added to the sand was leached after 10 successive 200 mL rinses with distilled water. In organic soil, however, (after 5 successive 200 mL rinses with distilled water) 0.0, 0.0, 0.03, 0.09, 0.11, and 1.2% of ethion leached from soil, respectively; and only 1.2% of ethion added to the organic soil was leached after 10 successive 200 mL rinses with distilled water. The amount leached from the sandy soil was over 10 times greater than that leached from the organic soil, although the leachability of ethion was far less than for many of the other organophosphates tested. While ethion can show high sorption in soils with high organic content (>3%), in most other soil types (sands), ethion has properties suggesting only a slight potential for leaching into groundwater (Sharom et al. 1980b).

In a study of groundwater contamination in California, ethion was detected, but not quantified in 5 out of an unspecified number of groundwater well samples (Cohen 1986). In the Great Lakes region of Ontario, Canada, Frank et al. (1982) reported that ethion was detected in only 0.4% of all surface water samples collected from 11 agricultural watersheds from 1975 to 1976 at a maximum concentration of 0.05 ppb. Ethion was not detected, however, during the 1976–1977 monitoring season (Frank et al. 1982).

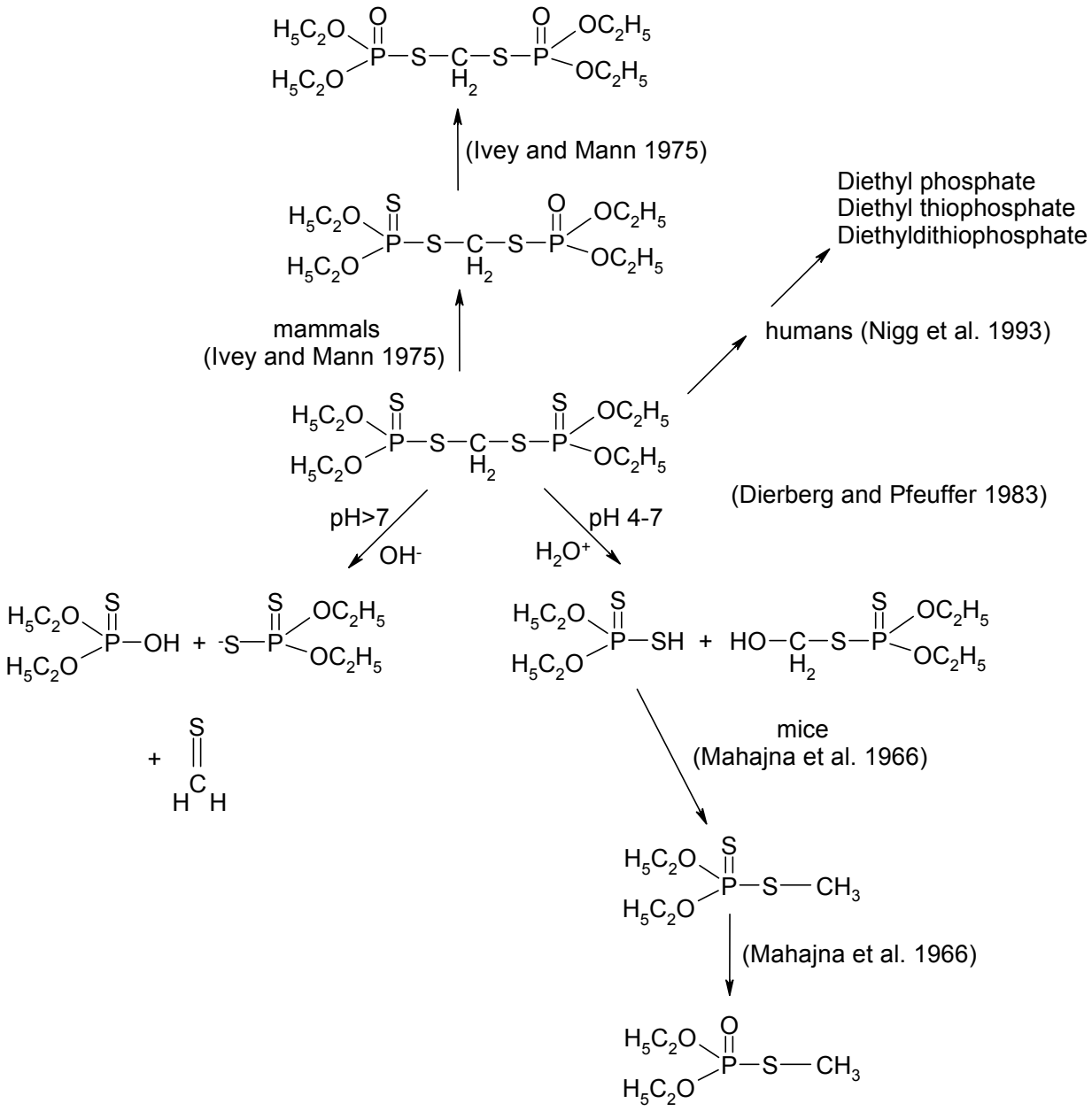
5.3.2 Transformation and Degradation

Ethion is subject to a variety of physical, chemical, and biological degradation processes in all environmental compartments. Some of these transformation pathways are shown in Figure 5-2.

5.3.2.1 Air

Ethion, once released to the atmosphere, may be subject to direct photolysis; however, because ethion does not absorb light in the spectrum above 290 nm (Gore et al. 1971), direct photolysis is likely to be only a minor fate process. In the vapor-phase, ethion can react rapidly, however, with photochemically produced hydroxyl radicals. The half-life (first-order kinetics) for the vapor-phase reaction of ethion with hydroxyl radicals in the atmosphere is estimated to be 40.13 minutes, assuming an atmospheric concentration of containing $5x10^5$ hydroxyl radicals/m^3 at 25 EC (Meylan and Howard 1993; SRC 1995). No other information on the transformation processes of ethion in the atmosphere was located.

Figure 5-2. Transformation of Ethion



5.3.2.2 Water

Ethion released to water may be subject to both abiotic degradation (i.e., hydrolysis and photolysis) and biotic degradation by microorganisms. The rate of abiotic degradation is influenced strongly by pH and temperature. Cowart et al. (1971) studied the rate of hydrolysis of 7 organophosphate pesticides, including ethion in distilled water samples at a pH of 6. Over a 6-week study period, these authors reported that the percentage of undegraded ethion was 92, 84.2, 71.3, 38.9, 37.9, 31.2, 13.4, 6, and 5.2% at 2 hours, 1 day, 2 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, and 6 weeks post-application, respectively. These authors found that ethion and parathion were the two most persistent organophosphates tested, and that as a general rule, the rate of hydrolysis in distilled water increases with decreasing sulfur content of the organophosphate tested. Chapman and Cole (1982) also studied the influence of pH on the degradation of ethion in sterile water at 25±3 EC. These authors reported estimated half-life values (first-order kinetics) for ethion of 99, 63, 58, 25, and 8.4 weeks at pH values of 4.5, 5, 6, 7, and 8, respectively. The lower temperature conditions of this study may account for the much slower ethion degradation rates in the acidic pH range. In a laboratory study, Dierberg and Pfeuffer (1983) reported that the hydrolysis half-life of ethion in buffered distilled water at 30 EC was 20.8 weeks at a pH ranging from 4 to 7 (first-order kinetics and independent of pH), 8.9 weeks at pH 8 (second-order kinetics), and 1 day at pH 10 (second-order kinetics). Degradation of ethion was most rapid under alkaline conditions.

Available studies conducted using natural water and sterilized natural water suggest that hydrolysis rather than microbial degradation is the most important degradation process for ethion in water. Dierberg and Pfeuffer (1983) reported that the half-life of ethion in natural and sterilized Florida canal water was very similar, between 24 and 26 days over a 12-week study period, which suggested that hydrolysis rather than microbial degradation was a significant mechanism of loss from Florida surface waters. This contrasts sharply with results obtained by Sharom et al. (1980a) using sterile and unsterile Ontario, Canada marsh water where half-lives of greater than 16 weeks were calculated. The incubation temperature of the Dierberg and Pfeuffer (1983) study was 4 EC higher and the initial ethion concentrations were lower; however, the similarity of the half-lives for the sterile and unsterile distilled water controls between the two investigations suggests that these differences were minor in accounting for the degradation rates in the two surface waters. Degradation was more affected by temperature, suggesting that hydrolysis was the primary mode of degradation. In contrast to the half-life of 26 days reported by Dierberg and Pfeuffer (1983) for unsterile canal water, is the half-life value (>8 weeks) given

by Eichelberger and Lichtenberg (1971) for water from the Little Miami River, Florida incubated under similar laboratory conditions (except for the presence of light). The inclusion of light in the latter study demonstrates that photolysis may not be a competitive degradation pathway for ethion compared to hydrolysis.

Gore et al. (1971) reported that ethion in a hexane solvent did not absorb ultraviolet light above 260 nm, which suggests that direct photolysis does not readily occur. Frank et al. (1991) investigated the degradation of ethion in surface and groundwater samples for 164 days, but found little difference in the rate of ethion degradation in light and dark conditions, indicating that photolysis was not a major fate process. The half-life (first-order kinetics) of ethion of 51 days (light) and 58 days (dark) suggests that photolysis was not a major factor in degradation. The ambient temperature during this degradation experiment ranged from -3.8 to 37.0 EC. These authors also compared the degradation of ethion in two controlled temperature regimes of 4 and 21 EC at a pH of 8. These authors calculated a half-life (first-order kinetics) for ethion of 34 days at 21 EC as compared to 84 days at 4 EC.

Sharom et al. (1980a) studied the degradation of ethion under laboratory conditions using both distilled water and natural water samples. The rate of degradation was comparable (half-life >16 weeks) in natural water (pH 7.7), sterilized natural water, sterilized distilled water, or distilled water, suggesting biodegradation of ethion was not occurring. Under these experimental microcosm conditions, hydrolysis appears to be the major transformation process operative in the natural water system. Discrepancies in the rates of ethion degradation in water reported in the literature appear to be influenced by both abiotic and biotic factors.

Although ethion has been detected in groundwater samples only rarely in the United States (Cohen 1986; HazDat 2000), no studies were identified dealing with ethion transformation and degradation processes within aquifers. Based on theoretical considerations, abiotic hydrolysis mechanisms would be expected to degrade ethion within a few months to years (99 weeks to 8.4 weeks at a pH of 4.5 and 8, respectively) (Chapman and Cole 1982).

5.3.2.3 Soil Transformation and Degradation

Once released to soils and sediments, ethion can be degraded by hydrolysis, photolysis, and biodegradation. Hydrolysis may be a significant degradation process under alkaline soil conditions. Photolysis, while possible, is not likely to be a significant degradation process because ethion does not absorb ultraviolet (UV) light above 260 nm (Gore et al. 1971). Microbial degradation appears to be the major pathway for the degradation of ethion in soils (Miles et al. 1979). Ethion degraded with a half-life of 69–102 days in an aerobic soil metabolism study (EPA 1989b).

Miles et al. (1979) studied the persistence of 8 organophosphate pesticides including ethion in sterile and nonsterile mineral (sandy loam) and organic soils. Ethion was the most persistent of the organophosphates tested. These authors reported that 50% of the initial concentration of ethion still remained at >24 weeks in sterile sandy loam and sterile organic soil. In nonsterile soil, however, 50% of the initial concentration remained after 7 and 8 weeks in sandy loam and organic soil, respectively. Ethion was slightly more persistent in organic soil than in the sandy loam. These authors concluded that microbial degradation played a major role in the degradation of ethion from the soils tested.

Miles et al. (1978) studied the use of ethion as a seed furrow treatment for the control of onion maggots in the Holland Marsh in Ontario, Canada from 1972 to 1975. These authors reported that a 25% carryover of ethion residues in the soil occurred from one yearly application to the next. Ethion soil residues were 1.83±1.42 ppm (dry weight basis) in 1972, 6.93±8.31 ppm in 1973, 5.75±4.98 ppm in 1974, and 3.47±2.83 ppm in 1975. Chapman et al. (1984) also reported that concentrations of ethion in field microplots over a 3-year period suggested that some carryover was occurring. These authors reported that in the fall of 1977, concentrations of ethion in soil treated with a granular formulation to control onion maggots were 4.36 ppm. Soil concentrations in the spring and fall of 1978 were 1.85 and 3.06 ppm, respectively. Ethion residues in the spring of 1979 were not analyzed, and the fall concentrations were 7.77 ppm, and fell only slightly to 7.6 ppm in the spring of 1980 indicating slow degradation in winter.

Sherman et al. (1974) studied iron sulfide production from ethion-enriched soils by bacteria found in lagoonal sediments of the Indian River-Banana River in Florida. These authors reported that ethion enriched sediment samples from the Indian River were used as the source of sulfur-utilizing bacteria (probably *Clostridium*) in culture tube experiments. Inoculated media that contained both an iron wire

and ethion gave evidence of darkening of the wire; but more significantly, they gave evidence of iron sulfide (FeS) production at the stab-line of the inoculation, after 12 hours of incubation. Upon further incubation, the FeS discoloration spread from the inoculation stab-line throughout the culture tube. The authors also concluded that this reaction was an anaerobic process because no FeS was found at the surface of the media slant. Inoculated media that contained iron wire, but had no ethion added, supported bacteria growth, but FeS was not produced. In uninoculated cultures containing both an iron wire and ethion, there was evidence of a chemical reaction of ethion with the wire as indicated by a darkening of the surface of the wire. However, there was no FeS production throughout the medium.

