TOXICOLOGICAL PROFILE FOR DISULFOTON

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

August 1995

DISCLAIMER

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

UPDATE STATEMENT

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

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

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and 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 being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but 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.

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 protect public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicologic information; therefore, we have included this information in the beginning of the document.

Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance in order 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.

(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.

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 the Agency for Toxic Substances and Disease Registry (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 Environmental Protection Agency (EPA). The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on February 28, 1994 (59 FR 9486). 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); and October 17, 1991 (56 FR 52166); and October 28, 1992 (57 FR 48801).

Foreword

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects our assessment of all relevant toxicologic testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

David Satcher, M.D., Ph.D.
Administrator
Agency for Toxic Substances and
Disease Registry

CONTRIBUTORS

CHEMICAL MANAGERS(S)/AUTHOR(S):

Nickolette Roney
ATSDR, Division of Toxicology, Atlanta, GA

Sharon Wilbur, M.A.
Research Triangle Institute, Research Triangle Park, NC

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1 . Green Border Review. Green Border review assures consistency with ATSDR policy.

2 . 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.

3 . 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.

4 . Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

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

1 . Dr. William Buck, Private Consultant, Consul-Tox, Inc., Tolono, Illinois;

2 . Dr. Lucia Costa, Professor and Director, Toxicology Program, School of Public Health and Community Medicine, Department of Environmental Health, University of Washington, Seattle, Washington; and

3 . Dr. Casey Robinson, Professor of Pharmacodynamics and Toxicology, College of Pharmacy, Health Science Center, University of Oklahoma, Oklahoma City, Oklahoma.

These experts collectively have knowledge of disulfoton'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.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about disulfoton and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,408 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. Disulfoton has been found in at least 7 of the sites on the NPL. However, the number of NPL sites evaluated for disulfoton is not known. As EPA evaluates more sites, the number of sites at which disulfoton is found may increase. This information is important because exposure to disulfoton may cause harmful health effects and because these sites are potential or actual sources of human exposure to disulfoton.

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 can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking substances containing the substance or by skin contact with it.

If you are exposed to substances such as disulfoton, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, gender, nutritional status, family traits, life-style, and state of health.

1.1 WHAT IS DISULFOTON?

Disulfoton is a manufactured substance used as a pesticide to control a variety of harmful pests that attack many field and vegetable crops. Disulfoton does not occur naturally. The common trade names for disulfoton are Di-syston, Disystox, Frumin AL, and Solvirex. Pure disulfoton is a colorless oil with no identifiable odor and taste. The technical product is dark

yellowish, and has an aromatic odor. It does not easily dissolve in water or evaporate to air. It is most likely to be present in hazardous waste sites with other wastes, either in drums or mixed with soil. Disulfoton is used to protect small grains, sorghum, corn, and other field crops; some vegetables, fruit, and nut crops; and ornamental and potted plants against certain insects. Although it is used primarily in agriculture, small quantities are used on home and garden plants. Small quantities also are used for other purposes, such as mosquito control in swamps. The use of disulfoton has decreased in recent years. Chapters 3 and 4 of this profile provide more information on the physical properties and uses of disulfoton.

1.2 WHAT HAPPENS TO DISULFOTON WHEN IT ENTERS THE ENVIRONMENT?

Disulfoton enters the environment principally when it is applied as a spray or as granules on field crops, vegetables, potted plants, and home gardens. Disulfoton also can enter the environment when it accidentally spills or leaks during storage and transport. Disulfoton may also enter the environment from hazardous waste sites. Environmental contamination by disulfoton mainly affects soil and water. Natural chemical reactions and bacterial attack remove disulfoton from soil and water. Such reactions form some by-products that are more toxic than disulfoton. Fish accumulate disulfoton in their bodies. The levels of disulfoton in fish can be hundreds of times higher than the level in water. Disulfoton binds moderately well to soil and typically does not travel deep into soil with rainwater. Disulfoton has been detected infrequently in groundwater from agricultural soil in California and Virginia. The estimated amount of time required for the concentration of disulfoton in river water to decrease to half of its initial level (half-life) is 7 days. The estimated half-life in soil ranges from 3.5 to 290 days, depending on the nature of the soil and climatic conditions. Chapter 5 provides more information about what happens to disulfoton in the environment.

1.3 HOW MIGHT I BE EXPOSED TO DISULFOTON?

You may be exposed to disulfoton by breathing contaminated air, drinking contaminated water, and eating contaminated food. Disulfoton is rarely detected in air. In 1980, a low level of disulfoton was detected in 1 of 123 air samples collected from 10 locations in the

United States. The average concentration at this site was 0.1 nanogram (ng) in 1 cubic meter of air (1 ng = 1/1,000,000,000th [one billionth] of a gram). Disulfoton has not been detected in drinking water. Low levels of disulfoton (0.05-1.0 milligram in a kilogram [mg/kg] of food) (1 mg = l/1,000 [one thousandth] of one gram) are sometimes found in some grains, fruits, and vegetables treated with this pesticide. Because the levels in food are higher than levels in air and water, you are more likely to be exposed to disulfoton by eating contaminated food. The Food and Drug Administration (FDA) estimated that the average intake of disulfoton in food per day for a 14- to 16-year-old male in the United States from 1986 to 1991 was 0.2 ng/kg (nanograms per kilogram) of body weight. The FDA estimate for disulfoton intake from foods is 0.07% or less than l/l,000th of the Food and Agriculture Organization/World Health Organization (FAO/WHO) acceptable daily intake (ADI) value of 300 ng/kg. The FAO/WHO AD1 value is the maximum amount of a chemical which if ingested over a person's lifetime appears to be without appreciable health risk. Workers in industries that manufacture and formulate disulfoton are at a higher risk of exposure. Workers who spray the pesticide in fields and some farm workers who enter the fields following spraying also are at a higher risk of exposure than the general population. Among the general population, people who frequently use the pesticide in their homes and gardens are potentially at higher risk. People who live near hazardous waste sites that contain disulfoton also are potentially at a higher risk of exposure. Children playing at or near these hazardous waste sites may be exposed by touching and eating soil that contains disulfoton. More information about disulfoton exposure can be found in Chapter 5 of this profile.

1.4 HOW CAN DISULFOTON ENTER AND LEAVE MY BODY?

Disulfoton can easily enter your body when you breathe it in, swallow it, or have skin contact with it. The amount of disulfoton that enters your body depends on the amount in air, food, and water, and the length of time you are exposed to it. In an oily mixture, disulfoton may enter the body through the skin, lungs, or stomach more easily than it would in a water mixture. After disulfoton enters your body, the blood carries it to your organs and tissues. Disulfoton generally does not build up in your organs and tissues, but is initially changed to more harmful substances, which quickly break down to harmless by-products. The harmful

breakdown products inhibit important enzymes (cholinesterases) in the nervous system, and this action can cause neurological effects. The harmless breakdown products do not have any known effects on the body. Studies in animals show that disulfoton and/or the breakdown products completely leave the body through the urine, feces, and exhaled air in about 10 days or less. More information on how disulfoton moves in the body can be found in Chapter 2.

1.5 HOW CAN DISULFOTON AFFECT MY HEALTH?

In people, disulfoton mainly causes harmful effects to the nervous system. The harmful breakdown products of disulfoton inhibit cholinesterase activity in the nervous system, which results in neurological effects. Depending on the amount of disulfoton that enters the body, neurological effects, such as inhibited cholinesterase activity, narrowing of the pupils, vomiting, diarrhea, drooling, difficulty in breathing, tremors, convulsions, and even death may occur. These effects can occur if you breathe in, swallow, or have skin contact with disulfoton. Exposure to small amounts of disulfoton can sometimes inhibit cholinesterase activity without causing obvious neurological effects. If you take in disulfoton from food or water for long periods, you may also become nearsighted. You are less likely to die from skin contact with disulfoton than from swallowing it, but you may become weak and tired after skin contact.

Breathing in, swallowing, or having skin contact with high levels of disulfoton can cause similar neurological effects in animals. The neurological effects of disulfoton are the most common effects. Animals that swallowed disulfoton for long periods became nearsighted, and the structures of their eyes were further damaged. Results of animal studies suggest that female rats and mice are more sensitive to disulfoton than male rats and mice.

We do not know whether disulfoton causes reproductive or birth defects, or cancer in people. However, some studies suggest that disulfoton may cause reproductive effects in animals. Some animals that swallowed disulfoton during pregnancy had newborns with underdeveloped bones, damaged livers and kidneys, and underdeveloped testes. Animals that swallowed disulfoton for long periods did not develop cancer. Chapter 2 provides more information on

the harmful effects of disulfoton. Disulfoton has not been classified for carcinogenic effects by the Department of Health and Human Services (DHHS), the International Agency for Research on Cancer (IARC), or the EPA.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO DISULFOTON?

Disulfoton and its breakdown products can be measured in the blood, urine, feces, liver, kidney, or body fat of exposed people. In cases of occupational or accidental exposure to disulfoton, the breakdown products are often measured in the urine. The breakdown products are relatively specific for disulfoton and a few other similar organophosphate pesticides and can be detected in urine for up to one week after people were last exposed. Because disulfoton inhibits cholinesterase in blood and in blood cells, inhibition of this enzyme activity may also suggest exposure to disulfoton. Cholinesterase activity in blood and in blood cells may remain inhibited for as long as l-2 weeks after the last exposure. Because other organophosphate pesticides also inhibit cholinesterase activity in blood and blood cells, this test is not specific for disulfoton. The measurement of cholinesterase in blood and blood cells and the amount of disulfoton breakdown products in the urine cannot always predict how much disulfoton you were exposed to. Your doctor can send samples of your blood or urine to special laboratories that perform these tests. Chapters 2 and 6 provide more information about medical tests.

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

The National Institute for Occupational Safety and Health (NIOSH) recommends an exposure limit of 0.1 mg disulfoton/ m^3 of air for a 10-hour workday within a 40-hour workweek.

EPA recommends that no more than 10 parts of disulfoton per billion parts (ppb) of water be present in drinking water that children drink for periods of up to 10 days. Disulfoton in drinking water should not exceed 3 ppb for children or 9 ppb for adults if they drink the

water for longer periods, and should not exceed 0.3 ppb for adults who will drink the water during an average lifetime. EPA has designated disulfoton as a hazardous substance, but it does not intend to cancel or restrict registration of pesticide products containing disulfoton. Federal regulations limit the amount of disulfoton that factories can release into waste water. EPA requires industries to report releases or spills of 1 pound or more.
For more information on recommendations by the federal government, please see Chapter 7.

1.8 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, Georgia 30333
(404) 639-6000

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances.

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

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for disulfoton. 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 A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding the lethal effects in humans after inhalation exposure to disulfoton.

In an acute inhalation study, l-hour exposure of male Sprague-Dawley rats to 202.2 mg/ m^3 disulfoton resulted in 60% mortality, while no deaths occurred in male rats exposed to ≤195.1 mg/ m^3 (Doull 1957). In Holtzman rats, a l-hour exposure resulted in death of 3 of 6 males at 180.1 mg/ m^3 and 2 of 6 females at 87.6 mg/ m^3 (DuBois 1971). No deaths occurred in males at 101.3 mg/ m^3 or in females at 75.1 mg/ m^3. LC_{50} values reported for Wistar rats were 290 mg/ m^3 in males and 63 mg/ m^3 for females exposed for 1 hour and 60 mg/ m^3 for males and 15 mg/ m^3 for females exposed for 4 hours (Thyssen 1978). When the rats were exposed to disulfoton 4 hours/day for 5 days, a concentration of 9.8 mg/ m^3 resulted in death of 9 of 10 females within l-8 days after exposure. No males died, and no deaths occurred in either sex at ≤l.8 mg/ m^3. In a 3-week study, 5 of 10 females exposed intermittently to 3.7 mg/ m^3 died after 3-12 exposures, while 3 of 20 females exposed intermittently to 3.1 mg/ m^3 intermittently died after 8-15 exposures (Thyssen 1980). No deaths occurred in the male rats in the 3-week study. Based on these data, strain differences in the lethal concentrations of disulfoton appear to exist in rats, and female rats are definitely more susceptible to the lethality of disulfoton than male rats. A l-hour exposure of female mice to 53.4 mg/ m^3 (lowest exposure concentration) resulted in 10% mortality, and 58.2 mg/ m^3 resulted in 70% mortality (Doull 1957). Male mice were not studied; therefore, data are insufficient to make comparisons of the inhalation lethality of disulfoton between male and female mice, and between rats and mice. The lethality of disulfoton appears to be related to the cholinergic effects, since such effects as tremors or convulsions were usually noted in the animals that died (see Section 2.2.1.5). The LC_{50} values in rats and the LOAEL values resulting in mortality in rats and mice are recorded in Table 2-l and plotted in Figure 2- 1.

2.2.1.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, or body weight effects in humans after inhalation exposure to disulfoton.

TABLE 2-1. Levels of Significant Exposure to Disulfoton - Inhalation

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	0.5-1 hr				202.2 M (60% died)	Doull 1957
2	Rat (Holtz- man)	1 hr				87.6 F (2/6 died) 180.1 M (3/6 died)	DuBois 1971
3	Rat (Wistar)	1 hr				290 M (LC50) 63 F (LC50)	Thyssen 1978
4	Rat (Wistar)	4 hr				60 M (LC50) 15 F (LC50)	Thyssen 1978
5	Rat (Wistar)	5 d 4 hr/d				9.8 F (9/10 died)	Thyssen 1978
6	Rat (Wistar TNO/W 74)	3 d-3 wk 5 d/wk 6 hr/d				3.7 F (5/10 died)	Thyssen 1980
7	Mouse (Carworth Farms)	1 hr				53.4 F (10% died)	Doull 1957
Neurological							
8	Rat (Sprague-Dawley)	.5- 1hr				65.1 M (muscle twitching and fibrillation, ataxia, salivation, urination, defecation, lacrimation)	Doull 1957
9	Rat (Wistar)	1 hr				133 M (sluggishness, failure to 27 F groom, typical signs of cholinesterase inhibition - not otherwise described)	Thyssen 1978

TABLE 2-1. Levels of Significant Exposure to Disulfoton - Inhalation (continued)

Key [a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)		LOAEL Serious (mg/m3)		Reference
10	Rat (Wistar)	4 hr					64 M 3.4 F	(sluggishness, failure to groom, typical signs of cholinesterase inhibition - not otherwise described)	Thyssen 1978
11	Rat (Wistar)	5 d 4 hr/d		0.5 [b]	1.8	(17-26% depression in erythrocyte cholinesterase activity; unspecified behavioral disorders)	9.8	(unspecified behavioral disorders and unspecified signs of cholinesterase activity depression)	Thyssen 1978
12	Mouse (Carworth Farms)	1 hr					53.4 F	(muscular twitches and fibrillations, ataxia; salivation, urination, defecation, lacrimation)	Doull 1957
INTERMEDIATE EXPOSURE									
Death									
13	Rat (Wistar TNO/W 74)	3 wk 5 d/wk 6 hr/d					3.1 F	(3/20 died)	Thyssen 1980
Systemic									
14	Rat (Fischer- 344)	3 wk 5 d/wk 6 hr/d	Bd Wt	0.7					Shiotsuka 1988

TABLE 2-1. Levels of Significant Exposure to Disulfoton - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference
15	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Resp	0.16 M 1.4 F	1.4 M (increased incidence of inflammation of the nasal turbinates)		Shiotsuka 1989
			Cardio	1.4			
			Gastro	1.4			
			Hemato	1.4			
			Musc/skel	1.4			
			Hepatic	1.4			
			Renal	1.4			
			Endocr	1.4			
			Derm	1.4			
			Ocular	1.4			
			Bd Wt	1.4			
16	Rat (Wistar TNO/W 74)	3 wk 5 d/wk 6 hr/d	Resp	0.1	0.5 (inflammatory changes in the respiratory tract)	3.7 F (mottled distended lungs in the rats that died)	Thyssen 1980
			Cardio	3.7			
			Gastro	0.5		3.7 F (bloated gastrointestinal tract and ulcer-like foci in the glandular mucosa in rats that died)	
			Hemato	3.7			
			Hepatic	3.7			
			Renal	3.7			
			Endocr	0.5	3.7 F (increased absolute and relative adrenal weight)		
			Ocular	3.7			
			Bd Wt	0.5	3.7 F (11-12% decreased body weight gain)		

TABLE 2-1. Levels of Significant Exposure to Disulfoton - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference
17	Rat (Wistar TNO/W 74)	3 wk 5 d/wk 6 hr/d	Resp	0.02		3.1 F (distention and discoloration of lungs in rats that died; increased inflammatory changes in the respiratory tract)	Thyssen 1980
			Cardio	3.1 F			
			Gastro	3.1 F			
			Hemato	0.02	3.1 F (decreased percentage of lymphocytes, increased percentage of polymorpho- nuclear leukocytes)		
			Hepatic	3.1 F			
			Renal	3.1 F			
			Endocr	0.02	3.1 F (increased absolute and relative adrenal weight)		
			Ocular	3.1 F			
			Bd Wt	3.1 F			
Immunological/Lymphoreticular							
18	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		1.4			Shiotsuka 1989
19	Rat (Wistar TNO/W 74)	3 wk 5 d/wk 6 hr/d		0.1	0.5 (minimal to definite bone marrow changes accompanied by inflammatory changes in the respiratory tract)		Thyssen 1980

TABLE 2-1. Levels of Significant Exposure to Disulfoton - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)		LOAEL Serious (mg/m3)		Reference
20	Rat (Wistar TNO/W 74)	3 wk 5 d/wk 6 hr/d		0.02	3.1 F	(decreased absolute and relative spleen weight, reactive bone marrow changes accompanied by inflammatory changes in the respiratory tract)			Thyssen 1980
	Neurological								
21	Rat (Fischer- 344)	3 wk 5 d/wk 6 hr/d		0.7					Shiotsuka 1988
22	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		0.16	1.4	(14-31% inhibition of plasma cholinesterase, 22-34% inhibition of erythrocyte cholinesterase, 28-29% inhibition of brain cholinesterase)			Shiotsuka 1989
23	Rat (Wistar TNO/W 74)	3 wk 5 d/wk 6 hr/d			0.1	(lethargy for a brief time after exposure during the last week)	3.7	(muscle tremors, convulsion, increased salivation, difficulty breathing, 48-58% inhibition of brain cholinesterase)	Thyssen 1980

TABLE 2-1. Levels of Significant Exposure to Disulfoton - Inhalation (continued)

Key [a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference
24	Rat (Wistar TNO/W 74)	3 wk 5 d/wk 6 hr/d		0.02 [c]		3.1 F (muscle tremors, convulsions, increased salivation, difficulty breathing)	Thyssen 1980

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive an acute-duration inhalation minimal risk level (MRL) of 0.006 mg/m^3; concentration adjusted for intermittent exposure, converted to a human equivalent concentration, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive an intermediate-duration inhalation MRL of 2x10^{-4} mg/m^3; concentration adjusted for intermittent exposure, converted to a human equivalent concentration, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Derm = dermal; Endocr = endocrine; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LC50 = lethal concentration-50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

Figure 2-1. Levels of Significant Exposure to Disulfoton – Inhalation

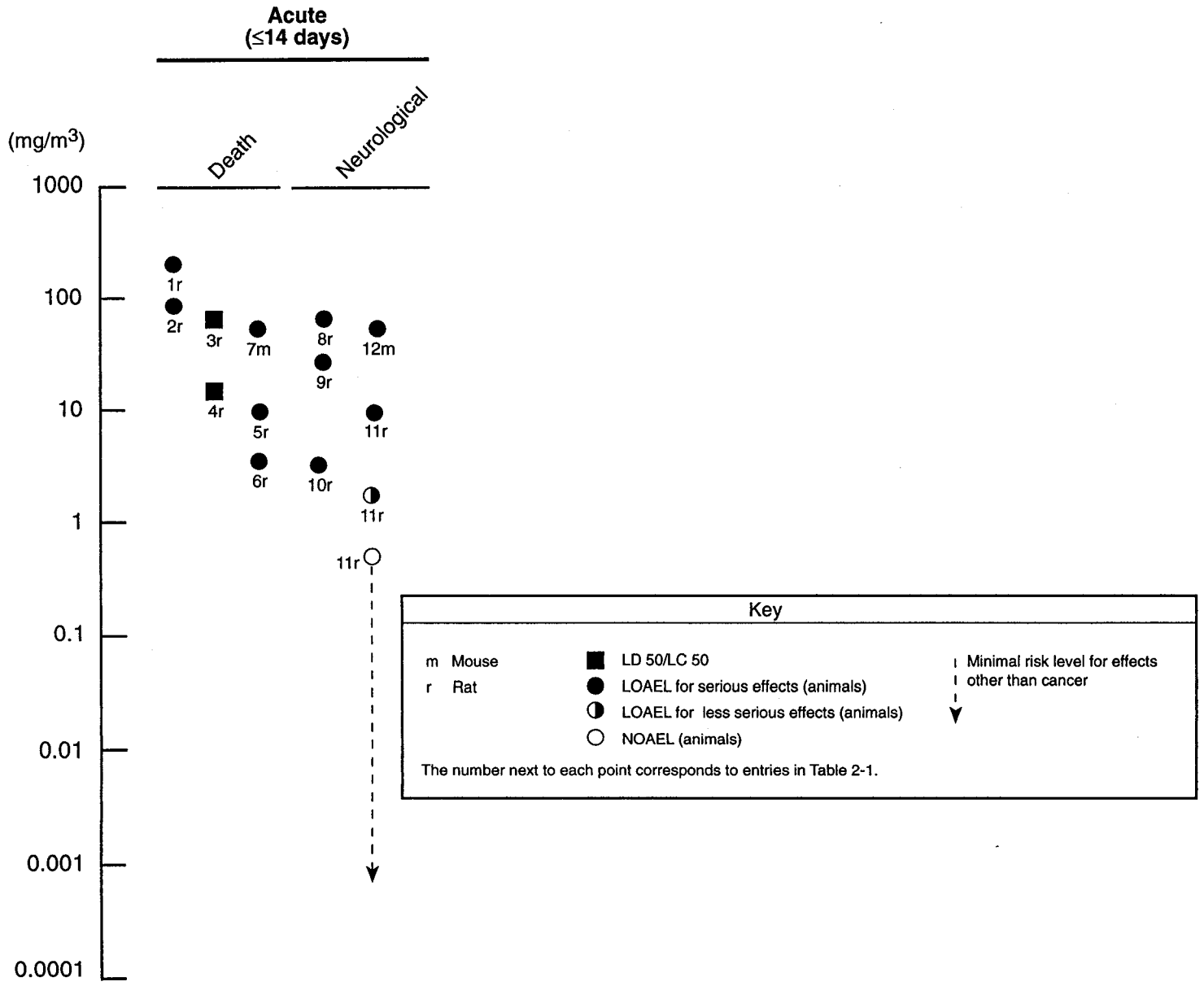
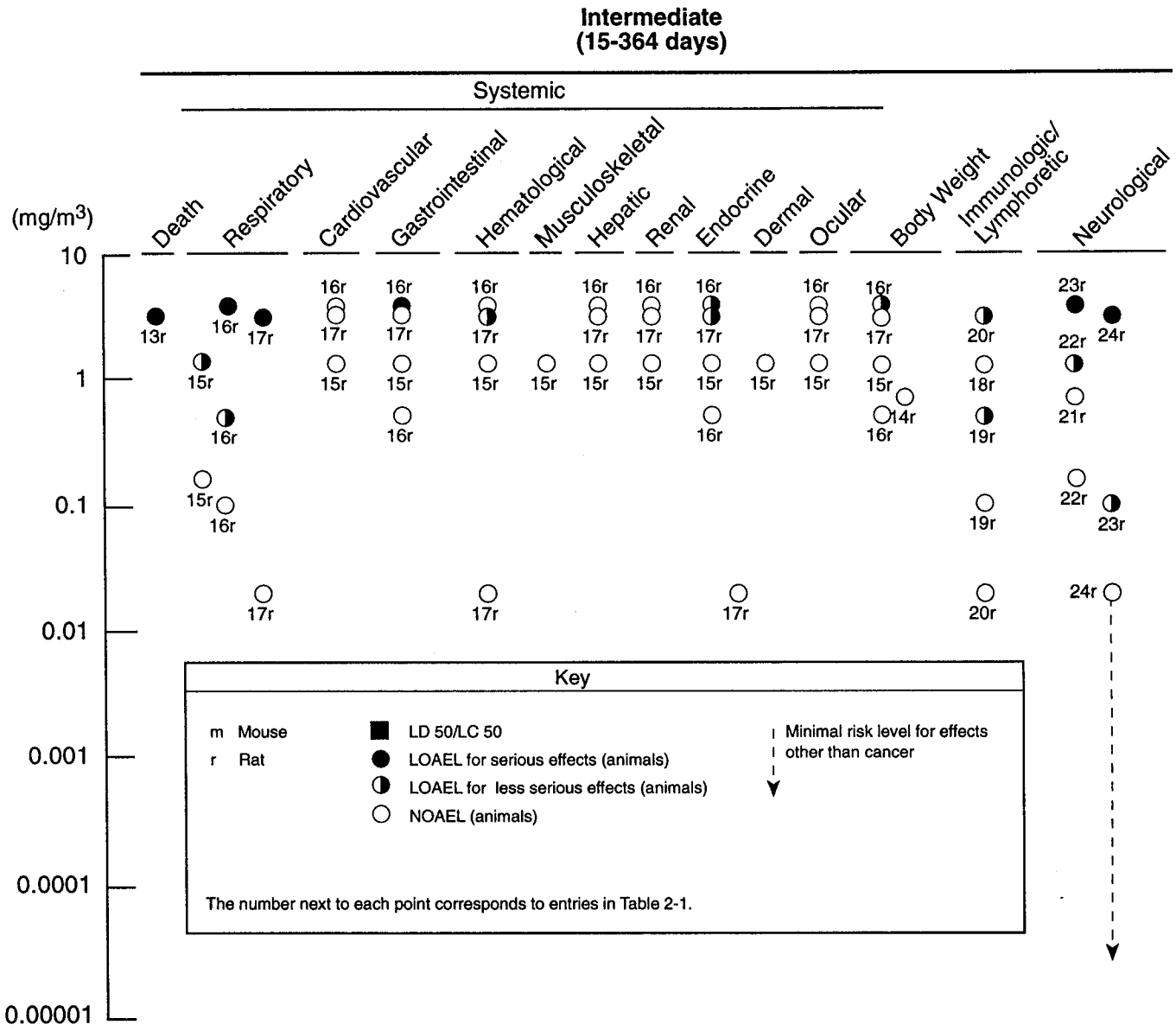


Figure 2-1. Levels of Significant Exposure to Disulfoton – Inhalation (continued)



Studies on these end points in animals exposed by inhalation to disulfoton are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for these end points in animals in each duration category are recorded in Table 2-l and plotted in Figure 2-l.

Respiratory Effects. In two separate experiments in which male and female rats were exposed intermittently for 3 weeks to 0.1, 0.5, or 3.7 mg/ m^3 in the first experiment, and to 0.02 mg/ m^3 (males and females) or 3.1 mg/ m^3 (females only) in the second experiment, inflammatory changes were found throughout the respiratory tract at 0.5, 3.1, and 3.7 mg/ m^3 (Thyssen 1980). These inflammatory changes were considered to be related to reactive bone marrow changes (see Section 2.2.1.3), which were minimal in male rats and definite in females in the first experiment. Deaths occurred in the female rats exposed to 3.1 or 3.7 mg/ m^3, and mottled, distended, and discolored lungs were found upon necropsy of the rats that died. Increased incidences of inflammation of the nasal turbinates were found in male rats, but not female rats, exposed to 1.4 mg/ m^3 intermittently for 13 weeks (Shiotsuka 1989). These lesions were not found at 0.16 mg/ m^3.

Cardiovascular Effects. No treatment-related microscopic lesions were found in the hearts of rats exposed intermittently to 3.7 mg/ m^3 for 3 weeks (Thyssen 1980) or to 1.4 mg/ m^3 for 13 weeks (Shiotsuka 1989).

Gastrointestinal Effects. In the female rats that died during intermittent exposure to 3.7 mg/ m^3 for 3 weeks, bloated gastrointestinal tracts and ulcer-like foci in the glandular mucosa were found upon necropsy (Thyssen 1980). Otherwise, no treatment-related histological effects in the gastrointestinal tract of the surviving females or in males exposed to ≤3.7 mg/ m^3 were found. Likewise, no gastrointestinal tract lesions were found in male or female rats exposed intermittently to ≤1.4 mg/ m^3 for 13 weeks (Shiotsuka 1989).

Hematological Effects. No effects on formed elements of the blood were found upon hematological examination in rats exposed intermittently to ≤3.7 mg/ m^3 for 3 weeks (Thyssen 1980). However, in a second experiment in which female rats were similarly exposed to 3.1 mg/ m^3, a relatively low percentage of lymphocytes and high percentages of polymorphonuclear leukocytes in the differential leukocyte counts were found. These effects were regarded as a first sign of a response to the inflammation in the respiratory tract and bone marrow changes observed in these rats (see

Section 2.2.1.3). No hematological effects were observed in rats exposed intermittently to 0.02-0.5 mg/ m^3 for 3 weeks (Thyssen 1980) or to 1.4 mg/ m^3 for 13 weeks (Shiotsuka 1989).

Musculoskeletal Effects. No gross or histological lesions were found in bones or skeletal muscle of rats exposed intermittently to ≤1.4 mg/ m^3 for 13 weeks (Shiotsuka 1989).

Hepatic Effects. Clinical chemistry tests and histological examination of livers revealed no hepatic effects in rats exposed intermittently to ≤3.7 mg/ m^3 for 3 weeks (Thyssen 1980) or to ≤1.4 mg/ m^3 for 13 weeks (Shiotsuka 1989).

Renal Effects. Clinical chemistry, urinalysis, and histological examination of kidneys revealed no renal effects in rats exposed intermittently to ≤3.7 mg/ m^3 for 3 weeks (Thyssen 1980) or to ≤1.4 mg/ m^3 for 13 weeks (Shiotsuka 1989).

Endocrine Effects. No histological lesions were found in the thyroid or adrenal glands of rats exposed interrnittently to ≤3.7 mg/ m^3 for 3 weeks, but females exposed to 3.1 and 3.7 mg/ m^3 in two separate experiments had significantly increased absolute and relative adrenal weights (Thyssen 1980). Since the increase in adrenal weights was consistently observed in both experiments, it was considered to be related to disulfoton exposure. No histological effects or effects on the weight of the adrenal gland and no histological effects on the thyroids, parathyroids, pituitary, or pancreas were observed in rats exposed intermittently to ≤1.4 mg/ m^3 for 13 weeks (Shiotsuka 1989).

Dermal Effects. No gross or histological lesions were found in the skin of rats exposed intermittently to 1.4 mg/ m^3 for 13 weeks (Shiotsuka 1989).

Ocular Effects. No histological or ophthalmological evidence of ocular effects were found in rats exposed intermittently to ≤3.7 mg/ m^3 for 3 weeks (Thyssen 1980) or to ≤1.4 mg/ m^3 for 13 weeks (Shiotsuka 1989).

Body Weight Effects. Female rats exposed intermittently to 3.7 mg/ m^3, but not 3.1 mg/ m^3, for 3 weeks had 12% and 11% lower body weights than controls during weeks 1 and 2, respectively, but only 5% lower body weight during week 3 (Thyssen 1980). Males similarly exposed to 3.7 mg/ m^3 had lower body weights than controls, but the difference was never >10%. No effects on body weight

were found in the rats exposed intermittently to 0.5 mg/ m^3 (Thyssen 1980) or 0.7 mg/ m^3 (Shiotsuka 1988) for 3 weeks, or 1.4 mg/ m^3 for 13 weeks (Shiotsuka 1989).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after inhalation exposure to disulfoton.

In two separate experiments in which male and female Wistar rats were exposed intermittently for 3 weeks to 0.1, 0.5, or 3.7 mg/ m^3 in the first experiment, and to 0.02 mg/ m^3 (males and females) or 3.1 mg/ m^3 (females only) in the second experiment, inflammatory changes were found throughout the respiratory tract at 0.5, 3.1, and 3.7 mg/ m^3 (Thyssen 1980). These inflammatory changes were considered to be related to reactive bone marrow changes. The reactive bone marrow changes were not specifically described in the study, but were regarded as minimal in male rats and definite in female rats in the first experiment. In the second experiment, but not in the first, female rats exposed to 3.1 mg/ m^3 had a relatively low percentage of lymphocytes and high percentages of polymorphonuclear leukocytes in the differential leukocyte counts. These effects were regarded as a first sign of a response to the inflammation in the respiratory tract and bone marrow changes observed in these rats. The female rats exposed to 3.1 mg/ m^3 also had decreased absolute and relative spleen weight, but histological examination of the spleen and bronchial lymph nodes revealed no treatmentrelated effects in males or females exposed to ≤3.7 mg/ m^3. In addition, histological examination of bone marrow, cervical lymph nodes, mesenteric lymph nodes, spleen, and thymus of Fischer 344 rats exposed intermittently to ≤1.4 mg/ m^3 for 13 weeks revealed no effects (Shiotsuka 1989). The highest NOAEL values and the LOAEL values for immunological and lymphoreticular effects in rats are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.4 Neurological Effects

Exposure to disulfoton can result in inhibition of cholinesterase activity in blood and at nerve synapses of muscles, secretory organs, and nervous tissue such as the brain and spinal cord (Murphy 1986). The accumulation of acetylcholine at these sites (specifically, the nerve synapses and ganglia in these organs) results in central nervous system, nicotinic, and muscarinic effects. Clinical signs and symptoms of neurotoxicity are usually observed in humans and animals that have been acutely

exposed to disulfoton or other organophosphate insecticides. Central nervous system signs and symptoms include anxiety, restlessness, depression of respiratory and circulatory centers, ataxia, convulsions, and coma. Nicotinic signs of disulfoton toxicity include muscle weakness, muscle tremors and fasciculations, and involuntary twitching. Muscle weakness that affects the respiratory muscles may contribute to dyspnea and cyanosis. Tachycardia may result from stimulation of sympathetic ganglia in cardiac tissue and may, therefore, mask the bradycardia due to the muscarinic action on the heart. Nicotinic action at the sympathetic ganglion may also result in pallor, high blood pressure, and hyperglycemia. Muscarinic signs of disulfoton toxicity include miosis, increased salivation, sweating, urination and defecation, vomiting and nausea, bronchoconstriction, increased bronchial secretions, and bradycardia that can progress to heart block.

Inhibition of the two principal human cholinesterases, acetylcholinesterase and pseudocholinesterase, may not always result in visible neurological effects (Sundlof et al. 1984). Acetylcholinesterase, also referred to as true cholinesterase, red blood cell cholinesterase, or erythrocyte cholinesterase is found in erythrocytes, lymphocytes, and at nerve synapses (Goldfrank et al. 1990). Inhibition of erythrocyte or lymphocyte acetylcholinesterase is theoretically a reflection of the degree of synaptic cholinesterase inhibition in nervous tissue, and therefore a more accurate indicator than pseudocholinesterase activity of inhibited nervous tissue acetylcholinesterase (Fitzgerald and Costa 1993; Sundlof et al. 1984). Pseudocholinesterase (also referred to as cholinesterase, butyrylcholinesterase, serum cholinesterase, or plasma cholinesterase) is found in the plasma, serum, pancreas, brain, and liver and is an indicator of exposure to a cholinesterase inhibitor.

Pseudocholinesterase and lymphocyte acetylcholinesterase activities are depressed before erythrocyte cholinesterase, suggesting that these cholinesterases are more sensitive than acetylcholinesterase (Fitzgerald and Costa 1993; Iyaniwura 1991; Sundlof et al. 1984). However, erythrocyte cholinesterase recovers more slowly (90-120 days) than pseudocholinesterase or lymphocyte acetylcholinesterase (days to weeks), and is therefore a better indicator after exposure ceases. Depression in pseudocholinesterase activity only indicates possible exposure to organophosphate(s), whereas depression in erythrocyte and lymphocyte cholinesterases also indicates a neurological effect, since they reflect inhibition of brain acetylcholinesterase activity. Recently, it was shown that the inhibition of lymphocyte acetylcholinesterase activity more closely paralleled the inhibition of brain acetylcholinesterase than did erythrocyte acetylcholinesterase activity (Fitzgerald and Costa 1993). In this profile, inhibition in lymphocyte or erythrocyte acetylcholinesterase activity and not

pseudocholinesterase activity is considered as an adverse neurological effect. Based on an evaluation by Kaloyanova and El Batawi (1991), ATSDR considers a 60% or greater acetylcholinesterase inhibition as a serious effect and less than 60%, but greater than 20%, acetylcholinesterase inhibition as a less serious effect.

Nervous system effects may occur in humans after occupational exposure to disulfoton (Wolfe et al. 1978). In this study, mean disulfoton concentrations of 0.460-0.633 mg/ m^3 caused a 22.8% depression in erythrocyte cholinesterase activity in workers at a pesticide-fertilizer mixing operation. The workers were exposed to disulfoton for 9 weeks, and there were no reports of adverse clinical signs due to disulfoton exposure. The study was limited in that baseline blood cholinesterase activities were obtained 2 weeks after the initial exposure and were compared with cholinesterase activities at 9 weeks. Therefore, the actual depression in cholinesterase activity over a 9-week period was probably >22.8%. In addition, these workers were also dermally exposed to disulfoton (see Section 2.2.3.4); therefore, the 22.8% depression in cholinesterase activity was probably due to both inhalation and dermal exposure. Despite these limitations, the study concluded that because this depression in cholinesterase activity was only associated with dry mixing operations, the wet mixing operations are less hazardous to workers.

Neurological effects, such as muscle twitching, ataxia, and increased salivation, urination, defecation, and lacrimation were observed in male Sprague-Dawley rats exposed to ≥65.1 mg/ m^3 and in female Carworth Farms mice exposed to ≥53.4 mg/ m^3 for 1 hour (Doull 1957). Female rats and male mice were not included in this study. However, the greater susceptibility of female rats to the cholinergic effects of disulfoton was demonstrated in several experiments in an acute inhalation study using Wistar rats (Thyssen 1978). In the LC_{50} determinations in this study, sluggishness, failure to groom, and typical signs of cholinesterase inhibition (not otherwise described) were observed in male rats exposed to ≥133 mg/ m^3 and in females exposed to ≥27 mg/ m^3 for 1 hour. These signs of toxicity were observed at lower exposure levels when rats were exposed for 4 hours (in males exposed to ≥64 mg/ m^3 and in females exposed to ≥3.4 mg/ m^3). These effects were transient, lasting for about 24 hours after exposure. In an experiment designed to examine cholinesterase activity in rats exposed to 0.5, 1.8, or 9.8 mg/ m^3 for 4 hours/day for 5 days, erythrocyte cholinesterase activity was depressed by 30-32% of controls in males exposed to 9.8 mg/ m^3 and by 17-26% in females at both 1.8 and 9.8 mg/ m^3. In addition, all rats were reported to display unspecified behavioral disorders at ≥1.8 mg/ m^3 and unspecified signs of cholinergic toxicity at 9.8 mg/ m^3. No inhibition of erythrocyte

cholinesterase activity and no signs of cholinergic toxicity were observed at 0.5 mg/ m^3. Based on this NOAEL of 0.5 mg/ m^3, an acute-duration inhalation MRL of 0.006 mg/ m^3 was calculated as described in footnote "b" in Table 2-l. No significant decrease in the activity of brain, serum, or submaxillary gland cholinesterase was found in female rats exposed to 0.14-0.7 mg/ m^3 disulfoton for 1 hour/day for 5-10 days (DuBois and Kinoshita 1971). No clinical signs of disulfoton toxicity or other details were reported.

Signs of cholinergic toxicity and depressions in cholinesterase activities were also observed in rats exposed to disulfoton for intermediate durations. In Wistar rats exposed intermittently to 0.1, 0.5, or 3.7 mg/ m^3 for 3 weeks, exposure to 0.1 mg/ m^3 resulted in brief periods of lethargy after exposure ended during the last week; exposure to 0.5 mg/ m^3 resulted in lethargy and failure to groom in males during the last week and in females during the second and last week; and exposure to 3.7 mg/ m^3 resulted in muscle tremors, convulsion, increased salivation, and dyspnea in males starting at the end of the first week and in females during the first week (Thyssen 1980). Erythrocyte cholinesterase activity was inhibited in males by 24-28% and in females by 27-32% at 3.7 mg/ m^3. Brain cholinesterase activity was inhibited in males by 48% at 3.7 mg/ m^3 and in females by 30% at 0.5 mg/ m^3 and 58% at 3.7 mg/ m^3. In a second 3-week experiment to determine a no-effect level for cholinesterase inhibition in Wistar male and female rats, no clinical signs of neurological effects and no effects on plasma, erythrocyte, or brain cholinesterase were observed at 0.02 mg/ m^3 (Thyssen 1980). Female rats exposed to 3.1 mg/ m^3 had muscle tremors, convulsion, increased salivation, and dyspnea, confirming the results in the first experiment. Male rats were not exposed to 3.1 mg/ m^3 in the second experiment. Based on the NOAEL of 0.02 mg/ m^3, an intermediate-duration inhalation MRL of $2x10^{-4}$ mg/ m^3 was calculated as described in footnote "c" in Table 2-l. In Fischer rats exposed intermittently to 1.4 mg/ m^3 for 13 weeks, erythrocyte cholinesterase activity was inhibited by 22-28% in males and 26-34% in females, and brain cholinesterase activity was inhibited by 29% in males and 28% in females (Shiotsuka 1989). Cholinesterase activities were not affected at $\leq$0.16 mg/ m^3, and no effects on brain weight or histological evidence of lesions in the brain, optic nerve, sciatic nerve, or spinal cord were found at any exposure level. In a similar study in Fischer 344 rats exposed to lower concentrations for 3 weeks, no significant differences in brain cholinesterase activities were found at 0.006-0.7 mg/ m^3 (Shiotsuka 1988). Erythrocyte cholinesterase activity was statistically consistently decreased at 0.7 mg/ m^3, but the decreases were never greater than 17% of control levels. The highest NOAEL values and all reliable LOAEL values for neurological effects in rats and mice for each duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to disulfoton.

In rats exposed intermittently to 0.02-3.7 mg/ m^3 for 3 weeks, measurements of the testes and ovary weights and histological examination of the testes and ovaries revealed no compound-related effects (Thyssen 1980). Similarly, no effects on testis or ovary weight and no compound-related histological lesions in epididymides, prostate, seminal vesicles, testicles, cervix, mammary glands, ovaries, or uterus were found in rats exposed intermittently to ≤1.4 mg/ m^3 for 13 weeks (Shiotsuka 1989). Reproductive studies in animals given disulfoton by the oral route have demonstrated that disulfoton produces effects on reproductive parameters (see Section 2.2.2.5); therefore, the above inhalation concentration levels cannot be considered NOAEL values for reproductive effects because these inhalation studies did not examine reproductive performance or outcomes.

2.2.1.6 Developmental Effects

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

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to disulfoton.