Mithyantha and Agnihothrodu (1984) studied the persistence of ethion in red, black, and laterite tropical soils under 2 moisture conditions (field capacity vs. submergence) using 2 application rates (25 and 50 ppm). These authors reported that ethion degraded more slowly in the acidic laterite soils followed by the red and black soils. Ethion degraded faster as the pH of the soil increased. The pH for the laterite, red, and black soils was 4.6, 6, and 7.8, respectively. Degradation rates for the 2 concentrations of ethion used were similar in each test. The half-life values (first-order kinetics) for ethion in these tropical soils ranged from 9 to 15.5 days when incubated at a temperature of 24±2 EC throughout the test period. The persistence of ethion in three different soil types at two treatment levels of ethion (25 and 50 ppm) is summarized in Table 5-1.

In a study of the fate of ethion in canals draining a Florida citrus grove, Dierberg and Pfeuffer (1983) reported that ethion adsorption to the sandy canal sediments was negligible following ethion applications to the citrus grove, and that ethion concentrations never exceeded 0.03 µg/g (ppm) (dry weight). Sharom et al. (1980b) reported that pesticides were desorbed to a greater degree from a sandy soil than a highly organic soil.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Most information on ethion concentrations in various environmental media derived from large-scale monitoring networks dates from before the mid-1980s and no longer reflects current environmental conditions. There is a noticeable lack of recent national or regional monitoring studies that would allow meaningful estimation of current ethion concentrations associated with various environmental media.

Table 5-1. Percentage of Ethion Remaining in Various Types of Tropical Soils over Time

Soil type (pH) treatment level	% Ethion[a]				
	10 Days	22 Days	35 Days	45 Days	57 Days
Laterite soils (pH 4.6) 25 ppm	66 (16.26)	30 (7.46)	13 (3.36)	7.6 (1.91)	3.3 (0.83)
Laterite soils (pH 4.6) 50 ppm	69 (34.70)	39 (19.25)	20 (10.05)	7.7 (3.87)	2.1 (1.03)
Submerged laterite soils (pH 4.6) 25 ppm	59 (14.82)	35 (8.83)	20 (5.08)	7.2 (1.98)	3.3 (0.83)
Submerged laterite soils (pH 4.6) 50 ppm	48 (24.22)	26 (13.11)	15 (7.32)	4.3 (2.16)	2 (0.98)
Red soils (pH 6) 25 ppm	65 (16.22)	42 (10.61)	17 (4.32)	2.6 (1.03)	3.3 (0.83)
Red soils (pH 6) 50 ppm	67 (33.62)	39 (19.28)	18 (9.10)	6.4 (3.18)	2.1 (1.03)
Submerged red soils (pH 6) 25 ppm	58 (14.60)	32 (8.00)	16 (3.96)	3.6 (0.90)	3.3 (0.83)
Submerged red soils (pH 6) 50 ppm	53 (26.26)	28 (14.13)	16 (7.98)	5.2 (2.16)	2.1 (1.03)
Black soils (pH 7.8) 25 ppm	50 (12.60)	28 (7.11)	16 (4.00)	3.3 (0.83)	2.4 (0.59)
Black soils (pH 7.8) 50 ppm	48 (24.22)	24 (11.82)	12 (5.88)	2.6 (1.03)	0.8 (0.41)
Submerged black soils (pH 7.8) 25 ppm	42 (10.48)	20 (5.10)	10 (2.58)	2 (0.52)	1.8 (0.45)
Submerged black soils (pH 7.8) 50 ppm	48 (24.22)	25 (12.66)	12 (5.88)	2.6 (1.03)	1.7 (0.83)

[a]Values in paratheses are ethion soil concentrations in ppm

Source: Mithyantha and Agnihothrodu 1984

5.4.1 Air

Ethion concentrations or concentrations of its metabolite, monoxon, in the atmosphere were not monitored in several major national and regional study (Glotfelty et al. 1990; Schomberg et al. 1991; Whitmore et al. 1994). Ethion also was not an analyte included in the National Pesticide Monitoring Program during the early 1970s (Kutz et al. 1976). No quantitative information was located on air samples collected either in rural or urban areas, near production or formulation facilities, or in indoor air associated with its use for pest control in greenhouses.

However, ethion was detected at 4 $\mu g/m^3$ in indoor air at a formulation plant in south Florida in 1974 (Lewis and Lee 1976). By contrast, ethion was not detected in indoor air of a storage shed where ethion was stored in sealed containers at the same pesticide formulation plant.

Ethion has been identified in air samples (outdoor air) collected at 1 of the 9 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2000).

5.4.2 Water

Although ethion is considered an extremely hazardous substance under Title III of the Superfund Amendments and Reauthorization Act (SARA) of 1986, also known as the Emergency Planning and Community Right-To-Know Act and is subject to reporting under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980, it has not been widely monitored in the United States in routine surface water or groundwater monitoring networks. Gilliom (1985) reported that as part of the USGS and EPA Pesticide Monitoring Network conducted between 1975 and 1980, ethion was monitored in surface water at 174 stations nationwide but was detected at only 0.6% of the stations sampled (detection limit=0.25 ppb).

In the Great Lakes region, ethion was detected in surface waters in several river basins in southern Ontario, Canada. Frank et al. (1982) monitored agricultural pesticide use and surface water concentrations in 11 agricultural watersheds in southern Ontario. All watersheds drained into the Great Lakes. During 1975, ethion use was estimated to range from 1 to 10 kg/ha. Ethion residues as a result of field use were detected rarely (0.4%) and were detected immediately during the spray season rather than throughout the year. The overall mean concentration of ethion in water collected from these watersheds

was <0.01 ppb (minimum [not detected] to maximum [0.4 ppb]) for 1975–1976 and the overall mean was not detected (minimum [not detected] to maximum [not detected]) for 1976–1977. In another study in the Great Lakes region, ethion was qualitatively identified in tributary stream feeding into Lake Ontario, Lake St. Clair, and Lake Huron (Great Lakes Water Quality Board 1983). In a study of the occurrence of pesticides in Spanish surface waters, ethion was detected in 1 out of 6 water samples from the Segre River Basin (west of Catalonia) at an estimated concentration of 0.01 µg/L (Planas et al. 1997). A group of research scientists recently completed a study of pesticide concentrations in the Arno river which supplies over 90% of the drinking water to Florence, Italy (Griffini et al. 1997). Water samples were collected from the river entering the drinking water treatment plant of Florence and from the finished drinking water. Of the 167 water samples analyzed from 1992 to 1995, none contained any detectable amount of ethion (detection limit = 0.010 µg/L).

In a groundwater contamination study of 28 of California's 58 counties that evaluated over 50 pesticides (from both point and nonpoint sources), ethion was detected (but not quantified) in 5 samples out of an unspecified number of groundwater samples (detection limit not specified) (Cohen 1986). Ethion however, was not included as an analyte of interest in the EPA Pesticides in Ground Water Database (EPA 1989c). This database was developed to compile the results of monitoring studies conducted by pesticide registrants, universities and government agencies and identified the pesticides that have been looked for in groundwater, the areas monitored, and the pesticides that have been detected.

Ethion has been identified in 1 surface water and 4 groundwater samples collected from the 9 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2000).

5.4.3 Sediment and Soil

Ethion has not been the focus of many recent national soil or sediment monitoring programs in the United States, but has been monitored in regional studies associated with agricultural applications in both the United States and Canada. Ethion was one of the organophosphate pesticides monitored in soils collected from 37 states as part of 1971 National Soils Monitoring Program (Carey et al. 1978). These authors reported that of 1,141 soil samples collected from 4 hectare sites throughout the US, ethion was detected in only 2 samples (0.2% positive detections) at concentrations ranging from 0.06 to 0.24 ppm. Ethion was detected only in samples collected in two states, California and Florida. Ethion was not detected in any crop samples that were analyzed for this study (detection limits 0.01–0.03 ppm).

Possibly because of its lack of detection in the 1971 National Soils Monitoring Program, ethion was not one of the 9 organophosphate pesticides monitored in soils collected as part of 1972 National Soils Monitoring Program (Carey et al. 1979).

Miles et al. (1978) reported on results of a regional study conducted on agricultural soils of high organic content in Holland Marsh, Ontario, Canada. These authors reported that ethion was used as a seed furrow treatment for control of first generation onion maggots and its use comprised 80% of the total organophosphate soil residues. Ethion was detected in soil at all 13 farms in the Holland Marsh study area from 1972 to 1975. Mean soil residues were 1.83±1.42 ppm, 6.93±8.31 ppm, 5.75±4.98 ppm, and 3.47±2.83 ppm (dry weight) for 1972, 1973, 1974, and 1975 respectively. The authors also demonstrated both in field and laboratory studies an ethion carryover rate of 25% from one planting season to the next when ethion was applied in a granular form.

Winterlin et al. (1984) reported that ethion was detected in soil collected from a lined evaporation bed used for disposal of pesticide wastes in California. Ethion was not detected in the soil horizon from the surface to a depth of 1 inch but was detected at concentrations of 4.1 to 4.6 ppm in the 1–6-inch soil horizon and was not detected in soil samples from the 6- to 12-inch soil horizon.

Gilliom (1985) reported that, as part of the USGS and EPA Pesticide Monitoring Network conducted between 1975 and 1980, ethion was monitored in bed sediments at 163 stations nationwide, but was detected at only 0.6% of the station (detection limit=0.25 ppb). Ethion has been detected in organic mud of the Holland Marsh drainage system in southern Ontario, Canada (Miles and Harris 1978b). Ethion was detected in these sediments at concentrations ranging from 0.043 to 0.073 ppm. Miles and Harris (1978a) also reported that ethion was detected in soil collected from 23 of 28 vegetable farms in southwestern Ontario, Canada. Soil concentrations ranged from trace amounts (<0.02 ppm) to 7.81 ppm at a maximum. On 15 of the farms, the ethion concentration in the soil was > 1.0 ppm and ethion was the major organophosphate residue reported.

Ethion has been identified in 8 soil and 2 sediment samples collected from the 9 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2000).

5.4.4 Other Environmental Media

Nigg et al. (1988) conducted a study of the distribution of ethion in Valencia oranges grown in Florida. The purpose of the study was to determine the distribution of ethion, ethion monoxon, and ethion dioxon between the peel and pulp of Florida Valencia oranges, and whether the concentration for the entire fruit was representative of ethion concentrations in the consumed portion (peeled orange). These authors found that ethion levels in whole mature fruit declined from 1.8 ppm at 3 days post-spraying to 0.6 ppm 35 days thereafter. The mature fruit samples collected prior to spraying ethion, contained ethion in the peel at 1.6 ppm. This mature harvestable crop, treated 9 months prior to sampling, contained ethion pulp residues below 0.02 ppm (unquantifiable trace level) and no detectable ethion monoxon or ethion dioxon. From these data, the authors concluded that the pulp (edible portion) contains a very small percentage of the whole fruit ethion.

MacNeil and Hikichi (1976) studied the degradation of ethion on pears and pear and grape foliage. Ethion concentration on pears treated with 8 lb/acre ethion (wettable powder–25%) decreased from 3.96±0.31 ppm at day 0 to 2.54±0.12 ppm, 1.95±0.08 ppm, 1.18±0.26 ppm, 1.19±0.01 ppm and 0.67±0.01 ppm after 1, 2, 3, 4, and 5 weeks, respectively. Pear leaves were treated with 8 lb/acre ethion (wettable powder–25%). Ethion concentrations on pear leaves declined from 3.34±0.56 ppm at day 0 to 3.41±1.78 ppm, 2.43±0.72 ppm, 1.21±0.26 ppm, 1.46±0.18 ppm, 0.40±0.19 ppm, 0.34±0.07 ppm, and 0.27±0.09 ppm at day 1, 3, 6, 14, 21, 28, and 35, respectively. Grape leaves were treated with 1 lb/acre ethion (wettable powder–25%). Ethion residues were 0.59±0.07 ppm on day 0 and declined to 0.40±0.07 ppm, 0.20±0.14 ppm, 0.10±0.06 ppm, 0.10±0.11, 0.02±0.01 ppm, 0.02±0.02 ppm, and 0.01±0.01 ppm at day 1, 3, 6, 14, 21, 28, and 35, respectively.

Ethion was found in 6 of 30 composite samples of fruit (at a maximum concentration of 0.265 ppm) collected from 30 markets in 24 different cities from June 1968 through April 1969. Corneliussen (1970) reported that average residues of ethion on fruit could be reduced from 0.024 ppm before processing to 0.014 ppm after processing. Furthermore, this author calculated the average retention of ethion residues on the fruit samples to be 58% after processing.

The FDA conducted a total diet study to determine dietary intake of selected pesticides, industrial chemicals, and heavy metals, including radionuclides, in 20 cities from October 1978 to September 1979 (Gartrell et al. 1985a). These authors reported that the average ethion concentrations (ppm) were

<0.0001 and 0.0014 for garden fruits and fruits, respectively, and that ethion exposures (µg/day) from garden fruits, fruits, and all groups of foods combined were 0.0018, 0.312 and 0.314, respectively. In a similar study conducted from October 1979 to September 1980, Gartrell et al. (1985b), reported that ethion was detected in root vegetables and fruits. The average ethion concentration (ppm) was 0.0008 and 0.0003, respectively, and the ethion exposures (µg/day) from root vegetables, fruits, and all foods combined were 0.0263, 0.0658, and 0.0921, respectively. Similarly, Gartrell et al. (1986) reported that ethion was detected in root vegetables, garden fruits, and fruits at 0.0001, 0.0007, and 0.0014 ppm, respectively. The average ethion exposures (µg/day) from root vegetables, garden fruits, fruits, and all groups of foods combined were 0.0021, 0.0482, 0.031, and 0.36, respectively, which rose slightly over the previous years.

Almost 20,000 samples of food and feed commodities were evaluated as part of a 5-year study from 1981 to 1986 conducted by the FDA Los Angeles District Laboratory to determine pesticide residues in domestic and imported foods and animal feeds (Hundley et al. 1988). These authors reported that ethion was detected in a wide variety of domestic foods: grapefruit, grapes, romaine lettuce, strawberries, and tomatoes; however, none of the samples exceeded EPA tolerance limits. Ethion was also detected in the following imported foods: apples, green beans, limes, cucumbers, pickling cucumbers, eggplant, Japanese eggplant, cantaloupe, honeydew melon, watermelon, nectarines, Chinese peas, peppers (Anaheim, bell, caribe, fresco, jalapeno, poblano, yellow) Italian squash, tomatoes, and cherry tomatoes; however, only residues in Chinese peas, bell peppers, and Serrano peppers exceeded the EPA tolerance limits. The overall violation rates for domestic and imported samples collected on a surveillance basis were 3.0 and 2.6%, respectively.

Luke et al. (1988) reported on a study of 19,851 samples of domestic and imported foods that were analyzed for pesticide residues by the FDA Los Angeles District Laboratory from 1982 through 1986. The authors reported that ethion was detected in 425 food samples; however, in only 2 of these samples did the concentrations of ethion exceed the 2 ppm tolerance limit.

Concentrations of ethion in ready-to-eat foods were monitored for 10 years from 1982 to 1991 through the FDA's Revised Market Basket Survey (KAN-DO Office and Pesticides Team 1995). Ethion was detected in 199 samples of 31 different foods at a mean concentration of 0.0053 µg/g (5.3 ppb), and the ethion oxygen analogue was detected eight times in five different foods at a mean concentration of 0.0029 µg/g (2.9 ppb). Ethion was detected in apples, cantaloupe, cherries, donuts, frankfurters, fruit

cocktail, grapefruit and grapefruit juice, grape jelly, oranges, orange juice, orange drink, tomatoes, tomato juice, plums, prunes, raisins, and summer squash, and was also detected in the following baby foods: apple sauce, Dutch apple Betty, meat, beef and vegetables, orange and orange pineapple juice, pears or pears and pineapples. The ethion oxygen analogue was detected in the following adult foods: grapefruit juice, orange juice, and pears and in the following baby foods: orange or orange-pineapple juice.

Minyard and Roberts (1991) reported pesticide residue data for 27,065 samples of foods collected and analyzed in 10 state food laboratories from 1988 to 1989. They reported in 1988, that ethion was detected in 15 of 13,980 samples analyzed with an occurrence frequency of 0.107%, but in only 1 sample was the residue at a significant level. Likewise in the 1989 study, ethion was detected in 25 of 13,085 samples for a frequency of occurrence of 0.0191%, but in only 2 of the samples were the residues at a significant level.

Schattenberg and Hsu (1992) reported on results of a pesticide screening program conducted for 111 different pesticides and performed on 6,970 produce samples collected from 1989 to 1991 at a major food chain in San Antonio, Texas. Ethion concentrations were detected (detection limit of 0.100 ppm) in 3.3% of apples, 0.5% of grapes, 1.8% of oranges, 0.6% of peppers, and 1.3% of strawberries tested. The actual concentrations of ethion detected were not specified.

More recently, Roy et al. (1995) evaluated ethion residues in domestic and imported pears and tomatoes. Ethion was found in <1% of the domestic pears sampled and the maximum concentration detected was 0.03 ppm. Ethion was not detected on any of the imported pears tested. With respect to tomatoes, ethion was detected in <1% of domestic tomatoes at a maximum concentration of 0.21 ppm, and it was also detected in 7% of the imported tomatoes at a maximum concentration of 0.09 ppm. The EPA tolerance limit for both pears and tomatoes is 2 ppm.

Most recently, Berry et al. (1997) conducted a study of human exposures in the lower Rio Grande Valley (in and around the city of Brownsville, Texas) to a variety of pollutants including ethion derived from the consumption of foods and beverages. Ethion was detected in only 1 food sample, at a concentration of 0.009 ppm, during the spring of 1993; and ethion was not detected in any food or beverage samples during the fall of 1993.

The frequency of detection of ethion was 3% in both the FDA adult total diet study conducted from 1978 to 1982 (Yess et al. 1991) and the FDA adult total diet study from 1982 to 1984 (Gunderson 1988). More recently, the frequency of occurrence of ethion detections in the FDA total diet study has remained relatively constant from 2% in 1987 (FDA 1988), 2% in 1988 (FDA 1989), 3% in 1989 (FDA 1990), 2% in 1990 (FDA 1991), 2% in 1991 (FDA 1992), averaged 2% from 1986 to 1991 (FDA 1993), averaged 2% from 1991 to 1993 (FDA 1994), and was 2% in 1994 (FDA 1995).

Gelardi and Mountford (1993) analyzed for the presence of 34 pesticides, including ethion in infant formula. The detection limit range for ethion was <0.001–0.016 ppm. These authors reported that of 110 milk-based formulae and of 59 soy-based formulae analyzed, ethion was not detected in any samples of either formula.

Pesticide residues were evaluated in infant and toddler total diet samples from August 1976 to September 1977 (Johnson et al. 1984). These authors reported that of 117 infant foods tested, ethion was detected in 2 samples in trace amounts, while ethion was detected in only 2 of 132 toddler foods at a concentration of 0.001 ppm. Positive detections were made only in foods in the fruit or fruit juice category.

Yess et al. (1993) summarized the results of a study to monitor pesticide residues in infant and adult foods eaten by infants and children. With respect to surveillance monitoring of domestic foods, these authors reported that ethion (total) was detected in 22 of 2464 apple samples at a maximum concentration of 1.7 ppm, in 1 of 13 orange juice samples at a maximum concentration of 0.03 ppm, in 42 of 862 samples of oranges at a maximum concentration of 1.1 ppm and in 7 of 571 pear samples at a maximum concentration of 0.22 ppm. The concentration of ethion (total), however, did not exceed the EPA tolerances level (2.0 ppm) for any of the domestic foods tested which might be eaten by infants and children. With respect to surveillance monitoring of imported foods, these authors reported that ethion (total) was detected in 9 of 735 apple samples at a maximum concentration of 0.23 ppm, in 1 of 64 orange juice samples at a maximum concentration of 0.02 ppm, in 89 of 474 samples of oranges at a maximum concentration of 0.61 ppm and in 1 of 816 pear samples at a maximum concentration of 0.17 ppm. The concentration of ethion (total), however, did not exceed the EPA tolerances level (2 ppm) for any of the imported foods tested which might be eaten by infants and children. With regard to prepared foods for infants and children, Yess et al. (1993) also reported that the maximum concentrations of ethion (total) detected in Dutch apple Betty were 0.001 ppm, in 3 samples of applesauce or applesauce with other fruits were 0.002 ppm, in 21 samples of orange or orange pineapple juice were 0.01 ppm, in

3 samples of pears or pears and pineapples were 0.003 ppm, in 24 samples of frozen orange juice were 0.008 ppm, and in 6 samples of raw pears were 0.280 ppm. Again, all of the adult foods that might be consumed by infants and children that were tested contained ethion residues well below the EPA tolerance level of 2 ppm.

Ethion residues have also been detected in a variety of fish species in two studies conducted during the 1970s; however, no more recent data on tissue concentrations of ethion were located. Butler and Schutzmann (1978) summarized results of the National Pesticide Monitoring Program conducted from July 1972 through June 1976, that analyzed residues of pesticides in 1,524 samples of juvenile fish collected semi-annually in 144 estuaries nationwide. Composite samples of 25 whole fish were screened for 20 pesticides and PCBs. Ethion was detected in composite samples of juvenile fish collected in two states. Ethion was detected at a mean concentration of 0.169 ppm in 19 of 140 samples collected in Maryland and at a concentration of 0.083 ppm in 1 of 51 samples collected in Texas. Ethion residues were also detected in a regional study of fish collected from 1972 to 1975 from the Holland Marsh, Ontario, Canada (Miles and Harris 1978a). These authors reported that ethion was only detected in fish collected during 1974 at 0.01 ppm in silver bass, 0.01 ppm in catfish, 0.02 ppm in whitefish, and 0.05 ppm in carp. All of the ethion detections were made in fish collected in the agricultural drainage system associated with Holland Marsh, and not in the fish collected downstream in Lake Simcoe.

Ethion residues have also been reported in honey from the northwestern portion of Spain (Garcia et al. 1995). These authors reported that 177 honey samples collected from 1988 to 1990 contained residues of 6 pesticides, including ethion. These pesticides were detected in 69 of the 177 samples tested; however, ethion was detected in only 23 (13%) of the samples at a mean concentration of 3 ppb (range, 1–8 ppb).

Because ethion has been used in veterinary application as a dip to control ticks and other skin parasites, there is the potential for residues to occur in some animal products (Mosha et al. 1990a, 1990b, 1991). Lino and da Silveira (1994) detected ethion residues in the muscle and skin tissue of chickens sampled in Portugal. Ethion concentrations in muscle tissue ranged from 31.32 to 51.37 ppb, and concentrations in skin tissue ranged from 361.3 to 1,796.8 ppb. These authors reported that chickens could be exposed to ethion and other pesticides via feeds or the direct treatment of ethion on the chickens by external application of dusts or sprays, by oral administration in the feed, and/or use of ethion in the chicken houses. Ivey et al. (1975) reported on tissue residues of ethion and its metabolites (ethion monoxon and

dioxon) in the body tissues of domestic turkeys reared in pens on soil treated with an emulsion of ethion (4 lb/gal effective concentration) at a rate of 4, 12, and 40 pounds active ingredient/acre or 4.48, 13.4, and 44.8 kg/ha, respectively. The maximum residues detected in turkey fat and skin, respectively, at 1 week post-application were 0.022 ppm (22 ppb) and 0.080 ppm (80 ppb)for the 4 lb/acre, 0.031 ppm (31 ppb) and 0.410 ppm (410 ppb)for the 12 lb/acre, and 0.295 ppm (295 ppb) and 0.666 ppm (666 ppb) for the 30 lb/acre application rates. Small residues of ethion monoxon were detected at 1–3 weeks post-application in the skin of turkeys only at a rate of 40 lb/acre, but no ethion dioxon was detected in any tissues. In an FDA study, Heikes and Craun (1992) reported the detection of 19 ppm ethion in 1 of 10 anhydrous lanolin samples analyzed in 1991. No ethion residues were detected in any lanolin samples analyzed in 1989. These same authors also detected ethion residues in two lanolin-containing pharmaceutical preparations: 0.28 ppm (280 ppb) in diaper rash ointment and 0.30 ppm (300 ppb) in ophthalmic ointment sampled in 1992. In an earlier 1988 study of the same pharmaceutical preparations, no ethion residues were detected.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

While no quantitative information is available on the percentage of ethion released to each environmental compartment, ethion can be emitted to any or all environmental media (air, surface water, groundwater, soil, and sediment), depending on the source of the release, formulation used, and prevailing environmental conditions. General population exposure to ethion typically occurs through two major routes; inhalation and ingestion of contaminated food or drinking water. The major route of exposure to ethion for the general population is through ingestion of foods contaminated with small residues of ethion or consumption of ethion-contaminated drinking water. The general population may also be exposed to ethion through inhalation of contaminated ambient (outdoor) air, specifically in agricultural areas where ethion is extensively used to control some agricultural pests or in veterinary applications to control external parasites (Lewis and Lee 1976).

A comparison of ethion intakes for various age groups of children and adults derived from FDA total diet studies over the past 25 years are summarized in Table 5-2. Johnson et al. (1984) reported ethion intakes in mg/kg body weight/day for the total diet analysis conducted (1976 and 1977) for infants as trace amounts and $1.1x10^{-6}$, respectively; and for toddlers, trace amounts and $1.1x10^{-6}$, respectively. Ethion intakes, in mg/kg body weight/day, estimated for total diet analyses (1982–1984) were $6.4x10^{-6}$, $1.15x10^{-5}$, $2.2x10^{-6}$, $2.7x10^{-6}$, $2.5x10^{-6}$, $2.0x10^{-6}$, $3.1x10^{-6}$, and $2.2x10^{-6}$ for 6–11-month-old infants,

Table 5-2. Ethion Intakes from Foods for Infants, Children, and Adults in the U.S. Population (in mg/kg/day)

Period of the Total Diet Study	6–11-month-old infants	2-year-old children	14–16-year-old females	14–16-year-old males	25–30-year-old females	25–30-year-old males	60–65-year-old females	60–65-year-old males	Source
1976	Trace	Trace	No data	No data	No data	No data	No data	No data	Johnson et al. 1984
1977	1.1×10^{-6}	1.0×10^{-6}	No data	No data	No data	No data	No data	No data	Johnson et al. 1984
1982–1984	6.4×10^{-6}	1.15×10^{-5}	2.2×10^{-6}	2.7×10^{-6}	2.5×10^{-6}	2.0×10^{-6}	3.1×10^{-6}	2.2×10^{-6}	Gunderson 1988
1987	1.68×10^{-5}	No data	No data	6.3×10^{-6}	No data	No data	7.0×10^{-6}	No data	FDA 1988
1988	1.19×10^{-5}	No data	No data	3.9×10^{-6}	No data	No data	3.3×10^{-6}	No data	FDA 1989
1989	1.67×10^{-5}	No data	No data	6.0×10^{-6}	No data	No data	6.0×10^{-6}	No data	FDA 1990
1990	1.44×10^{-5}	No data	No data	5.9×10^{-6}	No data	No data	5.1×10^{-6}	No data	FDA 1991
1991	1.28×10^{-5}	No data	No data	3.4×10^{-6}	No data	No data	3.5×10^{-6}	No data	FDA 1992
1992	1.46×10^{-5}	2.22×10^{-5}	4.0×10^{-6}	5.0×10^{-6}	4.5×10^{-6}	3.9×10^{-6}	4.9×10^{-6}	3.5×10^{-6}	FDA 1993

2-year-old children, 14–16-year-old females, 14–16-year-old males, 25–30-year-old females, 25–30-year-old males, 60–65-year-old females, and 60–65-year-old males, respectively (Gunderson 1988). Ethion intakes in mg/kg body weight/day, estimated for the total diet analyses for 1987–1992 also increase from intakes estimated in the 1982–1984 analysis and were $1.68x10^{-5}$, $6.3x10^{-6}$, and $7.0x10^{-6}$ in 1987 (FDA 1988); $1.19x10^{-5}$, $3.9x10^{-6}$, and $3.3x10^{-6}$ in 1988 (FDA 1989); $1.67x10^{-5}$, $6.0x10^{-6}$, and $6.0x10^{-6}$ in 1989 (FDA 1990); $1.44x10^{-5}$, $5.9x10^{-6}$, and $5.1x10^{-6}$ in 1990 (FDA 1991); and $1.28x10^{-6}$, $3.4x10^{-6}$, and $3.5x10^{-6}$ in 1991 (FDA 1992) for 6–11-month-old infants, 14–16-year-old males, and 60–65-year-old females, respectively. Ethion intakes in mg/kg body weight/day, estimated for the total diet study were $1.46x10^{-5}$, $2.22x10^{-5}$, $4.0x10^{-6}$, $5.0x10^{-6}$, $4.5x10^{-6}$, $3.9x10^{-6}$, $4.9x10^{-6}$, and $3.5x10^{-6}$ for 6–11-month-old infants, 2-year-old children, 14–16-year-old females, 14–16-year-old males, 25–30-year-old females, 25–30-year-old males, 60–65-year-old females, and 60–65-year-old males, respectively (FDA 1993).