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans after inhalation exposure to disulfoton.

In a 13-week study in rats exposed intermittently to ≤1.4 mg/ m^3, the author reported that comprehensive histological examination of organs and tissues revealed no treatment-related neoplastic

lesions (Shiotsuka 1989). However, chronic-duration inhalation studies, which would be more appropriate to assess possible carcinogenicity, were not located for disulfoton.

2.2.2 Oral Exposure

2.2.2.1 Death

Only one study was located involving death in humans after ingestion of disulfoton (Hattori et al. 1982). In this case report, a 30-year-old man was found dead after consuming an unknown amount of disulfoton. He was believed to have been dead for at least 24 hours. Autopsy and histopathological examination revealed miosis, bubbling saliva from the mouth, pulmonary edema and hemorrhage, swelling of the glomemlus, and congestion of most organs, which suggested that the man had ingested an organophosphate. Analysis of urine and blood samples confirmed that disulfoton was the toxicant responsible for the death.

The dose of disulfoton associated with death following acute oral exposure in animals depends on the sex, species, and the duration of the exposure. As seen from Table 2-2 and Figure 2-2, female rats and mice were generally more sensitive than male rats and mice, and rats generally appeared to be more sensitive than mice, to disulfoton given orally. LD_{50} values ranged from 1.9 to 3.2 mg/kg in female rats, 6.2-12.5 mg/kg in male rats (Bombinski and DuBois 1958; Crawford and Anderson 1974; Gaines 1969; Mihail 1978; Pawar and Fawade 1978), 2.7-8.2 mg/kg in female mice, and 5.8-19.3 mg/kg in male mice (Mihail 1978; Pawar and Fawade 1978; Stevens et al. 1972a). In one LD_{50} determination in rats, deaths occurred within 6 minutes to 2 days in males and 4 minutes to 3 days in females (Gaines 1969). Oral LD_{50} values of 10 mg/kg in rats of unspecified sex (Schafer 1972), of 8.9-10.8 mg/kg in male guinea pigs (Bombinski and DuBois 1958; Crawford and Anderson 1973), and of 12.7 mg/kg in female guinea pigs (Crawford and Anderson 1973) have also been reported. A dose of 18 mg/kg was determined to be the minimum dose at which mortality occurred in wild deer mice of unspecified sex given disulfoton by gavage (Schafer and Bowles 1985).

Deaths occurred on the day of treatment in 4 of 6 female rats at a dose of 2.5 mg/kg and in 1 of 9 female rats at a dose of 1.5 mg/kg, but no deaths occurred in male rats given ≤5.2 mg/kg (Sheets 1993a). However, in another study using the same strain of rats (Sprague-Dawley), 1 of 5 male rats died after receiving one dose of 3.5 mg/kg disulfoton, while two more rats died after receiving the

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral

Key [a] to figure	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 (Sprague-Dawley)	once (G)				12.5M (LD50) 2.6 F (LD50)	Bombinski and DuBois 1958
2	Rat (NS)	once (GW)				2.0 F (2/4 died)	Crawford and Anderson 1974
3	Rat (Sherman)	once (GO)				6.8M (LD50) 2.5 F (LD50)	Gaines 1969
4	Rat (Wistar)	once (GO)				6.2M (LD50) 1.9 F (LD50)	Mihail 1978
5	Rat (Hindustan antibiotics)	once (G)				7.2M (LD50) 3.2 F (LD50)	Pawar and Fawade 1978
6	Rat (NS)	once (GO)				10 (LD50)	Schafer 1972
7	Rat (Sprague-Dawley)	1-23 d 1x/d for 3 days at a time (GO)				3.5M (3/5 died)	Schwab et al. 1981
8	Rat (Sprague-Dawley)	once (GO)				1.5 F (1/9 died on the day of treatment)	Sheets 1993a
9	Mouse (MMRI)	once (GO)				7.0M (LD50) 8.2 F (LD50)	Mihail 1978

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
10	Mouse (Hindustan antibiotics)	once (G)				5.8M (LD50) 2.7F (LD50)	Pawar and Fawade 1978
11	Mouse (wild deer mouse)	once (G)				18 (mortality of an unspecified number of mice)	Schafer and Bowles 1985
12	Mouse (Swiss-Webster)	once (GO)				19.3M (LD50)	Stevens et al. 1972a
13	Mouse (Swiss)	1-10 d 1x/d (GO)				9.6M (2/8 died)	Stevens et al. 1972b
14	Gn pig (NS)	once (G)				10.8M (LD50)	Bombinski and DuBois 1958
15	Gn pig (NS)	once (GW)				8.9M (LD50) 12.7F (LD50)	Crawford and Anderson 1973
	Systemic						
16	Rat (Wistar)	once (GO)	Endocr		6.25 F (173 and 313% increase in urinary noradrenaline and adrenaline levels, respectively)		Brzezinski 1969
17	Rat (Wistar)	once (GO)	Endocr		5.0M (decrease in adrenal gland catecholamine levels, increase in plasma catacholamines)		Brzezinski 1972

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	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	Rat (Wistar)	once (GO)	Endocr		5.0M (increase in urinary adrenaline and noradrenaline)		Brzezinski 1973
19	Rat (Wistar)	once (GO)	Endocr		5.0M (increase in urinary catecholamines by 41-250%)		Brzezinski and Ludwicki 1973
20	Rat (Wistar)	once (GO)	Endocr		1.25 (increase in urinary levels of adrenalin and noradrenalin)		Brzezinski and Rusiecki 1970
21	Rat (Sprague-Dawley)	10 d 1x/d (GO)	Bd Wt		2.0M (32% reduction in weight gain)		Costa et al. 1984
22	Rat (Sprague-Dawley)	10 d 1x/d (GO)	Bd Wt			2.0M (50% reduced body weight gain)	Costa et al. 1986
23	Rat (Hindustan antibiotics)	once (GO)	Hepatic		2.0M (increased lipid peroxidation)		Fawade and Pawar 1983
24	Rat (Long-Evans)	1-2 wk 1x/d (GO)	Bd Wt		2.0M (temporary but significant ($p<0.025$) decreased body weight gain at day 3 with recovery by day 5-6)		Fitzgerald and Costa 1992
25	Rat (Long-Evans)	1-2 wk 1x/d (GO)	Bd Wt		2.0M (significantly ($p<0.025$) reduced body weight gain beginning at day 3 with recovery by day 5-6)		Fitzgerald and Costa 1993

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
26	Rat (Wistar)	once (GO)	Resp	0.5 F	1.0 (dyspnea)		Mihail 1978
27	Rat (Holtzman)	9 d (F)	Bd Wt	0.38 F	1.0 F (10-12% reduced body weight gain at all weighing times)		Schwab and Murphy 1981
28	Rat (Sprague-Dawley)	1-23 d 1x/d for 3 days at a time (GO)	Bd Wt		2.0 M (approximately 20% reduced body weight gain)		Schwab et al. 1981
29	Rat (Sprague-Dawley)	1-10 d 1x/d (GO)	Bd Wt		2.0 M (weight loss not otherwise specified)		Schwab et al. 1983
30	Rat (Sprague-Dawley)	once (GO)	Musc/skel	5.2			Sheets 1993a
			Ocular	5.2			
31	Rat (Wistar)	once (GO)	Endocr	0.26 F	0.52 F (increased excretion of 1.25 M 4-hydroxy-3-methoxy-mandelic acid in urine)		Wysocka-Parusz ewska 1971
32	Mouse (Hindustan antibiotics)	2-4 d 1x/d (GO)	Hepatic		0.5 M (increased lipid peroxidation)		Fawade and Pawar 1978
33	Mouse (Hindustan antibiotics)	3 d 1x/d (GO)	Hepatic		1.0 M (increased lipid peroxidation)		Fawade and Pawar 1980

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
34	Mouse (MMRI)	once (GO)	Resp	2.5	5.0 (dyspnea)		Mihail 1978
	Neurological						
35	Rat (Wistar)	once (GO)			5.0M (decrease in brain catecholamine levels)		Brzezinski 1972
36	Rat (Wistar)	once (GO)				5.0M (33.8 -96.7% inhibition of blood acetylcholinesterase activity)	Brzezinski and Ludwicki 1973
37	Rat (Sprague-Dawley)	10 d (GO)				2M (89% inhibition of brain acetylcholinesterase activity)	Costa and Murphy 1983
38	Rat (Sprague-Dawley)	10 d 1x/d (GO)				2M (50% reduction in pancreatic acetylcholinesterase activity, salivation, lacrimation, diarrhea)	Costa et al. 1984
39	Rat (Sprague-Dawley)	10 d 1x/d (GO)				2M (decreased number of muscarinic receptors in cerebral cortex 84% inhibition of brain acetyl cholinesterase)	Costa et al. 1986
40	Rat (NS)	once (GW)				0.5 F (tremors)	Crawford and Anderson 1974
41	Rat (Long-Evans)	1-2 wk 1x/d (GO)				2M (typical signs of cholinergic toxicity, not specified, including diarrhea, decrease in brain receptor density)	Fitzgerald and Costa 1992

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
42	Rat (Long-Evans)	1-2 wk 1x/d (GO)				2M (60-84% decrease in brain cholinesterase activity, diarrhea, flaccidity, malaise)	Fitzgerald and Costa 1993
43	Rat (CD)	10 d Gd 6-15 1x/d (G)		0.1 [b] F	0.3 F (41% inhibition of plasma and erythrocyte cholinesterase activity in dams)	1.0 F (82-90% inhibition of plasma and erythrocyte cholinesterase activity in dams)	Lamb and Hixson 1983
44	Rat (Wistar)	once (GO)		0.5 F		1.0 F (muscle twitching cramps, salivation)	Mihail 1978
45	Rat (Holtzman)	9 d (F)			0.38 F (30-35% inhibition of brain and diaphragm acetyl cholinesterase)	1.0 F (tremors, diarrhea, excessive urination, fasciculations, exophthalmia)	Schwab and Murphy 1981
46	Rat (Sprague-Dawley)	1-23 d 1x/d for 3 days at a time (GO)				2.0M (exophthalmia, salivation, excessive urination and defecation, tremors)	Schwab et al. 1981
47	Rat (Sprague-Dawley)	1-10 d 1x/d (GO)				2.0M (salivation, lacrimation, excessive urination and diarrhea, fasciculations, tremors, 15-51% inhibition of ileal acetylcholinesterase activity)	Schwab et al. 1983

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
48	Rat (Sprague-Dawley)	once (GO)		0.24		0.76 F (muscle fasciculations, decrease vocalization, minimal head or body movement, 53% decrease in erythrocyte cholinesterase activity) 1.5M (muscle fasciculation, tremors, minimal head or body movement)	Sheets 1993a
49	Rat (Holtzman)	1 wk (F)			0.26 F (50% inhibition of brain acetylcholinesterase activity)		Su et al. 1971
50	Mouse (MMRI)	once (GO)		2.5		5.0 (muscle twitches, clonic cramps, salivation)	Mihail 1978
	Reproductive						
51	Mouse (NMRI/ ORIG)	once (GO)		5M			Herbold 1980
	Developmental						
52	Rat (CD)	10 d Gd 6-15 1x/d (G)		0.3	1.0 (delayed ossification of parietal bones and sternebrae)		Lamb and Hixson 1983
53	Rabbit (New Zealand)	13 d Gd 6-18 1x/d (G)		1.5			Tesh et al. 1982

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	INTERMEDIATE EXPOSURE						
	Death						
54	Rat (Albino)	30 d (F)				2.5M (death of 4/71)	Robinson et al. 1978
55	Rat (Fischer 344)	48 d ad lib (F)				1.31 F (1/12 died)	Sheets 1993b
56	Mouse (Charles River)	4 wk (F)				26F (5/25 died)	Clark et al. 1971
	Systemic						
57	Rat (Wistar)	76 d 1x/d every 2d (GO)	Endocr		0.625 M (increase in urinary levels of adrenalin and noradrenalin)		Brzezinski and Rusiecki 1970
58	Rat (Fischer- 344)	6 mo ad lib (F)	Bd Wt	0.07			Christenson and Wahle 1993

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
59	Rat (Sprague-Dawley)	F0: 15 wk premating; F1b: 13 wk premating & through production and weaning of F2a & F2b (F)	Bd Wt	0.03	0.09 (6-10% and 9-11% decrease in body weight gain in F1 parental females and males, respectively, during premating period)		Hixson and Hathaway 1986
60	Rat (Wistar)	90 d (F)	Resp	0.55			Klotzsche 1972
			Cardio	0.55			
			Gastro	0.55			
			Hemato	0.55			
			Musc/skel	0.55			
			Hepatic	0.55			
			Renal	0.55			
			Endocr	0.55			
			Derm	0.55			
			Ocular	0.55			
			Bd Wt	0.55			
61	Rat (Albino)	30 d (F)	Bd Wt		2.5 M (29% reduced body weight gain)		Robinson et al. 1978
62	Rat (Holtzman)	30-62 d (F)	Bd Wt	0.38 F	1.0 F (10-12% reduced body weight gain at all weighing times)		Schwab and Murphy 1981

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
63	Rat (Fischer- 344)	13 wk ad lib (F)	Musc/skel	1.31			Sheets 1993b
			Ocular	1.31			
			Bd Wt	1.31			
64	Rat (Holtzman or Charles River)	141-178 d (F)	Bd Wt	0.5 F		1.25 F (40% reduced body weight gain)	Stavinoha et al. 1969
65	Mouse (CF-LP)	13 wk (F)	Resp	0.71			Rivett et al. 1972
			Cardio	0.71			
			Gastro	0.71			
			Hemato	0.71			
			Hepatic	0.71			
			Renal	0.71			
			Endocr	0.71			
			Ocular	0.71			
			Bd Wt	0.71			
	Immunological/Lymphoreticular						
66	Rat (Wistar)	90 d (F)		0.55			Klotzsche 1972
67	Mouse (CF-LP)	13 wks (F)		0.71			Rivett et al. 1972

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Neurological						
68	Rat (Fischer- 344)	6 mo ad lib (F)		0.03 F 0.06 M	0.07 F (22-29% inhibition in erythrocyte cholinesterase activity)		Christenson and Wahle 1993
69	Rat (Charles River)	3 mo (F)			0.5 M (59% inhibition of brain acetylcholinesterase activity)		Clark and Pearson 1973
70	Rat (NS)	2 mo (F)			2.5 (increased permeabilitiy of brain tissue to copper ferricyanide)		Clark and Stavinoha 1971
71	Rat (NS)	8-16 wk (F)		0.05	0.1 (inhibition of brain and red blood cell cholinesterase activity)		Doull and Vaughn 1958
72	Rat (Fischer 344)	3-6 mo (F)		0.05 M	0.18 M (46-50% inhibition of erythrocyte cholinesterase)	0.75M (71-82% inhibition of erythrocyte cholinesterase)	Hayes 1985
					0.06 F (14-22% inhibition of erythrocyte cholinesterase)	0.21 F (68-69% inhibition of erythrocyte cholinesterase)	

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
73	Rat (Sprague-Dawley)	F0: 15 wk premating; F1b: 13 wk premating & through production and weaning of F2a & F2b (F)		0.03		0.09 F (tremor in the F0 females during the production of the F1 generation)	Hixson and Hathaway 1986
74	Rat (Wistar)	90 d (F)		0.07 M 0.11 F	0.34 M (30-40% inhibition of 0.55 F plasma and erythrocyte cholinesterase)		Klotzsche 1972
75	Rat (Albino)	30 d (F)				2.5M (unspecified typical signs of anticholinesterase, poisoning, inhibition of cholinesterase activity of 77.2% in brain, 81.9% in the stomach, 70.3% in the diaphragm)	Robinson et al. 1978
76	Rat (Albino)	60-95 d (F)				0.5 (51.6% and 81.3% inhibition of male and female brain cholinesterase activity, respectively)	Ryan et al. 1970
77	Rat (Holtzman)	30-62 d (F)				0.38 F (75% inhibition of brain and 50% inhibition of diaphragm acetylcholinesterase)	Schwab and Murphy 1981

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
78	Rat (Fischer- 344)	13 wk ad lib (F)		0.071 F		0.351 F (muscle fasciculation, urine stain, 79-80% inhibition of erythrocyte cholinesterase activity, 64% inhibition of brain cholinesterase activity)	Sheets 1993b
				0.063 M		0.270M (61-67% inhibition of erythrocyte cholinesterase activity; 35% inhibition of brain cholinesterase activity)	
79	Rat (Holtzman or Charles River)	141-178 d (F)				0.5 F (72% inhibition of brain acetylcholinesterase activity)	Stavinoha et al. 1969
80	Mouse (NS)	2 mo (F)			19.5 (increased permeability of brain tissue to copper ferricyanide)		Clark and Stavinoha 1971
81	Mouse (Charles River)	4-12 wk (F)				21.7 (increased exploratory behavior)	Clark et al. 1971
82	Mouse (CF-LP)	13 wk (F)		0.14 F 0.63 M	0.71 F (27-37% inhibition of red blood cell and plasma cholinesterase activity)		Rivett et al. 1972
83	Dog (Beagle)	5 mo 5d/wk 1x/d (C)				0.5 (80% inhibition of erythrocyte cholinesterase)	Hikita et al. 1973

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference
84	Dog (Beagle)	40 wk (F)			0.06	(22-50% inhibition of erythrocyte cholinesterase; 33-36% inhibition of plasma cholinesterase)			Hoffman et al. 1975
	Reproductive								
85	Rat (Sprague-Dawley)	F0: 15 wk premating; F1b: 13 wk premating & through production and weaning of F2a & F2b (F)		0.009	0.03	(decreased F2b litter counts and litter weights)	0.09	(decreased % sperm-positive F0 & F1 females; decreased maternal F0 & F1 weight during gestation & lactation; decreased litter counts, viability & lactation indices, increased dead births & % dead births)	Hixson and Hathaway 1986
86	Rat (Albino)	60-95 d (F)					0.5	(2/5 females failed to become pregnant)	Ryan et al. 1970
	Developmental								
87	Rat (Sprague-Dawley)	F0: 15 wk premating; F1b: 13 wk premating & through production and weaning of F2a & F2b (F)		0.009 [c]	0.03	(24-32% inhibition of brain cholinesterase activity in F1a pups)			Hixson and Hathaway 1986

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
88	Rat (Albino)	60-95 d (F)			0.5 (32.1% inhibition of fetal brain cholinesterase activity)		Ryan et al. 1970
89	Rat (Holtzman)	3 generations (F)			0.1 (30-40% inhibition of erythrocyte cholinesterase in F3b weanlings) 0.5 (cloudy swelling and fatty livers, mild nephropathy, juvenile hypoplasia of testes in F3b weanlings)		Taylor 1965a
	CHRONIC EXPOSURE						
	Death						
90	Rat (Fischer 344)	104-106 wk (F)				1.02 F (increased mortality)	Hayes 1985

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Systemic						
91	Rat (Sprague-Dawley)	1.5-2yr (F)	Resp	0.1			Carpy et al. 1975
			Cardio	0.1			
			Gastro	0.1			
			Hemato	0.1			
			Musc/skel	0.1			
			Hepatic	0.1			
			Renal	0.1			
			Endocr	0.1			
			Derm	0.1			
			Ocular	0.1			
			Bd Wt	0.1			

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
92	Rat (Fischer 344)	104-106 wk (F)	Resp	0.21 F	1.02 F (granulomatous and suppurative inflammation of the lungs) 0.75 M		Hayes 1985
			Cardio	1.02 F			
			Gastro	0.21 F 0.75 M	1.02 F (mucosal hyperplasia and chronic inflammation of the forestomach)		
			Hemato	1.02 F			
			Musc/skel	0.21 F 0.75 M		1.02 F (skeletal muscle atrophy due to debilitation)	
			Hepatic	1.02 F			
			Renal	1.02 F			
			Endocr	0.18 M 1.02 F	0.75 M (pancreatic atrophy)		
			Derm	0.21 F 0.18 M	1.02 F (acanthosis, 0.75 M hyperkeratosis, ulcer of the skin)		
			Ocular	0.06 F 0.18 M	0.21 F (cystic degeneration of Harderian gland)	1.02 F (corneal neovascularization) 0.75M	
			Bd Wt	0.21 F 0.18 M	1.02 F (11-19% decrease in 0.75 M body weight gain)		

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference
93	Mouse (CD-1)	23 mo (F)	Resp	2.53				Hayes 1983
			Cardio	2.53				
			Gastro	2.53				
			Hemato	2.53				
			Musc/Skel	2.53				
			Hepatic	2.53				
			Renal	2.53				
			Endocr	2.53				
			Derm	2.53				
			Ocular	2.53				
			Bd Wt	2.53				
94	Dog (Beagle)	2 yr (F)	Resp	0.14				Hoffman et al. 1975
			Cardio	0.14				
			Gastro	0.14				
			Hemato	0.14				
			Musc/skel	0.14				
			Hepatic	0.14				
			Renal	0.14				
			Endocr	0.14				
			Ocular	0.14				
			Bd Wt	0.14				
95	Dog (Beagle)	2 yr 5 d/wk 1x/d (C)	Ocular			0.63	(myopia, astigmatism, degenerationof ciliary muscle cells)	Ishikawa and Miyata 1980

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Immunological/Lymphoreticular						
96	Rat (Sprague-Dawley)	1.5-2 yr (F)		0.1			Carpy et al. 1975
97	Rat (Fischer 344)	104-106 wk (F)		0.21 F 0.18 M	1.02 F (splenic lymphoid follicle depletion) 0.75 M (plasma cell hyperplasia in the mandibular lymph nodes)		Hayes 1985
98	Mouse (CD-1)	23 mo (F)		2.53			Hayes 1983
99	Dog (Beagle)	2 yr (F)		0.14			Hoffman et al. 1975
	Neurological						
100	Rat (Sprague-Dawley)	1.5-2 yr (F)		0.05 M	0.06 M (26-37%inhibition of brain cholinesterase) 0.09 F		Carpy et al. 1975
101	Rat (Fischer 344)	104-106 wk (F)		0.05 M		0.18M (46-67% inhibition of erythrocyte cholinesterase, 53% inhibtion of brain cholinesterase, optic nerve degeneration)	Hayes 1985
					0.06 F (14-24% inhibition of erythrocyte cholinesterase, 21% inhibition of brain cholinesterase)	0.21 F (57-77% inhibition of erythrocyte cholinesterase, 53% inhibition of brain cholinesterase, optic nerve degeneration, rough coat)	

TABLE 2-2 Levels of Significant Exposure to Disulfoton - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference
102	Mouse (CD-1)	23 mo (F)		0.5 M			2.13M 2.53 F	(significant inhibition of erythrocyte, plasma, and brain cholinesterase by 56-82%, 50-79%, and 44-46%, respectively)	Hayes 1983
103	Dog (Beagle)	2 yr (F)		0.03	0.14	(46-53% inhibition of erythrocyte cholinesterase, 54-70% inhibition of plasma cholinesterase, 34.4% inhibition of brain cholinesterase in males)			Hoffman et al. 1975
104	Dog (Beagle)	2 yr 5 d/wk 1x/d (C)					0.5	(necrosis and atrophy of optic nerve and retina)	Uga et al. 1977
	Reproductive								
105	Rat (Fischer 344)	104-106 wk (F)		0.21 F 0.75 M	1.02 F	(uterine cystic hyperplasia)			Hayes 1985

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.001 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive an intermediate-duration oral MRL of $9x10^{-5}$ mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[d]Used to derive a chronic-duration oral MRL of $6x10^{-5}$ mg/kg/day; dose divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Derm = dermal; Endocr = endocrine; F = female; (F) = feed; F0 = parental generation; F1 = first filial generation; F1a = first set of litters in the first filial generation; F1b = second set of litters in the first filial generation; F2a = first set of litters in the second filial generation; F2b = second set of litters in the second filial generation; F3B = second set of litters in the third filial generation; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage, oil vehicle; (GW) = gavage, water vehicle; Hemato = hematological; LD50 = lethal dose - 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time(s); yr = years(s)

Figure 2-2. Levels of Significant Exposure to Disulfoton – Oral

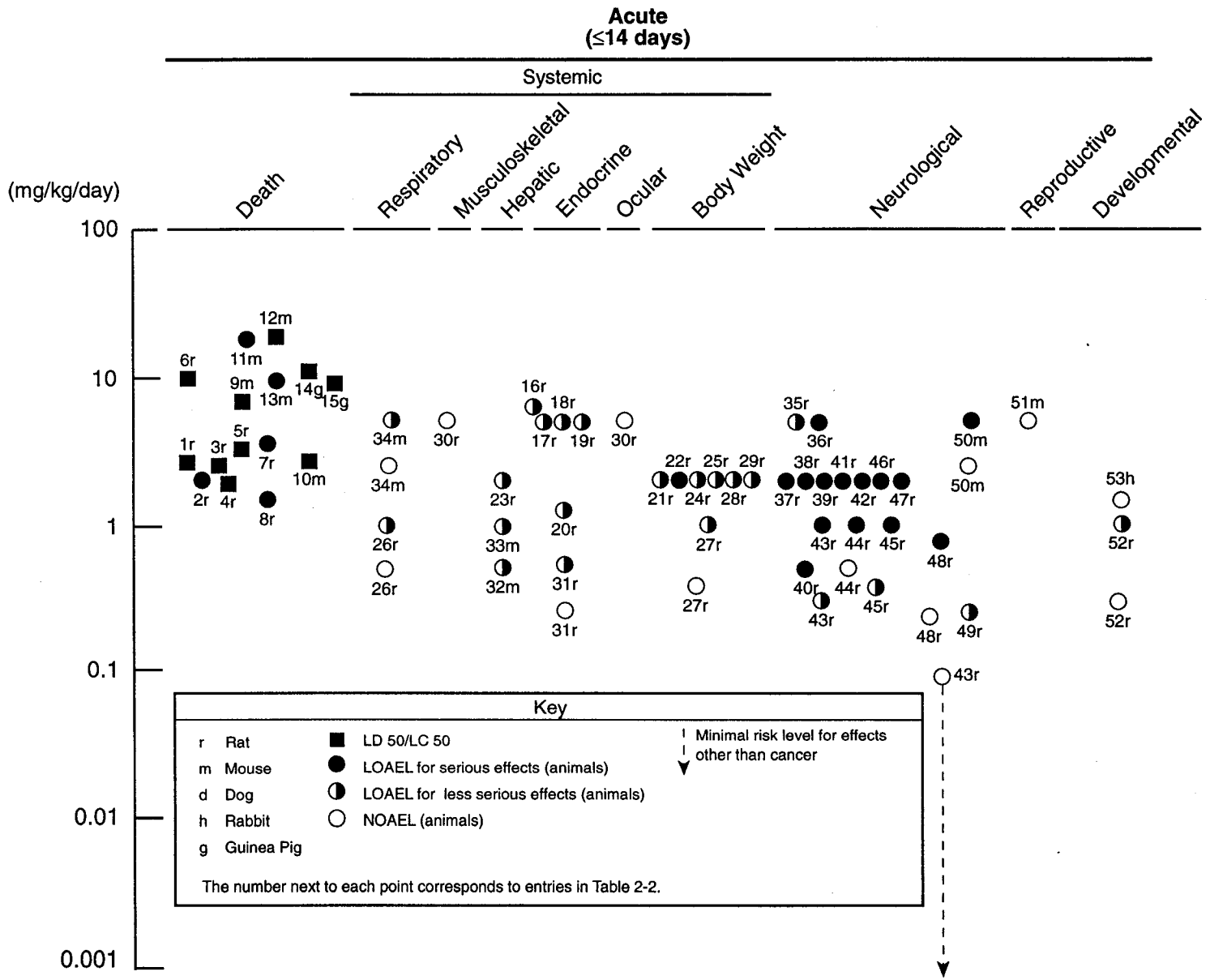


Figure 2-2. Levels of Significant Exposure to Disulfoton – Oral (continued)

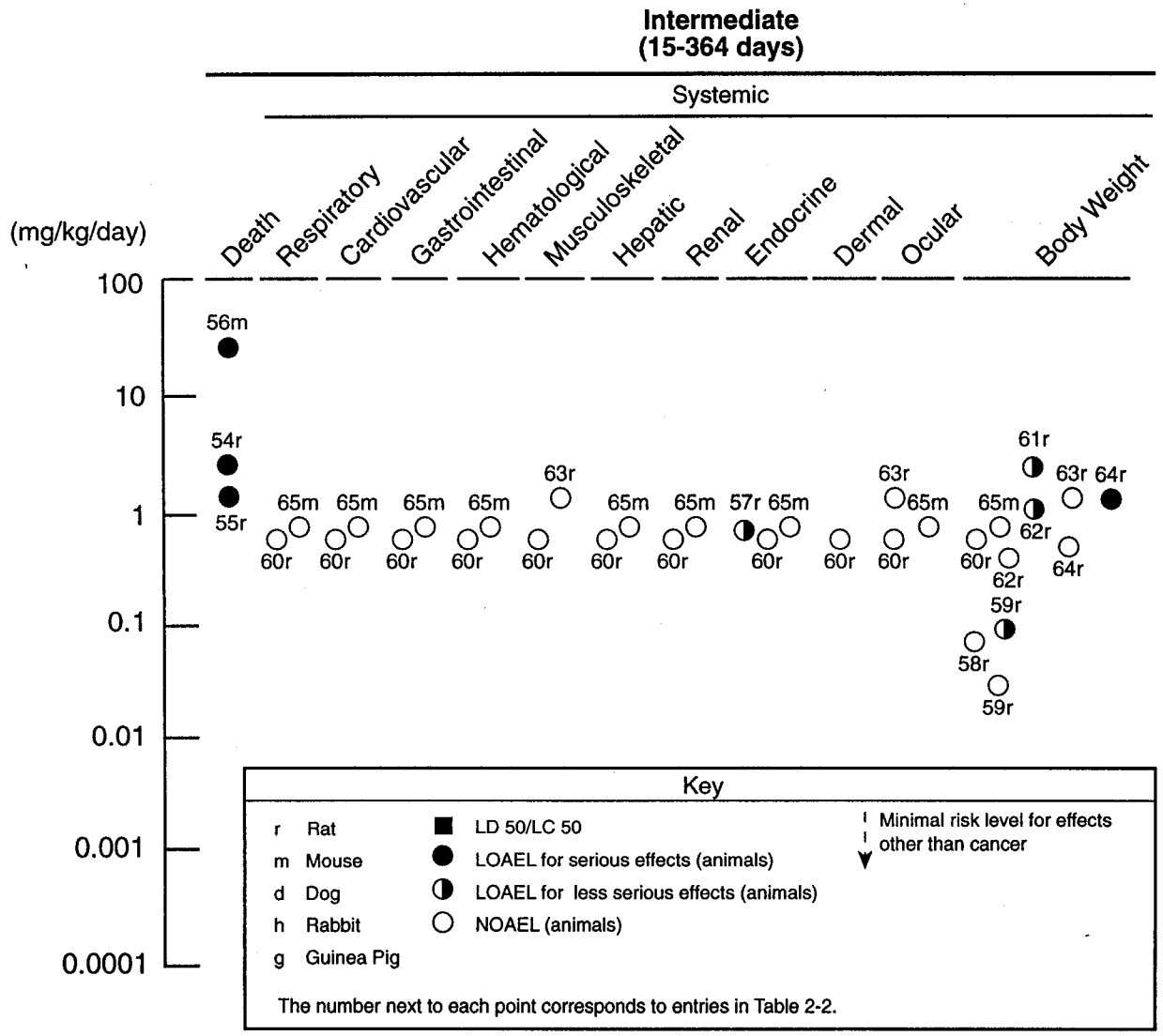


Figure 2-2. Levels of Significant Exposure to Disulfoton – Oral (continued)

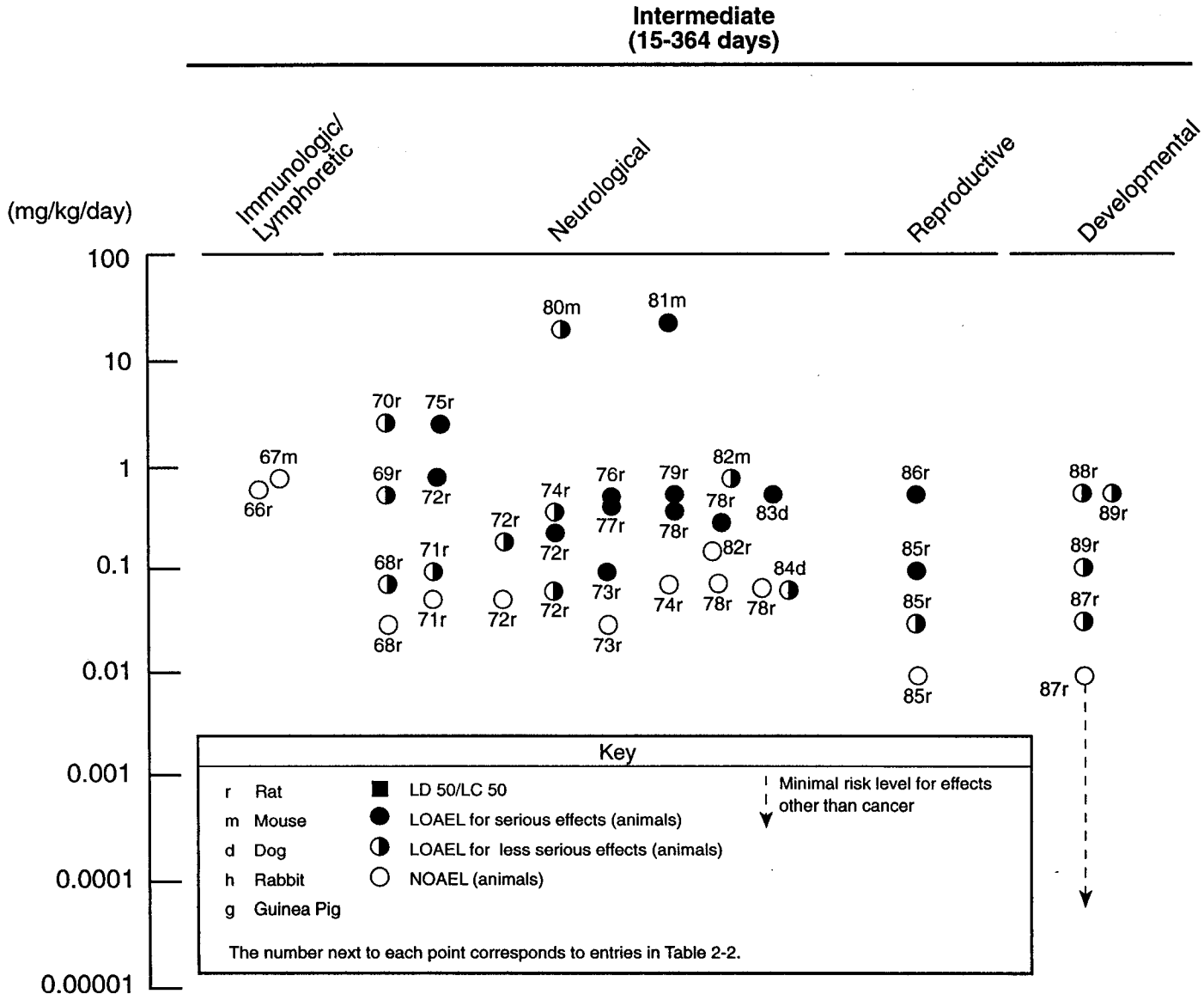
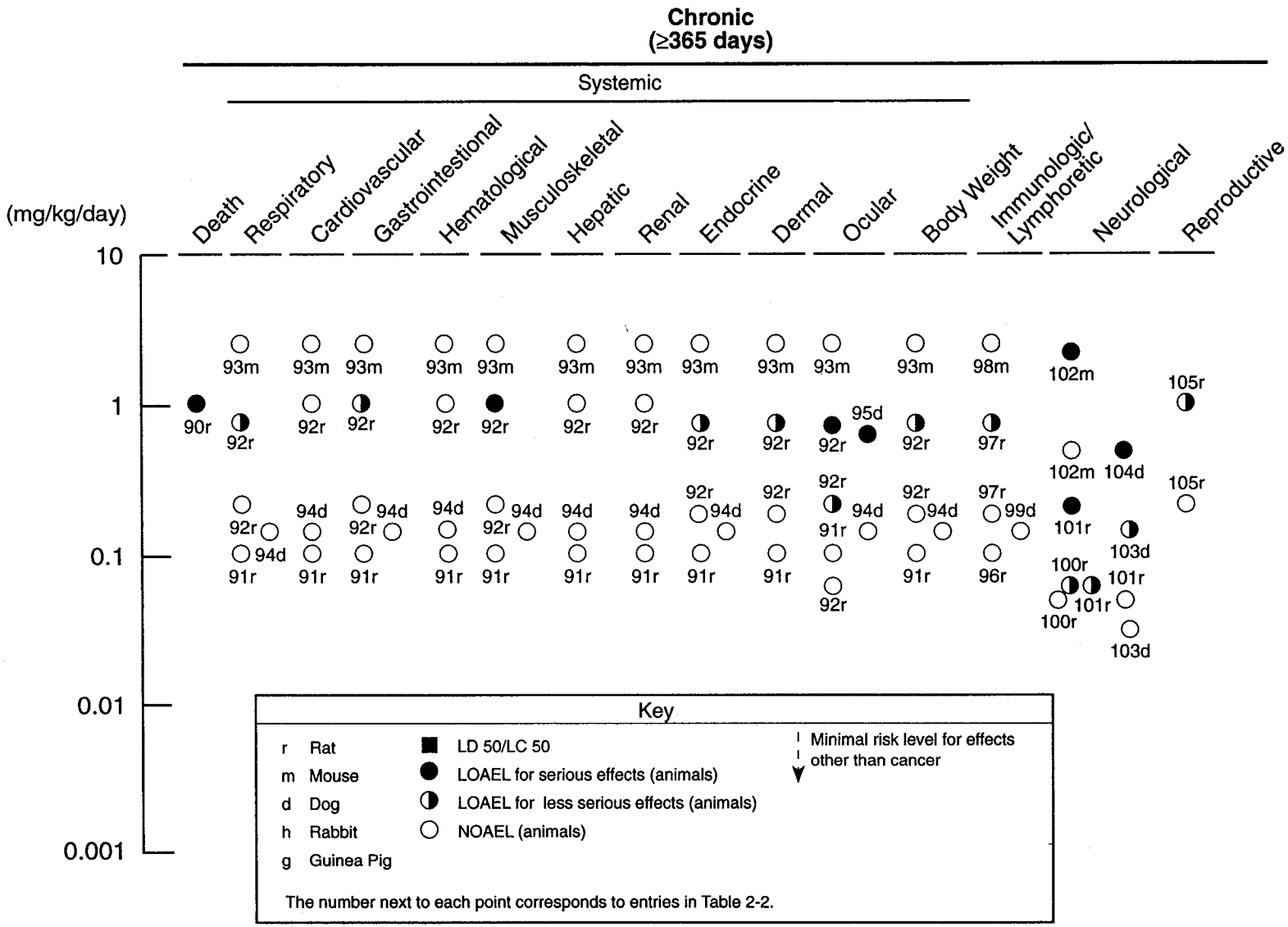


Figure 2-2. Levels of Significant Exposure to Disulfoton – Oral



same dose for 3 consecutive days (Schwab et al. 1981). In the same study, 1 of 8 rats died after receiving either 2.5 or 3.5 mgfkgfday for 6 days. When groups of mice were given 50% of the derived LD_{50} (9.6 mg/kg) for 3, 5, and 10 days, mortality was 2 of 8, 2 of 8, and 9 of 20, respectively (Stevens et al. 1972b). The results suggest that even at half the acute LD_{50} dose, almost half of the mice given disulfoton for 10 days died.

In intermediate-duration studies, 1 of 12 female rats given 1.3 1 mg/kg/day disulfoton in the diet was found dead on day 48 due to cholinergic effects (tremor, muscle fasciculation) (Sheets 1993b). In addition, 4 of 71 male rats died when given a diet providing 2.5 mg/kg/day for 30 days (Robinson et al. 1978), and 5 of 25 female mice died when given a diet providing 26 mg/kg/day disulfoton for 4 weeks (Clark et al. 1971). The reason that mice could tolerate a higher dose in the diet for 4 weeks compared with single dose LD_{50} values is probably related to the method of administration (i.e., continuous intermittent exposure during feeding versus a single bolus dose by gavage).

In a 2-year dietary study, female rats in the high dose group (1.02 mg/kg/day) had a 40% mortality rate during the last week of the study compared with 12% in controls (Hayes 1985). While the mortality rate in the control group was unusually low, the 40% mortality rate in the high dose female rats was also increased when compared with historical controls, in which the mortality rate ranged from 18 to 34%. No increase in the mortality rate of male rats was observed. Furthermore, no increase in the mortality was reported for mice exposed to 2.13 mg/kg/day (males) or 2.53 mg/kg/day (females) disulfoton in the diet for 23 months (Hayes 1983). These results support the conclusion that rats are more sensitive than mice and that female rats are more sensitive than male rats to the lethal effects of disulfoton.

The causes of death in these studies were not specifically mentioned, but disulfoton is a cholinesterase inhibitor, and animals exposed to disulfoton typically exhibit cholinergic signs of toxicity (see Section 2.2.2.4).

The LD_{50} values and the doses associated with death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

Studies regarding the systemic effects that have been observed in humans and animals after oral exposure to disulfoton are discussed below. 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 2-2 and plotted in Figure 2-2.

Respiratory Effects. Intra-alveolar bleeding, edema of the lungs, and blood in the bronchus were observed at autopsy in a man who had been dead for at least 24 hours after ingesting an unknown quantity of disulfoton (Hattori et al. 1982). This was the only information found regarding respiratory effects in humans after oral exposure to disulfoton.

Breathing difficulties were observed in rats given a single gavage dose of 1.0 mg/kg and in mice given 5.0 mg/kg disulfoton (Mihail 1978). Rats given 0.5 mg/kg and mice given 2.5 mg/kg did not display breathing disorders.

No histopathological lesions were found in the lungs of rats exposed to 0.34 mg/kg/day (males) or 0.55 mg/kg/day (females) (Klotzsche 1972) or mice exposed to 0.63 mg/kg/day (males) or 0.71 mg/kg/day (females) (Rivett et al. 1972) in the diet for 90 days, or in rats exposed to ≤0.21 mg/kg/day (Carpy et al. 1975; Hayes 1985), in mice exposed to 2.13 mg/kg/day (males) or 2.53 mg/kg/day (females) (Hayes 1983), or in dogs exposed to 0.14 mg/kg/day (Hoffman et al. 1975) in the diet for up to 2 years. In rats exposed to disulfoton in the diet for 2 years, granulomatous and suppurative inflammation of the lungs was found in the high dose groups (0.75 mg/kg/day in males and 1.02 mg/kg/day in females) (Hayes 1985). The lung inflammation was considered to be due to aspiration of the food particles, which in turn may have been associated with the debilitation observed in the high dose groups.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to disulfoton.