No information was located on the levels of ethion or its oxygen analogs in human tissues, adipose tissue, blood, urine, or breast milk in members of the general population. Ethion was not one of the pesticides monitored as part of the NHANES study (Needham et al. 1990), in the National Adipose Tissue Study (EPA 1986; Phillips and Birchard 1991), or in urine of the general population of the U.S. (Kutz and Cook 1992).

In occupational settings, dermal exposure and subsequent absorption through intact skin represent the most important route of exposure, while inhalation exposure is generally less important (Jeyaratnam and Maroni 1994). Inhalation of ethion depends on its volatility, the type of formulation used, and the application technique employed. Occupational ingestion may occur as a result of poor work practices and/or lack of personal hygiene. Workers employed in industries that manufacture, formulate, package, or apply ethion and workers involved in the disposal of ethion or ethion-containing wastes may be exposed to the highest concentrations of ethion.

Except for professional pesticide manufacturers, formulators, applicators, or farm workers, the exposure risks from ethion appear relatively minor as long as label instructions are followed and safeguards are taken to avoid extensive dermal contact (e.g., use of protective clothing). Studies of dermal exposure typical of ethion suppliers and applicators (spray crews) in Florida citrus spray operations were reported by Wojeck et al. (1981). These authors reported dermal and respiratory exposures for workers mixing and loading ethion for application and for those applying ethion to citrus trees. The suppliers' mean exposures were 1,799±3,793.2 mg/hour and 0.005±0.004 mg/hour for dermal and inhalation exposure,

respectively. The applicators' mean exposures were 1,972.5±244.6 mg/hour and 0.004±0.002 mg/hour for dermal and respiratory exposure, respectively. Dermal exposure accounted for 99% of total exposure, while respiratory exposure represented <1% for both the suppliers and applicators. For both suppliers and applicators, the hands received the highest exposures to ethion. These authors reported that dermal exposure of the hands represented 42% of the total body exposure for applicators and 76% for suppliers, and there were no significant differences in exposures to other areas of the body. A significant amount of variability existed between the groups of supplier and applicators tested, based on the procedures used. Ethion monoxon was detected in most samples, but did not exceed 5% of the total amount of toxicant. This study also points out that management of protective clothing worn by ethion applicators is important in reducing dermal exposures.

Kahn (1976) reported pesticide-related illness in California farm workers exposed to pesticide residues on the foliage of treated crops and in dusty soils of orchards, fields, and vineyards. Of the reported pesticide poisonings from 1949 to 1970, ethion was implicated in 4 separate incidents involving 46 farm workers; however, the incidence always involved ethion and 1 or more other pesticides.

Wolfe et al. (1978) conducted a study to determine the potential dermal and respiratory exposure of workers to ethion at an ethion formulating plant. The studies were conducted during the formulation of 25% water-wettable powder with adsorbed ethion. In order to determine the potential exposure in different work situations, exposure pad studies were carried out on (1) workers who inserted the proper proportions of ingredients into the formulating mixer (mixer), (2) workers who filled bags with the ethion formulation at the filler spout (bagger), and (3) workers who performed a combination of jobs such as packing bags into cartons for shipment or working at the mixing and bagging stations (mixer-bagger-carton packer). Dermal contamination was measured primarily by attaching absorbent pads to various parts of the workers' body and allowing them to be exposed during a timed period of work. Respiratory exposure was estimated from the contamination of special filter pads used in place of the usual outer absorbent filter pads which cover the filter cartridges of the respirators worn by the subjects. The authors calculated that the exposure to ethion for all workers was 126 mg/hour for dermal exposure and 1.71 mg/hour for respiratory exposure. However, the authors reported that dermal exposure at the bagging station (mean 116±234 mg/hour) was greater than at the mixing station (70±121 mg/hour), and exposure of the mixer-bagger-carton package was the highest exposure of all (237±324 mg/hour). Inhalation exposure followed a similar pattern whereby respiratory exposure at the bagging station (mean 1.63±1.56 mg/hour) was greater than at the mixing station (1.15±1.60 mg/hour), and exposure of the

mixer-bagger-carton package was the highest exposure of all (2.67±2.32 mg/hour). Dermal exposure of all workers typically represented 98.7% of the total exposure, while inhalation exposure represented 1.3% of the total exposure. Again, this study points out that management of clothing and respirators is important in reducing exposures.

Several studies have tested the use of various protective clothing or have made recommendations for reducing total dermal exposure to ethion. Wojeck et al. (1981) reported that exposure to the hands represented the largest percentage of total exposure to ethion in workers (suppliers and applicators) and recommended that the use of elbow-length vinyl gloves, washed inside and out with a strong alkaline detergent on a regular basis, would eliminate much of the potential hazard from dermal exposure. Davies et al. (1982) also reported that pesticide illness in agricultural workers often resulted from excessive dermal exposure to pesticides. These authors assessed the protection afforded by changing daily into freshly laundered 100% cotton coveralls. They reported that coveralls provided significantly greater protection from ethion exposure than did regular clothing and the use of respirators. Nigg et al. (1992) conducted a field evaluation of various coverall fabrics to assess heat stress and pesticide penetration. These authors reported that lighter weight, untreated fabrics marginally ameliorated heat stress under severe summer time temperatures in Florida citrus groves, but they also allowed more ethion penetration.

According to the National Institute for Occupational Safety and Health (NIOSH 1994), the Occupational Safety and Health Administration (OSHA), proposed an 8-hour time-weighted average (TWA) permissible exposure level (PEL) for ethion of 0.4 mg/m^3 for skin. However, this standard was vacated by a court decision. Two other organizations, however, adopted the proposed OSHA value. The National Institute for Occupational Safety and Health (NIOSH) recommends that the occupational exposure level not exceed 0.4 mg/m^3 (skin) for a 10-hour TWA workday (NIOSH 1997). In addition, the American Conference of Governmental Industrial Hygienists has recommended a TWA limit (TWA-TLV) of 0.4 mg/m^3 (skin) for occupational exposure to ethion (ACGIH 1997b).

5.6 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 2.7 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).

Information on the effects of ethion on humans is limited, and information on the effects of ethion on children is even more limited. One well documented case report of an acute poisoning incident was reported by Comstock et al. (1967) in which a 6-month-old infant received 6 ounces of milk from an 8-ounce bottle used previously to measure a concentrated solution of ethion in kerosene. The child's exposure represented a dose of 15.7 mg/kg. Ethion is not a pesticide that is used in the home, and no exposure studies on individuals likely to have significant exposure (formulators and applicators) are available in the literature. No information was located on measurements of ethion or its metabolite levels in amniotic fluid, meconium, cord blood, or neonatal blood that indicate prenatal exposure. Ethion and its active metabolite ethion monoxon are highly lipophilic molecules so there should be no significant barrier to crossing the placenta.

In addition, no information was located on measurements of ethion or its metabolite levels in breast milk that might result in post-natal exposure of an infant. Ethion and its active metabolite ethion monoxon are highly lipophilic molecules so their passage into breast milk is possible. This has been examined in animal models. Radioactivity derived from labeled ethion was present in goats' milk after oral exposure (Jobsis and Zeitlow 1985); however, the chemical identity of the radioactivity was not determined. Unchanged ethion (the monoxon was not measured) was detected in goats' milk after oral and dermal exposure to ethion (Mosha et al. 1990b). A total of 0.04–0.05% of the dose appeared in milk, after dermal exposure, and 1.4% after oral exposure.

Children may receive higher ethion doses from dermal exposures if they play on freshly treated grass or soil, or enter a treated agricultural area prematurely (Youngren et al. 1991). It is important that children not be allowed entry into ethion treated areas until the sprays have dried, dusts have settled, or vapors have dispersed to perform hand labor or to play. The reentry intervals described for farm workers should

be strictly adhered to with respect to all human exposures (EPA 1989d). In addition, children may receive potentially higher oral doses from ingestion of ethion treated soils from their hands while playing in contaminated areas. Because soil may be a reservoir for ethion in the environment, consumption of contaminated soil from unwashed hands during hand to mouth activity or from putting contaminated toys or other objects in their mouths could be a major source of ethion-contamination for children. Dermal absorption of ethion is not likely, however, to be significant based on the relatively low amount (3.3%) that is absorbed through the skin (Feldman and Maibach 1974). The vapor pressure of ethion is $1.5x10^{-6}$ mmHg (EPA 1989b; Merck 1989) suggesting that some of it may volatilize from soil surfaces. However, due to its high Koc value, vapor pressure is expected to be greatly attenuated (Haque and Freed 1974). Thus, children's exposure to vapor-phase ethion while playing outdoors on the ground is not expected to be significant. As time goes by, ethion is expected to degrade in the environment through both biodegradation and hydrolysis. Ethion degraded to 50% of its initial concentration after 7 and 8 weeks in nonsterile sandy loam and organic soils, respectively (Miles et al. 1979). Hydrolysis in moist soils may also contribute to the decrease in ethion concentration. Estimated half-life values for the first-order hydrolysis of ethion in sterile water at 25±3 EC was 99, 63, 58, 25, and 8.4 weeks at pH values of 4.5, 5, 6, 7, and 8, respectively (Chapman and Cole 1982). Based on these degradative processes, ethion concentrations in soil are not expected to persist unless there is a continuous source of ethion contamination.

Ethion is not intended for indoor use except within greenhouses (EPA 1989b, 1989d). Therefore, children are not expected to be exposed to ethion indoors unless it is transported inside through contaminated materials or applied illegally indoors.

It is important that children of occupational users of pesticides, not be exposed to the contaminated work clothes or shoes of their parent (NIOSH 1995). Worker protection statements for pesticides state that workers should take off all work clothes and shoes and shower using soap and water, and then put on clean clothes. Personal clothing worn during work must be laundered and stored separately from personal family clothing. Heavily contaminated clothing should be destroyed according to state and local regulations (EPA 1989b). Since some ethion is applied as a dust formulation (see Section 4.3) (liquid ethion adsorbed to a particle matrix), children may be exposed dermally, orally via hand to mouth activities, or via inhalation of dust particles while playing on contaminated floors or carpeting where ethion-contaminated particles may have fallen from contaminated work clothes. However, no literature

could be located documenting ethion's transfer to the home from contaminated work clothes or other articles.

Levels of ethion concentrations in infant and toddler foods and in baby formula are discussed in Section 5.4.4. Gelardi and Mountford (1993) analyzed for the presence of 34 pesticides including ethion in infant formula. The detection limit range for ethion was <0.001–0.016 ppm. These authors reported that of 110 milk-based formula and of 59 soy-based formula analyzed, that ethion was not detected in any samples of either formula. Similarly, pesticide residues were evaluated in infant and toddler total diet samples from August 1976 to September 1977 (Johnson et al. 1984). These authors reported that of 117 infant foods tested, ethion was detected in 2 samples in trace amounts, while ethion was detected in only 2 of 132 toddler foods at a concentration of 0.001 ppb. Positive detections were made only in foods in the fruit or fruit juice category. Yess et al. (1993) summarized the results of a study to monitor pesticide residues in infant and adult foods eaten by infants and children. These authors reported that ethion (total) was detected in 22 of 2,464 apple samples (maximum concentration of 1.7 ppm), in 1 of 13 orange juice samples (maximum concentration of 0.03 ppm), in 42 of 862 samples of oranges (maximum concentration of 1.1 ppm), and in 7 of 571 pear samples (maximum concentration of 0.22 ppm). These authors also reported that ethion (total) was detected in several imported foods including 9 of 735 apple samples (maximum concentration of 0.23 ppm), in 1 of 64 orange juice samples (maximum concentration of 0.02 ppm), in 89 of 474 samples of oranges (maximum concentration of 0.61 ppm), and in 1 of 816 pear samples (maximum concentration of 0.17 ppm). The concentration of ethion (total), however, did not exceed the EPA tolerances level (2 ppm) for any of the domestic or imported foods tested which might be eaten by infants and children.

With regard to prepared foods for infants and children, Yess et al. (1993) also reported that the maximum concentrations of ethion (total) detected in Dutch apple Betty were 0.001 ppm, in 3 samples of applesauce or applesauce with other fruits were 0.002 ppm, in 21 samples of orange or orange pineapple juice were 0.010 ppm, in 3 samples of pears or pears and pineapples were 0.003 ppm, in 24 samples of frozen orange juice were 0.008 ppm, and in 6 samples of raw pears were 0.280 ppm. Again, all of the adult foods that might be consumed by infants and children that were tested contained ethion residues well below the EPA tolerance level of 2 ppm. Concentrations of ethion in ready-to-eat foods were monitored for 10 years from 1982 to 1991 through the FDA's Revised Market Basket Survey (KAN-DO Office and Pesticides Team 1995). Ethion was detected in 199 samples of 31 different foods at a mean concentration of 0.0053 µg/g (5.3 ppb) and the ethion oxygen analogue was detected 8 times in 5

different foods at a concentration of 0.0029 µg/g (2.9 ppb). Ethion was detected in the following baby foods: apple sauce, Dutch apple Betty, meat, beef and vegetables, orange and orange pineapple juice, pears or pears and pineapples. The ethion oxygen analogue was detected in the following baby foods: orange or orange-pineapple juice. Based on these studies, it appears to be unlikely that food containing ethion residues will pose a major health risk to infants and young children except in those instances where the infants and children live on farms where large amounts of ethion are used and they consume large amounts of farm-raised fruits and vegetables.

A comparison of ethion intakes for various age groups of children and adults derived from FDA total diet studies over the past 25 years are summarized in Table 5-2. Trends for adults are discussed specifically in Section 5.5. Johnson et al. (1984) reported ethion intakes in mg/kg body weight/day for the total diet analysis conducted (1976 and 1977) for infants as trace amounts and $1.1x10^{-6}$, respectively; and trace amounts and $1.0x10^{-6}$ for toddlers, respectively. Ethion intakes, in mg/kg body weight/day, estimated for total diet analyses (1982–1984) increased and were $6.4x10^{-6}$ and $1.15x10^{-5}$, respectively, for 6–11-month-old infants, and 2-year-old children. Ethion intakes in mg/kg body weight/day, estimated for the total diet analyses for 1987–1992 also increased from intakes estimated in the 1982–84 analysis and were $1.68x10^{-5}$, in 1987 (FDA 1988); $1.19x10^{-5}$ in 1988 (FDA 1989); $1.67x10^{-5}$ in 1989 (FDA 1990); $1.44x10^{-5}$ in 1990 (FDA 1991); and $1.28x10^{-5}$ in 1991 (FDA 1992) for 6–11-month-old infants. Ethion intakes in mg/kg body weight/day, estimated for the total diet study were $1.46x10^{-5}$ and $2.22x10^{-5}$ for 6–11-month-old infants and 2-year-old-children, respectively (FDA 1993).

In comparison, ethion intakes for older children were more comparable to adult intakes and were $2.2x10^{-6}$ and $2.7x10^{-6}$ for 14–16-year-old females and 14–16-year-old males, respectively (see Table 5-2) (Gunderson 1988). Ethion intakes in mg/kg body weight/day, estimated for the total diet analyses for 1987–1992 also increased slightly from intakes estimated in the 1982–1984 analysis and were $6.3x10^{-6}$ in 1987 (FDA 1988); $3.9x10^{-6}$ in 1988 (FDA 1989); $6.0x10^{-6}$ in 1989 (FDA 1990); $5.9x10^{-6}$ in 1990 (FDA 1991); and $3.4x10^{-6}$ in 1991, (FDA 1992) and $5.0x10^{-6}$ in 1992 for 14–16-year-old males (FDA 1993). Ethion intakes in mg/kg body weight/day, estimated for the total diet study also increased in 1992 and were $4.0x10^{-6}$ for 14–16-year-old females (FDA 1993).

Infants and children receive approximately 2–3 times more ethion in their diets per unit body weight than adults due to higher consumption of fruits and fruit drinks (FDA 1993). Studies have not been done in infants and children on the relationship between dietary intake and the activity of cholinesterases in red blood cells and plasma.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to ethion during its production, formulation, packaging, distribution, use or disposal (see Section 5.5), there are several groups within the general population that have potentially high exposures (higher than background levels) to ethion. These populations include individuals living in proximity to sites where ethion is produced or processed or sites where ethion was disposed, and individuals living near one of the 9 NPL hazardous waste sites where ethion has been detected in some environmental media (HazDat 2000). Other populations at risk of exposure to ethion and its oxygen analogs include recreational and subsistence fishers who may fish in ethion-contaminated waters and who typically consume larger amounts of locally caught fish and shellfish than the general population. However, no fish consumption advisories are currently in effect in the United States for ethion (EPA 1995g). Subsistence farmers and their families living in areas where ethion is heavily used in agriculture who may consume their own farm-raised fruits and vegetables or who may unknowingly consume drinking water from a ethion-contaminated well are at greater risk of exposure.

5.8 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 ethion 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 ethion.

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.

5.8.1 Identification of Data Needs

Physical and Chemical Properties. While the principal properties of ethion are well characterized (Bowman and Sans 1983; Chapman and Cole 1982; Dierberg and Pfeuffer 1983; EPA 1989b; HSDB 1998; Merck 1989; Sax 1984; Sharom et al. 1980a, 1980b; Tomlin 1994), there are data gaps for odor thresholds, flammability limits, autoignition temperature, and flash point for the compound. Additional information on these properties would be helpful in assessing the compound's environmental fate. There are also data gaps for some spontaneously produced degradation products, some of which may be as toxic or more toxic than ethion.

Production, Import/Export, Use, Release, and Disposal. As with most pesticide agents, no current information was found on production or import and export volumes for ethion (FASE 1996). This lack of current information seriously compromises efforts to design monitoring programs to study fate and transport and can seriously jeopardize proper assessments of exposure opportunities and their associated health risks for this compound. Information on current production, import/export volumes, uses, releases to various environmental matrices, and disposal methods is needed to conduct a more accurate assessment of exposure pathways.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1996, will become available in May of 1998. This database will be updated yearly and should provide a list of industrial production facilities and emissions. No information was available on facilities involved in the production or processing of ethion because it is not one of the chemicals that facilities are required to report to the TRI (EPA 1995e).

Environmental Fate. In the atmosphere, ethion is subject to only minor degradation due to photolysis (Gore et al. 1971), however, reactions with hydroxyl radicals result in an estimated half-life of less than an hour (SRC 1995). No information was located on ethion’s reaction with ozone in the air. In water, ethion is subject primarily to hydrolysis, with photolysis and biodegradation being minor fate processes (Dierberg and Pfeuffer 1983; Eichelberger and Lichtenberg 1971; Frank et al. 1991; Gore et al. 1971). The rate of degradation of ethion in water is strongly influenced by pH (Chapman and Cole 1982; Dierberg and Pfeuffer 1983; Frank et al. 1991; Sharom et al. 1980a) and temperature (Dierberg and

Pfeuffer 1983; Gore et al. 1971; Sharon et al. 1980a). The rate of ethion degradation increases in alkaline pH and at higher temperatures. Ethion can be degraded in soils and sediment by hydrolysis (Chapman and Cole 1982) and by biodegradation by microorganisms (Miles et al. 1979; Sherman et al. 1974). Ethion is moderately to highly immobile in most soil types, particularly those with moderate amounts of organic matter (Kenaga 1980; Sharom et al. 1980b). Information on the mobility of ethion is available (Sharom et al. 1980b); however, no information was located on mobility of its major degradation products in various soil types. Additional information on the persistence and mobility of major degradation products of ethion would be useful. Additional information on environmental parameters governing the degradation rate of ethion in soil also would be helpful in evaluating the environmental fate of ethion and its degradation products.

Bioavailability from Environmental Media. Ethion can be absorbed following inhalation, dermal, or oral exposures. Absorption through the skin is of major concern for occupational exposures of manufacturers and formulators, farmers, farm workers, commercial applicators or homeowners related to the use of ethion as an insecticide or acaricide (Jeyaratnam and Maroni 1994; Kahn 1976; Wojeck and Nigg 1980; Wojeck et al. 1981; Wolfe et al. 1978). Additional information on the bioavailability of concentrations of ethion in soils, surface water, groundwater, and fish and shellfish, particularly from environments near hazardous waste sites, is needed to determine the bioavailability of ethion in these media.

Food Chain Bioaccumulation. Ethion has an estimated high bioconcentration potential (BCF=1,300) (Kenaga 1980) in aquatic organisms; however, there is little experimental or environmental monitoring data to confirm that bioaccumulation occurs in edible fish and shellfish species (Butler and Schutzmann 1978; Miles and Harris 1978a). Additional information on measured BCF values for edible fish and shellfish would be helpful, as would information on tissue residues of ethion and its major degradation products in edible tissues of livestock and poultry. Little information was found on studies associated with plant uptake (Leffingwell et al. 1975; Nigg et al. 1988), but ethion is rarely detected above EPA tolerance limits (Berry et al. 1997; Corneliussen 1970; FDA 1988, 1990, 1991, 1992, 1993, 1994, 1995; Gelardi and Mountford 1993; Gunderson 1988; Hundley et al. 1988; Johnson et al. 1984; KAN-DO Office of Pesticide Team 1995; Minyard and Roberts 1991; Roy et al. 1995; Schattenberg and Hsu 1992; Yess et al. 1991, 1993). Bioaccumulation of ethion in aquatic food chains appears to be potentially important. Based on results obtained from a BCF estimating equation using the compound's chemical and physical properties, a substantial BCF value as high as 1,300 was calculated (Kenaga

1980). However, experimental data on bioaccumulation and biomagnification of ethion in aquatic species are needed to verify that the estimated theoretical BCF values are actually attained.

Exposure Levels in Environmental Media. Ethion is distributed in all environmental media and has been detected in ambient air (HazDat 2000; Lewis and Lee 1976), indoor air at a manufacturing plant (Lewis and Lee 1976), surface water (Frank et al. 1982), groundwater (Cohen 1986; HazDat 2000), and sediment (Carey et al. 1978; HazDat 2000; Miles et al. 1978). While some information is available on historic levels of ethion in environmental media, current levels of ethion in air, water, groundwater, soil, and sediment in the United States have not been well documented. There is a need for more information from national or large regional studies on current exposure levels in these environmental matrices. Adequate information from the late 1960s through to the present time are available for various raw and prepared foods as ethion has been monitored in many FDA total diet studies as well as compliance and surveillance monitoring programs (Berry et al. 1997; Corneliussen 1970; FDA 1988, 1990, 1991, 1992, 1993, 1994, 1995; Gelardi and Mountford 1993; Gunderson 1988; Hundley et al. 1988; Johnson et al. 1984; KAN-DO Office of Pesticide Team 1995; Minyard and Roberts 1991; Roy et al. 1995; Schattenberg and Hsu 1992; Yess et al. 1991; Yess et. al. 1993). Additional information on tissue residues of ethion and on its major degradation products in edible fish and shellfish species would be particularly helpful in quantifying health risk from consumption of contaminated species.

Reliable monitoring data for the levels of ethion in contaminated media at hazardous waste sites are needed so that the information obtained on levels of ethion in the environment can be used in combination with the known body burden of ethion to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Monitoring information from piezometer and producing water wells around hazardous waste sites for ethion and monitoring of water wells in areas that have high agricultural usage of ethion are considered essential.

Exposure Levels in Humans. Recent and historic data regarding levels of ethion in human tissues (adipose tissue, blood, urine, breast milk) from environmental exposures of members of the general population, populations living near hazardous waste sites, or occupationally exposed groups are not available. It is arguable that these levels are knowable because of the rapid metabolism and clearance of ethion after it enters the body. Studies are needed to determine ethion and ethion monoxon residues in breast milk from women with high exposure risks (e.g., individuals that live near hazardous waste sites where ethion has been detected or in agricultural areas of high ethion use (particularly citrus-growing

regions). Data on the relationship between environmental exposure to ethion and effects on biomarkers (blood cholinesterases) are needed to estimate the extent of exposure to ethion. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Children may be exposed to ethion primarily from consumption of small amounts of ethion in contaminated fruits, by consumption of ethion-contaminated dirt and soil from unwashed hands or other contaminated objects put into the mouth, or via ingestion of ethion-contaminated well water. Exposure and body burden studies for children would be helpful. There is no information on ethion residues in breast milk of members of the general population nor in women residing in areas of high ethion usage in agriculture and in areas near hazardous waste sites. Well water surveys should be conducted in areas of high ethion usage. These pathways via ingestion of ethion- contaminated breast milk or drinking water could be important routes of exposure in children.

Young children might be exposed to ethion through both pica and hand-mouth activity if they play in or around contaminated vegetation and soil. Soil and sediment may be contaminated with ethion and there are no studies of the transfer of ethion via both oral and dermal routes of exposure in children nor are there studies of the bioavailability of the chemical from soil and sediment.

Current information on whether children are different in their weight-adjusted intake of ethion via oral and dermal exposures was not located; however, information from older studies was available. Children, specifically 6–10-month-old infants and 2-year-old toddlers, are different in their weight-adjusted intake of ethion from food as compared to 14-year-olds as demonstrated by intake data (FDA 1988, 1989, 1990, 1991, 1992, 1993; Gunderson 1988; Johnson et al. 1984). The highest intakes were for 2-year-old-toddlers and 6–11-month-old-infants respectively (FDA 1993; Gunderson 1988). Intakes for children (14-year-olds) were lower than in infants and toddler and were more comparable to data from 25-year-olds and 65-year-old adults (FDA 1993; Gunderson 1988).

Child health data needs relating to susceptibility are discussed in Section 2.12.2 Identification of Data Needs: Children's Susceptibility.

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

subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.8.2 Ongoing Studies

No additional information was located on current studies that would fill existing data needs for ethion (FEDRIP 1998).