No histopathological lesions were found in the hearts of rats exposed to ≤0.55 mg/kg/day (Klotzsche 1972) or mice exposed to ≤0.71 mg/kg/day (Rivett et al. 1972) in the diet for 90 days, or in rats exposed to 0.1 mg/kg/day (Carpy et al. 1975) or ≤1.02 mg/kg/day (Hayes 1985), in mice exposed to

≤2.53 mg/kg/day (Hayes 1983), or in dogs exposed to 0.14 mg/kg/day (Hoffman et al. 1975) in the diet for up to 2 years.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to disulfoton.

No histopathological lesions were found in the gastrointestinal tracts of rats exposed to 0.34 mg/kg/day (males) or 0.55 mg/kg/day (females) (Klotzsche 1972) or mice exposed to 0.63 mg/kg/day (males) or 0.71 mg/kg/day (females) (Rivett et al. 1972) in the diet for 90 days, or in rats exposed to 0.1 mg/kg/day (Carpy et al. 1975), in mice exposed to 2.13 mg/kg/day (males) or 2.53 mg/kg/day (females) (Hayes 1983), or in dogs exposed to 0.14 mg/kg/day (Hoffman et al. 1975) in the diet for up to 2 years. However, increased incidences of mucosal hyperplasia and chronic inflammation of the forestomach were observed in female rats given 1.02 mg/kg/day disulfoton in the diet for 2 years (Hayes 1985). The mucosal hyperplasia was usually diffuse but was sometimes more locally severe and accompanied by inflammation, fibrosis, and ulceration. The forestomach lesions were not observed in male rats at ≤0.75 mg/kg/day or in females at ≤0.21 mg/kg/day.

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

Limited information from animal studies suggests that intermediate- or chronic-duration exposure to disulfoton is not associated with hematological effects. No hematological effects were observed in rats fed ≤0.55 mg/kg/day of disulfoton (Klotzsche 1972) or in mice fed ≤0.71 mg/kg/day (Rivett et al. 1972) for 90 days. In 2-year feeding studies, disulfoton did not cause any hematological effects in rats (Carpy et al. 1975; Hayes 1985), mice (Hayes 1983), or dogs (Hoffman et al. 1975).

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

Degeneration of ciliary muscle cells was found in the eyes of dogs given disulfoton at doses ≥0.63 mg/kg/day for 2 years (Ishikawa and Miyata 1980; Suzuki and Ishikawa 1974). The degenerative changes consisted of the presence of unique membranous structures, displacement of myofilaments, and lack of clearly defined organelles. The authors suggested that the microsomal

oxidation of disulfoton to an active metabolite that can destroy microsomes may account for the destructive changes in the ciliary muscle cells (Suzuki and Ishikawa 1974) or that cholinergic innervation of the iris-sphincter and ciliary muscle by disulfoton resulted in edema of the ciliary muscles (Ishikawa and Miyata 1980). The degeneration of these cells was believed to be the cause of myopia (see Ocular Effects below) in these dogs.

Histological examination of the gastrocnemius muscle of rats given a single gavage dose of ≤5.2 mg/kg (Sheets 1993a) or ≤1.31 mg/kg/day disulfoton in the diet for 13 weeks (Sheets 1993b) revealed no treatment-related lesions. No histopathological muscular or skeletal lesions were found in rats exposed to 0.34 mg/kg/day (males) or 0.55 mg/kg/day (females) (Klotzsche 1972) or mice exposed to 0.63 mg/kg/day (males) or 0.71 mg/kg/day (females) (Rivett et al. 1972) in the diet for 90 days, or in rats exposed to ≤0.21 mg/kg/day (Carpy et al. 1975; Hayes 1985), in mice exposed to 2.13 mg/kg/day (males) or 2.53 mg/kg/day (females) (Hayes 1983), or in dogs exposed to 0.14 mg/kg/day (Hoffman et al. 1975) in the diet for up to 2 years. However, reduced skeletal muscle size and skeletal muscle atrophy were observed in female rats given 1.02 mg/kg/day disulfoton in the diet for 2 years (Hayes 1985). The skeletal muscle atrophy corresponded to the generalized debilitation in the high dose females.

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

In animals, the hepatic effects associated with oral exposure to disulfoton included alterations in liver microsomal enzyme activities, lipid peroxidation, and changes in liver weight. The ability of disulfoton to affect microsomal enzyme activities appears to depend upon the dose, the duration of dosing, and the time between dosing and enzyme assays. Microsomal enzyme induction is considered to be nonadverse unless the induction of enzymes can be linked to more serious liver effects. A single oral dose (9.6 mg/kg) of disulfoton caused a significant ($p<0.05$) decrease in *in vitro* mouse liver ethylmorphine N-demethylase and reduced nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome c reductase activities, but no significant effect on NADPH oxidase, when assayed 1 hour after dosing (Stevens et al. 1973). However, a significant increase in liver ethylmorphine N-demethylase and NADPH oxidase activities, but no significant effect on NADPH cytochrome c reductase activity or cytochrome P-450 content, was observed in mice given 9.6 mg/kg/day disulfoton for 3 days and sacrificed 24 hours later for *in vitro* enzyme assays. When mice were

treated with 8 mg/kg/day for 5 days, the content of cytochrome P-450 was also significantly increased. Treatment of mice with 9.6 mg/kg/day disulfoton for 3, 5, or 10 days resulted in significant shortening of the hexobarbital sleeping time, compared with controls, and stimulated the *in vitro* side chain oxidation of hexobarbital and the hydroxylation of aniline (Stevens et al. 1972b). Significant increases in microsomal protein content and delta-aminolevulinic acid synthetase activity, and significant decreases in ethylmorphine N-demethylase, aminopyrine N-demethylase, and acetanilide hydroxylase activities were found in the livers from rats given 2 mg/kg or mice given 0.5 or 1.0 mg/kg/day disulfoton for l-4 days (Fawade and Pawar 1978, 1980, 1983). Disulfoton also caused an increase in NADPH-dependent and ascorbate-promoted lipid peroxidation and a decrease in electron transport elements. The reduction in electron transport elements was thought to be due to loss of integrity of the membranes and structural alterations in the membrane phospholipids, leading to increased lipid peroxidation. Disulfoton or its oxygenated metabolite may also have changed the conformation of heme protein, leading to enhanced lipid peroxidation (Fawade and Pawar 1978).

In intermediate-duration studies, no effects on clinical chemistry indices of liver toxicity and no histopathological hepatic lesions were found in rats given 0.34 mg/kg/day (males) or 0.55 mg/kg/day (females) (Klotzsche 1972) or in mice given 0.63 mg/kg/day (males) or 0.71 mg/kg/day (females) (Rivett et al. 1972) in the diet for 90 days. However, a slight increase in liver weight was observed in female mice at 0.71 mg/kg/day (Rivett at al. 1972).

Similarly, in chronic feeding studies, no clinical chemistry or histological evidence of liver toxicity was found in rats (Carpy et al. 1975; Hayes 1985), mice (Hayes 1983), or dogs (Hoffman et al. 1975). However, trends towards increased liver weights in male rats and decreased liver weights in female rats fed disulfoton for 1.5-2.0 years were observed (Carpy et al. 1975). The reason for these opposite trends in male and female rats is not clear.

Renal Effects. The only information found regarding renal effects in humans after oral exposure to disulfoton was swelling of the glomerulus at autopsy in a man who had been dead for at least 24 hours after ingesting an unknown quantity of disulfoton (Hattori et al. 1982).

Few data were located regarding renal effects in animals after oral exposure to disulfoton, and the evidence for renal effects due to disulfoton ingestion is inconclusive. Urinalysis and histological examination revealed no renal effects in rats given ≤0.55 mg/kg/day disulfoton (Klotzsche 1972) or in

mice given ≤0.71 mg/kg/day disulfoton (Rivett et al. 1972) in the diet for 90 days, in rats given ≤1.02 mg/kg/day in the diet for 1.5-2 years (Carpy et al. 1975; Hayes 1985), in mice given ≤2.53 mg/kg/day in the diet for 23 months (Hayes 1983), or in dogs given 0.14 mg/kg/day in the diet for 2 years (Hoffman et al. 1975). Trends towards increased kidney weights in male rats and decreased kidney weights in female rats fed disulfoton for 1.5-2 years were observed (Carpy et al. 1975). The reason for these opposite trends in male and female rats is not clear. In another study, absolute and relative kidney weights were significantly increased in females mice fed 2.53 mg/kg/day, but not in male mice fed 2.13 mg/kg/day, disulfoton for 23 months (Hayes 1983). The increased kidney weight was thought to be associated with an insignificant increase in the incidence of malignant lymphoma in the kidney. Since the kidney tumors were not believed to be the result of disulfoton treatment, the toxicological significance of the increased kidney weight is not clear.

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

Disulfoton exposure altered catecholamine levels in animals, and this hormonal imbalance may be associated with elevated acetylcholine levels (Brzezinski 1969, 1972, 1973; Brzezinski and Ludwicki 1973; Brzezinski and Rusiecki 1970; Wysocka-Paruszewska 1970, 1971). In these studies, acute dosing with disulfoton caused increases in urinary and plasma noradrenaline and adrenaline levels, accompanied by decreases of adrenaline in the adrenal glands, in rats. In addition, the major urinary metabolite of catecholamine metabolism, 4-hydroxy-3-methoxymandelic acid (HMMA), was recovered in the urine from rats given acute doses of disulfoton (Wysocka-Paruszewska 1970, 1971). The maximum level of HMMA in the urine occurred 72 hours after exposure, which coincides with the time period for maximum urine catecholamine levels. There was a direct relationship between blood cholinesterase inhibition and catecholamine (adrenaline and noradrenaline) levels in the urine and blood (Brzezinski and Ludwicki 1973). Maximum inhibition of cholinesterase activity and maximum plasma catecholamine occurred during the first l-2 hours after exposure. However, catecholamine levels returned to normal more rapidly than cholinesterase activity. It was proposed that high levels of acetylcholine, which are normally associated with cholinesterase activity inhibition, caused a release of catecholamines from the stores in the adrenals.

Elevated catecholamine concentrations in the urine were also observed in rats dosed with 0.625 mg/kg/day of disulfoton every other day for 76 days (Brzezinski and Rusiecki 1970). Urinary

catecholamine levels plateaued between 16 and 36 days, followed by a gradual decline for the next 40 days. However, these levels were still elevated at day 76.

In 13-week dietary studies, measurement of organ weight and histological examination of adrenals, pancreas, pituitary, and thyroid revealed no effects in rats at doses ≤0.55 mg/kg/day (Klotzsche 1972) or mice at dose ≤0.1 mg/kg/day (Rivett et al. 1972)

There was a trend towards increased pituitary weights in male rats and decreased pituitary weights in female rats fed disulfoton for 1.5-2.0 years (Carpy et al. 1975). The reason for the opposite trends in organ weights in males and females and the toxicological significance for these effects is not clear. Male rats given a high dose (0.75 mg/kg/day) of disulfoton in the diet for 2 years had a significantly increased incidence of pancreatic atrophy, seen as small focal areas of shrunken acinar cells (Hayes 1985). No histopathological lesion in the pancreas were observed in females at doses ≤1.02 mg/kg/day, and no histopathological lesions in the adrenal, pituitary, thyroid, or parathyroid were found in the male or female rats at any dose. In other chronic dietary studies, no organ weight changes or histopathological lesions in the adrenals, pancreas, thyroid, parathyroid, or pituitary were found in mice at doses ≤2.53 mg/kg/day (Hayes 1983) or dogs at doses ≤0.14 mg/kg/day (Hoffman et al. 1975). The Hoffman study also found no changes or histopathological lesions in parotid in dogs.

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

In animals, histological examination of skin revealed no lesions in rats exposed to 0.34 mg/kg/day (males) or 0.55 mg/kg/day (females) (Klotzsche 1972) in the diet for 90 days, or in rats exposed to 0.1 mg/kg/day (Carpy et al. 1975) or in mice exposed to 2.13 mg/kg/day (males) or 2.53 mg/kg/day (females) (Hayes 1983) in the diet for up to 2 years. However, acanthosis, hyperkeratosis, ulceration of the skin, exudate formation, and epithelial inclusion cysts were increased in male rats exposed to 0.75 mg/kg/day and female rats exposed to 1.02 mg/kg/day disulfoton in the diet for 2 years (Hayes 1985). No increase in skin lesions was found in the male rats at 0.18 mg/kg/day or in female rats at 0.21 mg/kg/day.

Ocular Effects. The only information regarding ocular effects in humans comes from an epidemiological study in which a marked increase of myopia in young children was observed

(Ishikawa and Miyata 1980). The increase coincided with an increased use of disulfoton in combination with other organophosphates to treat food crops. As discussed below, disulfoton caused myopia in Beagle dogs, providing supportive evidence that disulfoton probably contributed to the development of myopia in the young children.

Ocular effects such as myopia and astigmatism have been observed in dogs. Myopia and astigmatism occurred after 12 months in Beagle dogs given ≥0.63 mg/kg/day disulfoton for 2 years (Ishikawa and Miyata 1980; Suzuki and Ishikawa 1974). The myopia became progressively worse until cessation of dosing. As discussed above for musculoskeletal effects, histological examination of the ciliary muscle cells revealed degenerative changes that were considered to be the cause of the myopia. Cystic degeneration of the Harderian gland was observed in male rats exposed to 0.75 mg/kg/day and in female rats exposed to ≥0.21 mg/kg/day disulfoton in the diet for 2 years (Hayes 1985). In the same study, the incidence of cornea1 neovascularization was significantly increased in the high dose rats (0.75 mg/kg/day in males and 1.02 mg/kg/day in females), while no ocular lesions were found in the male rats at 0.18 mg/kg/day or in the female rats at 0.06 mg/kg/day. In other studies, ophthalmological and histological examination of eyes revealed no lesions in rats given a single gavage dose of 5.2 mg/kg (males) or 1.5 mg/kg (females) (Sheets 1993a); or in rats exposed to ≤1.08 mg/kg/day (males) or ≤1.31 mg/kg/day (females) (Klotzsche 1972; Sheets 1993b) or mice exposed to 0.63 mg/kg/day (males) or 0.71 mg/kg/day (females) (Rivett et al. 1972) in the diet for 90 days; or in rats exposed to 0.1 mg/kg/day (Carpy et al. 1975), in mice exposed to 2.13 mg/kg/day (males) or 2.53 mg/kg/day (females) (Hayes 1983), or in dogs exposed to 0.14 mg/kg/day (Hoffman et al. 1975) in the diet for up to 2 years.

Body Weight Effects. Weight loss or decreased body weight gain is commonly observed in animals after acute exposure to disulfoton and is one of the typical signs of cholinergic toxicity of cholinesterase inhibitors (see Section 2.2.1.4). The weight loss or reduced weight gain usually occurs early in the dosing regimen, but the rate of weight gain recovers with repeated dosing as the animals become tolerant (Costa et al. 1984, 1986; Fitzgerald and Costa 1992, 1993; Schwab and Murphy 1981; Schwab et al. 1981). Many of the acute oral studies conducted in animals showing initial body weight loss were designed to study the phenomenon and mechanism of tolerance development (see Section 2.3.5). Rats treated with 2.0 or 2.5 mg/kg/day disulfoton by gavage for l-10 days initially exhibited a 20-50% reduction in weight gain (Costa et al. 1984, 1986; Schwab et al. 1981, 1983). In another study, rats exhibited an unspecified, but significant ($p<0.01$), decrease in body weight gain

within 3 days of a 9-day disulfoton feeding regimen that provided 1 mg/kg/day (Schwab and Murphy 1981). In all of these studies, the effect on weight gain diminished with repeated dosing, suggesting that the rats became tolerant to disulfoton. In addition, a more severe weight loss (≈20%) was observed in rats given 3.5 mg/kg/day of disulfoton for 3 days than in rats that had previously received a 2.5 mg/kg/day dose for 6 days and then a 3.5 mg/kg/day dose for an additional 6 days (Schwab et al. 1981). Although changes in neurological effects are more commonly employed, these studies suggested that body weight changes can be used to monitor the development of tolerance in rats.

Although the acute studies suggest that with repeated dosing body weight gain recovers after the initial decrease, the body weight remains lower than the control body weight, as demonstrated in intermediate-duration studies. Rats given 2.5 mg/kg/day disulfoton for 30 days gained 29% less in body weight gain than controls (Robinson et al. 1978). In a 62-day feeding study, significantly ($p<0.01$) lower body weights were seen in rats within 3 days at 1 mg/kg/day disulfoton (Schwab and Murphy 1981). Although the rats recovered some of the body weight, the body weights were still significantly depressed at all weighing times during the 62-day exposure. A 40% decrease in body weight gain was observed in rats given 1.25 mg/kg/day, but not 0.5 mg/kg/day, disulfoton in the diet for 141-178 days (Stavinoha et al. 1969). Weight changes were used as the major criterion for tolerance development rather than the less objective neurological signs of cholinergic poisoning. The time for tolerance development increased as the dose of disulfoton increased. In an extensive reproductive study, body weight gain was marginally depressed by 6-10% in F_1 parental females and 9-l 1% in F_1 parental males receiving 0.09 mg/kg/day disulfoton in the diet during the premating period of 13 weeks (Hixson and Hathaway 1986). In other intermediate-duration dietary studies, no effects on body weight gain were observed in rats given ≤l.3 1 mg/kg/day (Christenson and Wahle 1993; Klotzsche 1972; Sheets 1993b) or in mice given ≤0.71 mg/kg/day (Rivett et al. 1972).

In rats given disulfoton in the diet for 2 years, body weight gain was decreased by ll-19% in females at 1.02 mg/kg/day, but not at 0.21 mg/kg/day, and in males at 0.75 mg/kg/day, but not at 0.18 mg/kg/day (Hayes 1985). In other chronic-duration studies, no effects on body weight were observed in rats given 0.1 mg/kg/day in the diet (Carpy et al. 1975), in mice given ≤2.53 mg/kg/day in the diet (Hayes 1983), or in dogs given 0.14 mg/kg/day in the diet (Hoffman et al. 1975).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding the immunological or lymphoreticular effects in humans after oral exposure to disulfoton.

In 13-week feeding studies, histological examination of lymph nodes, spleen, and bone marrow of rats at doses ≤0.55 mg/kg/day (Klotzsche 1972) and of lymph nodes, spleen, and thymus of mice at ≤0.71 mg/kg/day (Rivett et al. 1972) revealed no treatment-related lesions. In rats given the high concentration of disulfoton in the diet for 2 years, males (0.75 mg/kg/day) had a significantly increased incidence of plasma cell hyperplasia in the mandibular lymph nodes, and females (1.02 mg/kg/day) had a significantly increased incidence of splenic lymphoid follicle depletion (Hayes 1985). The author suggested that plasma cell hyperplasia in the mandibular lymph nodes was probably a response to upper respiratory tract inflammation, which may have been due to aspiration of ingested food particles. Histological examination of the mesenteric lymph node or thymus revealed no treatment-related lesions in either sex at any dose. In other chronic dietary studies, no treatmentrelated lesions were found in the lymph nodes, spleen, thymus, or bone marrow of rats at ≤0.1 mg/kg/day (Carpy et al. 1975), mice at ≤2.53 mg/kg/day (Hayes 1983), or dogs at ≤0.14 mg/kg/day (Hoffman et al. 1975).

Down-regulation of cholinergic muscarinic receptors in T-lymphocytes and significantly inhibited acetylcholinesterase activity in T-lymphocytes were found in rats given 2 mg/kg/day disulfoton by gavage for l-2 weeks (Fitzgerald and Costa 1993). The inhibition of T-lymphocyte acetylcholinesterase activity paralleled that in the brain. The immunological significance of these neurological effects (see Section 2.2.2.4) is not known.

2.2.2.4 Neurological Effects

Exposure to disulfoton can result in inhibition of acetylcholinesterase activity, with consequent accumulation of acetylcholine at nerve synapses and ganglia leading to central nervous system, nicotinic, and muscarinic effects (see Section 2.2.1.4 for more extensive discussion).

In a human case-report study, a 30-year-old man was found dead after consuming an unknown amount of disulfoton (Hattori et al. 1982). Bubbling saliva in the oral cavity and constricted pupils were

evidence of muscarinic effects. Pulmonary edema and blood in the lungs and bronchus suggested that death was primarily due to respiratory failure brought on by disulfoton intoxication. Severe signs and symptoms of disulfoton toxicosis (miosis, salivation, masseteric spasms, and monoplegia) were observed in a man within 2-3 hours of consuming 34 heaping tablespoons of disulfoton (Yashiki et al. 1990). The coincidental depression in serum cholinesterase activity and the occurrence of severe clinical signs suggests that a very severe toxic dose of disulfoton was consumed, and death may have occurred were it not for the medical treatment.

Disulfoton can interfere with neurotransmitter levels (e.g., acetylcholine, catecholamines) in the brain of affected animals (Brzezinski 1972; Costa et al. 1986). A single dose of disulfoton caused a lower noradrenaline level in the brain of rats compared with the controls, with the greatest decreases (about 0.175 µg /mL and 0.1 µg /mL compared with 0.3 µg /rnL in control) at 15 and 120 minutes after dosing (Brzezinski 1972). Adrenaline levels in the brain, however, showed little difference from control levels, being slightly increased at 60 minutes and slightly decreased at 120 minutes. The rats exhibited typical cholinergic signs of disulfoton toxicosis (not otherwise specified). In other acute exposure studies, brain cholinesterase activity was significantly depressed when rats were given disulfoton for 7-10 days, suggesting elevated brain acetylcholine levels (Costa and Murphy 1983a; Costa et al. 1986; Schwab and Murphy 1981; Su et al. 1971).

Muscle twitching, clonic cramps, and increased salivation were observed in rats given a single gavage dose of 1.0 mg/kg and in mice given a single oral gavage dose of 5.0 mg/kg (Mihail 1978). Rats given 0.5 mg/kg and mice given 2.5 mg/kg did not develop these signs. However, in another study, rats given a single gavage dose of 0.5 mg/kg had tremors (Crawford and Anderson 1974). In an extensive neurotoxicity screening study, rats were given single gavage doses of disulfoton (0.24, 1.5, and 5.2 mg/kg in males; 0.24, 0.76, and 1.5 mg/kg for females) (Sheets 1993a). Clinical signs of cholinergic intoxication consisted of muscle fasciculation, tremors, ataxia, oral stain, urine stain, diarrhea, or decreased activity in the high dose males (5.2 mg/kg) and high dose females (1.5 mg/kg) and muscle fasciculation in the mid dose females (0.76 mg/kg). A battery of functional observational tests revealed effects in both males and female at the mid and high doses. At the mid dose and high dose, these effects included muscle fasciculation, ataxia, and minimal head or body movement during open field observation in both sexes and a lower incidence of vocalizations upon removal from the home cage in females. High dose males also had uncoordinated righting reflex. Results of motor and locomotor activity tests revealed a 55% and 51% reduced motor activity in high dose males and

females, respectively, and 64% and 62% reduced locomotor activity in high dose males and females, respectively. Erythrocyte cholinesterase activity was inhibited by 21% in high dose males, 75% in high dose females, and 53% in mid dose females. No treatment-related effects were observed for brain weight and extensive histopathological examination of the brain, spinal cord, peripheral nerves (sciatic, tibial, sural), optic nerves, or gasserian ganglion.

Animals exposed to disulfoton develop typical signs of cholinergic toxicity associated with inhibition of brain acetylcholinesterase activity after a few oral doses (Costa et al. 1984; Schwab and Murphy 1981; Schwab et al. 1981, 1983). However, with subsequent dosing, the severity of the overt cholinergic effects diminish, while cholinesterase remains inhibited. This phenomenon is known as tolerance (see Section 2.3.5). Male rats given 2.0 or 2.5 mg/kg/day of disulfoton for 1-14 days initially exhibited exophthalmia, excessive salivation, urination and defecation, diarrhea, fasciculations, generalized tremors, flaccidity, and malaise (Costa et al. 1984; Fitzgerald and Costa 1992, 1993; Schwab et al. 1981, 1983). Similar effects were observed in female rats after 3 days on a diet that provided 1 mg/kg/day disulfoton (Schwab and Murphy 1981). A diet that provided 0.38 mg/kg/day did not cause overt signs of toxicity, but brain acetylcholinesterase was inhibited by 30-35%. The severity of these signs diminished after an unspecified time with repeated dosing, but the signs did not completely disappear (Costa et al. 1984; Schwab and Murphy 1981; Schwab et al. 1981, 1983). When rats were given 3.5 mg/kg/day for 3-4 days, these clinical signs were more severe than those exhibited by rats pretreated with 2.5 mg/kg/day of disulfoton for 6 days and then given 3.5 mg/kg/day for 6 more days (Schwab et al. 1981). Thus, the rats pretreated with 2.5 mg/kg/day for 6 days became tolerant to even higher doses of disulfoton. In the same study, heart, ileum, forebrain, and hindbrain cholinesterase activity was moderately but significantly depressed in rats given seven daily doses of 2 mg/kg/day of disulfoton, followed by four daily doses of 3 mg/kg/day. Furthermore, a 50% reduction in pancreatic acetylcholinesterase activity was observed in rats given 2 mg/kg/day for 10 days despite the disappearance of clinical cholinergic signs after a few doses (Costa et al. 1984). This depression in cholinesterase activity suggests that the mechanism associated with disulfoton toxicity was not impaired, despite the disappearance of overt neurological signs of toxicity following repeated doses of disulfoton.

Disulfoton caused muscular tremors, unsteadiness, and ataxia in pregnant rabbits after exposure to 1.5-3.0 mg/kg/day on days 6-18 of gestation (Tesh et al. 1982). Doses of 0.3 or 1.0 mg/kg/day disulfoton did not affect the pregnant rabbits. In a reproductive study, tremors were observed in high

dose (0.09 mg/kg/day) F_0 female rats, but not the mid dose (0.03 mg/kg/day) F_0 females, during the production of the F_1 generation (Hixson and Hathaway 1986). Pregnant rats given disulfoton during gestation had significantly inhibited plasma and erythrocyte cholinesterase activity by 82-90% at 1 mg/kg/day and by 41% at 0.3 mg/kg/day, but not at 0.1 mg/kg/day (Lamb and Hixson 1983). Basec on this NOAEL (0.1 mg/kg/day), an acute oral MRL of 0.001 mg/kg/day was calculated as described in footnote "b" in Table 2-2.

An intermediate-duration extensive neurotoxicity screening study similar to the acute study described above was conducted in rats fed disulfoton in the diet that provided doses of 0.063, 0.270, or 1.08 mg/kg/day for males and 0.71, 0.315 or 1.31 mg/kg/day for females (Sheets 1993b). Clinical signs of cholinergic intoxication consisted of muscle fasciculation, perianal stains, and increased reactivity in high dose males and females and increased incidence of urine stains in mid and high dose females. A battery of functional observational tests revealed effects in high dose males and mid and high dose females. The effects in high dose rats included muscle fasciculations, tremors, increased defecation, decreased forelimb grip strength, decreased movement, and increased urine stain. Muscle fasciculations and increased urine stain were also seen in mid dose females. Automated measures of motor and locomotor activity were reduced on each test occasion (weeks 4, 8, and 13) in the high dose males and females. Erythrocyte cholinesterase activity was inhibited by 95100% in high dose rats and 61-80% in mid dose rats. Brain cholinesterase activity was inhibited by 35% in mid dose males and 64% in mid dose females and by 75% in high dose males and 87% in high dose females. No treatment-related effects were observed for brain weight and extensive histopathological examination of the brain, spinal cord, peripheral nerves (sciatic, tibial, sural), optic nerves, or gasserian ganglion.

In intermediate-duration studies, typical signs of cholinergic poisoning are generally seen only during the first few days, after which they diminish. However, cholinesterase activity usually remains inhibited during exposure. Characteristic signs (not otherwise specified) of anticholinesterase poisoning were observed in rats fed disulfoton for 30 days, and some of the rats recovered (Robinson et al. 1978). Brain, stomach, and diaphragm cholinesterase activity were severely depressed. In a 62-day feeding study, rats developed severe cholinergic signs of disulfoton toxicity after 3 days on a diet providing 1 mg/kg/day disulfoton (Schwab and Murphy 1981). The severity of these signs decreased but never completely disappeared after 62 days. Brain and diaphragm cholinesterase activity was depressed at day 6 and remained depressed throughout the study. Sex and strain differences in rats may influence the ability of disulfoton to inhibit cholinesterase or to elevate acetylcholine levels.

Brain cholinesterase activity was significantly depressed to about the same extent in Holtzman rats and Charles River rats fed disulfoton for 141-178 days, but only the Charles River rats had elevated brain acetylcholine levels (Stavinoha et al. 1969). Cholinesterase activity of erythrocytes and the brain was inhibited to a greater extent or at lower doses in female rats than in male rats given disulfoton in the diet for intermediate durations (Christenson and Wahle 1993; Doull and Vaughn 1958; Hayes 1985; Klotzsche 1972; Ryan et al. 1970). In mice fed diets providing 0.63 mg/kg/day (males) or 0.71 mg/kg/day (females), cholinesterase was inhibited in all tissues, especially in females, but the tissues were not specified (Rivett et al. 1972). In a chronic study in which dogs were given capsules containing disulfoton for 2 years, erythrocyte cholinesterase activity was inhibited by 80% after 5 months of exposure to ≥0.5 mg/kg/day and remained depressed throughout the 2-year duration (Hikita et al. 1973). A 22-50% inhibition of erythrocyte cholinesterase activity and a 33-36% inhibition of plasma cholinesterase activity were found in dogs given diets containing disulfoton at a dose of 0.06 mg/kg/day for 40 weeks (Hoffman et al. 1975).

Disulfoton has also been studied for behavioral effects. Rats fed ≥0.5 mg/kg/day disulfoton for 90 days had significantly depressed brain acetylcholinesterase levels (59-74% below control), but the treated rats had shorter maze running times and made fewer mistakes than the controls (Clark and Pearson 1973). This unexpected result (improved learning) at reduced brain cholinesterase levels led the authors to question the “critical level of 60% reduction” for neurobehavioral effects. In another behavioral experiment, there was an unexplained increase in exploratory behavior in mice fed disulfoton for 12 weeks (Clark et al. 1971). Dietary exposure of rats and mice to 2.5 mg/kg/day disulfoton for 2 months resulted in an increase in the permeability of spinal cord and brain stem tissues in both species (Clark and Stavinoha 1971). The nature of this change in permeability was not further investigated.

In a chronic-duration study, a decrease in relative and absolute brain weights was observed in male rats, but an increase in brain weights was observed in female rats fed disulfoton for 1.5-2.0 years (Carpy et al. 1975). The reason for and the toxicological significance of these opposite trends in males and females is not clear. In the same study, plasma, erythrocyte, and brain cholinesterase activity was significantly inhibited in both male and female rats. A dose of 0.1 mg/kg/day resulted in a 21% inhibition of brain cholinesterase activity in female rats. At 0.05 mg/kg/day, brain cholinesterase was inhibited by 11% in male rats. In another chronic dietary study in rats which provided doses of 0.05, 0.18, and 0.75 mg/kg/day in males and 0.06, 0.21, and 1.02 mg/kg/day in

females, erythrocyte cholinesterase activity was inhibited by ≤19% and 14-24% in low dose males and females respectively, 46-67% and 57-77% in mid dose males and females, respectively, and 71-82% and 75-86% in high dose males and females, respectively (Hayes 1985). Brain cholinesterase activity was inhibited by 15% and 21% in low dose males and females, respectively; 53% in both mid dose males and females; and 79% and 82% in high dose males and females, respectively. Relative brain weight was significantly increased in both high dose males and females. Histological examination revealed a dose-related increased incidence of optic nerve degeneration that was statistically significant in mid dose males and mid and high dose females. No treatment-related lesions were found in the brain, sciatic nerve, or spinal cord. Based on the LOAEL of 0.06 mg/kg/day for erythrocyte and brain cholinesterase inhibition in female rats, a chronic oral MRL of $6x10^{-5}$ mg/kg/day was calculated as described in footnote "d" in Table 2-2. Significant depression of erythrocyte, plasma, and brain cholinesterase activity was also found in mice fed disulfoton for 23 months at doses of 2.13 mg/kg/day (males) and 2.53 mg/kg/day (females) (Hayes 1983). Beagle dogs did not exhibit profound changes in general appearance or behavior when fed disulfoton (0.03 or 0.14 mg/kg/day) for 2 years (Hoffman et al. 1975). However, significant depression of plasma and erythrocyte and brain cholinesterase activity occurred at 0.14, but not at 0.03 mg/kg/day. No histological lesions were found in the brain. Necrosis and atrophy of the optic nerve and retina was observed in dogs given disulfoton (0.5-1.5 mg/kg/day) for 2 years (Uga et al. 1977). The authors regarded the pathological changes in the retina as mild; however, the nerve fibers in the optic nerve were reduced in number.

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

2.2.2.5 Reproductive Effects

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

In a dominant lethal test, treatment of male mice with a single oral dose of 5 mg/kg disulfoton had no effect on male fertility (Herbold 1980). In a three-generation reproductive study, exposure of male and female rats to disulfoton in the diet at 0.5 mg/kg/day resulted a "slight" reduction of litter sizes in the third generation (Taylor 1965a). This study was limited by data reporting deficiencies such as lack of statistical analysis, incomplete necropsy report, and insufficient histopathological data. A more extensive multigeneration study was conducted in male and female rats exposed to disulfoton in the

diet that provided doses of 0.009, 0.03, and 0.09 mg/kg/day (Hixson and Hathaway 1986). At 0.09 mg/kg/day, decreased reproductive performance occurred, evidenced by a decreased percentage of females placed for mating and decreased percentage of sperm-positive F_0 and F_1 parental females. In addition, decreased maternal weight of F_0 and F_1 dams during gestation and lactation, decreased litter counts, viability index, and lactation index, and increased dead births and percentage of dead births occurred in both generations at 0.09 mg/kg/day. A decrease in F_{2b} litter counts and litter weights occurred at 0.03 mg/kg/day. Gross and histological examination of the ovary, vagina, uterus, testes, epididymis, seminal vesicles, and prostate of the F_0 and F_1 parents revealed no treatment-related lesions. In an intermediate-duration study, exposure of male and female rats to diets providing 0.5 mg/kg/day disulfoton for 60 days prior to mating and/or during mating resulted in the failure of two of five females to become pregnant (Ryan et al. 1970). Histological examination of reproductive organs of males (testes, epididymides, seminal vesicles, prostate glands) and females (ovaries, uteri, mammary glands) did not reveal any treatment-related lesions in rats fed 0.34 mg/kg/day (males) or 0.55 mg/kg/day (females) (Klotzsche 1972) or in mice fed 0.63 mg/kg/day (males) or 0.71 mg/kg/day (females) (Rivett et al. 1972) for 90 days, or in rats fed 0.1 mg/kg/day (Carpy et al. 1975), in mice fed 2.13 mg/kg/day (males) or 2.53 mg/kg/day (females) (Hayes 1983), or in dogs fed 0.14 mg/kg/day (Hoffman et al. 1975) for up to 2 years. However, uterine cystic hyperplasia was observed in female rats given disulfoton in the diet at 1.02 mg/kg/day, but not at 0.21 mg/kg/day, for 2 years (Hayes 1985). Histological examination of the cervix, mammary glands, ovaries, prostate gland, seminal vesicles, and testes revealed no effects in the rats at any dose level. In the studies that did not assess reproductive function, the dose levels that were not associated with histopathological lesions in reproductive organs cannot be considered as NOAEL values.

The reliable NOAEL value for reproductive performance and the LOAEL values for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No studies were located regarding development effects in humans after oral exposure to disulfoton.

Pregnant rats given disulfoton on days 6-15 of gestation had decreased plasma and erythrocyte cholinesterase activity at ≥0.3 mg/kg/day (Lamb and Hixson 1983). Fetotoxic effects included increased incidences of incomplete ossified parietal bones and stemebrae at 1.0 mg/kg/day, but not at

0.3 mg/kg/day. This was considered as evidence of growth retardation due to maternal toxicity rather than specific fetotoxic effects. There was no evidence of soft tissue, external, or skeletal malformations. Pregnant rabbits given high doses of disulfoton (1.5-3.0 mg/kg/day) died or exhibited cholinergic signs of disulfoton toxicity (Tesh et al. 1982). Generally, there were no adverse effects on fetal survival, growth, or development. Because of the high mortality of the dams, the initial high dose (3.0 mg/kg/day) was reduced to 2.0 mg/kg/day and finally to 1.5 mg/kg/day. In animals that received doses in the range of 1.5-3.0 mg/kg or a combination of doses, no fetotoxic effects were observed in the offspring. Thus, 1.5 mg/kg/day is considered the NOAEL for developmental effects in this study. In an intermediate-duration study, exposure of male and female rats to diets providing 0.5 mg/kg/day disulfoton for 60 days prior to mating and/or during mating resulted in a 32.1% depression in fetal brain cholinesterase activity (Ryan et al. 1970). In a three-generation study in rats, cloudy swelling and fatty infiltration of the liver, mild nephropathy (females), and juvenile hypoplasia of the testes were observed in F_{3b} litters (Taylor 1965a). These litters also had significantly depressed erythrocyte cholinesterase activities. In another multigeneration study in rats, brain cholinesterase activity was inhibited by 24% and 32% in male and female F_{1a} pups, respectively, at 0.03 mg/kg/day and by 50% and 59% in male and female F_{1a} pups, respectively, at 0.09 mg/kg/day (Hixson and Hathaway 1986). No inhibition of brain cholinesterase was found in the F_{1a} pups at 0.009 mg/kg/day, and no grossly observable developmental abnormalities were found in any pups in the F_1 or F_2 generation. Based on this NOAEL of 0.009 mg/kg/day for brain cholinesterase inhibition in pups, an intermediate oral MRL of $9x10^{-5}$ mg/kg/day was calculated as described in footnote “c” in Table 2-2. The highest NOAEL values and all LOAEL values for developmental effects in each reliable study in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to disulfoton.

Disulfoton was negative in a dominant lethal test in male mice treated orally with a single dose of 5 mg/kg (Herbold 1980) and in an erythrocyte micronucleus test in mice dosed with 6 or 12 mg/kg/day for 2 days (Herbold 1981). Disulfoton also did not induce micronuclei in erythrocytes of mice dosed with 2, 4, or 8 mg/kg disulfoton (EPA 1984a; Sandhu et al. 1985), but whether disulfoton was administered by the oral or intraperitoneal route was not clear. Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to disulfoton.

No histological evidence of a carcinogenic effect was observed in rats fed ≤0.1 mg/kg/day disulfoton for 1.5-2.0 years (Carpy et al. 1975), in rats fed ≤1.02 mg/kg/day disulfoton for 2 years (Hayes 1985), or in mice fed ≤2.53 mg/kg/day disulfoton for 23 months (Hayes 1983). The study by Carpy et al. (1975) was limited by insufficient necropsy and histological data and by dosing manipulations. In addition, there was no evidence of carcinogenicity in Beagle dogs fed disulfoton (0.02-0.14 mg/kg/day) for 2 years (Hoffman et al. 1975).

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to disulfoton.

Dermal LD_{50} values suggest that, irrespective of strain, female rats are more sensitive than male rats when disulfoton is administered dermally. The dermal LD_{50} for disulfoton was determined to be 15.9 and 3.6 mg/kg in male and female Wistar rats, respectively (Mihail 1978). In Sherman rats, the dermal LD_{50} was determined to be 15 and 6 mg/kg in males and females, respectively (Gaines 1969). In male Sprague-Dawley rats, the dermal LD_{50} was determined to be 20 mg/kg (DuBois 1957). A dermal LD_{50} value of 0.285 mL/kg (187 mg/kg) was reported for rats given a liquid formulation containing 65.7% disulfoton (Weil et al. 1971). When a granular formulation containing 10% disulfoton was applied at a dose of 1,280 mg/kg, one of four rats died. The difference in dermal LD_{50} values is probably related to the different formulations of disulfoton. In a range-finding study, 2 of 2 rabbits died after 1 or 2 applications of 10 mg/kg/day disulfoton was applied to the shorn, unabraded skin and left for 6 hours (Flucke 1986). None of the rabbits similarly treated with 0.4 or 2.0 mg/kg/day for 5 days died. In a 3-week experiment, similar treatment of rabbits 5 days/week resulted in death of 5 of 5 females after l-6 treatments and of 5 of 5 males after 3-10 treatments with 6.5 mg/kg/day. None of the rabbits treated with ≤1.6 mg/kg/day for 3 weeks died. The rabbits that died in these experiments exhibited persistent cholinergic signs of intoxication (muscle spasms, dyspnea, salivation) before death.

The LD_{50} values in rats and the LOAEL values for death of rabbits after dermal exposure to disulfoton are recorded in Table 2-3.

2.2.3.2 Systemic Effects

No studies were located regarding musculoskeletal or ocular effects in humans or animals after dermal exposure to disulfoton. The highest NOAEL values and all LOAEL values from each reliable study for systemic end points in animals are recorded in Table 2-3.

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to disulfoton.

In rats exposed to disulfoton applied to clipped dorsal skin at doses of 2.5-20 mg/kg, breathing difficulties were noted (Mihail 1978), but it was not clear at which doses this effect was seen. In a 3-week study, in which disulfoton was applied to the shorn, unabraded skin of rabbits and left for 6 hours, 5 days/week, necropsy of the rabbits that died within 2 weeks during treatment (100%) with the high dose of 6.5 mg/kg/day revealed distended, pale, mottled, and fluid-containing lungs (Flucke 1986). The organs and tissues of the high dose rabbits were not examined histologically, but gross and histological examination of the lungs of rabbits similarly treated with ≤1.6 mg/kg/day for 3 weeks revealed no treatment-related lesions.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after dermal exposure to disulfoton.

Acute dermal exposure to unspecified doses of organophosphorus insecticides, including disulfoton, was reported to cause protein degeneration and significant circulatory disruptions in heart muscles of rats, cats, and rabbits (Kundiev and Rappoport 1967). This study is limited by reporting deficiencies regarding incidences, and by uncertainty about whether the effects were observed in all species and whether disulfoton was among the insecticides causing these effects. In a 3-week study in which disulfoton was applied to the shorn, unabraded skin of rabbits and left for 6 hours, 5 days/week, gross and histological examination of the heart revealed no treatment-related lesions at ≤1.6 mg/kg/day (Flucke 1986).

TABLE 2-3. Levels of Significant Exposure to Disulfoton - Dermal

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						
Rat (Sprague-Dawley)	once				20 M (LD50)	DuBois 1957
Rat (Sherman)	once				15 M (LD50) 6.0 F (LD50)	Gaines 1969
Rat (Wistar)	once				15.9 M (LD50) 3.6 F (LD50)	Mihail 1978
Rabbit (New Zealand)	1-2 d 6 hr/d				10 (2/2 died)	Flucke 1986
Rabbit (New Zealand)	1-2 wk 5 d/wk 6 hr/d				6.5 (10/10 died)	Flucke 1986

TABLE 2-3. Levels of Significant Exposure to Disulfoton - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference
Systemic							
Rabbit (New Zealand)	1-2 wk 5 d/wk 6 hr/d	Resp			6.5	(distended, pale, mottled, fluid containing lungs in rabbits that died)	Flucke 1986
		Gastro			6.5	(marked intussusception of the ileum in one female that died)	
		Hepatic			6.5	(lobular pattern in the liver of rabbits that died)	
		Renal			6.5	(pale kidneys, with reddened renal pelvis and indistinct structure in rabbits that died)	
		Derm	6.5				
		Bd Wt			6.5	(little or no feed intake and distinct weight loss up to time of death)	
Immunological/Lymphoreticular							
Rabbit (New Zealand)	1-2 wk 5 d/wk 6 hr/d				6.5	(small pale spleen in rabbits that died)	Flucke 1986
Neurological							
Rabbit (New Zealand)	1-5 d 6 hr/d		2		10	(2/2 rabbits exhibited unspecified cholinergic signs and died after 1 or 2 doses)	Flucke 1986
Rabbit (New Zealand)	1-2 d 6 hr/d				6.5	(muscle spasms, dyspnea, salivation)	Flucke 1986

TABLE 2-3. Levels of Significant Exposure to Disulfoton - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
INTERMEDIATE EXPOSURE						
Systemic						
Rabbit (New Zealand)	3 wk 5 d/wk 6 hr/d	Resp	1.6			Flucke 1986
		Cardio	1.6			
		Hemato	1.6			
		Hepatic	1.6			
		Renal	1.6			
		Endocr	1.6			
		Derm	1.6			
		Bd Wt	1.6			
Neurological						
Rabbit (New Zealand)	3 wk 5 d/wk 6 hr/d		0.4	1.6 F (21-33% inhibition of erythrocyte cholinesterase activity)		Flucke 1986

Bd Wt = body weight; d = day(s); Derm = dermal; Endocr = endocrine; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LD50 = lethal dose 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after dermal exposure to disulfoton.

In a 3-week study in which disulfoton was applied to the shorn, unabraded skin of rabbits and left for 6 hours, 5 days/week, necropsy of the rabbits that died within 2 weeks during treatment (100%) with the high dose of 6.5 mg/kg/day revealed marked intussusception of the ileum of one female (Flucke 1986). The gastrointestinal tract of the high dose rabbits or of rabbits similarly treated with ≤1.6 mg/kg/day for 3 weeks were not examined histologically.

Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to disulfoton. No hematological effects in rabbits were found at ≤1.6 mg/kg/day in a 3-week study in which disulfoton was applied to the shorn, unabraded skin and left for 6 hours, 5 days/week (Flucke 1986).

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to disulfoton.

Acute dermal exposure to unspecified doses of organophosphorus insecticides, including disulfoton, was reported to cause protein degeneration and significant circulatory disruptions in the livers of rats, cats, and rabbits (Kundiev and Rappoport 1967). This study is limited by reporting deficiencies regarding incidences, and by uncertainties about whether the effects were observed in all species and whether disulfoton was among the insecticides causing these effects. In a 3-week study in which disulfoton was applied to the shorn, unabraded skin of rabbits and left for 6 hours, 5 days/week, 100% of the rabbits died within 2 weeks during treatment. Necropsy of the rabbits treated with the high dose of 6.5 mg/kg/day revealed a lobular pattern in the liver (Flucke 1986). The organs and tissues of the high dose rabbits were not examined histologically, but clinical chemistry results and gross and histological examination of the liver of rabbits similarly treated with ≤1.6 mg/kg/day for 3 weeks revealed no treatment-related hepatic effects. Slight increases in the absolute and relative liver weights were found in male rabbits at 1.6 mg/kg/day, but the absence of clinical chemistry and histological effects indicates that the liver weight change was not toxicologically significant.

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to disulfoton.

Acute dermal exposure to unspecified doses of organophosphorus insecticides, including disulfoton, was reported to cause protein degeneration and significant circulatory disruptions in the kidneys of rats, cats, and rabbits (Kundiev and Rappoport 1967). This study is limited by reporting deficiencies regarding incidences, and uncertainties about whether the effects were observed in all species and whether disulfoton was among the insecticides causing these effects. In a 3-week study in which disulfoton was applied to the shorn, unabraded skin of rabbits and left for 6 hours, 5 days/week, 100% of the rabbits died within 2 weeks during treatment. Necropsy of the rabbits treated with the high dose of 6.5 mg/kg/day revealed pale kidneys, with reddened renal pelvis and indistinct structure (Flucke 1986). The organs and tissues of the high dose rabbits were not examined histologically, but clinical chemistry and urinalysis results and gross and histological examination of the kidney of rabbits similarly treated with ≤1.6 mg/kg/day for 3 weeks revealed no treatment-related renal effects.

Endocrine Effects. No studies were located regarding endocrine effects in humans after dermal exposure to disulfoton.

In a 3-week study in which disulfoton was applied to the shorn, unabraded skin of rabbits and left for 6 hours, 5 days/week, gross and histological examination of the adrenal and thyroid glands revealed no treatment-related lesions at ≤1.6 mg/kg/day (Flucke 1986).

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

Acute dermal exposure to unspecified doses of organophosphorus insecticides, including disulfoton, was reported to cause microscopic changes in the blood vessels and fibrous structures in the skin of rats, cats, and rabbits (Kundiev and Rappoport 1967). Collagen and elastin fibers in the skin and the blood vessels in the skin appeared to have been affected. These effects were thought to have further increased the absorption of the insecticides by the skin. This study is limited by reporting deficiencies regarding incidences, and questions about whether the effects were observed in all species and whether disulfoton was among the insecticides causing these effects. In a 3-week study in which disulfoton was applied to the shorn, unabraded skin of rabbits and left for 6 hours, 5 days/week, the treated areas of the skin were observed daily for signs of inflammation (redness and swelling) (Flucke 1986). In the rabbits that died within 2 weeks during treatment with the high dose of 6.5 mg/kg/day (100%) and in the rabbits treated with ≤1.6 mg/kg/day for 3 weeks, no indication of local irritation was found.

The skin of the high dose rabbits was not examined histologically, but histological examination of the skin of rabbits treated with ≤1.6 mg/kg/day for 3 weeks revealed no treatment-related lesions.

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

In a 3-week study in which disulfoton was applied to the shorn, unabraded skin of rabbits and left for 6 hours, 5 days/week, little or no feed intake and distinct weight loss occurred up to the time of death in the rabbits that died within 2 weeks during treatment. Necropsy of the rabbits treated with the high dose of 6.5 mg/kg/day (100%) (Flucke 1986). No effects on body weight were found in rabbits similarly treated with ≤1.6 mg/kg/day for 3 weeks.

2.2.3.3 Immunological and Lymphoreticular Effects

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

In a 3-week study in which disulfoton was applied to the shorn, unabraded skin of rabbits and left for 6 hours, 5 days/week, 100% of the rabbits died within 2 weeks during treatment. Necropsy of the rabbits treated with the high dose of 6.5 mg/kg/day revealed small and pale spleens in some cases (Flucke 1986). The organs and tissues of the high dose rabbits were not examined histologically, but gross and histological examination of the spleens of rabbits similarly treated with ≤1.6 mg/kg/day for 3 weeks revealed no treatment-related lesions. The NOAEL value and the LOAEL value for effects on the spleen in rabbits are recorded in Table 2-3.

2.2.3.4 Neurological Effects

Exposure to disulfoton can result in inhibition of acetylcholinesterase activity, with consequent accumulation of acetylcholine at nerve synapses and ganglia leading to central nervous system, nicotinic, and muscarinic effects (see Section 2.2.1.4 for more extensive discussion).

A farmer who had worn disulfoton~ontaminated gloves for several days developed signs of disulfoton toxicity (weakness, fatigue, and cyanosis) and had to be hospitalized (Savage et al. 1971). Because a

considerable amount (not otherwise specified) of disulfoton was detected in the serum and because blood cholinesterase activity was severely depressed, it can be assumed that the patient had absorbed a considerable amount of disulfoton through the skin. The patient recovered following treatment for the toxicosis. Severe neurological signs and symptoms were not reported by workers exposed to disulfoton during wet or dry mix operations at mean doses of 0.013-0.23 mg/kg/day for 9 weeks at a pesticide-fertilizer mixing plant (Wolfe et al. 1978). However, erythrocyte cholinesterase activity was depressed by 22.8% from week 2-9 of the study in workers involved in dry mix operations (0.23 mg/kg/day). No depression in blood cholinesterase activity was observed in workers involved with wet mix operations (0.013 mg/kg/day). These workers were also exposed to disulfoton by the inhalation route (see Section 2.2.1.4). Therefore, the depression in erythrocyte cholinesterase activity may be due to both absorption of disulfoton through the respiratory tract and through the skin. No significant reductions in plasma or erythrocyte cholinesterase activities occurred in three employees at a pesticide formulating plant exposed to disulfoton (unspecified doses) for 25 weeks (Brokopp et al. 1981). Similarly, no reductions in cholinesterase activity were found for eight employees exposed for shorter periods.

Disulfoton caused muscle twitching and clonic cramps in male and female rats after acute dermal exposure to doses 2.5-20 mg/kg (Mihail 1978), but it was not clear at which doses these signs were observed. These neurological effects persisted for an unspecified time after disulfoton was removed from the skin. Disulfoton also caused depression in skin cholinesterase activity in rats, cats, and rabbits given acute unspecified dermal doses (Kundiev and Rappoport 1967). This study is limited by reporting deficiencies regarding incidences and uncertainty about whether the effects were observed in all species. In a range-finding study, 2 of 2 rabbits died after 1 or 2 applications of 10 mg/kg/day disulfoton were applied to the shorn, unabraded skin and left for 6 hours (Flucke 1986). The rabbits exhibited cholinergic signs of intoxication (not otherwise specified) before death. None of the rabbits similarly treated with 0.4 or 2.0 mg/kg/day for 5 days showed cholinergic signs or died. In a 3-week experiment, similar treatment of rabbits 5 days/week resulted in death of 5 of 5 females after l-6 treatments and of 5 of 5 males after 3-10 treatments with 6.5 mg/kg/day. Persistent cholinergic signs (muscle spasm, dyspnea, salivation) were observed in the high dose females after 1 or 2 treatments and in high dose males after 2 treatments. No clinical signs of cholinergic intoxication were seen in the rabbits treated with 0.4 or 1.6 mg/kg/day, but erythrocyte cholinesterase activity was inhibited by 21-33% in the female rabbits treated with 1.6 mg/kg/day. The highest NOAEL values

and the LOAEL values for neurological effects in rabbits for the acute and intermediate duration are recorded in Table 2-3.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after dermal exposure to disulfoton. In a 3-week study, in which disulfoton was applied to the shorn, unabraded skin of rabbits and left for 6 hours, 5 days/week, gross and histological examination of the testes, epididymides, ovaries, and uterus revealed no treatment-related lesions at ≤1.6 mg/kg/day (Flucke 1986). Slight increases in the absolute and relative testes weights were found in male rabbits at 1.6 mg/kg/day, but the absence of histological effects indicates that the testes weight change was not toxicologically significant. Reproductive function was not evaluated.

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

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

2.3 TOXICOKINETICS

The toxicokinetics of disulfoton in humans and animals depends on its physicochemical characteristics and its metabolism. The lipophilicity of disulfoton indicates that the insecticide should be easily absorbed by oral, inhalation, and dermal routes. No bioavailability data were located for inhalation and dermal exposure. However, disulfoton is almost completely absorbed from the gastrointestinal tract within 2 days after oral exposure. Animal studies suggest that disulfoton is widely distributed primarily to the liver and in smaller quantities to the kidney, fat, skin, muscle, brain, and other organs.

Disulfoton and/or its metabolites are excreted mainly in the urine of humans and animals, with minor amounts excreted in the feces and expired air.

Disulfoton causes neurological effects in humans and animals. The mechanism of action on the nervous system depends on the metabolism of disulfoton to active metabolites. The liver is the major site of metabolic oxidation of disulfoton to disulfoton sulfoxide, disulfoton sulfone, demeton S-sulfoxide and demeton S-sulfone, which inhibit acetylcholinesterase in nervous tissue. These four active metabolites are more potent inhibitors of acetylcholinesterase than disulfoton. Cytochrome P-450 monooxygenase and flavin adenine dinucleotide monooxygenase are involved in this metabolic activation. The active metabolites ultimately undergo nonenzymatic and/or enzymatic hydrolysis to more polar metabolites that are not toxic and are excreted in the urine.

The inhibition of acetylcholinesterase increases the amount of acetylcholine at nerve synapses, which causes an overstimulation of cholinergic nerves and effector organs. Depending on the dose and its duration, the resulting cholinergic effects are usually reversible within several days to 2 weeks after disulfoton exposure has been discontinued. Prolonged exposure to disulfoton results in diminished cholinergic signs, and affected animals develop tolerance. The down-regulation of cholinergic receptors due to accumulation of acetylcholine may be associated with disulfoton-induced tolerance.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding absorption in humans or animals after inhalation exposure to disulfoton.

2.3.1.2 Oral Exposure

Disulfoton and/or its metabolites have been detected in the blood and urine of humans who consumed unknown amounts of disulfoton solution (Hattori et al. 1982; Yashiki et al. 1990). In one case, the concentration of disulfoton and the sum of its metabolites in the blood were 0.093 nmol/g (25.4 ng/g) and 4.92 nmol/g, respectively, at ≈2 hours after ingestion (Yashiki et al. 1990). The 4.92 nmol/g blood concentration corresponded to 1.35 µg disulfoton/g. Gastrointestinal absorption was not yet

complete, since 3.3 mg of disulfoton were recovered from the stomach contents, which was also collected at ≈2 hours after the ingestion. The concentration of metabolites in the urine was not quantitated. While these data indicate disulfoton is absorbed from the gastrointestinal tract of humans, the data are not sufficient to estimate the extent or rate of absorption.

Male rats given a single acute dose (1.2 mg/kg) of [^{14}C]-disulfoton eliminated an average of 84.3%, 6.1%, and 9.2% of the dose in the urine, feces, and expired air, respectively, in the 10 days following exposure (Puhl and Fredrickson 1975). Female rats given 0.2 mg/kg eliminated 78.9%, 7.8%, and 9.2% of the administered radioactivity in the urine, feces, and expired air, respectively, in the same time period. The data indicate that at least 88-91% of the administered dose was absorbed over the lo-day period. Absorption rates were not determined; however, 50% of the administered dose was recovered in the urine during the first 4-6 hours after exposure in males and the first 30-32 hours after exposure in females. Although it was not possible to quantitatively determine the absorption rate in female rats, the data from the male rats suggest that absorption was almost complete within 12-24 hours of dosing in males. As seen in Section 2.2, female rats are more sensitive to the toxic effects of disulfoton than male rats; therefore, the females were given a lower dose. Nevertheless, it took longer for females to excrete 50% of the dose than males. Whether this sex difference is due to differences in absorption, metabolism, retention, excretion, or a combination of factors is not known.

In another study, rats received [^{14}C]-disulfoton at a single oral dose of 0.2 mg/kg or 1.0 mg/kg or repeated oral doses 0.2 mg/kg/day for 14 days (Lee et al. 1985). In the rats given a single dose of 0.2 mg/kg, the respective percentages of administered radioactivity 72 hours later in females and males were: urine, 97.1% and 96.9%; feces, 1.1% and 1.4%; tissues, 0.1% in both sexes; carcass, 0.7% in both sexes; and cage rinses, 1.0% and 0.9%. In the rats given a single dose of 1.0 mg/kg, the respective percentages of administered radioactivity for females and males were: urine, 97.5% and 96.9%; feces, 1.7% and 1.9%; tissues, 0.1% and 0%; carcass, 0.5% and 0.4%; and cage rinse, 0.2% and 0.8%. In the rats given 14 daily doses of 0.2 mg/kg/day, the respective percentages in females and males were: urine, 97.1% and 98%; feces, 0.5% and 0.7%; tissues, 0.1% and 0.3%; carcass, 0.9% and 0.5%; and cage rinse, 1.4% and 0.5%. Based on the percentages of administered radioactivity in the urine, ≥97% of the administered dose was absorbed from the gastrointestinal tract within 72 hours. At least 90% of the administered dose was excreted in the urine in the first 24 hours, indicating rapid absorption. In a preliminary experiment, in which rats were given a single oral dose of 0.2 mg/kg

radioactive disulfoton, urinary excretion was essentially complete within 48 hours, with 61-72% excreted in urine of females and 31-48% excreted in the urine of males in the first 4 hours.

Gastrointestinal absorption of disulfoton was extensive following oral exposure of rats and guinea pigs, as evidenced by the small differences in the oral LD_{50} values versus the intraperitoneal LD_{50} values (Bombinski and DuBois 1958). However, the intraperitoneal LD_{50} values were slightly lower than the oral LD_{50} values, suggesting that gastrointestinal absorption is <100%.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals after dermal exposure to disulfoton. However, data on lethality, other signs of toxicity, and acetylcholinesterase inhibition in animals after dermal exposure (see Section 2.2.3) suggest that disulfoton can be absorbed from the skin.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals after inhalation exposure to disulfoton.

2.3.2.2 Oral Exposure

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

Analysis of tissues and blood for radioactivity at various time intervals after rats were dosed with [^{14}C]-disulfoton (1.2 mg/kg for males, 0.2 mg/kg for females) showed that peak levels occurred 6 hours after dosing (Puhl and Fredrickson 1975). The highest levels were found in the liver (peak was 3.6 mg/kg for males, 2.3 mg/kg for females). Peak levels in other tissues (kidney, plasma, fat, whole blood, skin, muscle, and brain in descending order) also generally occurred at 6 hours. At 10 days after dosing, the levels of radioactivity in all tissues decreased; however, low levels were found in the heart at this sampling time. In Beagle dogs dosed with 0.5-l.5 mg/kg/day disulfoton in

capsules for 2 years, disulfoton was detected in the kidney (0.06 ppm), urine (0.06 ppm), liver (0.02 ppm), serum (0.04 ppm), brain and spinal cord (0.01-0.02 ppm) (Hikita et al. 1973). Disulfoton and its metabolites (unidentified) were also detected in small intestine, pancreas, bile, fatty tissue, thymus, spleen, erythrocytes, extraocular muscle, and muscles of the extremities and torso.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to disulfoton.

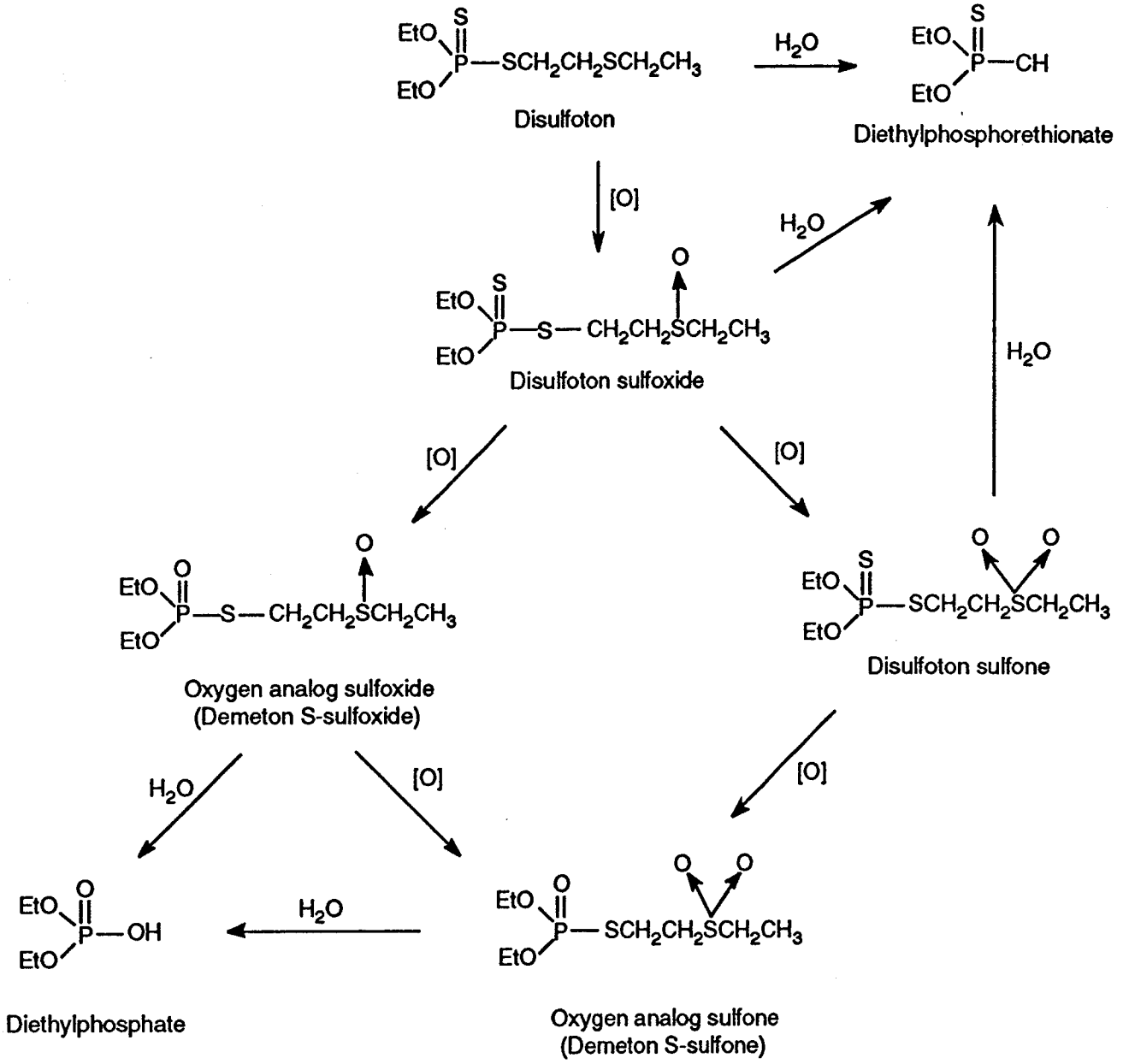
2.3.3 Metabolism

Three different pathways are associated with the metabolism of disulfoton: (1) oxidation of the thioether sulfur to produce sulfoxides and sulfones; (2) oxidation of the thiono sulfur to produce the oxygen analogs; and (3) hydrolysis of the P-S-C linkage to produce the corresponding phosphorothionate or phosphate (WHO 1976) (see Figure 2-3). These pathways have been elucidated from data obtained in humans exposed to disulfoton and from *in vivo* and *in vitro* metabolism studies in rats and mice.

The oxygen analog of disulfoton sulfoxide (demeton S-sulfoxide) and the oxygen analog of disulfoton sulfone (demeton S-sulfone) were identified in the urine from an 87-year-old man who accidentally drank an unknown amount of diluted disulfoton (Yashiki et al. 1990). Disulfoton sulfone and demeton S-sulfone were the only metabolites of disulfoton detected in the blood of this patient. The authors did not report whether they detected the products of disulfoton and/or sulfoxide/sulfone hydrolysis, diethyl phosphate (DEP), diethyl thiophosphate (DETP), and diethyl dithiophosphate (DEDPT) in the urine. From this case report, there is evidence of oxidation of the thioether and thiono sulfur, which produces sulfoxides or sulfones and oxygen analogs of disulfoton, respectively. Workers exposed mainly to disulfoton at a pesticide formulating plant had excreted the metabolites DEP, DETP, DEDPT, and diethyl phosphorothiolate (DEPTh) in urine after dermal and possibly inhalation exposure to disulfoton (Brokopp et al. 1981).

Studies in rats and mice indicate that the same pathways operate in humans and rodents. Unidentified urinary metabolites in mice injected intraperitoneally with 32ρ-disulfoton were described as hydrolysis

FIGURE 2-3. Metabolic Pathways for Disulfoton*



* Adapted from WHO 1976

products (March et al. 1957). The metabolites, disulfoton sulfoxide, disulfoton sulfone, demeton S-sulfoxide, and demeton S-sulfone were also identified as products of *in vitro* hepatic disulfoton metabolism. Disulfoton sulfoxide (11.3%), disulfoton sulfone (2.4%), demeton S-sulfoxide (26.7%), and demeton S-sulfone (59.6%) were also identified in the livers of rats 30 minutes after intraperitoneal injection with disulfoton (Bull 1965). Disulfoton sulfone was the only one of these metabolites not recovered from the liver 120 minutes after exposure. DEP and DETP, formed from the hydrolysis of disulfoton and/or its oxidation products, were identified as the major urinary metabolites in rats dosed orally or intraperitoneally in several studies (Bull 1965; Puhl and Fredrickson 1975; Wolfe et al. 1978). The minor urinary metabolites included disulfoton sulfoxide, demeton S-sulfoxide, and demeton S-sulfone (Puhl and Fredrickson 1975). Although disulfoton sulfone was not detected in the urine in this study, it can be assumed that, subsequent to its formation, it was quickly oxidized to demeton S-sulfone or quickly hydrolyzed to DETP. Furthermore, in another study, disulfoton sulfone was found in the urine of rats after oral exposure to disulfoton (Lee et al. 1985). These findings are consistent with the pathways in Figure 2-3, whereby disulfoton metabolism proceeds via the sequential oxidation of thioether sulfur and/or oxidative desulfuration followed by hydrolysis of the ester. The data also suggest that a greater percentage of disulfoton sulfoxide is oxidized to demeton S-sulfoxide, rather than disulfoton sulfone, to form demeton S-sulfone (Bull 1965). The relative importance of each of the pathways, however, cannot be deduced from relative percentages of metabolites formed because the final urinary metabolites are common products of several of the intermediate metabolites (see Figure 2-3). In addition, after a single dose of 0.2 mg/kg [^{14}C]-disulfoton, disulfoton sulfone, demeton S-sulfone, and demeton S-sulfoxide were found in urine of males, while only demeton S-sulfone was apparent in the urine of females (Lee et al. 1985). However, after dosing with 0.2 mg/kg/day for 14 days, the pattern in males and females was reversed. This reversed pattern after repeated dosing was more likely due to metabolic rate differences than to a difference in pathway, since disulfoton sulfone and demeton S-sulfoxide are precursors to the demeton S-sulfone.

The studies described above support the accepted theory (Eto 1974) that most thioether organophosphate insecticides, such as disulfoton, first undergo metabolic oxidation to sulfoxides, sulfones, and their respective oxygen analogs as part of the metabolic activation pathway. These active metabolites bind to ubiquitous cholinesterase and cause signs of disulfoton toxicity. In the detoxification pathway, these oxidation products and/or disulfoton subsequently undergo hydrolysis to more polar metabolites that are eliminated in the urine. Cytochrome P-450 monooxygenase and flavin

adenine dinucleotide (FAD) monooxygenase are thought to be involved in the metabolic activation pathways.

Generally, organophosphates serve as substrates for the hepatic cytochrome P-450 mixed-function oxidase (MFO) system. The components of the MFO system include cytochrome P-450, the terminal oxidase, and NADPH, and NADPH-dependent cytochrome c reductase (Stevens and Green 1974). Generally, anticholinesterase insecticides such as disulfoton bind to oxidized cytochrome P-450 to form a disulfoton:cytochrome P-450 complex, which usually produces some form of a Type I spectra (Stevens et al. 1973). An electron is then transferred from cytochrome c reductase to cytochrome P-450 (Gillette et al. 1972), thereby reducing the disulfoton:cytochrome P-450 complex. Molecular oxygen then binds to this complex to form a disulfoton:reduced cytochrome P-450:0_2 complex (Gigon et al. 1969). A second electron from NADPH or reduced nicotinamide adenine dinucleotide (NADH) then reduces this complex to form an active oxygen intermediate that decomposes with the formation of the product and oxidized cytochrome P-450 (Hildebrandt and Estabrook 1971).

Flavin monooxygenase specifically oxidizes sulfides to (R)-(+)-sulfoxide enantiomers, while cytochrome P-450-dependent oxidations yield predominantly sulfoxides in the (S)-(-) configuration (Light et al. 1982; Waxman et al. 1982). Disulfoton has three sulfur atoms that can be oxidized: the thiophosphoryl or thiono, the thiol, and the thioether. It has been proposed that flavin monooxygenase I cannot catalyze P=S to P=O conversions (Hajjar and Hodgson 1980). The flavin monooxygenase enzymes metabolize thioether-containing organophosphates to sulfoxides only; that is, there is no evidence for the formation of any other products such as disulfoton sulfones in the presence of only FAD monooxygenase (Hajjar and Hodgson 1980). Sequential oxidations by both monooxygenases (FAD-dependent and cytochrome P-450) may be required to form sulfones (Tynes and Hodgson 1985). Disulfoton interacted with cytochrome P-450 to markedly inhibit the metabolism of p-nitroanisole and parathion, both of which have rather high affinities for cytochrome P-450. These findings underscore the fact that cytochrome P-450 and flavin monooxygenase both have the potential to participate in the oxidation of the disulfoton.

FAD-dependent monooxygenase, purified from pig liver microsomes oxidized disulfoton (Hajjar and Hodgson 1982). The product of this reaction was disulfoton sulfoxide. However, disulfoton sulfoxide was not a substrate for this enzyme, as disulfoton sulfone was not detected. Structure-activity relationships suggest that substitution by oxygen of either the thiono or thiol sulfur atoms decreases

the activity of FAD-dependent monooxygenase and thus the rate of sulfoxidation. In addition, changes in the thioether sulfur have a similar effect. Structural changes on the thioether moiety may increase steric hindrance of the sulfur atom, affect enzyme-substrate binding, and decrease the rate of sulfoxidation. Thus, disulfoton sulfones were not formed, and further oxidation of the sulfoxides to sulfones did not involve FAD-dependent monooxygenase, but rather another oxidase or nonenzymatic reaction. Sulfoxidation was not inhibited by n-octylamine, a known inhibitor of cytochrome P-450-dependent oxygenation (Hajjar and Hodgson 1982). This finding further suggests that FAD-dependent monooxygenase may play a greater role than cytochrome P-450 monooxygenase in the oxygenation of thioether organophosphates. Compared to most other thioether compounds, it was concluded that disulfoton is among the best known flavin monooxygenase substrates (Poulsen 1981). Compared to most other organophosphate insecticides (parathion, diazinon, ethion, phorate, azinophosmethyl, methyl parathion, and ronnel), disulfoton was more rapidly metabolized in the hepatic microsomal oxidative system involving NADPH from rats, guinea pigs, and monkeys (Rao and McKinley 1969).

The metabolism of disulfoton appears to be similar among similar species. For example, liver homogenates from rats, guinea pigs, and monkeys were generally more active in metabolizing disulfoton than liver homogenates from chickens (Rao and McKinley 1969). In addition, pig liver flavin monooxygenase was more saturable by disulfoton than the mouse liver enzyme (Tynes and Hodgson 1985). Flavin monooxygenase in pig liver also had a higher affinity (lower K_m) than the mouse enzyme towards disulfoton (Smyser et al. 1985). Rat liver and lung microsomes have lower flavin monooxygenase activity towards disulfoton than liver or lung microsomes from the mouse or the rabbit (Tynes and Hodgson 1985). However, flavin monooxygenase activity was greater in rabbit and mouse lungs than in their respective livers. This disparity between lung and liver tissues was not observed in rats.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding the rate or extent of excretion in humans or animals after inhalation exposure to disulfoton.

2.3.4.2 Oral Exposure

No studies were located regarding the rate or extent of excretion in humans after oral exposure to disulfoton.

Male rats given a single acute dose (1.2 mg/kg) of [^{14}C]-disulfoton eliminated an average of 84.3%, 6.1%, and 9.2% of the dose in the urine, feces, and expired air, respectively, in the 10 days following exposure (Puhl and Fredrickson 1975). Female rats given 0.2 mg/kg eliminated 78.9%, 7.8%, and 9.2% of the administered radioactivity in the urine, feces, and expired air, respectively, in the same time period. Male rats excreted 50% of the administered dose in the urine during the first 4-6 hours after exposure, while females required 30-32 hours to excrete 50% of the dose in the urine. The female rats were given a lower dose than the males because female rats are more sensitive than male rats to the toxic effects of disulfoton (see Section 2.2). Nevertheless, it took longer for females to excrete 50% of the dose. Whether this sex difference is due to differences in absorption, metabolism, retention, excretion, or a combination of factors is not known.

In another study, rats received [^{14}C]-disulfoton at a single oral dose of 0.2 mg/kg or 1.0 mg/kg or repeated oral doses of 0.2 mg/kg/day for 14 days (Lee et al. 1985). In the rats given a single dose of 0.2 mg/kg, the respective percentages of administered radioactivity 72 hours later in females and males were 97.1% and 96.9% in urine and 1.1% and 1.4% in feces. In the rats given a single dose of 1.0 mg/kg, the respective percentages of administered radioactivity for females and males were 97.5% and 96.9% post-dosing in urine and 1.7% and 1.9% in feces. In the rats given 14 daily doses of 0.2 mg/kg/day, the respective percentages in females and males were 97.1% and 98% in urine and 0.5% and 0.7% in feces. Thus, the primary route of excretion in all dose groups was via the urine (at least 97% in each group), and excretion was essentially complete within 72 hours post-dosing, with at least 90% excreted in the first 24 hours. In a preliminary experiment in which rats were given a single oral dose of 0.2 mg/kg radioactive disulfoton, urinary excretion was essentially complete within 48 hours, with 61-72% excreted in urine of females and 3148% excreted in the urine of males in the first 4 hours. Analysis of expired gases at 24-hour intervals for 144 hours post-dosing in the preliminary experiment indicated that only 0.5% and 0.2% of the radioactivity in females and males, respectively, was present in the expired air.

2.3.4.3 Dermal Exposure

No studies were located regarding the rate or extent of excretion in humans or animals after dermal exposure to disulfoton.

2.3.4.4 Other Routes of Exposure

No studies were located regarding excretion in humans after other routes of exposure to disulfoton.

White rats given a single dose of radiolabeled disulfoton intraperitoneally eliminated the metabolites phosphoric acid (4.1%), DEP (61.2%), and DETP (24.8%) in urine as a percentage of excretory metabolites lo-12 hours after exposure (Bull 1965). Approximately 24 and 48 hours after exposure 14.1% and 28.6%, respectively, of the administered dose was excreted in the urine. Excretion rates for disulfoton and its metabolites were not determined. Mice eliminated 30-60% of the radiolabeled intraperitoneal dose of disulfoton in the urine and 2-3% in the feces within 96 hours of exposure (March et al. 1957).

2.3.5 Mechanisms of Action

Disulfoton is readily absorbed from the gastrointestinal tract (Hattori et al. 1982; Lee et al. 1985; Puhl and Fredrickson 1975; Yashiki et al. 1990). Although information regarding the rate and extent of absorption of disulfoton after inhalation and dermal exposure was not located, the lipophilic nature of disulfoton suggests that it is probably absorbed by passive diffusion by these routes as well.

Although there are no known intermediary proteins or other mechanisms associated with distribution of disulfoton to effector organs or to organs where the compound is likely to be metabolized, binding studies with other organophosphates suggest that serum albumin may be an important protein involved with distribution to effector organs (Braeckman et al. 1983). Available data suggest that more disulfoton is distributed initially to the liver than to any other organ (Puhl and Fredrickson 1975). The detection of disulfoton metabolites in the liver of rats is consistent with this observation (Bull 1965). The active metabolites of disulfoton are known to depress the activity of serum, erythrocyte, and brain cholinesterase (see Section 2.2.2.4).

Metabolism of disulfoton in humans and animals appears to be qualitatively and quantitatively similar (Brokopp et al. 1981; Bull 1965; Puhl and Fredrickson 1975; Yashiki et al. 1990). The intermediary products of disulfoton metabolism, rather than disulfoton itself, are responsible for the signs of toxicity observed in humans and animals exposed to the pesticide. These metabolites (disulfoton sulfoxide, disulfoton sulfone) and the oxygen analogs (demeton S-sulfoxide and demeton S-sulfone) are oxidation products of disulfoton and are formed primarily in the liver (Bull 1965; March et al. 1957). In an oral study in rats, the metabolites, disulfoton sulfoxide, disulfoton sulfone, demeton S-sulfoxide, and demeton S-sulfone resulted in mortality and signs of toxicity at lower doses than did disulfoton (Crawford and Anderson 1974).

No information was located regarding the mechanism of excretion of disulfoton and/or its metabolites. Because disulfoton and its active metabolites are relatively lipophilic, excretion by passive diffusion is the probable mechanism.

The acute toxic effects of organophosphate insecticides are due primarily to accumulation of acetylcholine at muscarinic and nicotinic cholinergic receptors (Costa et al. 1982b). The accumulation of this substrate is due to the inhibition of cholinesterase activity by the active metabolites of the organophosphate (Murphy et al. 1984). In many instances, humans and animals exhibit signs of toxicity resembling excessive stimulation of cholinergic nerves. Atropine, a cholinergic blocking agent, has been used to demonstrate that excessive acetylcholine accumulation is related to the mechanism of toxicity (Bombinski and DuBois 1958). Cholinesterase enzyme kinetics provide further evidence supporting the proposed mechanism. Studies indicate that the enzyme-acetylcholine complex and the enzyme-organophosphate complex usually are formed at the same rate (Murphy et al. 1984). However, the enzyme-acetylcholine complex is hydrolyzed at a much faster rate than the enzyme-organophosphate complex; the enzyme is therefore regenerated faster in the forrner case. Dephosphorylation of the enzyme is a slow reaction, and, therefore rate-limiting.

Signs of disulfoton toxicity, such as muscle tremors, fasciculations, lacrimation, and salivation, in animals are generally observed after a few daily doses, but begin to diminish in severity as exposure to disulfoton continues (Bombinski and DuBois 1958). This phenomenon is known as tolerance. Tolerance appears to be a reproducible phenomenon that does not depend on the organophosphate insecticide used, the route of administration, or the animal species (Costa et al. 1982b). Several possible mechanisms have been proposed to explain this phenomenon.

Evidence suggests that tolerance involves the cholinergic system and not the opiate system (Costa and Murphy 1986). Tolerance to chronic treatment with disulfoton was once thought to be due to refractoriness of the cholinergic receptor to acetylcholine (Brodeur and DuBois 1964). More recently, tolerance has been associated more specifically with alterations of cholinergic receptor density, rather than with changes in binding affinity (Costa et al. 1981, 1982a, 1990; McDonald et al. 1988). Radiolabeled ligands, such as [^{3}H] quinuclidinyl benzilate ([^{3}H] QNB), which are muscarinic antagonists that can bind to recognition sites on muscarinic receptors, were used in these studies to demonstrate that disulfoton caused a reduced number of receptor binding sites in central and peripheral nerve tissue. However, the binding affinity was not changed in disulfoton-tolerant animals. Furthermore, the alteration in cholinergic muscarinic receptors was not due to direct binding of disulfoton and/or its metabolites to the receptor, but due to an adaptive mechanism to overstimulation by endogenous acetylcholine (Costa et al. 1981). Disulfoton also caused modulation of Ml and M2 muscarinic receptor subtypes in the brain of disulfoton-tolerant rats (Fitzgerald and Costa 1992). However, recovery of M2 muscarinic receptor binding after termination of exposure was slower compared to the Ml subtype, particularly in the hippocampus. Alteration of muscarinic binding sites in lymphocytes was also demonstrated (Costa et al. 1990; Fitzgerald and Costa 1993). The rate of recovery of cholinesterase is much slower than the rate of recovery of [^{3}H] QNB binding in disulfoton- tolerant animals (Costa et al. 1981). McDonald et al. (1988) hypothesized that the decrease in muscarinic receptor densities in the hippocampus, cortex, and striatum of the brain was the reason for memory loss in animals that became tolerant to disulfoton after repeated intraperitoneal dosing (see Section 2.4). The data from earlier intraperitoneal behavioral studies are not consistent with this finding (Costa and Murphy 1982). However, these two studies measured different neurobehavioral end points in different species. In addition, this memory loss has not been reported in humans. While cholinergic muscarinic signs diminish in severity in disulfoton-tolerant animals, nicotinic cholinergic signs may persist (McPhillips 1969a). It was proposed that nicotinic receptors were stable, while muscarinic receptors were labile to acetylcholine accumulation in disulfoton-tolerant animals (Costa et al. 1982a). However, a decrease in nicotinic acetylcholine receptors in the brain was subsequently found after repeated administration of disulfoton in rats (Costa and Murphy 1983a).

As supporting evidence for this mechanism (i.e., reduced density of muscarinic receptor binding sites), subsensitivity to other cholinergic agonists was demonstrated in disulfoton-tolerant animals. The mechanism for the subsensitivity to cholinergic agonists is probably related to changes in agonist binding as well as loss of surface receptor labeling by hydrophilic ligands such as

N-methylscopolamine (Costa et al. 1982b; Schwab et al. 1983). Animals made tolerant to disulfoton were resistant to the lethal or adverse effects of cholinergic agonists, such as carbachol (Brodeur and DuBois 1964; Costa et al. 1981; Schwab and Murphy 1981) and oxotremorine (Costa et al. 1982b; McPhillips 1969a), which are not hydrolyzed by acetylcholinesterase. Tissues from animals tolerant to disulfoton such as the ilea (Foley and McPhillips 1973; McPhillips 1969b; McPhillips and Dar 1967) and the atria (Perrine and McPhillips 1970; Schwab et al. 1983), were resistant to the effects of carbachol and/or oxotremorine. Because the uterus and vas deferens have a relatively sparse parasympathetic innervation compared to the ileum and do not receive a steady flow of impulses via this system, these tissues were not as subsensitive to carbachol as the ileum (Foley and McPhillips 1973). Thus, acetylcholine accumulation may be a prerequisite for tolerance development.

Other hypotheses have been tested in attempts to explain the mechanism of tolerance. Tolerance may be associated with interference of acetylcholine synthesis at the presynaptic junction (Costa et al. 1982b). However, no difference in the uptake of choline occurred in the hippocampus from disulfoton-tolerant mice compared with controls, suggesting that the availability of choline was not limiting. Noncholinergic mechanisms may also be involved in the development of tolerance. In one study, the atria from disulfoton-tolerant rats were subsensitive to carbachol and oxotremorine, but there was no alteration in binding of [^{3}H] QNB when compared with the controls (Schwab et al. 1983). This finding is inconsistent with the "altered receptor" hypothesis that suggests tolerance is associated with a decrease in radioligand binding and a concomitant subsensitivity to cholinergic agonists. The authors proposed that in addition to receptor loss, other mechanisms distal to [^{3}H] QNB binding sites or removed from the receptor complex may contribute to the subsensitivity of the atria and other tissues to cholinergic agonist. These and other related mechanisms remain to be studied.

2.4 RELEVANCE TO PUBLIC HEALTH

The lipophilic properties of disulfoton suggest that the compound is likely to be absorbed readily by the lungs, gastrointestinal tract, and the skin. Toxicokinetic data in humans and animals show that disulfoton is readily and extensively absorbed by the gastrointestinal tract. Disulfoton and/or its metabolites are distributed rapidly to tissues such as the liver, kidney, brain, and adipose tissue. Although the compound is relatively lipophilic, its accumulation in these organs does not appear to be appreciable. Fifty to ninety percent of the dose administered to rats was eliminated in the urine within

4-32 hours. Disulfoton is rapidly metabolized to its oxygen analogs, which are in turn rapidly detoxified to water soluble nontoxic metabolites that are eliminated via the urine.