6. ANALYTICAL METHODS

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

6.1 BIOLOGICAL SAMPLES

Methods for the analysis of ethion and its metabolites in human biological samples are given in Table 6-1. Ethion can be recovered from saliva, urine, and plasma by extraction and analysis by gas chromatography with flame photometric detection (GC/FPD), or GC in conjunction with mass spectrometry (GC/MS) (Nigg et al. 1993; Singh et al. 1986). The metabolites of ethion for which methods have been developed include diethylphosphate (DEP), diethylthiophosphate (DETP), and diethyldithiophosphate (DEDTP). These metabolites are recovered from urine and saliva via extraction, solid phase extraction (SPE), and derivatization with tetrabutylammonium hydroxide before analysis using GC/FPD (Nigg et al. 1993). Ethion is also metabolized to form the oxygen analogs (monoxon, dioxon) but no methods for these compounds were found for biological samples of human origin. A method for the oxygen analogs in animal tissues has been described (Ivey and Mann 1975) and would serve as a good starting point for methods to be validated for human samples. A recent publication (Mahajna et al. 1996) has shown that O,O-dialkyl phophosphorodithioate insecticides (such as ethion) can undergo cleavage at the S-R (S-CH_3 of ethion) and be methylated. However, no methods have been described for human samples.

Table 6-1. Analytical Methods for Determining Ethion and Metabolites in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Saliva (Ethion, DEP, DETP, DEDTP)	Ethion: Extraction with hexane and addition of methanol followed by centrifugation (repeat 3 times); evaporation of solvent to dryness with re-dissolution in hexane just prior to analysis. Metabolites: Addition of NaOH to aqueous residue from ethion extraction; addition of methanol and removal of water; acidification and addition of ammonium sulfate; isolation using SPE; addition of tetrabutylammonium hydroxide just prior to GC analysis.	GC/FPD	Ethion: <1 ppm Metabolites: <260 ppb	80±10% at 1 ppm DEP: 68±3% DETP: 77±2% DEDTP: 69±1% at 260 ppb	Nigg et al. 1993
Urine (DEP, DETP, DEDTP)	Acidification and addition of ammonium sulfate; isolation using SPE; addition of 20% methanol in acetone to eluate; addition of tetrabutylammonium hydroxide just prior to GC analysis.	GC/FPD	<260 ppb	DEP: 81±3% DETP: 92±2% DEDTP 51±5%	Nigg et al. 1993
Plasma	Extraction with ethyl acetate followed by centrifugation; water removal and evaporation of solvent; re-dissolution in small volume of ethyl acetate	GC/MS (selected ion monitoring)	no data	57% at 200 ng/mL	Singh et al. 1986
Urine	Adjustment of pH to 7.4; centrifugation; extraction with ethyl acetate; centrifugation; evaporation of ethyl acetate, re-dissolution in small volume	GC/MS (selected ion monitoring)	<10 ng/mL	7,580% at 10 ng/mL	Singh et al. 1986

DEDTP = diethyl dithiophosphate; DEP = diethyl phosphate; DETP = diethyl thiophosphate; FPD = Flame photometric detector; GC = gas chromatography; MS = mass spectrometry; NaOH = sodium hydroxide; SPE = solid phase extraction

6.2 ENVIRONMENTAL SAMPLES

A variety of methods for the analysis of ethion, and to a lesser extent, ethion oxidation products (oxygen analogs), in environmental samples have been described. Ethion has limited volatility, so it is not typically measured in air. Methods have been reported for water (EPA 1992; EPA 1997c; Lopez-Avila et al. 1997; Valor et al. 1997) and are based on solvent extraction or solid phase microextraction (SPME). SPME is a technique in which a polymer-coated fiber is placed into the water and organic compounds adsorb to the film. The organic compounds are subsequently released via thermal desorption in the GC. The choice of fiber coating (polar vs. non-polar) can have a large impact on the recovery of the target analytes (Lopez-Avila et al. 1997) and is thus an important consideration in methods utilizing SPME.

Since ethion is used on plants, it is not surprising that analytical methods have been developed for many types of vegetative material, including many used as foods (see Table 6-2). The majority of methods are based on solvent extraction during or following homogenization of the sample (e.g., FDA 1997; Johnson et al. 1997; Sicbaldi et al. 1997; Torres et al. 1996) followed by GC with some form of selective detection. Supercritical fluid extraction (SFE) has also been reported as a means to isolate ethion from the plant matrix (Lehotay and Valverde-Garcia 1997; Pearce et al. 1997). The applicability of SFE has been reviewed by Lehotay (1997).

Foods of animal origin have also been investigated for ethion and some of its metabolites/decomposition products. Methods have been developed, for milk (Erney et al. 1997; Di Muccio et al. 1996); beef, turkey, and chicken (Ivey and Mann 1975; Lino and da Silveira 1994); and fatty foods, including dairy and meats (FDA 1997).

As with any analytical method, it is important to verify that the method blanks are free of interfering compounds; it is also important to be certain that the matrix does not have an impact on the recovery of the target analytes relative to solvent standards. Erney et al. (1997) have described how co-extracted matrix components can have a protective effect on the analytes. That is, these matrix components can reduce any thermal decomposition in the injector port and give rise to recoveries well in excess of 100% relative to solvent standards. The use of spiked matrix samples during method development and validation can bring such interferences to light.

Table 6-2. Analytical Methods for Determining Ethion in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Milk	Precipitation of protein using acetone and acetonitrile followed by extraction of the aqueous phase with dichloromethane.	GC/FPD	No data	No data	Erney et al.1997
Milk	Extraction with acetonitrile and acetone, cleanup using SPE; extract taken to dryness followed by redissolution in 1 mL acetone.	GC/FPD	0.005 mg/kg	90	DiMuccio et al. 1996
Water	Adjustment of pH of sample to 9, liquid-liquid extraction with hexane and water removal using sodium sulfate.	GC/MS	<10 ppt	113 at 10 ppt	Termonia and Termonia 1997
Water	SPME from aqueous phase	GC/TSD	No data	82 (18%RSD)	Lopez-Avila et al. 1997
Water, wastewater	SPME from aqueous phase	GC/NPD	30 ng/L	Tap water: 108±2%; Sea water: 98±2%; Wastewater: 103±8%	Valor et al. 1997
Leaves	Addition of water and wetting agent to pre-weighed leaf sections; extraction with hexane; water removal.	GC/FPD	0.5 ng	No data	Thompson and Brooks 1976
Oranges	Addition of water and wetting agent to pre-weighed leaf sections; extraction with hexane; water removal.	GC/ECD	0.5 ng	No data	Thompson and Brooks 1976

Table 6-2. Analytical Methods for Determining Ethion in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Oranges	Homogenization of oranges; addition of C_{18} to 0.5 g of homogentae, mixing (Matrix Solid Phase Dispersion). Introduce to column and elute with ethyl acetate; volume reduction	GC/ECD	95 µg/kg	93±7% at 539 µg/kg	Torres et al. 1996
Oranges, sweet potatoes, and green beans	Homogenization of sample with drying agent. Supercritical fluid extraction.	GC/ion trap MS	4 ng/g	74–77	Lehotay and Valverde-García 1997
Fruits and vegetables	Maceration of sample in presence of acetone; filtration and addition of sodium sulfate followed by extraction with hexane; extraction with ethyl acetate and cleanup using Florisil.	GC/Thermionic NPD	<0.1 mg/kg	peaches 88 at 0.2 mg/kg	Ferreira and Fernandes 1980
Grass	Homogenization with acetone; filtration; extraction with dichloromethane; evaporation to less than 1 mL, dilution to 5.0 m; filtration clean up using GPC.	GC/MS	2 µg/kg	87±2%	Johnson et al. 1997
Vegetation	Homogenization followed by mixing with diatomaceous earth; extraction with ethyl acetate; filtration; vaporization to dryness then redissolution in acetone.	GC/NPD	0.001 µg/g	Apples 90–95 at 1 µg/g	Sicbaldi et al. 1997
Rice grains	Using supercritical fluid extraction, ethion is extracted using CO_2 + 5% methanol, 45EC, 315 bar, and dynamic flow.	SFE/GC-AED	0.01 mg/kg	75-120%	Skopec ZV et al. 1993

Table 6-2. Analytical Methods for Determining Ethion in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Strawberries	Homogenization of sample and mixing with Extralute; supercritical fluid extraction and expansion into acetone	GC/FPD; GC/NPD	0.1 mg/kg	82–117 (3–12% RSD)	Pearce et al. 1997
Beef and turkey fat, skin, muscle, liver, kidney, heart, gizzard; (ethion, ethion mono-oxon, ethion di-oxon)	Fat: Blending of fat with sodium sulfate and 5% acetone in hexane; mixing with celite, heating; filtration; partitioning with acetonitrile; solvent evaporation; redissolution and column cleanup. Other tissue: blending of tissue with acetone followed by stirring with celite and filtration; residue extracted with hexane; volume reduction and combining of extracts, volume reduction; water removal. Partitioning with acetonitrile and clean up as for fat.	GC/FPD	Ethion: 0.002 ppm; ethion mono-oxon: 0.002 ppm; ethion dioxin: 0.005 ppm	Ethion: 86–100% ethion mono-oxon: 79–107% ethion dioxon: 63–98%	Ivey and Mann 1975
Chicken muscle and skin	Blending with acetonitrile followed by filtration; re-homogenization with acetonitrile-water; addition of zinc acetate, addition of sodium chloride and extraction with dichloromethane; removal of water from dichloromethane layer followed by extraction with hexane and cleanup using Florisil column.	GC/NPD	4.4–4.5 µg/kg	Mscle: 82±8.5% RSD at 39 µg/kg (ppb) skin: 91±8.5% RSD at 100 µg/kg (ppb)	Lino and da Silveira 1994

Table 6-2. Analytical Methods for Determining Ethion in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Orange leaves (ethion, ethion monooxon, ethion dioxon)	Addition of wetting agent and extraction with methylene chloride, water removal, evaporation to dryness; re-dissolution in benzene.	GC/FPD, GC/ECD	No data	Ethion: 98±3% ethion monooxone: 95±2% ethion dioxon: 90±2%	Nigg et al. 1988
Wastewater	Extraction with 15% methylene chloride in hexane, water removal, solvent exchange to hexane. Clean-up using column chromatography if needed. (EPA Method 614.1)	GC/NPD, GC/MS	0.1 µg/L (ppb)	89±4.5% RSD at 1.8 mg/L (ppm)	EPA 1992
Water, soil, sediment, sludge	Less than 1% solids: continuous extraction with methylene chloride; Greater than 1% solids: If solids #30%, dilution with water and sonication prior to continuous extraction with methylene chloride. If solids >30%, extraction with methylene chloride:acetone or acetonitrile followed by methylene chloride using sonication; volume reduction followed by GPC of SPE cleanup. (EPA Method 1657)	GC/FPD	13 ng/L (ppt) with no interferences	47–149 (15% RSD)	EPA 1997c
Fatty foods (Ethion)	Extraction of fat and residues using sodium sulfate/petroleum ether; column clean-up if needed (FDA PAM Method 304).	GC/FPD	No data (sub-ppm)	>80%	FDA 1997

Table 6-2. Analytical Methods for Determining Ethion in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Non-fatty foods (Ethion, ethion oxygen analog)	Extraction using acetone/water; filtration; extraction into organic solvent; column clean-up as needed depending on matrix (FDA PAM Method 302)	GC/FPD	No data (sub-ppm)	>80%	FDA 1997

FPD = flame photometric detector; GC = gas chromatography; GPC = gel permeation chromatography; ECD = electron capture detector; MS = mass spectrometry; NPD = nitrogen phosphorus detector; SPE = solid phase microextraction; SPE = solid phase extraction; TSD = thermionic selective detector

6.3 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 ethion 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 ethion.

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.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods exist for the determination of ethion in saliva (Nigg et al. 1993; LOD <1 ppm, 10% RSD) and urine (Singh et al. 1986; LOD <100 ng/mL). In the absence of a clear relationship between exposure concentrations and concentrations in biological samples, a definitive statement about the adequacy of the methods available is not possible. Methods for metabolites DEP, DETP, and DEDTP have also been described for saliva and urine (Nigg et al. 1993), but these compounds are not specific to ethion exposure. In addition, cholinesterase activity in plasma and red blood cells can be related to exposure to organophosphorus pesticides, but a decrease in activity is not unique to ethion effect.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for the determination of ethion in water have limits of detection of 0.1 µg/L (EPA 1992), 13 ng/L (EPA 1997c), and 10 ppt (0.01 µg/L; Termonia and Termonia 1997). Assuming a 2 L/day consumption of water, an exposure via drinking water of 0.02 µg/day could be quantified. The oral MRLs derived by ATSDR are 0.002 mg/kg/day for oral exposure in acute and intermediate conditions, and 0.0004 mg/kg/day for oral exposure in chronic conditions. These methods are adequate for determination of ethion at levels well below the MRL. Methods exist for the

determination of ethion in milk (DiMuccio et al. 1996; Erney et al. 1997, LOD=0.005 mg/kg), oranges, sweet potatoes, fruits and vegetables, strawberries, and meats (FDA 1997; Ferreira and Fernandes 1980; Ivey and Mann 1975; Lehotay and Valverde-García 1997; Lino and da Silveira 1994; Pearce et al. 1997; Torres et al. 1996). Sensitivities are as low as 4 µg/kg (ppb) (Lehotay and Valverde-García 1997). Assuming a total ingestion of 2 kg of food per day, potential exposures as low as 8 µg per day could be measured. Current methods are adequate to detect ethion in foods at the MRL levels. However, methods must be validated for other matrices before they can be used.

6.3.2 Ongoing Studies

No ongoing studies in which new methods for the measurement of ethion or its metabolites/breakdown products were identified.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding ethion in air, water, and other media are summarized in Table 7-1.

ATSDR has derived a Minimal Risk Level (MRL) of 0.002 mg/kg/day for oral exposure to ethion over the acute and intermediate durations based on a NOAEL of 0.06 mg/kg/day for inhibition of brain acetylcholinesterase in Beagle dogs (Bailey 1988). This same study was used to derive a chronic-duration MRL of 0.0004 mg/kg/day.