The most significant and sensitive effects resulting from acute, intermediate, or chronic exposure to disulfoton by the inhalation, oral, or dermal route are neurological. The neurological effects are the result of inhibition of acetylcholinesterase by active metabolites of disulfoton at nerve synapses; subsequent accumulation of acetylcholine results in overstimulation of the distal neuron, and more specifically, in cholinergic effects. Examples of cholinergic effects include salivation, miosis, muscle tremors, and urinary and fecal incontinence. Convulsions, coma, and death have been associated with severe disulfoton intoxication. Studies in chickens indicated that disulfoton does not cause delayed neurotoxicity. Body weight loss is also a common finding in animals and is associated with cholinesterase inhibition. In addition, disulfoton may alter catecholamine levels in body tissues. The effects on catecholamine levels appear to be related to the accumulation of acetylcholine. Optic nerve atrophy and necrosis have also been associated with chronic oral exposure to disulfoton in dogs.

The inhibition of erythrocyte acetylcholinesterase is a very sensitive biomarker of this acetylcholinesterase inhibition at the nerve synapses, and, therefore, can be regarded as a sensitive effect as well. Some of these effects have been observed in occupationally exposed individuals and in a man who accidentally ingested disulfoton. Results from several animal studies support these findings. The cholinergic effects are usually associated with acute exposure to disulfoton. Prolonged exposure to disulfoton (5-10 days) generally results in a decrease in the severity of the cholinergic toxicity, while cholinesterase remains inhibited. This phenomenon, known as tolerance, has been observed in animals exposed to disulfoton for prolonged periods. A number of studies have investigated the mechanism of tolerance development.

Hepatic effects have not been observed in humans, but mild hepatic effects were observed in animals after oral exposure to disulfoton. These hepatic effects include alterations in liver microsomal enzyme activities and lipid peroxidation. No concurrent histopathological changes in the liver were observed. Although hepatic effects should be of little concern to exposed humans, caution is advised with concomitant use of prescription or nonprescription drugs that share a common metabolic pathway with disulfoton. Results from oral studies suggest that disulfoton may cause myopia in animals and possibly humans. In one chronic dietary study in rats, effects on eyes (degeneration of the Harderian gland and cornea1 neovascularization), lungs (inflammation), stomach (mucosal hyperplasia and

inflammation of the forestomach), skeletal muscle (atrophy due to debilitation), pancreas (atrophy), ant spleen and lymph nodes were seen in some rats, mostly at the highest doses, but the most sensitive effects were associated with cholinesterase inhibition. Other than the cholinergic effects, none of the effects were seen in mice or dogs given chronic oral doses, and their relevance to humans are unknown. Other effects observed in rats exposed to disulfoton by the inhalation route include inflammation of the nasal turbinates and bone marrow changes, which were related to decreased lymphocytes and inflammatory changes in the lungs.

No data were located regarding reproductive or developmental effects in humans. However, disulfoton has caused lower pregnancy rates and reduced litter sizes in animals after oral exposure for intermediate durations. Fetotoxic effects, such as increased incidences of incomplete ossification of parietal bones and stemebrae, have been reported in the fetuses of rat dams exposed orally during gestation. In addition, depression of fetal brain and erythrocyte cholinesterase, fatty infiltration of the liver, mild nephropathy, and juvenile hypoplasia of the testes occurred in litters of rats exposed orally in multiple-generation reproductive studies. Although placental transfer of disulfoton and/or its active metabolites appears to occur, no data were located regarding transfer via the dam’s milk.

Disulfoton has been tested for genotoxicity in a variety of assays with mostly negative results; however, the few positive results indicate genotoxic potential. Carcinogenicity was not observed in Beagle dogs, rats, or mice fed disulfoton for 2 years.

Employees at hazardous waste sites, employees at pesticide mixing and formulating plants, and farm workers are more likely to be exposed to disulfoton than individuals in other occupations. Neurotoxic effects have been observed in occupationally exposed persons. However, no human data were located to identify susceptible subpopulations. Animal data suggest that female animals and young animals are more susceptible to disulfoton toxicosis. Based on the results from animal studies, women and children could also be more susceptible than men to toxic effects of disulfoton.

Minimal Risk Levels for Disulfoton

Inhalation MRLs

- An MRL of 0.006 mg/ m^3 has been derived for acute-duration inhalation exposure (14 days or less) to disulfoton.

The MRL is based on a NOAEL of 0.5 mg/ m^3 for decreased acetylcholinesterase activity in rats exposed to disulfoton 4 hours/day for 5 days in a study by Thyssen (1978). The NOAEL was adjusted for intermittent exposure, converted to a human equivalent concentration, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability). Inhibition of erythrocyte cholinesterase activity and unspecified behavioral disorders were observed at 1.8 mg/ m^3, and unspecified signs of cholinergic toxicity were observed at 9.8 mg/ m^3. Similar effects were observed in rats or mice exposed to higher concentrations for shorter durations (Doull 1957; Thyssen 1978). The NOAEL value of 0.5 mg/ m^3 is supported by another study, in which no significant decrease in the activity of brain, serum, or submaxillary gland cholinesterase was found in rats exposed to 0.14-0.7 mg/ m^3 for 1 hour/day for 5-10 days (DuBois and Kinoshita 1971). Mild depression of erythrocyte cholinesterase activity was reported in workers exposed by the inhalation and dermal routes (Wolfe et al. 1978).

- An MRL of $2x10^{-4}$ mg/ m^3 has been derived for intermediate-duration inhalation exposure (15-364 days) to disulfoton.

The intermediate MRL is based on a NOAEL of 0.02 mg/ m^3 for decreased acetylcholinesterase activity in rats exposed to disulfoton 6 hours/day, 5 days/week for 3 weeks in a study by Thyssen (1980). The NOAEL was adjusted for intermittent exposure, converted to a human equivalent concentration, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability). In the Thyssen (1980) study, 2 separate 3-week experiments were conducted. In the first experiment, rats exposed to 0.1, 0.5, or 3.7 mg/ m^3 showed concentrationrelated increased severity of cholinesterase inhibition and cholinergic signs of toxicity, with the lowest exposure level of 0.1 mg/ m^3 associated with lethargy during the last week of exposure. At 0.5 mg/ m^3, lethargy and failure to groom were observed during the second and third weeks; and at 3.7 mg/ m^3, muscle tremors, convulsions, inhibition of brain cholinesterase, and death were observed. Because a

NOAEL could not be established in the first experiment, the second experiment used an exposure level of 0.02 mg/m^3, which resulted in no inhibition of cholinesterase activity or signs of cholinergic toxicity, and an exposure level of 3.1 mg/ m^3 to confirm the effects seen at 3.7 mg/ m^3 in the first experiment. In a 13-week inhalation study, inhibition of erythrocyte and brain cholinesterase activity was observed in rats exposed to 1.4 mg/ m^3, but not 0.16 mg/ m^3, disulfoton 6 hours/day, 5 days/week (Shiotsuka 1989). Other effects of intermediate-inhalation exposure of rats to disulfoton include inflammatory changes in the respiratory tract associated with bone marrow changes at 20.5 mg/ m^3 and decreased percentages of lymphocytes with increased polymorphonuclear leukocytes at 3.1 mg/ m^3, increased absolute and relative adrenal weight at 3.1 and 3.7 mg/ m^3 (Thyssen 1980), and increased incidence of inflammation of the nasal turbinates at 1.4 mg/ m^3 (Shiotsuka 1989).

An MRL has not been derived for chronic-duration inhalation exposure to disulfoton because no chronic-duration inhalation studies were located.

Oral MRLs

- An MRL of 0.001 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to disulfoton.

The MRL was based on a NOAEL of 0.1 mg/kg/day for decreased cholinesterase activity in rats treated with disulfoton by gavage on gestation days 6-15 (Lamb and Hixson 1983). Erythrocyte and plasma cholinesterase activities were significantly inhibited at 0.3 mg/kg/day. Numerous acute oral studies in rats and mice have found significantly depressed brain or other tissue cholinesterase activities (Costa and Murphy 1983a; Costa et al. 1984, 1986; Schwab and Murphy 1981; Schwab et al. 1981, 1983; Su et al. 1971). Most of these studies used higher doses than those in the Lamb and Hixson (1983) study. However, a 50% inhibition of brain cholinesterase activity was found in rats exposed to disulfoton in the diet at 0.26 mg/kg/day for 1 week (Su et al. 1971), which supports the LOAEL of 0.3 mg/kg/day in the Lamb and Hixson (1983) study. In an extensive acute oral neurotoxicity study in rats, a NOAEL of 0.24 mg/kg for erythrocyte cholinesterase activity was found (Sheets 1993a); however this NOAEL value is essentially the same as the LOAEL values of 0.26 mg/kg/day in the Su et al. (1971) study and 0.3 mg/kg/day in the Lamb and Hixson (1983) study. Other effects of disulfoton in acute oral studies include depression of body weight gain (Schwab and Murphy 1981; Schwab et al. 1981, 1983), interference with catecholamine levels in body tissues

(Brzezinski 1969; Brzezinski and Ludwicki 1973; Brzezinski and Rusiecki 1970; Wysocka-Paruszewska 1970, 1971, 1972), and lipid peroxidation in the liver (Fawade and Pawar 1978, 1980, 1983). None of these effects occurred at doses lower than the acute oral NOAEL of 0.1 mg/kg/day for neurological effects. Furthermore, the NOAEL is an order of magnitude lower than the dose (1 mg/kg/day) associated with delayed ossification in fetal rats (Lamb and Hixson 1983).

- An MRL of $9x10^{-5}$ mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to disulfoton.

The MRL was based on a NOAEL of 0.009 mg/kg/day for decreased brain cholinesterase activity in F_{1a} pups in a multigeneration feeding study in rats by Hixson and Hathaway (1986). At the LOAEL of 0.03 mg/kg/day, the brain cholinesterase activity was inhibited 24-32% in the F_{1a} pups and litter counts and litter weights were decreased in F_{2b} litters. At 0.09 mg/kg/day, effects included tremors in the F_0 females during the production of the F_1 generation, decreased reproductive performance, decreased maternal F_0 and F_1 weight during gestation and lactation, decreased litter counts and viability and lactation indices, and increased dead births and percentage dead births. Numerous intermediate-duration oral studies in rats, mice, and dogs have found significantly depressed brain or other tissue cholinesterase activities (Clark and Pearson 1973; Doull and Vaughn 1958; Hayes 1985; Hoffman et al. 1975; Klotzsche 1972; Rivett et al. 1972; Robinson et al. 1978; Ryan et al. 1970; Schwab and Murphy 1981; Sheets 1993b; Stavinoha et al. 1969; Vaughn et al. 1958). All of these studies reported cholinesterase inhibition at higher doses than those in the Hixson and Hathaway (1986) study. In addition, other intermediate-duration oral developmental and reproductive studies in animals reported depression of brain or erythrocyte cholinesterase activity in the offspring of rats and reduced litter sizes or failure to produce litters at doses ≥0.1 mg/kg/day (Ryan et al. 1970; Taylor 1965a). In addition, cloudy swelling or fatty livers, mild nephropathy, and juvenile hypoplasia of the testes occurred in F_3 litters (Taylor 1965a).

- An MRL of $6x10^{-5}$mg/kg/day has been derived for chronic-duration oral exposure (≥365 days) to disulfoton.

The MRL is based on a LOAEL of 0.06 mg/kg/day for acetylcholinesterase inhibition in rats exposed to disulfoton in the diet for 2 years in a study by Hayes (1985) using an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to human, and 10 for human

variability). The chronic-duration oral studies have found inhibition of brain, erythrocyte, and plasma cholinesterase in rats given ≥0.06 mg/kg/day, but not ≤0.05 mg/kg/day, disulfoton in the diet for 1.5-2 years (Carpy et al. 1975; Hayes 1985) and in mice given 2.13 mg/kg/day (males) and 2.53 mg/kg/day (females), but not ≤0.5 mg/kg/day, disulfoton for 23 months (Hayes 1983). Dogs treated with 0.5 mg/kg/day disulfoton in capsules (Uga et al. 1977) and rats given ≥0.18 mg/kg/day in the diet (Hayes 1985) for 2 years had optic nerve degeneration. Systemic effects of disulfoton in chronic oral studies were ocular effects (degeneration of ciliary muscles cells, myopia, and astigmatism) in dogs at 0.63 mg/kg/day (Ishikawa and Miyata 1980) and cystic degeneration of the Harderian gland at 0.21 mg/kg/day and cornea1 neovascularization at 0.75 mg/kg/day in rats (Hayes 1985). In addition, rats given disulfoton in the diet for 2 years had granulomatous and suppurative inflammation of the lungs, pancreatic atrophy, dermal lesions, decreased body weight gain, and plasma cell hyperplasia in the mandibular lymph nodes at ≥0.75 mg/kg/day, and mucosal hyperplasia and chronic inflammation of the forestomach and splenic lymphoid follicle depletion at 1.02 mg/kg/day. In a a-year feeding study in dogs, erythrocyte and plasma cholinesterase activities were significantly inhibited at a time-weighted-average dose of 0.14 mg/kg/day, but not at 0.03 mg/kg/day (Hoffman et al. 1975). Although NOABL values of 0.03 mg/kg/day in dogs (Hoffman et al. 1975) and of 0.05 mg/kg/day in rats (Carpy et al. 1975; Hayes 1985) were found, the NOAEL values would result in MRLs higher than the intermediate-duration oral MRL. Thus, the chronic-duration oral MRL of $6x10^{-5}$ mg/kg/day was based on the LOAEL value of 0.06 mg/kg/day in female rats in the study by Hayes (1985), using an uncertainty factor of 1,000.

The chronic-duration oral MRL for disulfoton is $6x10^{-5}$ mg/kg/day, and the EPA chronic oral RfD is $4x10^{-5}$ mg/kg/day (IRIS 1994). Both of these values are based on the same study (Hayes 1985) and the identical end point. Even though the MRL and the RfD are essentially the same, they have minor differences due to the manner in which the exposure doses were calculated. The LOAEL of 0.04 mg/kg/day used by EPA was calculated by multiplying the analytical dietary concentration of 0.8 ppm (nominal concentration of 1 ppm) by the reference rat food consumption factor of 0.05. However, Hayes (1985) provided an equivalent dose of 0.08 mg/kg/day for the nominal concentration of 1 ppm, based on actual food consumption and body weight data. The LOAEL of 0.06 mg/kg/day used in deriving the chronic oral MRL was obtained by multiplying the 0.08 mg/kg/day dose, corresponding to the nominal concentration of 1 ppm, by the analytical concentration of 0.8 ppm.

Death. No studies were located regarding death in humans after inhalation or dermal exposure to disulfoton. One case report of human death after acute oral exposure to disulfoton was found (Hattori et al. 1982). Because an unknown amount was ingested, the lethal dose was not determined. Autopsy results suggested that death may have been due to asphyxia resulting from respiratory failure. Pulmonary edema is associated with disulfoton-induced overstimulation of secretory glands and bronchial secretions in the respiratory tract.

High mortality was found at 202.2 mg/ m^3 in male Sprague-Dawley rats (Doull 1957), at 180.1 mg/ m^3 in male Holtzman rats and 87.6 mg/ m^3 in female Holtzman rats (DuBois 1971), and at 53.4 mg/ m^3 in female mice (Doull 1957) after l-hour exposures; and in female Wistar rats, but not males, at intermittent exposures ≥3.1 mg/ m^3 for 3-15 exposures (Thyssen 1980). LC_{50} values reported for Wistar rats were 290 mg/ m^3 in males and 63 mg/ m^3 for females exposed for 1 hour, and 60 mg/ m^3 for males and 15 mg/ m^3 for females exposed for 4 hours (Thyssen 1978). Thus, strain-, sex-, and species-related differences in the inhalation lethality of disulfoton exist. Acute oral LD_{50} values for rats and mice also suggest that female rats and mice are more sensitive to disulfoton (1.9-8.2 mg/kg) than male rats and mice (5.8-19.3 mg/kg) (Bombinski and DuBois 1958; Crawford and Anderson 1974; Gaines 1969; Mihail 1978; Pawar and Fawade 1978; Stevens et al. 1972a) and that rats are generally more sensitive than mice to disulfoton. However, female guinea pigs appear to be less sensitive than male guinea pigs (LD_{50} of 12.7 mg/kg for females and 8.9 mg/kg for males) (Crawford and Anderson 1973). Acute dermal LD_{50} studies (Gaines 1969; Mihail 1978), and acute intraperitoneal LD_{50} studies (Bombinski and DuBois 1958) also indicate that female rats are more sensitive than male rats and that young animals are more sensitive than adult animals. The acute dermal LD_{50} in rats ranges from 3.6 to 187 mg/kg, depending on the formulation (Weil et al. 1971). Acute dermal exposure resulted in deaths in rabbits at doses of 6.5-10 mg/kg/day (Flucke 1986). In most of these studies, the cause of death was not reported, but may have been due to the cholinergic effects and hypoxia resulting from bronchoconstriction, excessive respiratory secretions, and erratic, slowed heart rate.

Although the dose levels of disulfoton that would cause death in humans are not known, disulfoton levels in the workplace, in the ambient environment, in drinking water, or at hazardous waste sites are probably not high enough to cause death.

Systemic Effects.

Respiratory Effects. Information on respiratory effects due to exposure to disulfoton is very limited. Exposure to disulfoton causes overstimulation of the muscarinic cholinergic receptors in the respiratory tract (Murphy 1986). This usually results in excessive bronchial secretions, bronchoconstriction, and eventually respiratory failure. Pulmonary edema and hemoptysis were recognized as probable causes of death in a man who ingested an unknown amount of disulfoton (Hattori et al. 1982). Studies regarding inhalation exposure were concerned primarily with lethality or cholinesterase inhibition. However, in intermediate-duration inhalation studies in rats, inflammation of the nasal turbinates at 1.4 mg/ m^3 (Shiotsuka 1989) and inflammatory changes throughout the respiratory tracts, possibly related to bone marrow changes, at 0.5 mg/ m^3 (Thyssen 1980) were observed. Breathing difficulties were observed in rats given a single gavage dose of 1.0 mg/kg, mice given a single gavage dose of 5.0 mg/kg, and rats given single dermal applications of disulfoton (Mihail 1978). In a chronic dietary study in rats, granulotamous and suppurative inflammation of the lungs occurred at the highest dietary concentration, but may have been due to aspiration of food particles, since the high dose rats showed considerable debilitation (Hayes 1885). However, no histopathological lesions were found in the lungs of rats (Klotzsche 1972) or mice (Rivett et al. 1972) exposed to disulfoton in the diet for intermediate durations, or in mice (Hayes 1983) or dogs (Hoffman et al. 1975) exposed in the diet for up to 2 years. The likelihood that respiratory effects would occur in humans exposed to disulfoton in the ambient environment or at hazardous waste sites is negligible.

Cardiovascular Effects. Exposure to disulfoton may cause acetylcholine-mediated overstimulation of muscarinic receptors in the heart, which can result in bradycardia progressing to fatal heart block (Murphy 1986). However, no studies were located regarding cardiovascular effects in humans after inhalation, oral, or dermal exposure to disulfoton. No histopathological lesions were found in the hearts of rats exposed by the inhalation route for intermediate durations (Shiotsuka 1989; Thyssen 1980), in rats (Klotzsche 1972) or mice (Rivett et al. 1972) exposed in the diet for intermediate durations, in rats (Carpy et al. 1975; Hayes 1985), mice (Hayes 1983), or dogs (Hoffman et al. 1975) exposed in the diet for chronic durations, or in rabbits exposed dermally for intermediate duration (Flucke 1986). However, acute dermal exposure to unspecified doses of organophosphorus insecticides, including disulfoton, reportedly caused protein degeneration and significant circulatory disruptions in heart muscles of rats, cats, and rabbits (Kundiev and Rappoport 1967). As discussed in Section 2.2.3, this study is limited by reporting deficiencies. No changes in blood pressure or heart

rate were found in rats injected intraperitoneally with disulfoton for ≤30 days (McPhillips and Dar 1967; Perrine and McPhillips 1970). This information is too limited, however, to allow any analysis of the likelihood of cardiovascular effects occurring in humans exposed to disulfoton in any scenario.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after exposure to disulfoton. Necropsy of rats that died after intermittent inhalation exposure to 3.7 mg/ m^3 for 3 weeks revealed bloated gastrointestinal tracts and ulcer-like foci in the glandular mucosa of the forestomach (Thyssen 1980). Mucosal hyperplasia and chronic inflammation of the forestomach was found in rats given 1.04 mg/kg/day disulfoton in the diet for 2 years (Hayes 1985). However, no histopathological lesions were found in the gastrointestinal tracts of rats exposed intermittently by inhalation to 3.1 mg/ m^3 for 3 weeks (Thyssen 1980) or 1.4 mg/ m^3 for 13 weeks (Shiotsuka 1989), in rats exposed to 0.55 mg/kg/day (Klotzsche 1972) or mice exposed to 0.71 mg/kg/day (Rivett et al. 1972) in the diet for 90 days, in rats exposed to ≤0.75 mg/kg/day (Carpy et al. 1975; Hayes 1985), mice exposed to 2.53 mg/kg/day (Hayes 1983), or dogs exposed to 0.14 mg/kg/day (Hoffman et al. 1975) in the diet for 2 years, or in rabbits treated dermally with 1.6 mg/kg/day for 3 weeks (Flucke 1986). The likelihood that gastrointestinal effects would occur in humans exposed to disulfoton in the ambient environment or at hazardous waste sites is negligible.

Hematological Effects. No studies were located regarding hematological effects in humans after exposure to disulfoton. Rats exposed intermittently for 3 weeks to 3.1 mg/ m^3, but not 3.7 mg/ m^3, had decreased percentages of lymphocytes and increased percentages of polymorphonuclear leukocytes, which represented an early response to the bone marrow changes (see Immunological and Lymphoreticular Effects below) (Thyssen 1980). No hematological effects were found in rats exposed by inhalation to lower concentrations for 13 weeks (Shiotsuka 1989); in 90-day dietary studies in rats (Klotzsche 1972) and mice (Rivett et al. 1972); in the 2-year dietary studies in rats (Carpy et al. 1975; Hayes 1985), mice (Hayes (1983), or dogs (Hoffman et al. 1975); or in the 3-week dermal study in rabbits (Flucke 1986). The results of the animal studies indicate that the potential for hematological effects is not a concern for humans exposed to disulfoton.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after exposure to disulfoton. Disulfoton injected intraperitoneally in rats for 10 days had no effect on the contractile mechanism of smooth muscle of the ileum (McPhillips 1969b). No histopathological muscular or skeletal lesions were found in rats dosed once by gavage with disulfoton (Sheets 1993a),

rats (Klotzsche 1972) or mice (Rivett et al. 1972) exposed to disulfoton in the diet for 90 days, or in rats (Carpy et al. 1975), mice (Hayes 1983), or dogs (Hoffman et al. 1975) exposed in the diet for up to 2 years. However, female rats exposed to the highest dietary concentrations of disulfoton for 2 years had skeletal muscle atrophy, which was probably related to the general debilitation of these rats (Hayes 1985). Degenerative changes in the ciliary muscle cells of the eye were observed in dogs exposed orally to disulfoton for 2 years (Ishikawa and Miyata 1980; Suzuki and Ishikawa 1974). These histopathological changes in the muscle were thought to be associated with myopia, also observed in the dogs (see Ocular Effects below). Since high incidences of myopia found in children corresponded with an increased use of disulfoton in combination with other organophosphates to treat food crops (Ishikawa and Miyata 1980), the possibility that degeneration of ciliary muscle cells occurs in humans exposed to disulfoton cannot be ruled out.

Hepatic Effects. No studies were located regarding hepatic effects in humans after exposure to disulfoton. No hepatic effects were found in rats exposed by inhalation (Shiotsuka 1989; Thyssen 1980) or dermally (Flucke 1986) to disulfoton for intermediate durations. However, acute dermal exposure to unspecified doses of organophosphorus insecticides, including disulfoton, reportedly caused protein degeneration and significant circulatory disruptions in the liver of rats, cats, and rabbits (Kundiev and Rappoport 1967). As discussed in Section 2.2.3, this study is limited by reporting deficiencies. Acute oral exposure of animals to disulfoton has resulted in alterations in hepatic microsomal enzymes (Fawade and Pawar 1978, 1980, 1983; Stevens et al. 1972b, 1973). Although inhibition or induction of hepatic microsomal enzymes by disulfoton in the absence of liver pathology is not an adverse effect, animal studies have demonstrated that disulfoton-pretreated animals are more susceptible to the toxic effects of several drugs and anesthetics (see Section 2.6). In addition, lipid peroxidation was also observed in animals after oral exposure to disulfoton (Fawade and Pawar 1978). Fatty infiltration of the liver was observed in F_{3b} offspring in a three-generation oral study (Taylor 1965a). Although no histopathological changes were observed, increased liver weights were observed in female mice exposed orally for intermediate durations (Rivett et al. 1972) and in male rats exposed orally for chronic durations (Carpy et al. 1975). The increased liver weight may be associated with liver enzyme induction. However, an unexplained decrease in liver weights was observed in female rats (Carpy et al. 1975). Clinical chemistry and histological examination revealed no hepatic effects in rats (Carpy et al. 1975; Hayes 1985), dogs (Hoffman et al. 1975), or mice (Hayes 1983) exposed to disulfoton in the diet for up to 2 years. In an intraperitoneal study, injection of rats, but not mice, rabbits, or guinea pigs, resulted in a dose-related increase in serum β-glucuronidase activity at

≥2 mg/kg, but no histopathological lesions in the liver (Kikuchi et al. 1981). In another intraperitoneal study, injection of rats with 1 mg/kg/day for 10 days resulted in cytoplasmic RNA in much smaller clumps in the periportal and centrilobular areas of the liver than in control rats (Clark and Stavinoha 1969). The results from these animal studies indicate that hepatic effects in humans exposed to disulfoton would be mild, if they occurred.

Renal Effects. Glomerular swelling was among the postmortem changes observed in a man who died after he drank an unknown amount of disulfoton (Hattori et al. 1982). However, most organs were congested at autopsy, suggesting that the renal pathology was one of the sequelae of death. Inconclusive evidence that disulfoton causes renal effects was found in animals. In one study, kidney weights of male rats increased while kidney weights of female rats decreased during a 2-year feeding study (Carpy et al. 1975). The toxicological significance of these opposite trends is not clear. Urinalysis and histological examination of kidneys from animals exposed to disulfoton in the diet for intermediate (Klotzsche 1972; Rivett et al. 1972) and chronic durations (Carpy et al. 1975; Hayes 1983, 1985; Hoffman et al. 1975), by inhalation for intermediate durations (Shiotsuka 1989; Thyssen 1980), or dermally for intermediate duration (Flucke 1986) revealed no renal effects. However, acute dermal exposure to unspecified doses of organophosphorus insecticides, including disulfoton, reportedly caused protein degeneration and significant circulatory disruptions in the kidneys of rats, cats, and rabbits (Kundiev and Rappoport 1967). As discussed in Section 2.2.3, this study is limited by reporting deficiencies. These animal studies suggest that the potential for renal effects is not a concern for humans exposed to disulfoton.

Endocrine Effects. No studies were located regarding endocrine effects in humans after exposure to disulfoton. No histopathological evidence of lesions in endocrine organs, such as adrenals, thyroids, pituitary, and pancreas, were found in animals exposed dermally (Flucke 1986) or by inhalation (Shiotsuka 1989; Thyssen 1980); however, female rats exposed to 3.1 and 3.7 mg/ m^3 in two separate intermediate-duration inhalation experiments had significantly increased absolute and relative adrenal weights (Thyssen 1980). Since the increase in adrenal weights was consistently observed in both experiments, it was considered to be related to disulfoton exposure. Oral and intraperitoneal exposure of animals to disulfoton has also resulted in increased urinary or plasma levels of adrenaline or noradrenaline or their metabolites, accompanied by decreases in adrenaline in the adrenal glands (Brzezinski 1969, 1972, 1973; Brzezinski and Ludwicki 1973; Brzezinski and Rusiecki 1970; Wysocka-Pamszewska 1970, 1971), indicating interference with catecholamine levels in body tissues.

These effects may be related to elevated acetylcholine levels, which may cause a release of catecholamines from the stores in the adrenals. Various scenarios involving human exposure to disulfoton might result in an increase in the amount of adrenaline released from the adrenals.

Histological examination of endocrine tissues in animals exposed orally to disulfoton for intermediate (Klotzsche 1972; Rivett et al. 1972) or chronic durations (Carpy et al. 1975; Hayes 1983, 1985; Hoffman et al. 1975) has generally shown no treatment-related lesions. However, male rats exposed chronically to the high dietary concentration had pancreatic atrophy (Hayes 1985). Increased pituitary weight in male rats and decreased pituitary weight in female rats were reported in another chronic feeding study (Carpy et al. 1975). The toxicological significance of these findings is unknown.

Dermal Effects. No studies were located regarding dermal effects in humans after exposure to disulfoton. Dermal lesions consisting of acanthosis, hyperkeratosis, ulceration of the skin, exudate formation, and epithelial inclusion cysts were found in male and female rats exposed chronically to the high dietary concentration of disulfoton (Hayes 1985). However, in intermediate-duration studies, histological examination of skin revealed no lesions in rats exposed by inhalation (Shiotsuka 1989), in rabbits exposed dermally (Flucke 1986), or in rats (Klotzsche 1972) or mice (Rivett et al. 1972) exposed in the diet for 90 days. In a chronic-duration study in rats (Carpy et al. 1975), mice (Hayes 1983), or dogs (Hoffman et al. 1975) exposed in the diet for up to 2 years, histological examination of the skin also revealed no lesions. Acute dermal exposure to unspecified doses of disulfoton appeared to have caused microscopic changes in the blood vessels and fibrous structures in the skin of rats, cats, and rabbits (Kundiev and Rappoport 1967). As discussed in Section 2.2.3, this study is limited by reporting deficiencies. Therefore, exposure to disulfoton in the workplace, in the environment, in drinking water or food, or at hazardous sites might cause dermal lesions in humans.

Ocular Effects. An epidemiological study suggests that the increased use of disulfoton in combination with other organophosphates to treat food crops may have increased the incidence of myopia in children (Ishikawa and Miyata 1980). To determine whether the myopia was associated with disulfoton exposure specifically, dogs were given disulfoton orally for 2 years. Myopia, astigmatism, and associated degenerative changes in the ciliary muscle (see Musculoskeletal Effects above) were observed (Ishikawa and Miyata 1980; Suzuki and Ishikawa 1974). The dog studies support the evidence for disulfoton-induced myopia in humans. Although other factors may have contributed to the occurrence of myopia, histopathological changes in the ciliary muscle of the dogs suggest a strong

cause and effect relationship. Cystic degeneration of the Harderian gland and comeal neovascularization were observed in rats exposed chronically to disulfoton in the diet (Hayes 1985). However, in other studies, histological or ophthalmological examination of the eyes revealed no lesions in rats (Klotzsche 1972) or mice (Rivett et al. 1972) exposed in the diet for 90 days, or in rats (Carpy et al. 1975), mice (Hayes 1983), or dogs (Hoffman et al. 1975) exposed in the diet for up to 2 years. The rats in the study by Carpy et al. (1975) received lower doses than the rats in the Hayes (1985) study. The possibility that myopia or other ocular effects may occur in humans exposed to disulfoton cannot be ruled out.

Body Weight Effects. Weight loss or decreased body weight gain were commonly observed in animals exposed to disulfoton for acute and intermediate durations (Costa et al. 1984, 1986; Fitzgerald and Costa 1992, 1993; Robinson et al. 1978; Schwab and Murphy 1981; Schwab et al. 1981, 1983; Stavinoha et al. 1969; Thyssen 1980). This decrease in weight gain is consistent with disulfoton neurological toxicosis since cholinergic signs (e.g., nausea, emesis, or diarrhea) will reduce food ingestion, absorption, and assimilation. Like the other overt signs of disulfoton toxicosis (see Neurological Effects below), the weight loss is usually transient. In a chronic feeding study, an 11-19s depression of body weight gain occurred in the rats exposed to the high concentration of disulfoton (Hayes 1985). The decrease in body weight gain was partially due to decreased food consumption, which was probably related to the general debilitation of the high dose rats. Intraperitoneal studies also have reported weight loss in animals injected with disulfoton (Costa and Murphy 1982; Costa et al. 1981; McDonald et al. 1988). Based on the results from animal studies, weight loss in humans following moderate to severe disulfoton exposure is possible.

Immunological and Lymphoreticular Effects. No studies were located regarding immunological effects in humans after exposure to disulfoton. However, down-regulation of cholinergic muscarinic receptors in T-lymphocytes and significantly inhibited acetylcholinesterase activity in T-lymphocytes were found in rats given 2 mg/kg/day disulfoton orally for l-2 weeks (Fitzgerald and Costa 1993). The inhibition of T-lymphocyte acetylcholinesterase activity paralleled that in the brain. Similar results were found in rats injected intraperitoneally with 2 mg/kg/day disulfoton for 2 weeks (Costa et al. 1990). The immunological significance of these neurological effects (see Section 2.2.2.4) is not known. Inflammatory changes throughout the respiratory tract, associated with bone marrow changes and low percentages of lymphocytes and high percentages of polymorphonuclear leukocytes in the differential leukocyte counts, were observed in rats exposed to

disulfoton by inhalation for intermediate duration (Thyssen 1980). Female rats exposed by inhalation to a high concentration in this study also had decreased spleen weights (Thyssen 1980), and rats given the high concentration of disulfoton in the diet for 2 years had a significantly increased incidence of plasma cell hyperplasia in the mandibular lymph nodes (males) and a significantly increased incidence of splenic lymphoid follicle depletion (females) (Hayes 1985). The plasma cell hyperplasia in the mandibular lymph nodes was probably a response to upper respiratory tract inflammation, which may have been due to aspiration of ingested food particles. In other inhalation (Shiotsuka 1989), dietary (Carpy et al. 1975; Hayes 1983; Hoffman et al. 1975; Klotzsche 1972; Rivett et al. 1972), and dermal (Flucke 1986) studies in animals exposed to disulfoton, histological examination of spleen, thymus, lymph nodes,‘and bone marrow revealed no treatment-related lesions. The relevance of the various lymphoreticular and possible immunological effects to humans exposed to disulfoton is not clear.

Neurological Effects. The neurological effects of disulfoton depend on its metabolism to active metabolites which, in turn, inhibit acetylcholinesterase activity at nerve synapses. Inhibition of acetylcholinesterase activity results in excessive accumulation of acetylcholine which, in turn, stimulates muscarinic cholinergic receptors located in various organ tissues. The response of these effector organs to overstimulation is recognized as a neurological effect, and the severity will depend on such factors as dose, sex, species, and age of the human or animal exposed. Despite mild depression of erythrocyte cholinesterase activity, neurological effects were not observed in pesticide-fertilizer mixers after inhalation exposure to 0.46-0.633 mg/ m^3 disulfoton and dermal exposure to 0.23 mg/kg/day disulfoton (Wolfe et al. 1978). One case of accidental ingestion of disulfoton resulted in cholinergic signs including miosis, salivation, masseteric spasms, monoplegia, and depressed serum cholinesterase activity (Yashiki et al. 1990). Weakness, fatigue, and cyanosis were observed in a farmer who, for several days, had worn gloves that were soaked in disulfoton (Savage et al. 1971).

Neurological effects observed in humans have also been demonstrated in animals after acute and intermediate oral exposure (Costa et al. 1984; Crawford and Anderson 1974; Mihail 1978; Schwab and Murphy 1981; Schwab et al. 1981, 1983; Sheets 1993a, 1993b), acute and intermediate inhalation exposure (Doull 1957; Shiotsuka 1989; Thyssen 1978, 1980), and acute dermal exposure (Flucke 1986; Mihail 1978) to disulfoton. Inhibition of brain acetylcholinesterase and other tissue acetylcholinesterase activities (Carpy et al. 1975; Christenson and Wahle 1993; Clark and Pearson 1973; Doull and Vaughn 1958; Flucke 1986; Hayes 1983, 1985; Hikita et al. 1973; Hixson and Hathaway 1986; Hoffman et al. 1975; Klotzsche 1972; Robinson et al. 1970, 1978; Schwab and

Murphy 1981; Schwab et al. 1981; Sheets 1993a, 1993b; Shiotsuka 1989; Thyssen 1978, 1980) also have been observed in animals in numerous studies regardless of the route, duration, or animal species. Female animals appear to be more sensitive than males to the cholinergic effects of disulfoton. Chronic oral exposure of animals to disulfoton has resulted in necrosis and atrophy of the optic nerve and retina (Hayes 1983; Uga et al. 1977) and unexplained changes in brain weight (Carpy et al. 1975). A 2-month dietary study in rats and mice found that disulfoton exposure increased the permeability of spinal cord and brain stem tissues (Clark and Stavinoha 1971).

Limited evidence indicates that disulfoton does not cause organophosphate-induced delayed neurotoxicity in chickens. This syndrome is caused by some phosphate, phosphonate, and phosphoramidate esters, which are not usually used as insecticides (Ecobichon 1990). Axonal degeneration followed by myelin degeneration in nerve fibers distal to the nerve cell body are common histopathological findings in hens with organophosphate-induced delayed neurotoxicity. However, oral doses of 0, 0.1, 0.6, or 1.5 mg/kg disulfoton for 30 days did not cause demyelination in White Leghorn hens (Taylor 1965b). Furthermore, White Leghorn hens given two 30 mg/kg oral doses of disulfoton 21 days apart displayed no signs of delayed neurotoxicity (Hixson 1983). While clinical signs of cholinergic intoxication (loss of equilibrium, decreased activity, diarrhea, and locomotor ataxia) were observed on the first treatment day, these signs disappeared within 5 days of treatment. Histological examination of the sciatic nerve, spinal cord, and brain revealed no treatment-related lesions. It should be noted that the disulfoton-treated hens in the Hixson (1983) study were also treated with 0.5 mg/kg atropine intramuscularly 10 minutes prior to disulfoton and with 12.5 mg/kg pralidoxime chloride (2-PAM) intramuscularly 30 minutes after disulfoton. These antidotes were given to prevent lethality, but 2-PAM also reverses cholinesterase inhibition, and atropine blocks the muscarinic and central nervous system toxicity (see Section 2.8.3). Therefore, the administration of these antidotes may have confounded the conclusion that disulfoton does not cause delayed neurotoxicity.

Numerous studies indicate that animals develop a tolerance to the cholinergic effects of disulfoton after a few days of oral exposure (Costa et al. 1981; Fitzgerald and Costa 1992, 1993; Schwab and Murphy 1981; Schwab et al. 1981, 1983). Animals exposed to disulfoton initially developed cholinergic signs of toxicity, but with subsequent dosing (5-10 days) these signs almost disappeared, even though cholinesterase activity remained depressed. Inhibition of brain, erythrocyte, or other tissue cholinesterase, and typical signs of cholinergic poisoning have also been reported in numerous studies

in which animals received intraperitoneal injections of disulfoton (Bombinski and DuBois 1958; Brodeur and DuBois 1963, 1964; Costa and Murphy 1982, 1983a, 1986; Costa et al. 1981, 1982a, 1986, 1990; Foley and McPhillips 1973; LeFever and Green 1975; Llorens et al. 1993; McDonald et al. 1988; McPhillips 1969a; McPhillips and Dar 1967; Perrine and McPhillips 1970; Schwab et al. 1981; Smith et al. 1968; Stavinoha et al. 1969; Westfall et al. 1974).

Animal studies suggest that disulfoton causes neurobehavioral changes; however, most of these changes do not appear to be adverse. Unexpected faster maze running times and fewer errors were made by rats fed disulfoton for 90 days, despite a significant depression in brain cholinesterase (Clark and Pearson 1973). Furthermore, an unexpected increase in exploratory behavior was observed in mice fed disulfoton (Clark et al. 1971). Disulfoton did not result in impaired memory (assessed by shock treatment sensitivity and passive avoidance retention) in mice made tolerant by intraperitoneal injections of disulfoton for 14 days (Costa and Murphy 1982). However, McDonald et al. (1988) hypothesized that a decrease in muscarinic receptor densities in brain tissues of disulfoton-tolerant rats was the reason for the observed impairment of spatial memory after intraperitoneal injection with disulfoton for 14 days. In rats given daily intraperitoneal injections of disulfoton for 30 days, reduced motor activity occurred at 2.0 mg/kg/day, but tolerance to this effect did not develop (Llorens et al. 1993). Disulfoton had no effect on acquisition or retention of passive avoidance, but impaired performance in a spatial memory water maze occurred at 2.0 mg/kg/day. This deficit in cognitive performance occurred at a time when tolerance to overt signs of cholinergic toxicity developed.

Data from the few available case reports and the numerous animal studies strongly suggest that disulfoton exposure may cause mild to severe neurological effects in humans. Although disulfoton-associated memory loss has not been reported in humans, there should be concern that occupational exposure and exposure at hazardous waste sites may interfere with the performance of cognitive and complex tasks.

Reproductive Effects. No studies were located regarding reproductive effects in humans after exposure to disulfoton. No effect on male fertility was found in mice treated orally in a dominant lethal study (Herbold 1980). A 3-generation study demonstrated that a disulfoton diet providing 0.5 mg/kg/day resulted in slightly reduced litter sizes in the third generation of rats (Taylor 1965a). In a study where males or females were fed disulfoton prior to and/or during mating, the failure of two of five females to become pregnant indicated that reproductive function in males as well as females may

have been severely affected (Ryan et al. 1970). A more extensive multigeneration feeding study in rats found decreased reproductive performance, evidenced by a decreased percentage of females placed for mating and decreased percentage of sperm-positive F_0, and F_1 parental females, decreased maternal weight of F_0 and F_1 dams during gestation and lactation, decreased litter counts, decreased viability and lactation indices, increased dead births and percentage of dead births in both generations, and decreases in F_{2b} litter counts and litter weights (Hixson and Hathaway 1986). Histological examination of male and female reproductive organs generally did not reveal any treatment-related lesions in rats (Carpy et al. 1975; Hayes 1985; Klotzsche 1972; Shiotsuka 1989; Thyssen 1980), mice (Hayes 1983; Rivett et al. 1972), dogs (Hoffman et al. 1975), or rabbits (Flucke 1986) exposed to disulfoton by any route. The only exception was uterine cystic hyperplasia in female rats fed the high dietary concentration of disulfoton for 2 years (Hayes 1985). Reproductive function was not assessed in these studies. Based on the reproductive studies in animals, the possibility for reproductive effects in humans exposed to disulfoton cannot be ruled out.

Developmental Effects. No studies were located regarding developmental effects in humans after exposure to disulfoton. Incomplete ossification of the parietal bones and the stemebrae, but no tissue malformations were observed in the offspring of rats fed disulfoton during gestation (Lamb and Hixson 1983). Erythrocyte acetylcholinesterase depression, cloudy swelling and fatty infiltration of the liver, mild nephropathy, and juvenile hypoplasia of the testes were found in F_{3b} litters in a threegeneration feeding study (Taylor 1965a). Brain cholinesterase depression was also observed in the fetuses of rat dams fed disulfoton (Ryan et al. 1970) and in the F_{1a} pups of male and female rats in a dietary reproduction study (Hixson and Hathaway 1986). Intraperitoneal injection of pregnant mice with disulfoton on gestation day 11 resulted in 71.4% fetal mortality and decreased litter size (Uzokwu 1974). No malformations were seen. Nevertheless, rabbit fetal survival, growth, and development was not affected by oral exposure of the dams to disulfoton during gestation (Tesh et al. 1982). Based on the animal data, the potential for disulfoton to cause fetotoxic and developmental effects in humans cannot be ruled out.

Genotoxic Effects. No studies were located regarding genotoxicity of disulfoton in humans after inhalation, oral, or dermal exposure or in animals after inhalation or dermal exposure. The results of in viva studies are summarized in Table 2-4. Disulfoton did not induce micronuclei in the erythrocytes of mice treated orally at 6 or 12 mg/kg/day for 2 days (Herbold 1981) or orally or intraperitoneally at 2, 4, or 8 mg/kg disulfoton (EPA 1984a; Sandhu et al. 1985). Disulfoton was also negative in a

TABLE 2-4. Genotoxicity of Disulfoton *In Vivo*

Species (test system)	End point	Results	Reference
Drosophila melanogaster	Sex-linked recessive lethal	–	EPA 1981a; Sandhu et al. 1985; Waters et al. 1981, 1982
Mouse (intraperitoneal or oral, not otherwise specified)	Induction of micronuclei	–	EPA 1984a; Sandhu et al. 1985; Waters et al. 1981, 1982
Mouse (oral)	Induction of micronuclei in bone marrow polychromatic erythrocytes	–	Herbold 1981
Mouse (oral	Dominant lethal	–	Herbold 1980

– = negative result

dominant lethal test in mice given a single oral dose of 5 mg/kg (Herbold 1980). Furthermore, disulfoton did not induce sex-linked recessive lethal mutations in *Drosophila melunogaster* (EPA 1981a; Sandhu et al. 1985; Waters et al. 1981, 1982).

Disulfoton has been tested in numerous types of *in vitro* assays, mainly with negative results (see Table 2-5). Disulfoton was negative in most assays for reverse mutation in most strains of *Salmonella typhimurium* with or without metabolic activation (EPA 1980a; Inukai and Iyatomi 1976; Moriya et al. 1983; Sandhu et al. 1985; Waters et al. 1981, 1982); but positive results were obtained in LT-2 strains (Hanna and Dyer 1975) and in one assay with strain TA1535 (Moriya et al. 1983; Shirasu et al. 1982, 1984) of *S. typhimurium* without activation. Results of reverse mutation assays in *Escherichia coli* were equivocal; positive results without activation in WP2 strains were reported in one study (Hanna and Dyer 1975), but negative results in WP2 uvrA with and without activation were found in another study (EPA 1980a, 1984a; Sandhu et al. 1985; Waters et al. 1981, 1982). Disulfoton was negative in assays of differential toxicity in *S. typhimurium, E. coli,* and *Bacillus subtilis* with or without activation (EPA 1980a; Herbold 1983; Inukai and Iyatomi 1976; Sandhu et al. 1985; Waters et al. 1981, 1982). Negative results were obtained in assays for reverse mutation, gene conversion, mitotic crossing over and recombinants, and for primary DNA damage in eukaryotic yeast, *Succhuromyces cerevisiue,* with and without activation (Brusick 1981; EPA 1984a; Jagannath 1981; Sandhu et al. 1985; Waters et al. 1981, 1982). However, positive results without activation were obtained in assays for chiasma frequency (genetic recombinants), mitotic index, chromosomal aberrations, and pollen fertility in barley *(Hordeurn vulgaris)* (Murty et al. 1983; Panda 1983; Singh et al. 1977). Some positive and some negative results have been obtained in cultured mammalian cells. Positive or weakly positive results were obtained for sister chromatid exchanges in Chinese hamster ovary cells with metabolic activation in two assays (EPA 1984a; Sandhu et al. 1985; Waters et al. 1981, 1982), but negative results were found in another study (Chen et al. 1981, 1982). Conversely, disulfoton induced sister chromatid exchanges in Chinese hamster ovary cells without metabolic activation, but not with metabolic activation, in another study (Putnam 1987). Disulfoton was negative for HGPRT mutations in Chinese hamster ovary cells with and without activation (Yang 1988). Positive results without activation were obtained for forward mutations in mouse lymphoma cells, for unscheduled DNA synthesis in human lung fibroblasts (EPA 1984a; Sandhu et al. 1985; Waters et al. 1981, 1982), and for growth inhibition and increased protein synthesis in human HeLa cells (Litterst et al. 1969). However, negative results were found for chromosomal aberrations in human hematopoietic cell lines (Huang 1973) and for alterations of DNA or RNA synthesis in human HeLa cells (Litterst et al. 1969).

TABLE 2-5. Genotoxicity of Disulfoton *In Vitro*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium LT-2 strains	Reverse mutation	No data	+	Hanna and Dyer 1975
S. typhimurium TA1535	Reverse mutation	No data	+	Moriya et al. 1983; Shirasu et al. 1982, 1984
S. typhimurium	Reverse mutation			Moriya et al. 1983
WP2hcr		No data	–	
TA100		No data	–	
TA1537		No data	–	
TA1538		No data	–	
TA98		No data	–	
S. typhimurium TA100	Reverse mutation	–	–	Sandhu et al. 1985
S. typhimurium	Reverse mutation			EPA 1980, 1984a; Waters et al. 1981, 1982
TA1535		–	–	
TA1537		–	–	
TA1538		–	–	
TA98		–	–	
TA100		–	–	
S. typhimurium	Reverse mutation			Inukai and Iyatomi 1976
TA1535		–	–	
TA1537		–	–	
TA98		–	–	
TA100		–	–	
S. typhimurium SL4525(rec$^+$)/ SL4700(rec$^-$)	Differential toxicity	No data	–	EPA 1984a; Waters et al. 1981, 1982
Escherichia coli WP2 strains	Reverse mutation	No data	+	Hanna and Dyer 1975

TABLE 2-5. Genotoxicity of Disulfoton *In Vitro* (continued)

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium LT-2 strains	Reverse mutation	No data	+	Hanna and Dyer 1975
E. coli WP2 uvrA	Reverse mutation	–	–	EPA 1980, 1984a; Sandhu et al. 1985; Waters et al. 1981, 1982
E. coli W3110/p3478	Differential toxicity	–	–	Herbold 1983
E. Coli W3110/p3478	Differential toxicity	No data	–	EPA 1980
Bacillus subtilis H17/MW5	Differential toxicity	No data	–	EPA 1980
B. subtilis NIG17/NIG45	Differential toxicity	No data	–	Inukai and Iyatomi 1976
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae D7	Reverse mutation	–	–	EPA 1984a; Sandhu et al. 1985; Waters et al. 1981, 1982
S. cerevisiae	Reverse mutation			
S138		–	–	Jagannath 1981
S211		–	–	
S. cerevisiae D7	Gene conversion and mitotic crossing-over	–	–	Sandhu et al. 1985; Waters et al. 1981, 1982
S. cerevisiae D3	Induction of mitiotic recombinants	–	–	EPA 1980; Sandhu et al. 1985
S. cerevisiae D3	Primary DNA damage	No data	–	Waters et al. 1981, 1982
S. cerevisiae D6	Mitotic non-disjunction	–	–	Brusick 1981

TABLE 2-5. Genotoxicity of Disulfoton *In Vitro* (continued)

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium LT-2 strains	Reverse mutation	No data	+	Hanna and Dyer 1975
Plants:				
Barley (*Hordeum vulgare*) seeds	Chiasma frequency (genetic recombinants)	No data	+	Murty et al. 1983
Barley (*H. vulgare*) seeds	Mitotic index	No data	+	Panda 1983
	Chromosomal aberrations in embryonic shoots and pollen mother cells	No data	+	Panda 1983
Barley (*H. vulgare*) seeds	Pollen fertility	No data	+	Singh et al. 1977
Barley (*H. vulgare*) seeds	Chromosomal aberrations	No data	+	Singh et al. 1977
Mammalian cells:				
Chinese hamster ovary cells	HGPRT mutation	–	–	Yang 1988
Chinese hamster ovary cells	Sister chromatid exchange	(+)	–	Sandhu et al. 1985
Chinese hamster ovary cells V79	Sister chromatid exchange	–	–	Chen et al. 1981, 1982
Chinese hamster ovary cells	Sister chromatid exchange	+	–	EPA 1984a; Waters et al. 1981, 1982
Chinese hamster ovary cells	Sister chromatid exchange	–	+	Putnam 1987
Mouse lymphoma cells L517874	Forward mutation	–	+	EPA 1984a; Sandhu et al. 1985
Mouse lumphoma cells L5T	Forward mutation	No data	+	Waters et al. 1981, 1982

TABLE 2-5. Genotoxicity of Disulfoton *In Vitro* (continued)

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium LT-2 strains	Reverse mutation	No data	+	Hanna and Dyer 1975
Human lung fibroblasts WI-38 cells	Unscheduled DNA synthesis	–	+	EPA 1980a, 1984a; Sandhu et al. 1985
Human hematopoietic cell lines	Chromosomal aberrations			Huang 1973
B411–4		No data	–	
RPMI–1788		No data	–	
RPMI–7191		No data	–	
Human HeLa cells	Growth inhibition	No data	+	Litterst et al. 1969
Human HeLa cells	DNA synthesis	No data	–	Litterst et al. 1969
Human HeLa cells	RNA synthesis	No data	–	Litterst et al. 1969
Human HeLa cells	Protein synthesis	No data	+	Litterst et al. 1969

DNA = Deoxyribonucleic acid; HGPRT = hypoxanthine–guanine phosphoribosyl transferase; RNA = Ribonucleic acid; – = negative result; + = positive result; (+) = weakly positive result

While many of the studies on genotoxicity of disulfoton were negative, the positive results indicate a potential for mutagenic and clastogenic effects in humans exposed to disulfoton.

Cancer. No studies were located regarding cancer in humans after exposure to disulfoton. Carcinogenic effects were not observed in rats (Carpy et al. 1975; Hayes 1985), mice (Hayes 1983), or dogs (Hoffman et al. 1975) fed disulfoton for 1.5-2.0 years. There is no reason to believe that disulfoton is carcinogenic.

2.5 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).

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 disulfoton are discussed in Section 2.5.1. 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 (NAUNRC 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 disulfoton are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism3s 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 2.7, Populations That Are Unusually Susceptible.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Disulfoton

Disulfoton and its metabolites have been measured in various tissues and body fluids (blood, urine, feces, liver, kidney, and body fat) from humans or animals exposed to disulfoton (Brokopp et al. 1981; Hattori et al. 1982; Puhl and Fredrickson 1975; Yashiki et al. 1990). Because disulfoton is quickly metabolized, it is rarely detected in the blood or plasma of exposed individuals, but detection of the insecticide in blood provides conclusive evidence of previous exposure. At ≈2-3 hours after a man accidentally ingested disulfoton, 0.093 nmol/g (4.92 ng/g) of disulfoton and 4.92 nmol/g of total metabolites were detected in his blood (Yashiki et al. 1990). In another study, 1.45 nmol/g of disulfoton was detected in the blood of a man found dead at least 24 hours after he had ingested disulfoton (Hattori et al. 1982). In both cases, the original dose was unknown; therefore, a correlation between disulfoton exposure and blood concentration cannot be made.

The presence of disulfoton and/or its metabolites in the liver appears to be a sensitive indicator of disulfoton exposure, despite the limited data. Supporting evidence from animal studies indicates that disulfoton exposure will result in detectable levels in the liver (Bull 1965; Puhl and Fredrickson 1975). However, monitoring of liver levels would require biopsy, which is not practical.

The presence of disulfoton and/or its metabolites in urine is usually a reliable biomarker of disulfoton exposure. Specimens of urine collected from 64 locations across the United States, comprising the sample areas of the Second Health and Nutrition Examination Survey (NHANES II), reported detection (detection limit 0.02 ppm) of DEP and DETP at a frequency of 6-7% and DEDPT at a frequency of <1% of those tested (Murphy et al. 1983). Although no human data were located on the

relationship between the concentration of urinary metabolites and the exposure dose, data from several animal studies demonstrate that 28.6-98% of the dose was accounted for in the urine 2-10 days postexposure (Bull 1965; Lee et al. 1985; Puhl and Fredrickson 1975). An unknown amount of disulfoton sulfoxide and/or demeton S-sulfone was detected in the urine from a person exposed to an unknown amount of disulfoton (Yashiki et al. 1990). Results from a human occupational study of pesticide formulators who had worked with disulfoton for 25 weeks showed that the metabolites DEP (0.01-4.4 ppm), DETP (0.01-1.57), DEDPT (<0.01-0.05 ppm), and DEPTh (<0.01-0.55 ppm) were detected in the urine (Brokopp et al. 1981). The mean preformulation urinary levels were 0.05 ppm DEP, 0.04 ppm DETP, 0.01 ppm DEDPT, and 0.008 ppm DEPTh. Threshold levels of these metabolites, defined as two standard deviations above the mean, were 0.13 ppm DEP, 0.12 ppm DETP, 0.06 ppm DEDPT, and 0.06 ppm DEPTh. Although the excretion of DEP varied considerably among the individuals, this metabolite was more commonly detected above the threshold level among these employees. The dialkyl phosphate metabolites are not only very sensitive indicators of disulfoton exposure, but their presence strongly suggests previous exposure to a diethyl organophosphate ester. One animal study demonstrated that a greater percentage of the disulfoton dose was eliminated as DEP (Bull 1965). This provides limited but supporting evidence that DEP is a more sensitive urinary biomarker than the other metabolites discussed.

A combination of neurological signs is usually a biomarker of organophosphate exposure. Neurological signs such as pupil miosis, muscular tremors, and increased salivation have been observed in humans accidentally exposed to disulfoton (Yashiki et al. 1990) and in animals given disulfoton (Schwab et al. 1981).

Inhibition of erythrocyte acetylcholinesterase activity or serum cholinesterase activity with or without concomitant neurological signs is usually a good indicator of organophosphate exposure. In addition, T-lymphocyte acetylcholinesterase activity was found to be rapidly and greatly depressed in rats during a 14-day daily exposure to disulfoton, but rapidly recovered after exposure (Fitzgerald and Costa 1993). Therefore, T-lymphocyte acetylcholinesterase activity could be used as a biomarker of exposure to organophosphorus pesticides during exposure, but not once exposure has ceased. The acetylcholinesterase activity recovered more slowly in erythrocytes than in lymphocytes, indicating the erythrocyte activity is a better biomarker of exposure once exposure has ceased. However, the severity of the signs and symptoms and the degree of cholinesterase depression are not always correlated. Standards for serum cholinesterase activity (175-440 IU) have been established for humans (Yashiki et

al. 1990), but there is a wide normal range due to the variation in the human population. A man had depressed blood cholinesterase activity (<10 IU for 5 days and <40 IU for 8 days after exposure) as well as cholinergic signs of toxicity following accidental ingestion of disulfoton (Yashiki et al. 1990). As demonstrated in this case, cholinesterase activity can remain depressed for at least a week after neurological signs have disappeared; therefore, other parameters (e.g., urine metabolites) may help with the diagnosis. Cholinesterase depression was not observed in 11 employees exposed to disulfoton for ≤2.5 weeks (Brokopp et al. 1981). The presence of urinary metabolites of disulfoton was the only biomarker of disulfoton exposure. Employees occupationally exposed to disulfoton for 9 weeks had marked depression of the erythrocyte acetylcholinesterase activity, but no neurological signs (Wolfe et al. 1978). Urinary metabolites were not reported; therefore, cholinesterase depression was the only biomarker of exposure. Because organophosphates other than disulfoton and carbamates can depress cholinesterase activity (Osweiler et al. 198.5) cholinesterase activity is not specific for disulfoton exposure. Furthermore, liver dysfunction, pregnancy, malnutrition, neoplasia, infection, and certain drugs such as codeine and morphine may lower plasma pseudocholinesterase activity, while hemoglobinopathies such as sickle cell disease and thalassemia and other anemias may lower erythrocyte cholinesterase activity (Goldfrank et al. 1990).

Urine catecholamines may also serve as biomarkers of disulfoton exposure. No human data are available to support this, but limited animal data provide some evidence of this. Disulfoton exposure caused a 173% and 313% increase in urinary noradrenaline and adrenaline levels in female rats, respectively, within 72 hours of exposure (Brzezinski 1969). The major metabolite of catecholamine metabolism, HMMA, was also detected in the urine from rats given acute doses of disulfoton (Wysocka-Paruszewska 1971). Because organophosphates other than disulfoton can cause an accumulation of acetylcholine at nerve synapses, these chemical compounds may also cause a release of catecholamines from the adrenals and the nervous system. In addition, increased blood and urine catecholamines can be associated with overstimulation of the adrenal medulla and/or the sympathetic neurons by excitement/stress or sympathomimetic drugs, and other chemical compounds such as reserpine, carbon tetrachloride, carbon disulfide, DDT, and monoamine oxidase inhibitors (MAO) inhibitors (Brzezinski 1969). For these reasons, a change in catecholamine levels is not a specific indicator of disulfoton exposure.

Disulfoton induced the liver MFO system in animals (Stevens et al. 1973). In the same study, exposure to disulfoton orally for 3 days also increased ethylmorphine N-demethylase and NADPH

oxidase activities, but had no effect on NADPH cytochrome c reductase. Thus, the induction of the MFO system required repeated dosing with relatively high doses. Furthermore, these changes are not specific for disulfoton exposure, and these subtle liver effects require invasive techniques in humans to obtain liver tissue for performance of these enzyme assays.

2.5.2 Biomarkers Used to Characterize Effects Caused by Disulfoton

Disulfoton exposure results in cholinergic signs such as salivation, diarrhea, pupil constriction, muscle tremors, and weight loss. Ataxia, convulsions, coma, respiratory distress, and death are common signs associated with a more severe toxicosis. Nervous tissue is evidently the most sensitive target organ.

Because cholinesterase inhibition is a very sensitive biomarker for other chemicals, it is not always conclusive evidence of disulfoton exposure. However, depression of cholinesterase activity can alert a physician to the possibility of more serious neurological effects. Erythrocyte acetylcholinesterase activity more accurately reflects the degree of synaptic cholinesterase inhibition in nervous tissue, while serum cholinesterase activity may be associated with other sites (Goldfrank et al. 1990). In addition, a recent study showed that after rats received oral doses of disulfoton for 14 days, acetylcholinesterase levels in circulating lymphocytes correlated better with brain acetylcholinesterase activity than did erythrocyte cell cholinesterase activities during exposure (Fitzgerald and Costa 1993). However, recovery of the activity in lymphocytes was faster than the recovery of activity in the brain, which correlated better with the activity in erythrocytes. Animal studies have also demonstrated that brain acetylcholinesterase depression is a sensitive indicator of neurological effects (Carpy et al. 1975; Costa et al. 1984; Schwab and Murphy 1981; Schwab et al. 1981, 1983); however, the measurement of brain acetylcholinesterase in humans is too invasive to be practical.

Serum β-glucuronidase activity was increased in a dose-related manner when disulfoton was given intraperitoneally to rats (Kikuchi et al. 1981). In the same study, this effect was not observed in mice, rabbits, or guinea pigs. This enzyme appears to be a useful biomarker of hepatic function in rats exposed to disulfoton, but may not be a useful biomarker in humans.

Increased levels of urinary catecholamines may also be associated with accumulation of acetylcholine that resulted from acetylcholinesterase inhibition by disulfoton. No human data were located to support this, but limited animal data provide some evidence. Disulfoton exposure caused a 173% and

313% increase in urinary noradrenaline and adrenaline levels in rats, respectively, within 72 hours (Brzezinski 1969). The major metabolite of catecholamine metabolism, HMMA, was also detected in the urine from rats given acute doses of disulfoton (Wysocka-Paruszewska 1971).

Additional information regarding biomarkers for effects can be found in OTA (1990) and CDC/ATSDR (1990). A more detailed discussion of the health effects caused by disulfoton can be found in Section 2.2 of Chapter 2.

2.6 INTERACTIONS WITH OTHER SUBSTANCES

Disulfoton can function as an inhibitor of MFO when given in one or two doses and can potentiate the toxicity of similarly related compounds. Disulfoton exhibits Type I binding, that is, binding to the oxidized form of cytochrome P-450, and when given as a single dose, competitively inhibits the metabolism of other Type I substrates (Stevens et al. 1973). However, it was also reported that disulfoton was a noncompetitive inhibitor of rat and mouse ethylmorphine N-demethylase (Stevens and Green 1974; Stevens et al. 1972a). When given as a single dose, disulfoton also appears to inhibit NADPH cytochrome c reductase (Stevens et al. 1973). Disulfoton was reported to inhibit hexobarbital metabolism, thereby prolonging hexobarbital sleeping time in mice (Stevens et al. 1972a). This effect was not due to inhibition of cholinesterase nor was it due to an altered sensitivity of the brain to barbiturates, but it was associated with inhibition of hepatic MFO metabolism. These investigators also determined that disulfoton depressed microsomal metabolism of aniline as well as ethylmorphine in the mouse. A significant decrease in N-demethylase activity of aminopyrine and hydroxylase activity of acetanilide was observed in animals pretreated orally with disulfoton for 2 successive days, compared to the control group (Fawade and Pawar 1978). Disulfoton also caused decreased levels of cytochrome P-450 and cytochrome b, and an increase in NADPH-linked and ascorbate-promoted lipid peroxidation.

In contrast to the inhibitory effects of acute exposure, repeated dosing with disulfoton induces the cytochrome P-450 MFO system (Stevens et al. 1973). Disulfoton (1/2 LD_{50}) given orally to mice for 3 days resulted in increased activities of ethylmorphine N-demethylase and NADPH oxidase activities, but not the activity of NADPH cytochrome c reductase, the rate of reduction of cytochrome P-450, or the content of cytochrome P-450. The 5-day treatment regimen resulted in increased activities of ethylmorphine N-demethylase and NADPH oxidase activities, as well as increased cytochrome P-450

content. Apparently, the duration of exposure determines the effect of disulfoton on the various components of the MFO system. In another study, treatment of mice orally with disulfoton (1/2 LD_{50}) for 5 days followed by administration of hexobarbital resulted in an increase in hexobarbital hydroxylase activity (Stevens et al. 1972b). Therefore, disulfoton-treated mice had shorter hexobarbital sleeping times. Microsomes from disulfoton-treated mice also had increased activity of aniline hydroxylase when aniline was added to the incubation mixture. Lower doses of disulfoton for similar time periods of exposure did not result in significant hepatic enzyme induction. The results from these studies suggest that depending on the duration of exposure, disulfoton may increase or decrease the severity of toxicity associated with chemicals that are similarly metabolized.

The toxicity of disulfoton may be altered by pretreatment with inducers or inhibitors of the hepatic microsomal drug metabolizing system. Phenobarbital causes enzyme repression of flavin-containing monooxygenase, but it also causes induction of cytochrome P-450 activity (Sipes and Gandolfi 1986). Therefore, pretreatment with phenobarbital will not result in flavin monooxygenase-mediated activation of disulfoton to its active metabolite. Cytochrome P-450 can activate disulfoton to its toxic metabolites as well as detoxify disulfoton by oxidative dearylation and dealkylation to less toxic metabolites (Ecobichon 1990). However, pretreatment with phenobarbital induced cytochrome P-450 enzymes that functioned more as detoxification enzymes than as activation enzymes (DuBois and Kinoshita 1968; Pawar and Fawade 1978). Although phenobarbital affects both enzyme systems differently, the net result is protection from the toxicity of disulfoton. One hundred percent protection against the toxicity of disulfoton was achieved both in mice and rats pretreated with phenobarbital and then given disulfoton orally at the LD_{85} dose level (Pawar and Fawade 1978). Pretreatment with another enzyme inducer, 3-methylcholanthrene, resulted in only 73% protection against disulfoton toxicity in both rats and mice. The authors proposed that the different levels of protection were due to the induction of two different interconvertible forms of cytochrome P-450. Rats pretreated with phenobarbital were less susceptible to the toxicity of disulfoton (DuBois and Kinoshita 1968). In this study, the LD_{50} value for the pretreated group (16.3 mg/kg) was greater than that for the control group (6.7 mg/kg), suggesting that phenobarbital pretreatment reduced the toxic effects of disulfoton by way of hepatic microsomal enzyme induction. A 3-day phenobarbital pretreatment also resulted in increased microsomal protein content and increased aminopyrine N-demethylase activity, but decreased acetanilide hydroxylase activity, in mice given disulfoton for 3 more days (Fawade and Pawar 1980).

Pretreatment with the Type I substrate, ethylmorphine, resulted in 100% mortality in both rats and mice, and aminopyrine pretreatment resulted in 100% and 64% mortality in rats and mice, respectively, exposed to disulfoton (Pawar and Fawade 1978). Nickel chloride, cobalt chloride, or cycloheximide decreased the levels of cytochrome b,, cytochrome c reductase, and total heme in rats (Fawade and Pawar 1983). These electron transport components were further decreased in rats pretreated with these inhibitors and given a single dose of disulfoton. Data from this study suggests an additive effect, since disulfoton also decreases the activities of these components. Evidence of an additive effect between disulfoton and these metabolic inhibitors was suggested by the decrease in ethylmorphine N-demethylase and acetanilide hydroxylase activities when rats were given an inhibitor followed by disulfoton. In another experiment, these inhibitors decreased the activity of delta-aminolevulinic acid synthetase, but this decrease was reversed when disulfoton was administered.

Although some steroids have been reported to reduce the toxic effects of some insecticides, the steroid ethylestrenol decreased the rate of recovery of depressed cholinesterase activity in disulfoton-pretreated rats (Robinson et al. 1978). The exact mechanism of this interaction was not determined. Ethylestrenol alone caused a small decrease in cholinesterase activity, and, therefore, resulted in an additive effect. Rats excreted less adrenaline and more noradrenaline when given simultaneous treatments of atropine and disulfoton compared with rats given disulfoton alone (Brzezinski 1973). The mechanism of action of disulfoton on catecholamine levels may depend on acetylcholine accumulation. In the presence of atropine, the acetylcholine effect on these receptors increases the ability of atropine to liberate catecholamines.

Cross-tolerance between disulfoton and another organophosphate, chlorpyrifos, was observed in mice (Costa and Murphy 1983b). Because of this cross-tolerance, a benefit is derived as a result of this interaction. In the same study, propoxur-tolerant mice were tolerant to disulfoton but not vice versa. Propoxur (a carbamate) is metabolized by carboxylesterases, and these enzymes are inhibited in disulfoton-tolerant animals; disulfoton-tolerant animals are more susceptible to propoxur and/or carbamate insecticides than are nonpretreated animals. In another study, disulfoton-tolerant rats were tolerant to the cholinergic effects of octamethyl pyrophosphoramide (OMPA) but not parathion (McPhillips 1969a, 1969b). The authors were unable to explain why the insecticides OMPA and parathion caused different effects.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to disulfoton than will most persons exposed to the same level of disulfoton in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

No data were located that identify subpopulations of humans more susceptible to the toxic effects of disulfoton. Animal studies demonstrate that there are sex, age, and liver function differences in the susceptibility of animals to disulfoton toxicosis. Data from LC_{50} and LD_{50} studies suggest that female rats and mice are more sensitive than male rats and mice to disulfoton after inhalation (Thyssen 1978), oral (Bombinski and DuBois 1958; Crawford and Anderson 1974; Gaines 1969; Mihail 1978; Pawar and Fawade 1978), dermal (Gaines 1969; Mihail 1978), or intraperitoneal (Bombinski and DuBois 1958) exposure. Erythrocyte and brain cholinesterase activity was more depressed in female rats than in male rats (Klotzsche 1972; Ryan et al. 1970; Thyssen 1980). While absolute and relative brain weights generally increased in male rats exposed to disulfoton, the trend was reversed in female rats (Carpy et al. 1975). In the same study, liver, spleen, kidney, and pituitary weights were increased in male rats and decreased in female rats. The toxicological significance of these observations is unknown. Results from toxicokinetic studies showed that male rats eliminated disulfoton faster than female rats (Lee et al. 1985; Puhl and Fredrickson 1975). This apparent difference in the toxic responses of the sexes may have been due to differences in absorption, retention, metabolism, or a combination of factors.

Animal studies suggest that younger animals are more susceptible to disulfoton toxicosis than older animals. The intraperitoneal LD_{50} of disulfoton was lower in weanling rats than in adult rats (Brodeur and DuBois 1963). These investigators proposed that the relatively slow rate of metabolic

detoxification and/or incomplete development of detoxification enzymes in weanlings accounted for the difference in the effects. Calves were more sensitive to disulfoton than yearling cattle, as indicated by an increase in severe clinical signs and a greater depression of cholinesterase activity in calves (McCarty et al. 1969).

Data suggest that animals pretreated with disulfoton or hepatic enzyme inducers were less susceptible to disulfoton toxicosis than those subpopulations that were not pretreated. Disulfoton-tolerant animal populations are generally less sensitive to subsequent disulfoton exposure than are nontolerant animals (Costa et al. 1984; Schwab and Murphy 1981; Schwab et al. 1981, 1983). In addition, animals pretreated with chemicals that induce MFO (e.g., phenobarbital) were less susceptible to disulfoton toxicosis (DuBois and Kinoshita 1968; Pawar and Fawade 1978).

2.8 METHODS FOR REDUCING TOXIC EFFECTS

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

2.8.1 Reducing Peak Absorption Following Exposure

If disulfoton is inhaled, the victim should be removed to a fresh air environment. Artificial respiration and the use of oxygen has been recommended (Sittig 1991). Not much can be done to reduce absorption of disulfoton from the respiratory tract. If disulfoton is ingested, the stomach should be emptied by inducing emesis or by gastric lavage (Haddad and Winchester 1990). If the patient is unconscious, means to prevent aspiration are recommended prior to gastric lavage. Because most organophosphates contain hydrocarbon solvents, which are severe aspiration hazards, the use of emetics may be contraindicated (Ellenhom and Barceloux 1988). Activated charcoal and a cathartic should then be given to adsorb any of the remaining disulfoton. Repeated treatment with activated charcoal may be useful to prevent reabsorption following enterohepatic circulation. In the event of dermal exposure, contaminated clothing should be removed and the victim should be bathed with soap

and water in an attempt to decontaminate the skin. The eyes should be rinsed with water or physiological saline if disulfoton entered the eye.

2.8.2 Reducing Body Burden

No information is available regarding methods for specifically reducing the body burden of disulfoton. Diuresis, dialysis, and hemoperfusion have been used to reduce the body burden of other organophosphates in humans and animals (Ellenhorn and Barceloux 1988). Because disulfoton is rapidly metabolized to its active metabolites which bind to ubiquitous cholinesterases in nervous tissue, these methods may not be effective unless started immediately after exposure. However, repeated administration of activated charcoal/cathartics may prevent possible enterohepatic recirculation of disulfoton or its metabolites. Administration of oximes, such as 2-PAM, may also increase the excretion of disulfoton metabolites, since oximes accelerate the hydrolysis of phosphorylated cholinesterase (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Haddad and Winchester 1990; Morgan 1982). However, “aging” of the phosphorylated enzyme may occur after l-2 days (Ecobichon 1990). Because 2-PAM is unable to reverse cholinesterase inhibition once “aging” has started, 2-PAM should be administered as soon as possible after exposure or any time following exposure when clinical signs or symptoms are present.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of action of disulfoton depends on active metabolites of disulfoton binding to acetylcholinesterase and causing an accumulation of acetylcholine at the synapse that results in muscarinic (e.g., salivation) and nicotinic (e.g., muscle tremors) effects. Atropine sulfate has been used as a therapeutic agent to reduce the severity of disulfoton toxicosis by binding to muscarinic receptors, thus blocking the muscarinic and central nervous system manifestations (Goldfrank et al. 1990). Atropine also reduces excessive bronchial secretions that can result in bronchopneumonia. This drug was also used successfully to treat a patient with severe signs of disulfoton toxicosis (Yashiki et al. 1990). Pretreatment of rats with atropine protected them against an intraperitoneal LD_{50} dose (Bombinski and DuBois 1958). Oxime derivatives (e.g., 2-PAM), accelerate the hydrolysis of phosphorylated cholinesterase and hence accelerate regeneration of the active cholinesterase (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Haddad and Winchester 1990; Morgan 1982). The oximes usually reduce both the muscarinic and nicotinic effects of poisoning when administered within

36 hours after organophosphate exposure (Goldfrank et al. 1990; Morgan 1982). However, "aging" of the phosphorylated enzyme may occur after l-2 days (Ecobichon 1990). Because 2-PAM is unable to reverse cholinesterase inhibition once "aging" has started, 2-PAM should be administered as soon as possible after exposure. Atropine and 2-PAM synergistically alleviate the manifestations of cholinesterase inhibition when co-administered (Goldfrank et al. 1990). While atropine blocks the muscarinic effects, 2-PAM regenerates cholinesterase enzymes in sympathetic, parasympathetic, and central nervous system sites.

2.9 ADEQUACY OF THE DATABASE

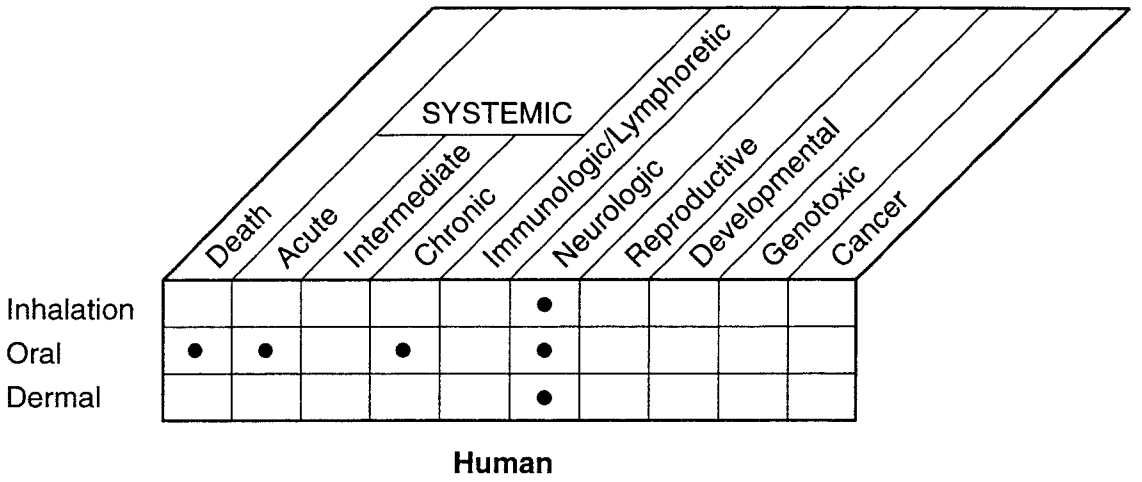
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of disulfoton is available. Where adequate information is not 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 disulfoton.

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.

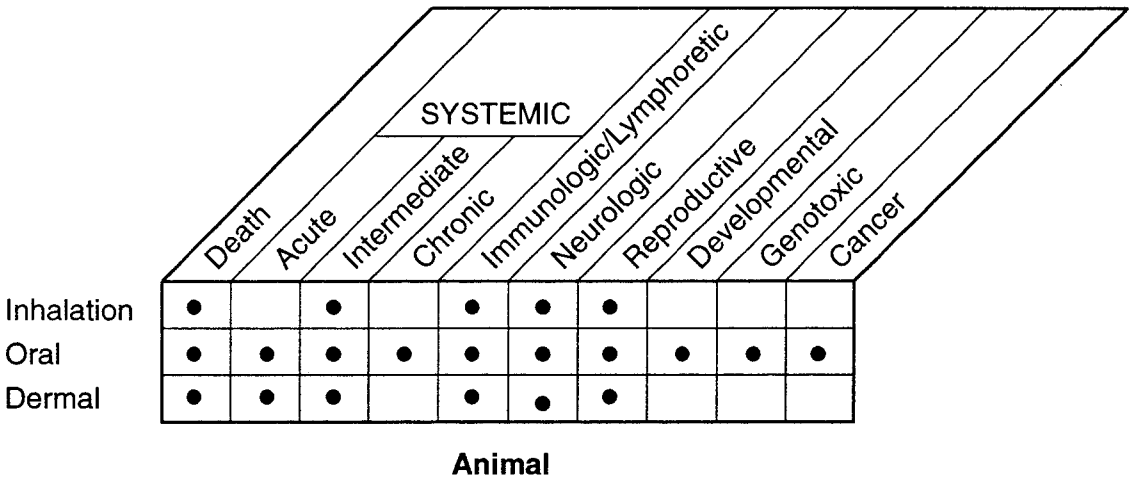
2.9.1 Existing Information on Health Effects of Disulfoton

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to disulfoton are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of disulfoton. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs." 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

FIGURE 2-4. Existing Information on Health Effects of Disulfoton



Human



Animal

● Existing Studies

more broadly as any substance-specific information missing from the scientific literature.

As seen from Figure 2-4, data exist regarding neurological effects in humans after inhalation exposure to disulfoton. The data for neurological effects were derived from medical evaluations of workers at a pesticide-fertilizer mixing operation. Neurological effects consisted of >22.8% depression in erythrocyte cholinesterase activity after 9 weeks of exposure to disulfoton. Other severe neurological effects were not reported. Systemic and neurological effects were observed in humans after accidental or intentional ingestion of disulfoton. Respiratory and renal effects, more associated with postmortem changes, were reported in a man who died after ingesting disulfoton. Neurological effects consisted of miosis, increased salivation, masseteric spasms, and monoplegia. Epidemiological studies suggest that disulfoton causes myopia in children. Neurological effects were observed in humans after dermal exposure to disulfoton for acute or intermediate durations. Neurological effects after acute exposure included weakness, fatigue, and depressed cholinesterase activity. Intermediate dermal exposure resulted only in erythrocyte cholinesterase depression.

Death and neurological effects were observed in animals after acute- and intermediate-duration inhalation exposure to disulfoton. Intermediate-duration inhalation studies that investigated systemic end points, effects in lymphoreticular organs, and effects in reproductive organs were conducted in rats. Effects consisted of cholinergic signs of disulfoton toxicity, depressed erythrocyte and brain cholinesterase activity, inflammation in respiratory organs, increased adrenal weight, hematological effects, and bone marrow changes. Death, systemic effects of acute-, intermediate-, and chronicduration exposure, lymphoreticular, neurological, developmental, reproductive, genotoxic, and carcinogenic effects were investigated in animals after oral exposure to disulfoton. Systemic effects consisted of respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, and body weight effects. Ocular effects consisted of myopia development in dogs and cornea1 neovascularization in rats after chronic exposure to disulfoton. Neurological effects consisted of cholinergic signs of disulfoton toxicity, depressed erythrocyte and brain acetylcholinesterase activity, and pathology of the optic nerve and retina. Reproductive effects were observed in male and female rats, and fetotoxicity was reported in several developmental studies. Mostly negative results were obtained for genotoxicity, and negative results were found in carcinogenicity studies. Death and cholinergic toxicity were the only reliable effects reported in animal studies regarding acute dermal exposure to disulfoton. Rabbits that died showed gross effects in the lungs, stomach, liver, kidney,

and spleen upon necropsy. An intermediate-duration dermal study examined all systemic end points, effects in lymphoreticular and reproductive organs, and neurological effects.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. No studies were located regarding systemic effects in humans after inhalation or dermal exposure to disulfoton for acute durations. Acute oral ingestion by a man resulted in death, and respiratory and renal damage were found at autopsy performed at least 24 hours after death (Hattori et al. 1982). No studies were located regarding systemic effects in animals after inhalation exposure for acute durations. Information regarding systemic effects after dermal exposure is limited to reports of breathing difficulties in rats (Mihail 1978), and degenerative changes in heart, liver, kidney, and skin of rats, rabbits, and cats (Kundiev and Rappoport 1967). However, these studies were not very reliable. In addition, gross effects in the lungs, stomach, liver, kidney, and spleen were observed on necropsy of rabbits that died from cholinergic toxicity after a few dermal doses in a 3-week study (Flucke 1986). Acute inhalation lethality data are available for rats and mice (Doull 1957; DuBois 1971; Thyssen 1978, 1980); acute oral LD_{50} values are available for rats (Bombinski and DuBois 1958; Crawford and Anderson 1974; Gaines 1969; Mihail 1978; Pawar and Fawade 1978), mice (Mihail 1978; Pawar and Fawade 1978; Stevens et al. 1972a), and guinea pigs; (Bombinski and DuBois 1958; Crawford and Anderson 1973); acute dermal lethality data are available for rabbits (Flucke 1986); and dermal LD_{50} values are available for rats (DuBois 1957; Gaines 1969; Mihail 1969). Acute oral studies in animals have identified the liver as a possible target organ, evidenced by induction or inhibition of liver enzymes (Stevens et al. 1972a, 1972b, 1973) and lipid peroxidation (Fawade and Pawar 1978). Weight loss in animals also resulted from acute oral exposure to disulfoton (Costa et al. 1984, 1986; Schwab and Murphy 1981; Schwab et al. 1981, 1983). An acute inhalation MRL of 0.006 mg/ m^3 was derived based on a NOAEL for acetylcholinesterase inhibition in rats (Thyssen 1978). An acute oral MRL of 0.001 mg/kg/day was derived from animal data for acetylcholinesterase inhibition in rat dams exposed during gestation (Lamb and Hixson 1983). Acute-duration inhalation, oral, and dermal animal studies that perform comprehensive histological examination and look for other sensitive effects using several exposure concentrations or doses will provide dose-response data on possible end points other than neurological effects. Attempts to identify other target organs in animals after acute exposure will increase the weight of evidence that neurological effects (cholinesterase inhibition) are the most sensitive end points. This information is

important because there are populations surrounding hazardous waste sites that might be exposed to disulfoton for brief periods of time.