The Environmental Protection Agency (EPA) has not established a reference concentration (RfC) for ethion. The reference dose (RfD) for ethion is 0.0005 mg/kg/day. This RfD is based on a study in humans conducted by Palazzolo (1970) for the FMC Corporation (IRIS 1999).

Ethion has not been classified for carcinogenicity by the Department of Health and Human Services (DHHS), the International Agency for Research on Cancer (IARC), or the EPA. The National Toxicology Programs (NTP) Management Status Report does not list ethion as a candidate for general toxicology studies (NTP 1998).

Between June 27, 1974 and January 18, 1989, the Occupational Safety and Health Administration (OSHA) had promulgated protective, permissible exposure limits (PELs) for approximately 264 toxic substances (OSHA 1993). The OSHA PELs were established to protect workers against adverse health effects resulting from exposure to hazardous substances. An employer must ensure that an employee's exposure to a toxic substance in any 8-hour work shift of a 40-hour week does not exceed the 8-hour time-weighted average (TWA) established for the substance (OSHA 1993). On January 18, 1989, OSHA promulgated more protective PELs for approximately 376 toxic substances. Ethion was included among 164 toxic substances not previously regulated (OSHA 1989). The newly established PEL for ethion was set at 0.4 mg/m^3 (OSHA 1989). OSHA also provided a "skin designation" for ethion. The skin designation would indicate a potential for dermal absorption and the need for employers to implement the use of good work practices including providing workers with gloves, coveralls, goggles, and other appropriate equipment in order to prevent skin exposures (NIOSH 1997). Because the 1989 promulgation was rescinded by the 11^{th} Circuit Court Appeals in July 1992, only those PELs in place prior to the 1989 rule are currently enforced by OSHA. On June 30, 1993, OSHA published in the

Federal Register a final rule announcing the revocation of the 1989 exposure limits, including the newly established limits for ethion (OSHA 1993). Currently, there is no OSHA PEL for ethion. However, the National Institute for Occupational Safety and Health (NIOSH) and approximately twenty-five states have adopted the 0.4 mg/m^3 exposure limit for ethion that was initially promulgated by OSHA (NIOSH 1992, 1997; OSHA 1993). The American Conference of Governmental Industrial Hygienists (ACGIH) also adopted the 0.4 mg/m^3 exposure limit for ethion (ACGIH 1998).

Ethion has been designated as a hazardous substance pursuant to the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980 (EPA 1995a, 1996a). The statutory source for this designation is section 311(b)(4) of the Clean Water Act (CWA) (EPA 1995a). The owner and operator of any facility that produces, uses, or stores a CERCLA hazardous substance in an amount exceeding the "threshold planning quantity" are required to immediately report any release to any environmental media, if the amount released is equal to or exceeds the specified "reportable quantity" assigned to the substance. The threshold planning quantity for ethion is 1,000 pounds, and the reportable quantity is 10 pounds (4.54 kg) (EPA 1999c).

Under the authority of the CWA ethion is regulated as a wastewater pollutant in discharges from new and existing facilities that formulate, package, and repackage pesticide products. Facilities of this type make up two subcategories of the Pesticide Chemicals Point Source Category—Subcategory C: Pesticide Formulating, Packaging and Repackaging which includes facilities that also manufacture pesticide active ingredients (PAIs) and Subcategory E: Repackaging of Agricultural Pesticides Performed at Refilling Establishments (EPA 1996c). As of January 6, 1997, the regulatory limit for Subcategory C facilities on the discharge of wastewater pollutants into navigable waters and into publicly owned treatment works (POTWs) is a choice between zero discharge or compliance with the pollution prevention alternative provided in Table 8 of 40 CFR 455 (EPA 1996c). Subcategory E facilities are required to achieve the "zero" criterium for discharge of wastewater pollutants (EPA 1996c). Some of the PAIs to which these effluent guidelines and standards do not apply are sanitizers, including pool chemicals; microorganisms, such as *Bacillus thuringiensis*; and certain liquid chemical sterilants that are used on critical or semi-critical medical devices (EPA 1996c). Complete listings of PAIs that are not required to meet the Subcategory C and E guidelines and standards can be found in 40 CFR 455.40 and 40 CFR 455.60, respectively. As a pesticide, ethion is regulated under the section 408 of the Federal Food, Drug, and

Cosmetics Act as amended by the Food Quality Protection Act (EPA 1998a). The EPA has set tolerance limits for the amount of ethion residue that can be found raw agricultural products and animal feeds (EPA 1997a, 1998a).

Table 7-1. Regulations and Guidelines Applicable to Ethion

Agency	Description	Information	Reference
International Guidelines:			
IARC	Cancer classification	None	IARC 1997
National Regulations and Guidelines:			
a. Air			
ACGIH	Threshold limit value (TLV)	0.4 mg/m^3	ACGIH 1999
NIOSH	Exposure limit (TWA)—skin	0.4 mg/m^3	NIOSH 1999
OSHA	Permissible exposure limit (PEL) 8-hour time weighted average (TWA)	None 0.4 mg/m^3 was the vacated 1989 PEL	OSHA 1989[a] NIOSH 1997[a]
b. Water			
	No available data		
c. Food			
EPA	Pesticide classification for ethion	Cholinesterase inhibiting pesticide	40 CFR 180.3 EPA 1999a
	Tolerances for ethion residues in or on raw agricultural commodities	0.2-10 ppm	40 CFR 180.173 EPA 1999b
d. Other			
ACGIH	Biological exposure indices (BEI) organophosphorus cholinesterase inhibitors	70% of individual's baseline	ACGIH 1999
EPA	RfD Cancer classification	5x10^{-4} mg/kg/day Not determined	IRIS 1999
	Reportable quantities of hazardous substances Ethion—designated CERCLA hazardous substance under sections 311(b)(4) Clean Water Act	10 lbs.	40 CFR 302.4 EPA 1999c
	Statutory source for designation as a CERCLA hazardous substance	Yes	Clean Water Act U.S. Congress 1977

Table 7-1. Regulations and Guidelines Applicable to Ethion (*continued*)

Agency	Description	Information	Reference
EPA (cont.)	Designated hazardous substance in accordance with section 311(b)(2)(a) of the act	Yes	40 CFR 116.4 EPA 1998a
	Included in the list of organic pesticide active ingredients	Yes	40 CFR 455 Sub E EPA 1998b
STATE Regulations and Guidelines:			
a. Air			
Colorado	5 CCR1001-5 Regulation No. 3-Air contaminant emissions notices for HAP	Yes	BNA 1998
Connecticut	8-hour 30-minute	8 µg/m^3 40 µg/m^3	
Idaho	Screening emissions level Emissions in pounds per hour	0.4 mg/m^3 0.0267	
	Acceptable concentration Occupational exposure level	0.02 mg/m^3 0.4 mg/m^3	Idaho Department of Health and Welfare 1999
Maryland	Toxic air pollutants for existing sources	Yes	BNA 1998
New Mexico	Screening emissions levels Emissions in pounds per hour	0.4 mg/m^3 0.0267	
Washington	Toxic air pollutants and acceptable source impact levels	1.3 µg/m^3	
Wisconsin	Air contaminant emission inventory reporting requirements	147 pounds/year	
	Acceptable emission levels <25 feet 25 feet	 3.4x10^{-2} lbs/hour 0.14 lbs/hour	Wisconsin Department of Natural Resources 1997
b. Water			
Arizona	Human health based guidance levels (HBGLS)for ingestion of contaminants in drinking water—Oral HBGL	3.5 µg/L	Arizona Department of Health Services 1999
c. Other			
Hawaii	Restricted use pesticide	Yes	BNA 1998

Table 7-1. Regulations and Guidelines Applicable to Ethion (*continued*)

Agency	Description	Information	Reference
Indiana	Restricted use pesticide	All products 80% or greater	
Vermont	Restricted use pesticide	All products	
Washington	Pesticide regulations	Not for distribution to home and garden users	

[a]Prior to setting a protective PEL of 0.4 mg/m^3 for ethion in 1989, OSHA had not established a protective level for this substance. In July 1992, the 11th Circuit Court Appeals rescinded the 1989 PELs promulgated by OSHA for 212 substances, including ethion. Only PELs in place prior to the 1989 rule are currently allowed.

ACGIH = American Conference of Governmental Industrial Hygienists; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act of 1980; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; IARC = International Agency for Research On Cancer; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; RfD = Reference Dose; TLV = Threshold Limit Value; TWA = Time-Weighted Average; USDA = United States Department of Agriculture; WHO = World Health Organization

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9. GLOSSARY

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

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

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

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

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

Benchmark Dose (BMD)—is 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—is 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—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.

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Immunological Effects—are functional changes in the immune response.

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

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

***In Vivo*—**Occurring within the living organism.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related

endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

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

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

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

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

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

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

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

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

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

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

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

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from

data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using Lowest-Observed-Adverse-Effect Level (LOAEL) data rather than No-Observed-Adverse-Effect Level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

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

APPENDIX A

ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Ethion
CAS number: 563-12-2
Date: June 14, 2001
Profile status: Third Draft Post-Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Key to figure: 24
Species: Dog

MRL: 0.002 [x] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Bailey DE. 1988. 90-day subchronic toxicity study of ethion technical in dogs. Unpublished revised final report dated June 21, 1988 by Hazelton Laboratories America, Inc., Vienna VA, for FMC Corporation, Princeton NJ. Hazelton Study No. 104-229, FMC Study No. A86-1990, EPA MRID No. 40773301. [Available from EPA. Write to FOI, EPA, Washington, DC 20460]

Experimental design: See MRL Worksheet for intermediate-duration oral exposure, page A-5.

Effects noted in study and corresponding doses: See MRL Worksheet for intermediate-duration oral exposure, page A-5.

Dose end point used for MRL derivation: 0.06 mg/kg/day; brain acetylcholinesterase inhibition

[x] NOAEL [ ]LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [x] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

The acute oral MRL for ethion is derived as follows:

MRL = NOAEL ÷ UF
MRL = 0.06 mg/kg/day ÷ 30
MRL = 0.002 mg/kg/day

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Dose was calculated using mean daily compound consumption reported in the study (Table 5).

Was a conversion used from intermittent to continuous exposure? If so, explain: Not applicable

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

Other additional studies or pertinent information that lend support to this MRL: This MRL should be protective against health effects in individuals potentially exposed to ethion at hazardous waste sites. A

study in volunteers (Palazzollo 1970) has determined the sensitivity of humans to the effects of ethion on blood cholinesterase activities. A group of six male volunteers were given ethion in corn oil solutions in three divided doses (9:00 a.m., noon, and 5:00 p.m.) of 0.05, 0.075, 0.1, and 0.15 mg/kg/day via gelatin capsule. Subjects received 0.05, 0.075 , and 0.1 mg/kg/day for 3 weeks each and then 0.15 mg/kg/day for 3 days. No adverse clinical signs (blood pressure, pulse rate, pupil size, light reflex, eye accommodation, chest sound, muscle tone, knee jerk, tongue tremor and finger tremor) or effects on erythrocyte acetylcholinesterase were observed at any time during the study. Absorption of ethion by the volunteers was confirmed by a decrease in plasma cholinesterase levels. While no effect on plasma cholinesterase was observed at the 0.05 mg/kg/day dose level, a 16% decrease was seen in the 0.075 mg/kg/day group. Decreases of 23 and 31% were seen in the 0.1 and 0.15 mg/kg/day groups.

The NOAEL of the Bailey study for inhibition of brain acetylcholinesterase was adjusted by a factor of 10 for human variability and a factor of 3 for extrapolation of an animal study to humans. A factor of 3 was used for extrapolation rather than the full uncertainty factor of 10 because the results of the Palazzollo (1970) study indicated that dogs appear to be at least as sensitive to the neurological effects of ethion as humans when exposed to comparable doses.

The MRL value of 0.002 mg/kg/day for intermediate-duration oral exposure to ethion was extended to acute-duration oral exposure based on the toxicokinetics of ethion. Cholinesterase inhibition occurs quickly and there are no indications of progressive inhibition over time at a given dose in either the Palazzollo (1970) study in humans or the Bailey (1988) study in dogs. A similar lack of progression of inhibition was seen in 2-year studies in rats and mice where brain and erythrocyte acetylcholinesterase and plasma cholinesterase were measured at 6-month intervals (Morrow et al. 1985a, 1985b). The toxicity database indicates no change in ethion toxicity over time, i.e., toxicity is dependent on the dose, not the duration of exposure. Because the toxicological effects of ethion are due to a series of repeated acute exposures, the intermediate-duration oral MRL should be protective for this endpoint for acute exposure durations.