Intermediate-Duration Exposure. No studies were located regarding systemic effects in humans after inhalation, oral, or dermal exposure to disulfoton for intermediate durations. Intermediateduration inhalation studies in rats using several exposure concentrations and that included clinical chemistry, urinalysis, hematology, and comprehensive gross and histological examinations have been conducted (Shiotsuka 1989; Thyssen 1980). Inflammation in respiratory tissues, increased adrenal weight, decreased spleen weight, decreased lymphocytes, body weight gain reductions, bone marrow changes, and neurological effects were identified. An intermediate-duration inhalation MRL of $2x10^{-4}$ mg/ m^3 was derived based on a NOAEL for cholinergic effects and acetylcholinesterase inhibition in rats (Thyssen 1980). Intermediate-duration oral studies that used several dietary concentrations and conducted clinical chemistry, urinalysis, hematology, and performed comprehensive gross and histological examination in rats (Klotzsche 1972) and mice (Rivett et al. 1972) have been conducted. The liver was identified as a possible target organ, evidenced by a slight increase in liver weight in female mice (Rivett et al. 1972). Body weight gain reduction, in addition to neurological effects, also resulted from intermediate oral exposure in animals (Hixson and Hathaway 1986; Robinson et al. 1978; Schwab and Murphy 1981; Stavinoha et al. 1969). An intermediate-duration oral MRL of $9x10^{-5}$ mg/kg/day was derived based on a NOAEL for acetylcholinesterase inhibition in rat pups (Hixson and Hathaway 1986). A 3-week dermal study that used several dose levels and conducted clinical chemistry, urinalysis, hematology, and performed comprehensive gross and histological examination has been conducted on rabbits (Flucke 1986). No effects other than erythrocyte cholinesterase inhibition were found at 1.6 mg/kg/day, but the next higher dose of 6.5 mg/kg/day resulted in 100% deaths. A dermal study that uses doses between these extremes might provide dose-response information on systemic end points. Additional intermediate-duration animal studies by the oral and inhalation routes of exposure using doses intermediate between NOAEL values for effects other than cholinesterase inhibition and doses associated with death and severe neurotoxicity may be helpful for identifying thresholds for systemic effects. This information is important because there are populations surrounding hazardous waste sites that might be exposed to disulfoton for intermediate periods of time.

Chronic-Duration Exposure and Cancer. No studies were located regarding systemic effects in humans or animals after inhalation or dermal exposure to disulfoton for chronic durations. Results

from an epidemiological study suggest that oral exposure to disulfoton caused myopia in children (Ishikawa and Miyata 1980). Clinical evidence of myopia in dogs (Ishikawa and Miyata 1980; Suzuki and Ishikawa 1974) and histopathology of the ciliary muscles in the eyes of dogs (Ishikawa and Miyata 1980) were observed after chronic oral exposure. Another 2-year oral study was conducted in dogs, in which clinical chemistry, hematology, and gross and comprehensive histological examinations, including ophthalmology were performed; no effects for any systemic end points, including ocular, were found (Hoffman et al. 1975). The doses in this study were about 5 times lower than the doses that caused myopia and effects in the ciliary muscles. In addition to the 2-year oral studies in dogs, chronic oral studies have been conducted in rats (Carpy et al. 1975; Hayes 1985) and mice (Hayes 1983). These studies also used several dose levels and conducted clinical chemistry, hematology, urinalysis and gross and comprehensive histology. No systemic end points were found in the mice. One study in rats identified the liver and the kidney as possible target organs, suggested by an increase in liver and kidney weights in male rats (Carpy et al. 1975). The other study in rats found granulomatous and suppurative inflammation in the lungs, which may have been due to aspiration of the food particles; mucosal hyperplasia and chronic inflammation of the forestomach, skeletal muscle atrophy (due to debilitation); pancreatic atrophy; dermal lesions; and decreased body weight gain (Hayes 1985). In addition, ocular effects consisting of cystic degeneration of the Harderian gland and cornea1 neovascularization were observed. The chronic oral dietary studies in rats (Carpy et al. 1975; Hayes 1985), mice (Hayes 1983), and dogs (Hoffman et al. 1975) established LOAEL and NOAEL values for acetylcholinesterase inhibition. A chronic inhalation MRL was not derived because no studies were located. A chronic oral MRL of $6x10^{-5}$ mg/kg/day was derived based on a LOAEL for erythrocyte and brain cholinesterase inhibition in female rats in the study by Hayes (1985). Welldesigned chronic-duration inhalation and dermal studies in rats and mice, in which several dose levels are used and comprehensive end points are examined, might identify systemic target organs for these routes and establish dose-response relationships. Although cholinesterase inhibition is the most sensitive end point, additional chronic dietary studies in mice and dogs could be conducted that use doses to establish LOAEL and NOAEL values for end points other than cholinesterase inhibition, that is for systemic target organs. This information is important because there are populations surrounding hazardous waste sites that might be exposed to disulfoton for long periods of time.

No studies were located regarding cancer in humans after inhalation, oral, or dermal exposure to disulfoton or in animals after inhalation or dermal exposure. A 13-week inhalation study in rats reported that comprehensive histological examination of organs and tissues revealed no treatment-

related neoplastic lesions (Shiotsuka 1989); however, a chronic-duration inhalation study would be more appropriate to assess possible carcinogenicity. Carcinogenicity was not observed in rats (Carpy et al. 1975; Hayes 1985), mice (Hayes 1983) or dogs (Hoffman et al. 1975) that had been fed a diet of disulfoton for 1.5-2.0 years. Although there is little reason to suspect that disulfoton is carcinogenic, chronic inhalation, oral, or dermal studies should include comprehensive histology to confirm that disulfoton is not carcinogenic.

Genotoxicity. Disulfoton has been tested in numerous types of assays for genotoxicity. Disulfoton was positive for unscheduled DNA synthesis in human lung fibroblasts (EPA 1984a; Sandhu et al. 1985) and for growth inhibition in human HeLa cells (Litterst et al. 1969). Disulfoton was negative in assays for chromosomal aberrations in human hematopoietic cell lines (Huang 1973) and for alterations in DNA or RNA synthesis in human HeLa cells (Litterst et al. 1969). Disulfoton did not induce micronuclei in mice exposed orally or intraperitoneally (EPA 1984a; Herbold 1981; Sandhu et al. 1985), dominant lethality in mice exposed orally (Herbold 1980), or sex-linked recessive lethal mutation in *D. melunogaster* (EPA 1981a; Waters et al. 1981). Mostly negative results were obtained in in vitro tests in bacteria and yeast (Brusick 1981; EPA 1980a, 1984a; Herbold 1983; Jagannath 1981; Moriya et al. 1983; Sandhu et al. 1985; Waters et al. 1981, 1982), but a few positive results were obtained in some strains of *S. typhimurium* and *E. coli* (Hanna and Dyer 1975; Moriya et al. 1983; Shirasu et al. 1982, 1984). Disulfoton also produced positive results in several assays in barley (Murty et al. 1983; Panda 1983; Singh et al. 1977). Some positive and some negative results have been obtained in cultured mammalian cells. Positive results were found for sister chromatid exchange in Chinese hamster ovary cells in some studies (EPA 1984a; Putnam 1987; Sandhu et al. 1985; Waters et al. 1981, 1982), but negative results were obtained in another study (Chen et al. 1981, 1982). Negative results were also obtained for HGPRT mutations in Chinese hamster ovary cells (Yang 1988). Disulfoton was positive for forward mutation in mouse lymphoma cells (EPA 1984a; Sandhu et al. 1985; Waters et al. 1981, 1982). Although most assays were negative, the few positive results suggest a genotoxic potential. However, it is doubtful that additional testing would add meaningful data.

Reproductive Toxicity. No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to disulfoton. Disulfoton did not affect male fertility in mice in an oral dominant lethal study (Herbold 1980). Slightly reduced litter sizes in third generations were the findings of a three-generation oral reproductive study in rats (Taylor 1965a). When males and females

were exposed to disulfoton for 60 days prior to and/or during mating, 2 of 5 females failed to become pregnant (Ryan et al. 1970). Although complete gross anatomical and histopathological examinations were lacking, the data do suggest that the male and/or female reproductive system may be affected. A more extensive multigeneration feeding study in rats found decreased reproductive performance of males and females; decreased maternal weight of F_0 and F_1 dams during gestation and lactation; decreased litter counts, viability index; and lactation index; increased dead births and percentage of dead births in both generations; and decreases in F_{2b} litter counts and litter weights (Hixson and Hathaway 1986). However, negative histopathological results were generally obtained from the examination of male and female reproductive systems in rats exposed by inhalation for 3 or 13 weeks (Shiotsuka 1989; Thyssen 1980); in rabbits treated dermally for 3 weeks (Flucke 1986); in rats (Klotzsche 1972) or mice (Rivett et al. 1972) fed disulfoton for 90 days; or in rats (Carpy et al. 1975; Hayes 1985), mice (Hayes 1983), or dogs (Hoffman et al. 1975) fed disulfoton for ≈2 years, with the exception of uterine cystic hyperplasia in female rats fed the high dietary concentration of disulfoton for 2 years (Hayes 1985). Studies on reproductive function in animals exposed by the inhalation or dermal routes will help clarify whether disulfoton affects reproduction by these routes as well as the oral route.

Developmental Toxicity. No studies were located regarding developmental effects in humans after inhalation, oral, or dermal exposure to disulfoton or in animals after inhalation or dermal exposure. Developmental effects have been found in animals after acute- and intermediate-duration oral exposure to disulfoton. Plasma and erythrocyte cholinesterase depression and increased incidences of incomplete ossified parietal bones and sternebrae were observed in fetuses from rats fed disulfoton on days 6-15 of gestation (Lamb and Hixson 1983). Bone and soft tissue malformations were not observed. Effects in fetuses or pups, such as depressed brain cholinesterase activity (Hixson and Hathaway 1986; Ryan et al. 1970), renal and hepatic pathology, and juvenile hypoplasia of testes (Taylor 1965a) were also observed in reproductive studies. However, disulfoton did not cause any fetotoxic effects in the fetuses from pregnant rabbits treated orally with disulfoton during gestation (Tesh et al. 1982). Additional developmental studies involving inhalation or dermal exposure of animals to disulfoton might indicate whether fetotoxic effects are route-dependent.

Immunotoxicity and Lymphoreticular Effects. No studies were located regarding immunological effects in humans after inhalation, oral, or dermal exposure to disulfoton. In two acute animal studies (Costa et al. 1990; Fitzgerald and Costa 1993), repeated intraperitoneal or oral doses of

disulfoton caused a down-regulation of cholinergic muscarinic receptors in lymphocytes. Although the effect on lymphocytes is regarded as a neurological effect, secondary effects due to neuroimmuno interactions are possible and warrant further investigation. After inhalation exposure of rats, inflammatory changes throughout the respiratory tract (associated with bone marrow changes and low percentages of lymphocytes and high percentages of polymorphonuclear leukocytes) and decreased spleen weight were observed (Thyssen 1980). In a chronic dietary study in rats, increased incidence of plasma cell hyperplasia in the mandibular lymph nodes and a significantly increased incidence of splenic lymphoid follicle depletion were observed (Hayes 1985). In other inhalation (Shiotsuka 1989), dietary (Carpy et al. 1975; Hayes 1983; Hoffman et al. 1975; Klotzsche 1972; Rivett et al. 1972), and dermal (Flucke 1986) studies in animals exposed to disulfoton, histological examination of lymphoreticular organs revealed no treatment-related lesions. However, immunological data collected from animals exposed to disulfoton by all three routes for acute, intermediate, or chronic durations might indicate whether disulfoton affects the immune system. A battery of immune function tests would clarify whether disulfoton is an immunotoxicant.

Neurotoxicity. Exposure to disulfoton by the inhalation, oral, or dermal routes has resulted in neurological effects in humans. Disulfoton can cause erythrocyte cholinesterase depression in humans after inhalation exposure without other overt neurological effects (Wolfe et al. 1978). The more overt neurological effects have been observed in humans after oral exposure to disulfoton (Hattori et al. 1982; Yashiki et al. 1990). The clinical signs consisted of muscle tremors and incoordination, increased salivation, pupil miosis, and even death. Weakness and fatigue (Savage et al. 1971) and depressed erythrocyte acetylcholinesterase activity (Wolfe et al. 1978) were observed in humans after dermal exposure to disulfoton. No significant depression in brain, serum, or submaxillary gland cholinesterase activity and no overt signs of neurotoxicity were observed in rats after acute inhalation (5-10 days) exposure (DuBois and Kinoshita 1971). Inhalation, oral, and dermal exposures of animals to disulfoton resulted in signs of cholinergic toxicity (Costa et al. 1984; Doull 1957; Flucke 1986; Mihail 1978; Schwab and Murphy 1981; Schwab et al. 1981, 1983; Shiotsuka 1989; Thyssen 1980). These cholinergic signs were similar to those observed in humans and are associated with inhibition of acetylcholinesterase. Inhibition of brain, erythrocyte, and other tissue acetylcholinesterase activities (Carpy et al. 1975; Christenson and Wahle 1993; Clark and Pearson 1973; Doull and Vaughn 1958; Flucke 1986; Hayes 1983, 1985; Hikita et al. 1973; Hixson and Hathaway 1986; Hoffman et al. 1975; Klotzsche 1972; Robinson et al. 1978; Ryan et al. 1970; Schwab and Murphy 1981; Schwab et al. 1981; Sheets 1993a, 1993b; Shiotsuka 1989; Thyssen 1978, 1980) have been observed in animals in

numerous studies regardless of the route, duration, or animal species. The acute and intermediate inhalation MRLs and the acute, intermediate, and chronic oral MRLs are based on cholinesterase inhibition. Tolerance was also observed in animals exposed to disulfoton for ≥5-10 days (Costa et al. 1984; Schwab and Murphy 1981; Schwab et al. 1981, 1983). Neurobehavioral changes were observed in rats (Clark and Pearson 1973) and mice (Clark et al. 1971) exposed orally for intermediate durations. Necrosis and atrophy of the optic nerve and retina in dogs (Uga et al. 1977) were observed after oral exposure. Based on the results of the human and animal studies, neurological effects (subtle and/or overt) may occur regardless of the route of exposure. Additional animal studies do not seem to be warranted at this time.

Epidemiological and Human Dosimetry Studies. Epidemiological studies are limited. A coincidental increase in the incidence of myopia was observed in young children thought to be orally exposed to disulfoton (Ishikawa and Miyata 1980). Although there is clinical and histopathological evidence from animal studies to support the association between myopia and disulfoton exposure, other neurological effects (i.e., depressed acetylcholinesterase activity) were not reported. Employees exposed to disulfoton by inhalation and dermal routes (Brokopp et al. 1981; Wolfe et al. 1978) did not show overt signs of toxicity, but disulfoton exposure was confirmed in part by depressed cholinesterase activity and/or urinary metabolite identification. These studies are limited because it is not clear whether inhalation or dermal exposure contributed the most to the observed effects. Future human epidemiological studies should look for subtle neurological indicators of exposure (i.e., erythrocyte or lymphocyte acetyl cholinesterase depression) in addition to the ocular effects already described. The data would be useful for establishing cause/effect relationships and for future monitoring of individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect

Exposure. Disulfoton and its metabolites have been detected in the blood and the urine of humans exposed to disulfoton either accidentally or in the workplace (Brokopp et al. 1981; Hattori et al. 1982; Wolfe et al. 1978; Yashiki et al. 1990). Whereas, disulfoton and its metabolites were detected in the blood of humans who ingested unknown quantities of disulfoton (Hattori et al. 1982; Yashiki et al. 1990), urinary metabolites were a better indicator of occupational exposure to the pesticide (Brokopp et al. 1981; Wolfe et al. 1978). Although no animal studies reported the detection of disulfoton or its metabolites in blood, data from animal studies demonstrated that urinary metabolites were a reliable

indicator of disulfoton exposure (Bull 1965; Lee et al. 1985; Puhl and Fredrickson 1975). These animal studies also demonstrated that DEP was a more sensitive urinary biomarker than other metabolites. DEPs are specific for diethyl organophosphates such as disulfoton. A combination of neurological signs is usually a biomarker of disulfoton exposure, as demonstrated in humans (Yashiki et al. 1990) and animals (Schwab et al. 1981). Inhibition of serum cholinesterase and/or erythrocyte acetylcholinesterase are usually reliable biomarkers of exposure in humans (Wolfe et al. 1978; Yashiki et al. 1990). Since blood cholinesterase depression was not observed, but urinary metabolites were detected in exposed employees (Brokopp et al. 1981), urinary metabolites may be a more sensitive biomarker of disulfoton exposure. Urinary metabolites are generally eliminated within 2 weeks after the last exposure and are not usually detected beyond this period. However, cholinesterase depression may be a better biomarker, because the enzyme may remain inhibited for >2 weeks. A recent study showed that T-lymphocyte acetylcholinesterase activity was rapidly and greatly depressed in rats during a 14-day exposure to disulfoton, but rapidly recovered after exposure (Fitzgerald and Costa 1993). Therefore, T-lymphocyte acetylcholinesterase levels could be used as a biomarker of exposure to organophosphorus pesticides during exposure, and could be investigated for use in biomonitoring worker exposure. Animal studies indicate that nonspecific biomarkers of disulfoton exposure may include increased urinary levels of catecholamines (Brzezinski 1969) or their metabolite HMMA (Wysocka-Paruszewska 1971) and increased MFO enzymes (Stevens et al. 1973). No human data were located to support these findings. Although available biomarkers of exposure for disulfoton are nonspecific, it is doubtful that further research will identify a more useful and specific biomarker.

Effect. Disulfoton exposure in humans or animals causes characteristic cholinergic effects such as increased salivation, diarrhea, muscle tremors, and pupillary miosis (Costa et al. 1984; Schwab et al. 1981, 1983; Yashiki et al. 1990). These effects are also associated with exposure to other organophosphates and are, therefore, not specific to disulfoton. Inhibition of erythrocyte acetylcholinesterase can alert the physician to the possibility of more serious neurological effects. In rats, acetylcholinesterase levels in circulating lymphocytes correlated better with brain acetylcholinesterase activity than did erythrocyte cell cholinesterase activities during exposure, but not during recovery after exposure (Fitzgerald and Costa 1993). Thus, lymphocyte acetylcholinesterase activity may be a better biomarker of effect than erythrocyte acetylcholinesterase activity during exposure, but erythrocyte acetylcholinesterase probably remains the better sentinel for brain acetylcholinesterase activity after exposure has ceased. However, other organophosphates and also carbamates can cause this neurological effect. Although animal studies have demonstrated that brain

acetylcholinesterase inhibition is a sensitive indicator of a neurological effect (Carpy et al. 1975), this measurement is not practical in humans. Increased β-glucuronidase activity (Kikuchi et al. 1981) and increased urinary catecholamine levels (Brzezinski 1969) observed in animals may be useful nonspecific biomarkers of effects in humans. There does not appear to be a need for additional biomarkers of effect.

Absorption, Distribution, Metabolism, and Excretion. No studies were located regarding the absorption, distribution, metabolism, and excretion of disulfoton by humans or animals after inhalation or dermal exposure. Limited data exist regarding the absorption, distribution, and excretion after oral exposure to disulfoton. Data on levels of disulfoton and metabolites excreted in urine and expired air suggest that some almost complete absorption of an administered dose of disulfoton over 3-10 days (Lee et al. 1985; Puhl and Fredrickson 1975). The data are limited regarding the relative rate and extent of absorption. Animal data suggest that disulfoton and/or its metabolites are rapidly distributed to the liver, kidney, fat, skin, muscle, and brain, with peak levels occurring within 6 hours (Puhl and Fredrickson 1975). Elimination of disulfoton and metabolites occurs primarily in the urine, with >90% excreted in the urine in 3-10 days (Lee et al. 1985; Puhl and Fredrickson 1975). Evidence further suggests that male rats eliminate disulfoton at a faster rate than females. This difference may be due to differences in absorption, metabolism, retention, excretion, or a combination of factors. The metabolic pathways of disulfoton are relatively well understood based on data from animal studies (Bull 1965; Lee et al. 1985; March et al. 1957; Puhl and Fredrickson 1975). Similar metabolites have been detected in the urine and tissues from humans exposed to disulfoton (Brokopp et al. 1981; Yashiki et al. 1990). One study suggests that a greater percentage of disulfoton sulfoxide is oxidized to demeton S-sulfoxide, rather than disulfoton sulfone to form demeton S-sulfone (Bull 1965). Additional studies in animals, designed to measure the rate and extent of absorption, distribution, and excretion of disulfoton after inhalation or dermal exposure would be useful for predicting the toxicokinetics of disulfoton in humans at an occupational or hazardous waste site.

Comparative Toxicokinetics. The primary target organ for disulfoton in animals and humans is the nervous system. Other organs, such as the liver, are hardly affected. Since there have been no toxicokinetic studies in animals or humans exposed by inhalation or dermal routes, it is impossible to compare animals and humans by these two routes of exposure. Data from occupational studies suggest that disulfoton was absorbed via inhalation and/or dermal routes of exposure (Brokopp et al. 1981; Wolfe et al. 1978); however, the data from these studies on the rate and extent of absorption are

limited. No animal studies were available for comparison. Although the rate and extent of absorption was unknown, disulfoton was readily absorbed by two men as demonstrated in two separate studies (Hattori et al. 1982; Yashiki et al. 1990). In animals, toxicokinetic data are available only in rats exposed by the oral route (Lee et al. 1985; Puhl and Fredrickson 1975). No studies were located regarding the distribution of disulfoton following inhalation or dermal exposure in humans or animals. Although no studies were located regarding the distribution of disulfoton following oral exposure in humans, data from animal studies were located. Disulfoton and its metabolites were detected in the liver, kidney, adipose tissue, muscle, skin, and brain (Puhl and Fredrickson 1975). Data from human (Brokopp et al. 1981; Wolfe et al. 1978; Yashiki et al. 1990), rat (Bull 1965; Lee et al. 1985; Puhl and Fredrickson 1975), and mouse (March et al. 1957) studies indicate that similar metabolic pathways operate in humans and rodents. No studies were located regarding the rate or extent of excretion of disulfoton in humans or animals after inhalation or dermal exposure. Although no studies were located regarding the rate or extent of excretion of disulfoton after oral exposure in humans, limited data for animal studies were located. Data from the only animal study located suggested that most of the disulfoton was eliminated within 3-10 days of exposure and that male rats eliminated disulfoton at a faster rate than females (Lee et al. 1985; Puhl and Fredrickson 1975). With intraperitoneal administration, rats eliminated 28% of the original dose within 48 hours (Bull 1965), and mice eliminated 30-60% of the original dose within 96 hours (March et al. 1957). There appears to be insufficient toxicokinetic data to use as a basis for comparison of animals and humans. Additional studies comparing the rate and extent of absorption, distribution, and elimination in several different animal species after inhalation, oral, and dermal exposure to disulfoton could be useful.

Methods for Reducing Toxic Effects. No data were located regarding the mechanism of absorption via the respiratory tract, gastrointestinal tract, or the skin. Besides moving the exposed individual to a fresh air environment and/or administering oxygen, very little can be done if disulfoton is inhaled (Sittig 1991). Induction of emesis, gastric lavage, and administration of a saline cathartic immediately after oral exposure help reduce absorption. Since diuresis, dialysis, and hemoperfusion have been used to reduce the body burden of other organophosphates (Ellenhorn and Barceloux 1988), it seems reasonable that these methods may also be used to treat disulfoton intoxication. Repeated administration of activated charcoal and cathartics may prevent possible enterohepatic recirculation of the parent compound and its metabolites. The treatment protocol also includes interfering with the known mechanism of action of disulfoton. Atropine is used to block the muscarinic effects of disulfoton (Goldfrank et al. 1990; Yashiki et al. 1990), and an oxime (e.g., 2-PAM) is given to

accelerate the hydrolysis of phosphorylated cholinesterase, which accelerates regeneration of the active cholinesterase (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Haddad and Winchester 1990; Morgan 1982). There are numerous treatment protocols that successfully use some or all of the methods described. Therefore, further studies regarding the reduction of toxic effects for disulfoton exposure may not be warranted.

2.9.3 Ongoing Studies

A study by S.C. Soderholm of the University of Rochester is in progress to relate the deposition efficiency of volatile aerosols of disulfoton in humans to physical properties of the airborne system, including exposure concentration, saturation vapor concentration, particle size, and blood/gas partition coefficient (CRISP Database 1994). Disposition efficiency will be determined from laboratory experiments and computer modelling. The results of computer models will be compared to measure disposition efficiencies of disulfoton aerosols in humans. With this information, the inhaled dose in humans can be estimated.

Studies on particular organophosphates are currently being conducted by EPA to substantiate the findings that these organophosphates, including disulfoton, are associated with the development of myopia in humans, as reported in Japanese populations (Dementi 1994).

3. CHEMICAL AND PHYSICAL INFORMATION

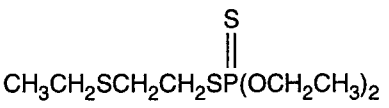
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of disulfoton is located in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Disulfoton is a systemic insecticide/acaricide that belongs to the organophosphate class of pesticides. Pure disulfoton is a colorless oil with low volatility and water solubility, but is readily soluble in most organic solvents (Worthing 1987). Information regarding the physical and chemical properties of disulfoton is located in Table 3-2.

TABLE 3-1. Chemical Identity of Disulfoton

Characteristic	Information	Reference
Chemical name	O, O-Diethyl S-[2-(ethylthio)ethyl]-phosphorodithioate	Worthing 1987
Synonym(s)	Ethylthiodemeton; M-74; thiodemeton	Worthing 1987
Registered trade name(s)	Di-Syston; Dithiosystox; Solvirex ENT 23347; Frumin AL	Worthing 1987 Merck 1989
Chemical formula	$C_8H_{19}O_2PS_3$	Worthing 1987
Chemical structure		Worthing 1987
Identification numbers:		
CAS Registry	298-04-4	Sittig 1985
NIOSH RTECS	TD9275000	Sittig 1985
EPA hazardous waste	PO39	HSDB 1994
OHM/TADS	7800012	HSDB 1994
DOT/UN/NA/IMCO shipping	NA2783/IMO 6.1	HSDB 1994
HSDB	379	HSDB 1994
NCI	No data	HSDB 1994

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 from National Library of Medicine; 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 Disulfoton

Property	Information	Reference
Molecular weight	274.38	HSDB 1994
Color	Colorless (pure); yellow (technical)	Sanborn et al. 1977
Physical state	Oily liquid	HSDB 1994
Melting point	No data	
Boiling point	113 °C at 0.4 mm Hg; 62 °C at 0.01 mm Hg	Melnikov 1971; Sanborn et al. 1977
Density: at 20 °C at 25 °C at 30 °C	 1.144 g/cm^3 No data No data	 Worthing 1987
Odor	Aromatic (technical product)	HSDB 1994
Odor threshold: Water Air	 No data No data	
Solubility: Water at 20 °C	 25 mg/L; 15.2 mg/L	 Sanborn et al. 1977; Lord and Burt 1964
Organic solvent(s)	Readily soluble in most	Sanborn et al. 1977
Partition coefficients: Log K_{ow} Log K_{oc}	 4.02 3.2; 2.78	 Bowman and Sans 1983 Rao and Davidson 1982; Wauchope et al. 1992
Vapor pressure at 20 °C	1.8x10^{-4} mm Hg	Melnikov 1971
Henry's law constant: at 20 °C at 30 °C	 2.17x10^{-6} atm-m^3/mol No data	 Domine et al. 1992
Autoignition temperature	No data	
Flashpoint	>180 °F (TOC)	EPA 1984b
Flammability limits	No data	
Conversion factors	1 mg/m^3 = 0.089 ppm (air at 25 °C)	EPA 1990b
Explosive limits	No data	

EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank from National Library of Medicine; TOC = Tag open cup

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

4.1 PRODUCTION

Disulfoton is produced commercially by a reaction of the sodium salt of O,O'-diethylhydrogen phoshorodithioate with 2-chloroethylthioethyl ether (VonRumker et al. 1974). Disulfoton is produced in the United States by a subsidiary of Bayer AG, Germany. Chemagro of Kansas City, Missouri, a subsidiary of Bayer AG, produced an estimated 5 million pounds of disulfoton in 1972 (VonRumker et al. 1974). Disulfoton production has declined in recent years as a result of restricted use due to its toxicity (EPA 1984b). In 1986, Mobay Corp., Kansas City, Missouri, produced over 2.1 million pounds of disulfoton in the United States (Goodrich et al. ld!Jl). Since the annual use of disulfoton in the United States from 1989 to 1991 was 3.06 million pounds (Gianessi and Puffer 1992), the production volume during this period must have exceeded 3.1 million pounds. In 1994, Miles Inc., Agriculture Division, Kansas City, Missouri, a subsidiary of Bayer AG of Germany, produced disulfoton; however, information on current production volume is not available (SRI 1994).

4.2 IMPORT/EXPORT

In 1972, disulfoton was not imported into the United States, and the exports of disulfoton from the United States to other countries were negligible (VonRumker et al. 1974). Import/export data for disulfoton in recent years were not located; however, since the recent yearly consumption of disulfoton in the United States is substantially lower than the estimated yearly production capacity of 7 million pounds at the Kansas City plant (VonRumker et al. 1974), it is unlikely that disulfoton is being imported.

4.3 USE

Disulfoton is a systemic organophosphate insecticide/acaricide (i.e., it is absorbed and translocated by treated plants) effective for controlling a variety of harmful insects that attack many field and vegetable crops. As emulsifiable concentrates and in granular or pelleted/tableted forms, disulfoton is used to treat seeds and is applied to soils or plants. Disulfoton is also available in a ready-to-use liquid formulations (EPA 1984b). Disulfoton is used to protect small grains, sugar cane, sorghum, corn, cotton, Cole, root, seed, forage, and other field crops; some vegetable, fruit (strawberry,

pineapple), and nut crops; and forest plantings, ornamental and potted plants (EPA 1984b; VonRumker et al. 1974). Agricultural uses account for most of its consumption; small quantities are used on home and garden plants and for other purposes, such as mosquito abatement (VonRumker et al. 1974; Warnick and Eldredge 1972). Use of disulfoton has declined since the early 1970s. In 1972, 4.9 million pounds of disulfoton were used for agricultural purposes, and only 0.1 million pounds were used in homes and gardens (VonRumker et al. 1974). Based on state usage data from 33 states for 1982, California use data for 1981, and the EPA Office of Pesticide Programs national survey of pesticide usage by urban applicators and nurseries, Gianessi (1986) estimated that 2.1 million pounds of disulfoton were used annually in agriculture during 1981 and 1982. The estimated annual agricultural use of disulfoton was 2.1 million pounds in 1986 (Goodrich et al. 1991) and 3.1 million pounds in 1989-1991 (Gianessi and Puffer 1992). The use of disulfoton in the production of corn, wheat, potatoes, and cotton accounted for the largest annual use during 1989-1991 (Gianessi and Puffer 1992).

4.4 DISPOSAL

The two preferable methods for disposing of wastes containing disulfoton are incineration and alkaline hydrolysis (HSDB 1994). For disposal of low-viscosity wastes (permitting atomization in the combustion chamber) containing disulfoton, liquid injection incineration at 650-1,600 ºC and a residence time of 0.1-2 seconds are recommended. For the disposal of viscous and solid wastes, rotary kiln incineration at 820-1,600 ºC and a residence time of seconds to hours, or fluidized bed incineration at 450-980 ºC with a residence time of seconds or longer are recommended. The effluent gases from the incineration units should pass through scrubbers or other air pollution control devices (HSDB 1994). Alkaline hydrolysis leads to the complete degradation of disulfoton to non-toxic end products (alkaline salts of O,O-dimethylphosphorothioic acid and ethylthioethyl mercaptan). Disulfoton is resistant to hydrolysis in acid media (Sittig 1980). Acid hydrolysis produces essentially the same end products; however, the reaction rate is much slower (IRPTC 1985). Fifty percent hydrolysis at 70 ºC requires 60 hours at pH 5, but only 7.2 hours at pH 9 (Sittig 1980). In the alkaline hydrolysis method, the waste should be subjected to hydrolysis with 6% potassium hydroxide in isopropanol under reflux for 30 minutes (IRPTC 1985) or 5% sodium hydroxide in ethanol for 3 hours (for 2%,10%, and 50% granular formulations) (Dillon 1981). The hydrolyzed product should be adsorbed on vermiculite, then incinerated or disposed of in a landfill (IRPTC 1985).

The EPA has proposed incineration as the best demonstrated available technology (BDAT) for treating organophosphorus nonwaste waters (waste containing >l% by weight total suspended solids and >l% by weight total organic carbon). EPA has demonstrated that rotatory kiln incineration at 1,000°C was satisfactory for attaining the proposed treatment standard of a maximum 0.1 mg/kg disulfoton in treated nonwaste waters (Berlow and Cunningham 1989).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Disulfoton enters the environment primarily during its use as an insecticide/acaricide in crops and vegetables, and in homes and gardens. Other important pathways for disulfoton's entry into the environment are the disposal of liquid disulfoton wastes into soil evaporation pits, ditches, ponds (Winterlin et al. 1989), and hazardous waste sites. Thus, soil is the environmental medium most likely to be contaminated with disulfoton. The processes that may transport disulfoton from soil to other environmental media include leaching to groundwater, runoff to surface water, and absorption by plants (Holden 1986; Mostaghimi et al. 1993; Nash 1974; Plumb 1991; Sanbom et al. 1977; Spalding and Snow 1989). Biodegradation, abiotic hydrolysis and, to a lesser extent, sensitized oxidation are principally responsible for the loss of disulfoton from water (Cape1 et al. 1988; Mossman et al. 1988; Wanner et al. 1989). In a chemical spill in the Rhine River where an initial disulfoton concentration of 5 µ/L was observed, the estimated biodegradation half-life of disulfoton in 10 ºC river water was 7-41 days (Wanner et al. 1989). The measured whole-body bioconcentration factor for disulfoton in carp was 450, but disulfoton residues disappeared rapidly from the fish when they were placed in uncontaminated water (Takase and Oyama 1985). Biodegradation and photosensitized oxidation play major roles in the loss of disulfoton from soil (Gohre and Miller 1986; Wanner et al. 1989; Zepp et al. 1981). The estimated half-life of disulfoton in soil ranges from 3.5 to ≤290 days (Chapman et al. 1993, 1994a; Garg and Sethi 1980; GreenhaIgh 1978; Harris et al. 1988; Jury et al. 1987a; Menzie 1972).

Disulfoton was detected at a maximum of 4.7 ng/m^3 in 1 of 123 ambient air samples from 10 locations in the United States (Carey and Kutz 1985). Disulfoton was qualitatively detected in groundwater samples from 1 of 479 hazardous waste sites (Plumb 1991) and in runoff water in an agricultural watershed at concentrations ranging from trace to 0.4 µg /L (Spalding and Snow 1989). Disulfoton was also detected in groundwater samples from the Nomini Creek Watershed in Virginia at a mean and maximum concentration of 0.39 µg/L and 2.87 µg /L respectively (Mostaghimi et al. 1993). A core soil sample taken from a waste evaporation pit at a depth of 90 cm contained disulfoton at a concentration of 44 mg/kg (Winterlin et al. 1989). The mean concentration of disulfoton in the bottom soil of an agricultural tail water pit used to collect irrigation runoff was 13.4 µg /kg.

The Food and Drug Administration (FDA) estimated the average dietary intake of disulfoton from 1986-1991 for a 14- to 16-year-old male in the United States at 0.2 ng/kg body weight/day, a quantity over 1,000 times lower than the Food and Agricultural Organization of the United Nations/World Health Organization's (FAO/WHO) acceptable daily intake (ADI) of 300 ng/kg body weight/day (EPA 1993b; FAO/WHO 1991; Winter 1992; Yess 1991).

Workers in industries that manufacture and formulate disulfoton, farm workers who enter treated fields after the insecticide has been applied and, in particular, applicators of the insecticide are at a higher risk of exposure than the general population. Among the general population, people who use the insecticide in homes and garden applications are at a higher risk of exposure, as are people who live near hazardous waste sites containing disulfoton.

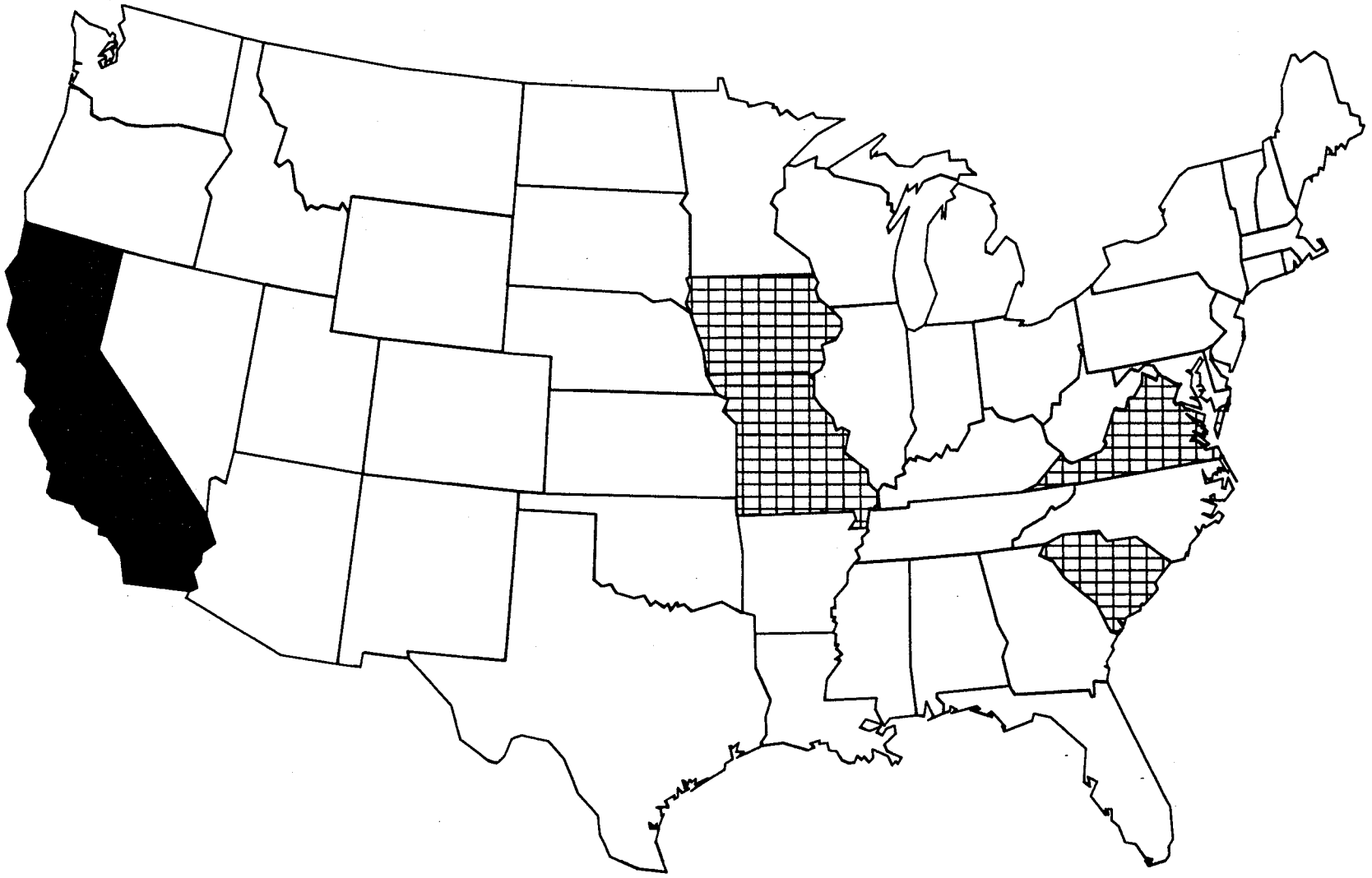
Disulfoton has been identified in 7 of the 1,408 hazardous waste sites on the NPL (HazDat 1994). The frequency of these sites within the United States can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Disulfoton may enter the atmosphere during its production and its use as an insecticide/acaricide. Air emissions from disulfoton production have been reported to be 0.5 kg per 1,000 kg (one metric ton) (Sittig 1980). Assuming a minimum production volume of 3.1 million pounds (1.4 million kg) per year, based on Gianessi and Puffer (1992) use estimates for 1989 through 1991, approximately 1,500 pounds (700 kg) are emitted to the atmosphere from production annually. Disulfoton is primarily released to the atmosphere during application of the granular insecticide by ground broadcast or aerial application (CPCR 1992). Disulfoton also enters the atmosphere when the emulsifiable insecticide is sprayed on crops and soil (CPCR 1992), and when the insecticide is aerially applied as a fog for controlling mosquitos (Racke 1992; Warnick and Eldredge 1972). Although not as significant a source, unintentional releases of disulfoton into the atmosphere include volatilization of applied insecticide from soil and plant surfaces, and accidental spills.

FIGURE 5-1. FREQUENCY OF NPL SITES WITH DISULFOTON CONTAMINATION *



*Derived from HazDat 1994

5.2.2 Water

Other than aerial application over swamps for mosquito abatement, disulfoton is not known to be used over water. Potential sources of release into surface water include discharge of waste water from disulfoton manufacturing, formulation, and packaging facilities (HSDB 1994). Leaching and runoff from treated fields, pesticide disposal pits, or hazardous waste sites may contaminate both groundwater and surface water with disulfoton. Entry into water can also occur from accidental spills. Small amounts of volatilized disulfoton may be removed from the atmosphere as a result of wet deposition and may enter surface water (Racke 1992).

5.2.3 Soil

Disulfoton is released to agricultural, home, and garden soil during direct soil or foliar treatment with the insecticide and from disposal of disulfoton-containing wastes in hazardous waste sites (HSDB 1994). Much of the foliar-applied disulfoton or its metabolites eventually reach the soil (Racke 1992). Soil in waste disposal sites may include manufacturing wastes containing disulfoton. A primary method for disposing of liquid pesticide wastes has been dumping liquid materials into soil evaporation pits, ditches, and ponds. Topsoil from such discharge areas can be expected to be contaminated with pesticides, as the soil from one such discharge pit contained disulfoton (Winterlin et al. 1989). Soil from tail water pits used for collecting irrigation runoff may also be a source of disulfoton if the soil has been treated with this insecticide (Kadoum and Mock 1978). Small amounts of disulfoton may enter soil by deposition of aerial disulfoton on land (Racke 1992). Entry may also occur from spills during storage, transport, or equipment loading and cleaning, although contemporary management practices significantly reduce the quantities of disulfoton accidentally released during its use (Racke 1992).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

There is a paucity of experimental data regarding the transport and partitioning of disulfoton in air. Given the vapor pressure of 1.8×10^{-4} mm Hg at 20 ºC (Melnikov 1971), disulfoton should exist almost entirely in the vapor phase in the atmosphere (Eisenreich et al. 1981). Because of low particle

diameter, the removal rate by dry deposition is low for compounds that exist in the vapor phase in the atmosphere (Schroeder et al. 1987); therefore, depending on its reactivity characteristics, vapor-phase disulfoton may travel long distances in the air. The solubility of 25 mg/L (Sanborn et al. 1977) ensures that at least partial removal of atmospheric disulfoton will occur by wet deposition.

The transport of disulfoton from water to air can occur due to volatilization. Compounds with a Henry's law constant (H) of <10m^{-5} atm-m^3/mol volatilize slowly from water (Thomas 1990). Therefore, disulfoton, with an H value of 2.17x10^{-6} atm- m^3/mol (Domine et al. 1992), will volatilize slowly from water. The rate of volatilization increases as the water temperature and ambient air flow rate increases and decreases as the rate of adsorption on sediment and suspended solids increases (Dragan and Carpov 1987). The estimated gas-exchange half-life for disulfoton volatilization from the Rhine River at an average depth of 5 meters at 11 ºC was 900 days (Wanner et al. 1989). The estimated volatilization half-life of an aqueous suspension of microcapsules containing disulfoton at 20 ºC with still air was >90 days (Dragan and Carpov 1987).