Agency Contact (Chemical Manager): Nickolette Roney

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Ethion
CAS number: 563-12-2
Date: June 14, 2001
Profile status: Third Draft Post-Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 24
Species: Dog

MRL: 0.002 [x] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Bailey DE. 1988. 90-day subchronic toxicity study of ethion technical in dogs. Unpublished revised final report dated June 21, 1988 by Hazelton Laboratories America, Inc., Vienna VA, for FMC Corporation, Princeton NJ. Hazelton Study No. 104-229, FMC Study No. A86-1990, EPA MRID No. 40773301. [Available from EPA. Write to FOI, EPA, Washington, DC 20460]

Experimental design: The purpose of this study was to evaluate the subchronic toxicity of Ethion Technical when administered orally to dogs for 13 weeks. Groups of Beagle dogs (n=4/sex/group, 20-28 weeks old) received ethion (purity 93.4%)in the diet at target concentrations of 0, 0.5, 2.5, 25.0, and 300 ppm for 90 days. Food was available for 2 hours a day, water was available *ad libitum*. The average compound consumed was 0, 0.01, 0.06, 0.71 and 6.9 mg/kg/day for males and 0, 0.012, 0.07, 0.71 and 8.25 mg/kg/day for females. All dogs were observed twice daily for mortality and moribundity. Animals were observed once daily for clinical signs. Body weights were recorded during acclimation and quarantine, on day 0 (one day prior to treatment initiation), and weekly thereafter. Food consumption was measured weekly. Detailed physical exams were performed at each weighing interval. Ophthalmoscopic examinations were performed prior to initiation and during week 13. Clinical pathology parameters were evaluated for all dogs prior to initiation of treatment (day -16) and during weeks 5, 9, and 13 and included the following: cholinesterase (plasma, erythrocyte, brain) activity, hematology (leukocyte count, erythrocyte count, hemoglobin, corrected leukocyte count, hematocrit, platelet count, differential leukocyte count), and clinical chemistry (sodium, potassium, chloride, total protein, albumin, calcium, phosphorus, total bilirubin, urea nitrogen, creatinine, glucose, alanine aminotransferase, aspartate aminotransferase, globulin). All surviving animals were sacrificed following the 13-week treatment period. Necropsies were performed, terminal body weights taken, and liver (with drained gallbladder), kidneys, testes (with epididymides), thyroid (with parathyroid) and brain weights were taken. Histopathological examination of the following tissues was conducted: lesions, brain (with medulla/pons, cerebellar cortex, and cerebral cortex), gallbladder, pituitary, thyroid (parathyroid), thymus, lungs, trachea, heart, bone (femur), salivary glands (mandibular), bone marrow (sternum), kidneys, uterus, adrenals, liver, spleen, pancreas, testes (with epididymides), ovaries, aorta, esophagus, stomach, duodenum, jejunum, ileum, colon, cecum, rectum, urinary bladder, mesenteric lymph node, sciatic nerve, spinal cord (cervical, thoracic, lumbar), skin, mammary gland, and eyes.

Effects noted in study and corresponding doses: One female dog in the 8.25 mg/kg/day group was sacrificed on day 90 (one day before schedule). Clinical signs exhibited by this animal prior to sacrifice included emesis, dehydration, and thin body mass. All other animals survived until terminal sacrifice. In the highest dose group (6.9 mg/kg/day for males, 8.25 mg/kg/day for females) clinical signs included miosis (all animals), emesis (all animals), dehydration (3M, 2F), salivation (2M, 2F), and tremors (3M, 4F). Animals in this group appeared to be in generally poor condition at the end of the study. Erythrocyte acetylcholinesterase was strongly inhibited at weeks 5 (94%M, 96%F), 9 (95%M, 93%F),

and 13 (94%M, 93%F) in the highest dose groups, but not in any of the other groups. Mean percent brain acetylcholinesterase activity inhibition at termination was 64% in males and 61% in females at the highest dose. Male brain acetylcholinesterase was inhibited 23% at 0.71 mg/kg/day but no inhibition of brain acetylcholinesterase occurred in females at this dose. Plasma cholinesterase inhibition was dose-related in both males and females. No significant differences in absolute organ weights were observed between treated and control animals. No compound-related histopathological effects were observed in any organ, including brain, sciatic nerve and spinal cord. The no-observed-adverse-effect level for inhibition of brain acetylcholinesterase is 0.06 mg/kg/day.

Cholinesterase Inhibition vs. Control at 13 Weeks (In Percentages)

Dose (mg/kg/day)	Plasma cholinesterase	Erythrocyte acetylcholinesterase	Brain acetylcholinesterase
0.01 (M)	3	4	10
0.012 (F)	5	0	0
0.06 (M)	15*	5	1
0.07 (F)	13	0	0
0.71 (M)	58*	12	23*
0.71 (F)	52*	5	2
6.9 (M)	84*	94*	64*
8.25 (F)	84*	93*	61*

* significantly different from control ($p<0.05$).

Dose end point used for MRL derivation: 0.06 mg/kg/day; brain acetylcholinesterase inhibition

[x] NOAEL [ ]LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [x] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

The intermediate oral MRL for ethion is derived as follows:

MRL = NOAEL ÷ UF
MRL = 0.06 mg/kg/day ÷ 30
MRL = 0.002 mg/kg/day

Was a conversion factor used from ppm in food or water to a mg/body weight dose? If so, explain: Dose was calculated using mean daily compound consumption reported in the study (Table 5).

Was a conversion used from intermittent to continuous exposure? If so, explain: Not applicable.

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

Other additional studies or pertinent information that lend support to this MRL: This MRL should be protective against health effects in individuals potentially exposed to ethion at hazardous waste sites. A study in volunteers (Palazollo 1970) has determined the sensitivity of humans to the effects of ethion on blood cholinesterase activities. A group of six male volunteers were given ethion in corn oil solutions in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) of 0.05, 0.075, 0.1, and 0.15 mg/kg/day via gelatin capsule. Subjects received 0.05, 0.075 , and 0.1 mg/kg/day for 3 weeks each and then 0.15 mg/kg/day for 3 days. No adverse clinical signs (blood pressure, pulse rate, pupil size, light reflex, eye accommodation, chest sound, muscle tone, knee jerk, tongue tremor and finger tremor) or effects on erythrocyte acetylcholinesterase were observed at any time during the study. Absorption of ethion by the volunteers was confirmed by a decrease in plasma cholinesterase levels. While no effect on plasma cholinesterase was observed at the 0.05 mg/kg/day dose level, a 16% decrease was seen in the 0.075 mg/kg/day group. Decreases of 23 and 31% were seen in the 0.1, and 0.15 mg/kg/day groups.

The NOAEL of the Bailey study for inhibition of brain acetylcholinesterase was adjusted by a factor of 10 for human variability and a factor of 3 for extrapolation of an animal study to humans. A factor of 3 was used for extrapolation rather than the full uncertainty factor of 10 because the results of the Palazzollo (1970) study indicated that dogs appear to be at least as sensitive to the neurological effects of ethion as humans when exposed to comparable doses.

The MRL value of 0.002 mg/kg/day for intermediate-duration oral exposure to ethion was extended to acute-duration oral exposure based on the toxicokinetics of ethion. Cholinesterase inhibition occurs quickly and there are no indications of progressive inhibition over time at a given dose in either the Palazzollo (1970) study in humans or the Bailey (1988) study in dogs. A similar lack of progression of inhibition was seen in 2-year studies in rats and mice where brain and erythrocyte acetylcholinesterase and plasma cholinesterase were measured at 6 month intervals (Morrow et al. 1985a, b). The toxicity database indicates no change in ethion toxicity over time, i.e. toxicity is dependent on the dose, not the duration of exposure. Because the toxicological effects of ethion are due to a series of repeated acute exposures, the intermediate-duration oral MRL should be protective for this endpoint for acute exposure durations.

Agency Contact (Chemical Manager): Nickolette Roney

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Ethion
CAS number: 563-12-2
Date: June 14, 2001
Profile status: Third Draft Post-Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Key to figure: 24
Species: Dog

MRL: 0.0004 [x] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Bailey DE. 1988. 90-day subchronic toxicity study of ethion technical in dogs. Unpublished revised final report dated June 21, 1988 by Hazelton Laboratories America, Inc., Vienna VA, for FMC Corporation, Princeton NJ. Hazelton Study No. 104-229, FMC Study No. A86-1990, EPA MRID No. 40773301. [Available from EPA. Write to FOI, EPA, Washington, DC 20460]

Experimental design: See MRL Worksheet for intermediate-duration oral exposure, page A-5.

Effects noted in study and corresponding doses: See MRL Worksheet for intermediate-duration oral exposure, page A-5.

Dose end point used for MRL derivation: 0.06 mg/kg/day; brain acetylcholinesterase inhibition

[x] NOAEL [ ]LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [x] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)
[ ] 1 [x] 5 [ ] 10 (Modifying Factor)

The chronic oral MRL for ethion is derived as follows:

MRL = NOAEL ÷ (UF * MF)
MRL = 0.06 mg/kg/day ÷ (30 * 5)
MRL = 0.0004 mg/kg/day

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Dose was calculated using mean daily compound consumption reported in the study (Table 5).

Was a conversion used from intermittent to continuous exposure? If so, explain: Not applicable

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

Other additional studies or pertinent information that lend support to this MRL: This MRL should be protective against health effects in individuals potentially exposed to ethion at hazardous waste sites. A study in volunteers (Palazollo 1970) has determined the sensitivity of humans to the effects of ethion on

blood cholinesterase activities. A group of six male volunteers were given ethion in corn oil solutions in 3 divided doses (9:00 a.m., noon, and 5:00 p.m.) of 0.05, 0.075, 0.1, and 0.15 mg/kg/day via gelatin capsule. Subjects received 0.05, 0.075 , and 0.1 mg/kg/day for 3 weeks each and then 0.15 mg/kg/day for 3 days. No adverse clinical signs (blood pressure, pulse rate, pupil size, light reflex, eye accommodation, chest sound, muscle tone, knee jerk, tongue tremor and finger tremor) or effects on erythrocyte acetylcholinesterase were observed at any time during the study. Absorption of ethion by the volunteers was confirmed by a decrease in plasma cholinesterase levels. While no effect on plasma cholinesterase was observed at the 0.05 mg/kg/day dose level, a 16% decrease was seen in the 0.075 mg/kg/day group. Decreases of 23 and 31% were seen in the 0.1, and 0.15 mg/kg/day groups.

The NOAEL of the Bailey study for inhibition of brain acetylcholinesterase was adjusted by a factor of 10 for human variability and a factor of 3 for extrapolation of an animal study to humans. A factor of 3 was used for extrapolation rather than the full uncertainty factor of 10 because the results of the Palazzollo (1970) study indicated that dogs appear to be at least as sensitive to cholinesterase inhibition by ethion as humans when exposed to comparable doses. An additional modifying factor of 5 was applied to the chronic duration to protect against possible long-term effects, seen in structurally-related cholinesterase inhibitors, which might be the result of mechanisms other than cholinesterase inhibition, and to protect against possible susceptibility in children.

Agency Contact (Chemical Manager): Nickolette Roney

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

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint 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 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

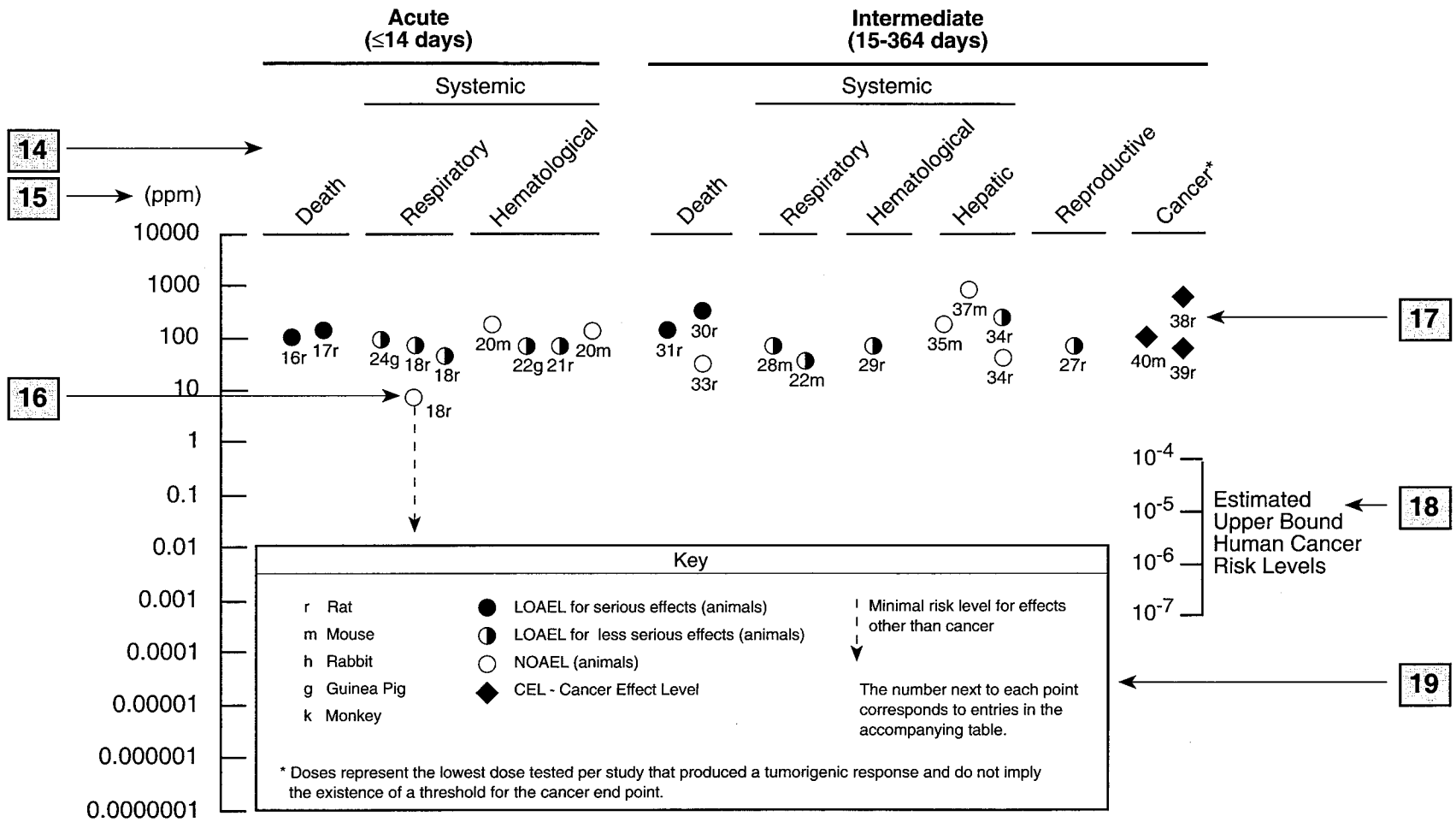
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic	9	9	9	9	9		9
18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					9		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

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

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

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint 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 endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level
ECD	electron capture detection

ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram

min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic

PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short-term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha

β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result