Adsorption to particulate matter will transport disulfoton from water to suspended solids and sediment in water. The estimated organic carbon-adjusted soil sorption coefficient (Koc) for disulfoton varies between 600 and 1,603 (Jury et al. 1987a; Rao and Davidson 1982; Wauchope et al. 1992). This range of K_{oc} values suggests that disulfoton in water adsorbs moderately to suspended solids and sediments (Swann et al. 1983), and this process may transport considerable amounts of disulfoton from water to particulate matter.

Based on structure activity relationships, certain regression equations have been developed to estimate disulfoton's bioconcentration factor (BCF) from its water solubility and K_{oc} values. Based on these regression equations, the estimated BCF for disulfoton in aquatic organisms is 100-l 10 (Kenaga 1980). A microcosm, simulating paddy fields containing water, sweet potato, tobacco cutworm *(Spodoptera litura),* algae *(Spirogyra crassa),* red snail *(Indoplanorbis exustus), Daphnia,* mosquito larvae *(Culex pipiens),* and guppies *(Labistes reticulatus),* was used to assess disulfoton accumulation in aquatic organisms over a 33-day period (Tomizawa 1980). Whole-body BCF values of 9 and 2,487 were reported for snails and guppies, respectively. The bioconcentration of disulfoton and its oxidation products (sulfoxide and sulfone) in *carp (Cyprinus carpio)* was investigated in a continuousflow water system for ≤56 days (Takase and Oyama 1985). The whole-body BCF values in carp were

≈450 for disulfoton, <l for the sulfoxide, and <6 for the sulfone. Disulfoton disappeared rapidly from fish tissues when the fish were transferred to uncontaminated fresh water.

The transport processes that may move disulfoton from soil to other media are volatilization, leaching, runoff, and absorption by plants. Volatilization of disulfoton from wet soil may be greater than from relatively dry soil (Gohre and Miller 1986). Like other pesticides, disulfoton in soil partitions between soil-sorbed and soil-water phases (Racke 1992). This latter phase may be responsible for the volatilization of disulfoton from soil; however, due to the low Henry's law constant value, the rate of disulfoton volatilization from the soil-water phase to the atmosphere would be low.

The reported K_{oc} values of 600-1,603 suggest that the adsorption of disulfoton to soil is moderately strong and that the rate of leaching may be minor in most soils. Batch-type adsorption tests and soil column studies showed that the disulfoton adsorption rate in soil increases as the clay content of the soil increases (King and McCarty 1968; McCarty and King 1966). Disulfoton leaching through Hugo sandy loam soil was initially rapid, but very little further leaching was observed with an increase in eluent volume (McCarty and King 1966). For example, 27.5% of disulfoton applied to a 6-inch soil column eluted with a total of 4 feet of buffered water (pH 7), but only 29% eluted with a total of 110 feet of buffered water. Other investigators concluded from soil column and soil thin-layer chromatography studies that disulfoton is only very slightly to moderately mobile in soil (Harris 1969; Helling et al. 1974; Thornton et al. 1976). Mobility may decrease with an increase in soil pH and organic content (Thornton et al. 1976). The oxidation products of disulfoton (sulfone and sulfoxide) are less mobile in soils than the parent compound (EPA 1989b). Due to increased polarity, the mobility of the oxidation products is expected to depend on the soil's cation exchange properties; mobility would decrease as the soil's cation exchange potential increases. Disulfoton has been detected infrequently and at low concentrations in groundwater from agricultural soil (Holden 1986; Mostaghimi et al. 1993) and in groundwater from disposal sites (Plumb 1991). These observations suggest that small amounts of disulfoton can leach through certain soils into groundwater.

Disulfoton is also transported through soils or from soil to surface water (streams or rivers) via runoff. Pesticides with water solubilities >10 mg/L move mainly.in solution phase in runoff water (Racke 1992). Disulfoton, with a water solubility of 25 mg/L (Sanbom et al. 1977), is expected to be found mainly in runoff water. In a runoff event from agricultural soil in Nebraska, low levels of disulfoton

were detected both in the dissolved state and in eroding soil particles in the sorbed state (Spalding and Snow 1989).

Disulfoton is absorbed from soil by the root systems of plants and is translocated to the plant top (Nash 1974). Plants metabolize disulfoton to its sulfone, sulfoxide, and oxons (Szeto et al. 1983a, 1983b). The concentrations of disulfoton and its metabolites in plant tops depend on the applied dosage in soil and the type of plants. The level of parent compound and its metabolites reaches a maximum concentration in plants within days or weeks and then tends to decrease (Nash 1974; Szeto et al. 1983a, 1983b). When disulfoton was applied to a soil at levels of 0.5 and 4.0 kg active ingredient per hectare in asparagus field plots, the levels of sulfone, sulfoxide, and oxons in asparagus ferns increased steadily to maximums of 14 and 61 mg/kg (fresh weight) in 70-85 days and then declined to 0.4 and 17.1 mg/kg in 147 days; no parent compound was detected at any time after 14 days following application (Szeto et al. 1983a). Similarly, the metabolites of disulfoton were detected in lettuce grown in a treated field (Szeto et al. 1983b). The residual levels of disulfoton and its metabolites in vegetables grown on treated soil were highest in carrots, intermediate in Chinese cabbage, and lowest in turnips (Sanbom et al. 1977). Recently, Chapman et al. (1994b) studied the effects of multiple soil applications of disulfoton (one treatment each year for 3 years) on enhanced microbial degradation in soil and subsequent uptake by seed potatoes and foliage. Disulfoton was the major insecticidal component detected in soil, a minor component of seed potatoes, and was not detected (<0.02 ppm) in potato foliage during all three treatment years. Disulfoton sulfoxide and sulfone were the major insecticidal degradation products detected in the seed potatoes and foliage.

In the first year, the maximum concentrations of sulfoxide and sulfone in soil, seed potatoes, and foliage were approximately 2, 2, and 6 times, respectively, the concentrations of those metabolites measured in the second and third year treatments. These results demonstrated that enhanced microbial degradation of relatively minor insecticidal compounds in the soil can significantly affect insecticide levels in the plant (when these degradation products are the major insecticidal component accumulated). As the sulfoxide and the sulfone metabolites are the major toxicants in the foliage of potato plants grown in disulfoton-treated soil, this reduction in toxicant residues over time can be expected to reduce insecticide efficacy.

5.3.2 Transformation and Degradation

5.3.2.1 Air

One of the important reactions for most organic pollutants in the atmosphere is with hydroxyl radicals. Using an estimation method (Atkinson 1988), the estimated rate constant for the vapor-phase reaction of disulfoton with hydroxyl radicals is 13.2×10^{-11} cm3/molecule-sec. Based on this value and assuming an average atmospheric hydroxyl radical concentration of 5×10^5 radicals/cm^3 (Atkinson 1988), the estimated half-life of disulfoton in the atmosphere due to this reaction is 3 hours. Therefore, disulfoton is short-lived in the atmosphere. Disulfoton is not susceptible to direct photolysis in sunlight (Gohre and Miller 1986). As with soil and water (Gohre and Miller 1986; Zepp et al. 1981), it is possible that disulfoton reacts with singlet oxygen in the atmosphere. The importance of this reaction for the transformation of disulfoton cannot be assessed because a reaction rate is unavailable.

5.3.2.2 Water

The three processes responsible for the transformation and degradation of disulfoton in water are abiotic hydrolysis, photosensitized oxidation, and biodegradation. Disulfoton is most stable towards hydrolysis in the pH range l-5 (Muhlmann and Schrader 1957). The experimentally estimated rate constants for the hydrolysis of disulfoton at 70 ºC were 1.16×10^{-2}/hour, 1.56×10^{-2}/hour, 2.50×10^{-2}/hour, 3.22×10^{-2}/hour, and 9.61×10^{-2}/hour at pH of 5, 6, 7, 8, and 9, respectively (Muhlmann and Schrader 1957). The corresponding estimated half-lives are 60, 44, 27.6, 21.5, and 7.2 hours. The estimated hydrolysis half-life of disulfoton at 70 ºC and pH 6.9 in ethanol-aqueous buffer solution (20:80) was 32 hours (Ruzicka et al. 1967). Other investigators reported the hydrolysis half-life of disulfoton under more realistic environmental conditions. For example, estimated hydrolysis half-lives were 103 days at 25 ºC and pH 7 (Ellington et al. 1988) and 170 days at 11 ºC and pH 7.9 (Wanner et al. 1989). Hydrolysis products of disulfoton are diethylthiophosphoric acid and 2-ethylmercaptothio ether (Muhlmann and Schrader 1957).

Direct photolysis of disulfoton is negligible, since it does not significantly absorb sunlight (Wanner et al. 1989). Disulfoton is more likely to react with singlet molecular oxygen ($^1O_2$) produced from the reaction of certain photochemically excited dissolved organic matters (e.g., humic and fulvic

substances) with molecular oxygen in water (Zepp et al. 1981). The estimated near-surface half-life for photosensitized oxidation of disulfoton by sunlight available during midwinter in the southern United States was 3 hours (Zepp and Baughman 1978). Due to light attenuation with increasing water depth, the half-life of disulfoton due to the oxidation reaction is expected to increase with increasing water depth. Estimated half-lives due to photosensitized oxidation are 1,000 days at a depth of 5 meters for a winter day and 100 days for a summer day (Wanner et al. 1989). The products of photosensitized oxidation are disulfoton sulfone and disulfoton sulfoxide (Mitchell et al. 1968). Hydroxyl radicals in natural water also oxidize disulfoton. When a 13 umol solution of disulfoton was exposed to October sunlight (Davis, California) in the presence of 100 umol hydrogen peroxide, 49% of the insecticide disappeared in 10.2 days due to reaction with hydroxyl radicals (Draper and Crosby 1984). The rate of this reaction will be slower in natural surface water where the concentration of available hydroxyl radicals is lower than that available from the photolysis of 100 pmol hydrogen peroxide (levels ≤30 pmol hydrogen peroxide are generated in eutrophic water) (Draper and Crosby 1984).

Following an accidental discharge of stored chemicals including disulfoton, the estimated biodegradation half-life of disulfoton in Rhine River water was between 7 and 41 days at 10 ºC (Wanner et al. 1989). Therefore, biodegradation of disulfoton is expected to be important in water, and the rate will depend on the initial concentration. A theoretical model predicted that over 12 days biodegradation and photolysis would account for an 80% mass loss of disulfoton in the Rhine River after an accident spill incident (Mossman et al. 1988); however, the removal of disulfoton by chemical processes was much slower than by biodegradation (Cape1 et al. 1988).

5.3.2.3 Sediment and Soil

Disulfoton in soil and sediment may undergo degradation and transformation by hydrolysis, photoinduced oxidation, and biotic processes. The hydrolysis of disulfoton may occur in the soil/sediment-water phase, as opposed to the soil/sediment-sorbed phase. As a result, the rate of hydrolysis is expected to be comparable to that in water. Based on slow hydrolysis rates observed in water (see Section 5.3.2.2), hydrolysis of disulfoton in soil is not expected to be significant. A group of investigators reported the oxidation of disulfoton on soil surfaces by singlet oxygen produced from sunlight irradiation (Gohre and Miller 1986; Hebert and Miller 1990; Miller et al. 1989). The initial loss of disulfoton on soil surfaces by photooxidation is quite rapid and slows down as the reaction

proceeds. Thus, attributing the loss to a first-order rate process and assigning a half-life to this process is misleading (Miller et al. 1989). Although the most rapid oxidation occurred in soil with the lowest organic carbon, half of the original concentrations of disulfoton in four different soil samples was lost in ≈3 days (Gohre and Miller 1986). The rate substantially decreased over the course of irradiation. The photooxidation of disulfoton occurred appreciably deeper than optical depths (depths for sunlight penetration in soil) of 0.2-0.3 mm (Hebert and Miller 1990). In aerated and moisture-unsaturated soil, the photooxidation can proceed up to a soil depth of 2 mm (Hebert and Miller 1990). The primary photooxidation product was the sulfoxide with trace amounts of the sulfone (Gohre and Miller 1986).

In laboratory tests, several fungi and cultures of actinomycetes isolated from garden soil readily degraded disulfoton (Bhaskaran et al. 1973). In flooded soil under anaerobic conditions, the reduction of disulfoton sulfoxide to disulfoton was due to biological conversion (Tomizawa 1975). The reduction of sulfone to either sulfoxide or sulfide (i.e., disulfoton) was not observed under the same conditions. Since the bacterial populations in sediments and soils are higher than in typical surface waters (Mossman et al. 1988), biodegradation is expected to play a major role in the loss of disulfoton in soil and sediment, as occurred in the disulfoton spill in the Rhine River (Cape1 et al. 1988; Wanner et al. 1989).

Several investigators have reported the rate of overall loss of disulfoton from soil due to all biotic and abiotic processes. The estimated half-life of disulfoton in soil ranged from 3.5 to 14 days (Chapman et al. 1993; Garg and Sethi 1980; Greenhalgh 1978; Harris et al. 1988; Jury et al. 1987a; McCarty and King 1966; Rao et al. 1985; Shaw 1975), although half-life values of 17 days and 42 days were reported for loam and Plainfield sand respectively (Chapman et al. 1994a). A half-life value of ≤290 days was also reported for soil (soil type unspecified) (Menzie 1972). The estimated persistence of disulfoton in soil varied between 28 and >64 days (Belanger and Hamilton 1979; Clapp et al. 1976; Jury et al. 1987b; Keamey et al. 1969). Soil type and soil temperature influenced the degradation rate of disulfoton. Disulfoton degraded almost twice as fast over the first 12 weeks post-application in loam as compared to Plainfield sand; however, the authors believe that lower temperatures may have contributed to the slower disappearance of disulfoton in the Plainfield sand study (Chapman et al. 1994a). Since the compound degraded faster during winter in Evesboro loamy sand soil than during summer in Chillum silt loam soil, the authors (Menzer et al. 1970) concluded that soil type was predominantly responsible, rather than temperature.

The presence of light and higher soil pH (pH 8 versus 5) also accelerated degradation of disulfoton in soil (Shaw 1975). The only metabolites isolated from disulfoton degradation in soil were the sulfoxide and sulfone (Chapman et al. 1994a, 1994b); only minute amounts of oxons were found (Clapp et al. 1976; Greenhalgh 1978; Shaw 197.5; Szeto et al. 1983a). Diethyl phosphorothioate was identified as the major metabolite in the aqueous fraction of soil (Shaw 1975). Disulfoton and disulfoton sulfoxide degraded in ≤32 days in soil, while disulfoton sulfone persisted for >64 days (Clapp et al. 1976; Greenhalgh 1978).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Disulfoton was detected at maximum and mean concentrations of 4.7 and 0.1 ng/ m^3 in only 1 of 123 ambient air samples collected from 10 locations in the United States in 1980 (Carey and Kutz 1985; Kutz 1983; Kutz and Carey 1986). No other air monitoring data were located.

5.4.2 Water

Disulfoton was detected in 7 groundwater samples from 28 California counties at a maximum of 6 µg /L from May 1979 to April 1984 (Cohen 1986; Hallberg 1989; Holden 1986). In an earlier survey of 48 municipal and 6 private groundwater supply systems in California, no disulfoton was detected at a minimum detection limit of 5 µg /L (Maddy et al. 1982). Disulfoton was not detected (detection limit of 1 µg /L) in over 1,508 samples from 358 groundwater wells in Wisconsin during 1980-1984 (Holden 1986; Krill and Sunzogni 1986). As of 1983, disulfoton was not detected (detection limit not given) in three samples of groundwater from Suffolk County, New York (Holden 1986). Disulfoton was detected in a 1985 survey of groundwater in the Nomini Creek Watershed in Virginia. The mean and maximum concentrations detected were 0.39 ppb and 2.87 ppb respectively. The frequency of detection of disulfoton in this watershed was 2.6% (Mostaghimi et al. 1993). Disulfoton was qualitatively detected (detection limit of 0.1 µg /L) in three groundwater samples from 1 of 479 hazardous waste disposal sites in the United States (Plumb 1991).

Recently, levels of disulfoton in an agricultural watershed were monitored during a spring runoff event in Shell Creek, an eastern tributary of the Platte River in Nebraska. The concentrations of disulfoton in this agricultural watershed ranged from trace to 0.4 µg /L (Spalding and Snow 1989).

During 1981-1985, disulfoton and other pesticides were monitored at three watersheds adjacent to agricultural production areas: the mouths of the Grand River, the Saugeen River, and the Thames River, Ontario, Canada (Frank and Logan 1988). At a detection limit of <0.1 µg /L, no disulfoton was detected in the river water samples. Disulfoton was also not detected (detection limit of 0.003 µg /L) in samples of water collected from Lakes Superior and Huron, including Georgian Bay, in 1974 (Glooschenko et al. 1976).

5.4.3 Sediment and Soil

The primary method for the disposal of liquid pesticide wastes in California in the past has involved soil evaporation pits, ditches, and ponds (Winterlin et al. 1989). A core soil sample taken from one such pit in northern California contained 44 mg/kg disulfoton at a depth of 90 cm (Winterlin et al. 1989). Disulfoton was detected in six of seven bottom soil samples from tail water pits used to collect irrigation runoff in Haskell County, Kansas, in 1974. The maximum and mean concentrations of disulfoton in these samples were 32.7 and 13.42 µg /kg respectively (Kadoum and Mock 1978). At a detection limit of 0.01 mg/kg, disulfoton was not detected in sediment samples collected from Lakes Superior and Huron, including Georgian Bay, in 1974 (Glooschenko et al. 1976).

5.4.4 Other Environmental Media

Disulfoton was detected in 1 of 360 food composites collected from different locations in the United States in fiscal year 1969. The positive sample was a composite of leafy vegetables collected from Boston, Massachusetts, that contained 2 µg /kg of disulfoton (Comeliussen 1970). From this data, the estimated daily adult human intake of disulfoton was <l µg /day in 1969 (Duggan and Comeliussen 1972). During fiscal year 1976, the FDA identified disulfoton in one sample each of cereal byproducts and leaf and stem vegetables, and in four samples of oilseed byproducts (Duggan et al. 1983). Disulfoton was also detected in one sample of whole grains for animal use and four miscellaneous animal feed samples (Duggan et al. 1983). The FDA’s monitoring program for domestic and imported food commodities during fiscal years 1978-1982 detected disulfoton in

unspecified foods at unspecified concentrations (Yess et al. 1991). During 1982-1986, the FDA Los Angeles District Laboratory analyzed 19,851 samples of domestic and imported food and feed commodities (Luke et al. 1988). Disulfoton sulfone was detected in 45 samples of 6,391 domestic agricultural commodities and in 1 sample of 12,044 imported agricultural commodities at concentrations ranging from 0.05-1.0 mg/kg. In domestic foods, disulfoton sulfone was detected in broccoli, cabbage, Boston lettuce, butter lettuce, green leaf lettuce, iceberg lettuce, red leaf lettuce, romaine lettuce, potatoes, and spinach; it was also detected in imported tomatillos (Hundley et al. 1988). Disulfoton was not detected in 14,492 domestic and imported food samples analyzed as part of the FDA pesticide monitoring program for 1986-1987 (FDA 1988). Disulfoton was not detected in various domestic food commodities by state regulatory monitoring activities during fiscal year 1988-1989 (Minyard et al. 1991). In a pesticide residue screening program conducted in 1989-1991 in San Antonio, Texas, on 6,970 produce samples, disulfoton was detected (0.1 ppm detection limit) in two produce samples (one sample of broccoli and one sample of cabbage) (Schattenburg and Hsu 1992). As part of the FDA's Pesticide Monitoring Program for domestic and imported foods, disulfoton residues have been detected in unspecified foods at unspecified concentrations during 1988-1989, 1989-1990, 199&1991, and 1991-1992 (FDA 1990, 1991, 1992, 1993).

Processing raw food reduced disulfoton levels in some potato products (Kleinschmidt 1971). Total residues were reduced by 35% with lye peeling. Lye peeling plus the first water blanching reduced the total disulfoton residue on a dry weight basis by 58, 74 and 61% for french fries, dehydrated potato cubes and dehydrated mashed potatoes, respectively.

In a study of pesticide residue contamination of processed milk-based and soy-based infant formula, disulfoton was not detected (detection limit <0.02 µg /g [ppm]) (Gelardi and Mountford 1993). The EPA Office of Water has recommended that disulfoton residues be monitored by states in their fish and shellfish contaminant monitoring programs in watersheds where this pesticide is currently used extensively in agriculture (EPA 1993a). While no fish or shellfish consumption advisories are currently in effect for disulfoton, this contaminant has not been widely monitored in national fish contaminant monitoring programs (e.g., the EPA National Study of Chemical Residues in Fish or the U.S. Fish and Wildlife Service National Contaminant Biomonitoring Program) (EPA 1993a).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is exposed to disulfoton by inhaling air and ingesting drinking water and food containing disulfoton. Toxicokinetic data show that disulfoton is readily and extensively absorbed by the gastrointestinal tract (see Section 2.4). The urinary metabolites of disulfoton are DEP, DETP, DEDPT, and DEPTh (see Section 2.3). Although the occurrence of these phosphate esters in human urine may not result specifically from exposure to disulfoton, detection of these metabolites in human urine indicates the possibility of exposure to disulfoton or several other organophosphate insecticides. Specimens of urine collected at 64 locations across the United States, comprising the sample areas in NHANES II, reported detection (detection limit 20 µg /L or ppb) of DEP and DETP at a frequency of 6-7% and DEDPT at a frequency of <1% of those tested (Murphy et al. 1983). Other than during home and garden insecticide application, exposure of the general public to disulfoton from skin contact with consumer products is not expected. Those among the general population who use the insecticide for homes and gardens are potentially at higher risk of exposure to disulfoton. It has been estimated that application to rose plants and other omamentals constitute by far the largest home and garden use of disulfoton (Whitmore et al. 1992).

Disulfoton has been very infrequently detected in ambient air (0.8% of air samples from 10 cities) and at very low concentrations (mean of 0.1 ng/ m^3 in detectable samples) (see Section 5.4.1). Therefore, the exposure of the general population to disulfoton from inhaling ambient air is probably insignificant. Disulfoton has never been detected in drinking water (see Section 5.4.2), possibly because of it occurs at very low concentrations and has only infrequently been detected in groundwater (Cohen 1986; Hallberg 1989; Holden 1986; Mostaghimi et al. 1993; Plumb 1991). Therefore, general population exposure to disulfoton from consumption of drinking water is negligible.

Disulfoton has been detected in some foods (see Section 5.4.4); thus, consumers can be exposed to disulfoton by ingesting contaminated food. The FDA has estimated daily food intakes of disulfoton for different age/sex groups in the United States for fiscal years 1982-1984 as follows:
6-11 months = 0.6; 2 years = 1.1; 14-16-year-old females = 0.4; 14-16-year-old males = 0.3; 25-30-year-old females = 0.3; 25-30-year-old males = 0.3; 60-65-year-old females = 0.5; and 60-65-year-old males= 0.6 (ng/kg body weight/day) (Gunderson 1988). The reported corresponding values for combined disulfoton and its metabolites (e.g., sulfone, sulfoxide, etc.) are 2.2, 4.8, 2.3, 1.8, 2.4, 2.2, 2.9, and 3.0 (ng/kg body weight/day) (Gunderson 1988). The FDA reported the following

dietary intakes of disulfoton for different age/sex groups in fiscal year 1990: 6-11 months, <0.1; 14-16-year-old males, 0.2; and 60-6.5year-old females, 0.3 (ng/kg body weight/day) (FDA 1991, Winter 1992; Yess 1991). Most recently, the FDA reported the following dietary intakes of disulfoton (total) for different age/sex groups averaged over 1986-1991: 6-11 months, 0.1; 2 years, 0.3; 14-16-year-old males, 0.2; 14-16-year-old females, 0.2; 25-30-year-old females, 0.4; 25-30-year-old males, 0.3; 60-65year-old females, 0.4; and 60-65-year-old males, 0.3 (ng/kg body weight/day) (FDA 1993). These 1982-1984, 1990, and 1986-1991 intakes estimated from the FDA Total Diet Study Program show a declining trend in the estimated daily food intakes of disulfoton over the past 10 years. All of the FDA estimated daily food intakes for the various sex and age groups are more than 1,000 times lower than the FAO/WHO Acceptable Daily Intake (ADI) value of 2,000 ng/kg body weight/day and an EPA revised reference dose of 40 ng/kg body weight/day ((FAO/WHO 1991; FDA 1991, 1993; Winter 1992; Yess 1991).

Workers involved in the manufacture, formulation, handling, or application of disulfoton, or those involved in the disposal of disulfoton-contaminated wastes are likely to be exposed to higher concentrations by dermal contact and inhalation than the general population. When granular disulfoton was applied at 0.75 active ingredient per acre to a field by air, the estimated inhalation exposure to disulfoton was 0.02 mg/8-hour day for the pilot and 0.03 mg/8-hour day for the ground staff (Myram and Forrest 1969). The estimated inhalation exposure to disulfoton for workers using ground machines was 0.33 mg/8-hour day (Myram and Forrest 1969).

No information was found in the National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 on the number of workers and the number of facilities where workers could be potentially exposed to disulfoton in the United States (NOES 1990). NIOSH (1992) recommends that the exposure level to skin not exceed 0.1 mg/ m^3 for a l0-hour time weighted average workday.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Other than individuals who are occupationally exposed to disulfoton during its production, formulation, packaging, distribution, use, or disposal, populations exposed to higher than background concentrations of disulfoton in ambient air include those living near chemical manufacturing or processing sites, individuals living on farms or in the vicinity of agricultural areas where disulfoton is extensively used,

and individuals living near hazardous waste sites. Individuals living near these sites may also be exposed to potentially higher concentrations of disulfoton or its metabolites in their drinking water if they obtain tap water from wells near these sources. Children may receive higher disulfoton doses from dermal exposures if they play on freshly treated soils. In addition, children may receive potentially higher oral doses from ingestion of disulfoton contaminated soils from their hands while playing in contaminated areas.

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

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.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. As seen in Table 3-2, the relevant physical and chemical properties of disulfoton are known (Bowman and Sans 1983; Domine et al. 1992; HSDB 1994; Kenaga and Goring 1980; Melnikov 1971; Merck 1989; Sanbom et al. 1977; Worthing 1987) and predicting the environmental fate and transport of disulfoton based on K_{ow}, K_{oc}, and H is possible.

Production, Import/Export, Use, Release, and Disposal. Knowledge of production and use data for a chemical is important in predicting its potential for environmental contamination and human exposure. Since disulfoton is produced by only one manufacturer (SRI 1994), to maintain confidentiality, its recent production volume is not known. Similarly, data concerning the import and

export volumes for disulfoton in recent years are not available. Estimates of its yearly use in the United States are available (Gianessi 1986; Gianessi and Puffer 1992; Goodrich et a1.1991; VonRumker et al. 1974). No information in the available literature was located that indicates disulfoton's use in any consumer products other than edible crops and vegetables during and after their planting (EPA 1984b; VonRumker et al. 1974). Disulfoton enters the environment primarily during its use as an agricultural insecticide/acaricide on a variety of field and vegetable crops and in its use in home and garden applications. Disulfoton wastes have been disposed of in soil evaporation pits, ditches, and ponds (Winterlin et al. 1989) and in hazardous waste sites. Thus, soils are most likely to be contaminated with this pesticide. Although some information regarding the disposal of wastes containing disulfoton is available (Berlow and Cunningham 1989; HSDB 1994; IRPTC 1985; Sittig 1980), more detailed information on the method used for the disposal of aqueous wastes would be helpful. The standards promulgated by the EPA for the disposal of wastes containing disulfoton are available (Berlow and Cunningham 1989).

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 1988-1992, became available in May of 1994. This database will be updated yearly and should provide a list of industrial facilities and emissions. However, no TRI data were located for disulfoton because this chemical is not required to be reported by chemical producers (EPA 199313).

Environmental Fate. Information regarding the fate of disulfoton in the air was not located in the literature. Although the available data indicate that the concentration of disulfoton in air will be low (Carey and Kutz 1985), more information would help predict the distance of its aerial transport. The fate of disulfoton in water is better studied (Wanner et al. 1989). Although it has been estimated that sorption onto particulates and settling into the sediment may not be important for disulfoton in Rhine River water, more information regarding the relative importance of sorption for disulfoton' s removal from water to sediment would be helpful (Wanner et al. 1989). There is conflicting evidence in the literature (Harris 1969; Helling et al. 1974; King and McCarty 1968; McCarty and King 1966) regarding disulfoton's mobility in soil. Disulfoton is degraded in soil by hydrolysis, photoinduced oxidation, and biodegradation (Bhaskaran et a1.1973; Cape1 et al. 1988; Chapman et al. 1993, 1994b; Gohre and Miller 1986; Hebert and Miller 1990; Miller et al. 1989; Tomizawa 1975; Wanner at al.

1989). Additional information on degradation of disulfoton in water and air and the fate of the degradation products in soil would be helpful.

Bioavailability from Environmental Media. Available information regarding the rate of disulfoton absorption following inhalation, oral, or dermal contact has been discussed in the Toxicokinetics section (see Section 2.3). Although no data on disulfoton's bioavailability from contaminated air are available, the bioavailability from inhalation exposure is expected to be high because disulfoton is likely to be present in the vapor phase (Eisenreich et al. 1981) and not in the particulate phase in the adsorbed state. Similarly, no data on the bioavailability of disulfoton from water and soil or plant material are available; however, disulfoton adsorbs rather strongly to soil (Harris 1969; Helling et al. 1974; Wauchope et al. 1992). Since the part that remains adsorbed to soil or sediments may, at most, be partially bioavailable, disulfoton is expected to have reduced bioavailability from soil and water. Data on the bioavailability of disulfoton from actual environmental media need further development.

Food Chain Bioaccumulation. Disulfoton bioconcentrates to a moderate extent in fish (Takase and Oyama 1985; Tomizawa 1980); however, measured bioconcentration factor (BCF) values are not available for a large number of edible invertebrate and fish species. EPA (1993a) has recently recommended that states monitor disulfoton in fish and shellfish in watersheds where it is extensively used, and additional information on disulfoton residues may be available in the future. There is also a lack of data in the literature regarding the biomagnification potential of disulfoton through aquatic food chains. Available data on terrestrial food chains indicate that disulfoton is translocated from the root to aerial parts of the plants, where it is quickly metabolized to sulfone and sulfoxide (Nash 1974; Szeto et al. 1983a, 1983b). Data regarding the biomagnification potential of disulfoton in terrestrial and aquatic food chains would be desirable. These data would be helpful in assessing the potential for human exposure as a result of ingestion of contaminated food.

Exposure Levels in Environmental Media. Although some data on the levels of disulfoton in ambient air are available (Carey and Kutz 1985), these data are neither current nor general enough to estimate inhalation exposure to disulfoton for the general population in the United States. No data on the level of disulfoton in drinking water were located in the literature, although disulfoton has been detected in groundwater (Cohen 1986; Hallberg 1989; Holden 1986; Mostaghimi et al. 1993). More recent data regarding the levels of disulfoton in ambient air, in drinking water, and in soil are needed.

Data on disulfoton levels in food and recent estimates of human intake of disulfoton from foods are available (Duggan et al. 1983; FDA 1990, 1991, 1992, 1993; Gelardi and Mountford 1993; Gunderson 1988; Luke et al. 1988; Schattenburg and Hsu 1992; Yess 1991).

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

Exposure Levels in Humans. No data on disulfoton levels in various human tissues and body fluids of a control population, populations near hazardous waste sites, or occupationally exposed groups in the United States are available. The levels of disulfoton metabolites (DEP [0.05 ppm], DETP [0.04 ppm], DEPTh [0.005 ppm], dimethyl phosphate [0.04 ppm], dimethyl thiophosphate [0.180 ppm], and dimethyl phosphorothiolate [0.004 ppm]) in the urine of disulfoton formulators have been measured (Brokopp et al. 1981). Data on the levels of disulfoton and its metabolites in body tissues and fluids are needed to estimate the extent of exposure to disulfoton.

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

Exposure Registries. No exposure registries for disulfoton 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.

5.7.2 Ongoing Studies

A search of federal research programs in progress indicates a few projects that would fill some of the existing data gaps. Drs. Singmaster and Acin-Diaz of the University of Puerto Rico are developing methods for determining disulfoton residue levels in food commodities and for disulfoton disposal. Dr. Brady of the University of Georgia is conducting a study to determine disulfoton’s dissipation on peach fruit, on foliage, in soil, in tank mixes, and in building interiors.

6. ANALYTICAL METHODS

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

Several methods are available for analyzing disulfoton in biological media; some of the commonly used methods are reported in Table 6-l. A variety of detectors may be used for the gas chromatographic analysis of disulfoton, but flame photometric detectors are superior because of low background interference and good reproducibility (Holstege et al. 1991). Mass spectrometric detectors show high specificity (Kawasaki et al. 1992) and may also be used to confirm detection by other methods.

The stability of disulfoton must be considered at all stages of sample storage and analysis. Organophosphorus insecticides, including disulfoton, react with natural esterases in human tissue and may reduce the level of free organophosphates (Singh et al. 1986). Besides the esterases, phosphorylphosphatase in natural tissue hydrolyzes and inactivates organophosphorus compounds (Singh et al. 1986). As a result, the amount of organophosphates in blood and excreted in urine will be considerably less than the amount expected from its concentration at the time of exposure (Hattori et al. 1982; Singh et al. 1986).

As discussed in Section 2.5.1, the detection of certain thiophosphate esters in human urine may indicate exposure to disulfoton and/or other organophosphate insecticides. Several methods are

TABLE 6-1. Analytical Methods for Determining Disulfoton in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Cow feces (disulfoton and 5 metabolites as total residue)	Extraction with chloroform; concentration then oxidation with m-chloroperbenzoic acid; clean-up by column chromatography	GC/FPD	1 µg/kg[a]	74	Bowman and Beroza 1969
Bovine liver and rumen (disulfoton only)	Extraction with methanol-methylene chloride; clean-up by column chromatography; concentration	Capillary GC/FPD	10–50 µg/kg	90–109	Holstege et al. 1991
Plasma and urine (disulfoton only)	Plasma: extraction with ethyl acetate; urine: adjustment to pH 7.4, centrifugation, extraction with ethyl acetate	Capillary GC/MS (SIM)	No data	>75 (urine) <10 (blood)	Singh et al. 1986
Blood, urine, and stomach content (disulfoton and its metabolites)	Dilution with 2% saline; fractionation by column chromatography; analysis; then oxidation with potassium permanganate; fractionation by column chromatography	Capillary GC/FPD; GC/MS	No data	101–105	Yashiki et al. 1990
Blood and urine	Homogenization of sample with acetonitrile; extraction with hexane; concentration; dissolution in acetonitrile	GC/MS (SIM)	No data	70–90	Hattori et al. 1982

[a]Instrumental detection limit

GC = gas chromatography; FPD = flame photometric detection; MS = mass spectrometry; SIM = selected ion monitoring

available for the quantitation of organophosphorus metabolites from urine (Bradway et al. 1981; Daughton et al. 1976; Lores and Bradway 1977; Shafik et al. 1973).

6.2 ENVIRONMENTAL SAMPLES

Analytical methods for determining disulfoton in environmental samples are reported in Table 6-2. The steps included in the methods are solvent extraction, purification and fractionation, and gas chromatographic analysis. Other analytical techniques, including capillary gas chromatography with mass selective detection (Stan 1989), high-performance liquid chromatography with either mass spectrometric (MS) or MS-MS detection (Betowski and Jones 1988), have been used to determine disulfoton in environmental samples.

Precautions should be taken to avoid disulfoton loss from stored water, soil, sediment, crop, and vegetable samples (Belisle and Swineford 1988; Miller et al. 1981; Munch and Frebis 1992; Szeto and Brown 1982). Disulfoton, disulfoton sulfone, and disulfoton sulfoxide were not recovered from spiked well water stored 14 days; however, sample extracts were stable for 14 days (84-92% recovery) (Munch and Frebis 1992). In most environmental samples, disulfoton will be present along with its environmental transformation products, disulfoton sulfone, disulfoton sulfoxide, disulfoton oxon, disulfoton oxon sulfone, and disulfoton oxon sulfoxide (Szeto and Brown 1982). Disulfoton and its oxon are very unstable, and they oxidize rapidly to the corresponding sulfoxides. The sulfoxides are relatively stable, but they oxidize slowly to their sulfones, which are most stable (Szeto and Brown 1982). Several methods for determining the metabolites of disulfoton in environmental samples are included in Table 6-2.

Few methods were located for determination of disulfoton in air. Ambient air monitoring data were reported for samples collected by ethylene glycol impinger samplers with subsequent gas chromatographic analysis; however, no performance data were reported (Kutz et al. 1976). A method for determination of organophosphorus pesticides, including disulfoton, in workplace air involves collection using a combined filter/XAD-2 sorbent sampler and gas chromatography/flame photometric (FPD) detection (Kennedy et al. 1994). Recovery is very good (>90%) and samples are stable for 30 days when stored cold.

TABLE 6-2. Analytical Methods for Determining Disulfoton in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Workplace air	Collection on filter/XAD-2 sorbent; desorption with solvent	capillary GC/FPD	0.07 µg/mL[a]	91-94	Kennedy et al. 1994
Water	Addition of bromine water; incubation with lyophilized bovine acetyl-cholinesterase; addition of indophenol acetate; incubation	Colorimetric (field screening method)	0.01–0.12 ppm for sulfur-containing compounds	No data[b]	Zweig and Devine 1969
Water	Extraction with petroleum ether; concentration	Dual column GC/thermoionic detection	0.04 µg/L	94	Zweig and Devine 1969
Water	Micro-extraction with hexane	GC/FPD	0.1 µg/L	97	Bourgeois et al. 1993
Water	Adjustment of pH to 6.0; SPE extraction	Capillary GC/NPD	≤20 ng/L	92–113	Borburgh and Hammers 1992
Drinking water	Extraction with methylene chloride; solvent exchange to methyl tert-butyl ether	Capillary GC/NPD (EPA method 507)	0.3 µg/L (disulfoton) 3.8 µg/L (sulfone) 0.38 µg/L (sulfoxide)	87–107 (disulfoton) 92–104 (sulfone) 54–95.1 (sulfoxide)	Edgell et al. 1991; EPA 1988c
Groundwater	Extraction with methylene chloride; clean-up by column chromatography if required	GC/FPD (EPA method 8140)	0.2 µg/L (disulfoton)	82	EPA 1986a
Waste water	Extraction with methylene chloride; clean-up by column chromatography if required	GC/FPD	0.2 µg/L (disulfoton)	111	Miller et al. 1981
Waste water	Extraction with methylene chloride; solvent removal; optional clean-up using GPC and/or SPE columns (Method 1657)	Capillary GC/FPD, confirmation using second GC column	32 ng/L	No data	EPA 1992c
Sediment	Extraction with acetone-methylene chloride; passage through anhydrous sodium sulfate; concentration	Capillary GC/FPD	≤0.1 mg/kg	95–100	Belisle and Swineford 1988

TABLE 6-2. Analytical Methods for Determining Disulfoton in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil, asparagus tissue	Extraction with ethyl acetate; clean-up by column chromatography; oxidation of fraction containing sulfoxide and oxon sulfoxide by potassium permanganate	GC/FPD	0.01 mg/kg	83.5–110 (for disulfoton and metabolites)	Szeto and Brown 1982
Cow milk (disulfoton and 5 metabolites as total residue)	Extraction with methylene chloride; dried residue oxidize with m-chloroperbenzoic acid; clean-up by column chromatography	GC/FPD	1 μg/kg[c]	80	Bowman and Beroza 1969
Various crops and processed foods	Extraction with suitable solvent; precipitation of pigments by addition of ammonium chloride-orthophosphoric acid; oxidation with potassium permanganate	GC/thermoionic detection	0.02 mg/kg	75–100	Thornton and Anderson 1968
Fresh fruits and vegetables	Extraction of homogenized sample with acetonitrile; partition with sodium chloride solution; concentration of extract	Capillary GC/MS	0.05 mg/kg	84	Liao et al. 1991
Rice, wheat, buckwheat, and dried beans	Extraction of powdered sample with n-hexane; clean-up by liquid-liquid partition and column chromatography	GC/FPD	0.3 μg/kg	68–75	Aoki et al. 1975
Tobacco plants	Extraction finely chopped samples with chloroform-methanol; concentration; separation into three fractions by column chromatography	GC/FPD	0.01–0.04 mg/kg	88–100	Bowman et al. 1969

TABLE 6-2. Analytical Methods for Determining Disulfoton in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Produce	Homogenization; extraction with acetonitrile; concentration; solvent exchange	Dual capillary GC/AFID and FPD	0.1 mg/kg	76–118 (all organophosphates)	Hsu et al. 1991
Hair dyes	Extraction with acetone/-hexane; clean-up by GPC and silica gel chromatography	Dual capillary GC/ECD	0.01 mg/kg	No data	Cetinkaya 1993

[a]Instrumental detection limit; method detection limit ($\mu g/m^3$) will depend upon volume of air sampled.
[b]Test is qualitative: positive or negative
[c]Instrumental detection limit

AFID = alkali flame ionization detector; ECD = Electron capture detection; EPA = Environmental Protection Agency; FPD = flame photometric detection; GC = gas chromatography; GPC = gel permeation chromatography; HRGC = high resolution gas chromatography; NPD = nitrogen-phosphorus detection; SPE = solid phase extraction device

Overall recoveries are good (>80%) and detection limits are in the low to sub-parts-per-billion (ppb) range for determination of disulfoton in water (Borburgh and Hammers 1992; Bourgeois et al. 1993; EPA 1986a, 1988c). Methods for soil and sediment also provide good recovery (>80%) and detection limits are in the ppb range (Belisle and Swineford 1988; Szeto and Brown 1982). Methods for determination of disulfoton in food matrices generally provide acceptable recovery (≥75%) and detection limits in ppb range (Hsu et al. 1991; Liao et al. 1991; Szeto and Brown 1982).

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

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. Analytical methods are available to determine the concentrations of disulfoton and its metabolites in blood, urine, and other body tissue and fluids (Bowman and Beroza 1969; Brokopp et al. 1981; Hattori et al. 1982; Holstege et al. 1991; Singh et al. 1986; Yashiki et al. 1990). The accuracy of the methods in terms of percent recovery has been determined. A reasonably low detection limit can be obtained when flame photometric detection is used to determine disulfoton (Bowman and Beroza 1969; Holstege et al. 1991). When blood samples were spiked with 0.3 μg /g (ppm) of disulfoton, phosphorodithioate sulfone, and phosphorothiolate sulfone, and quantitated by gas-chromatography-flame photometric detection (GC/FPD) method, the recovery of disulfoton and two of its metabolites were in the range of

101.0-104.6% (Yashiki et al. 1990). In spiked urine samples, the detection limits of four metabolites of disulfoton (DEP, DETP, DEDPT, and DEPTh) were 0.01 ppm by a GC/FPD method (Brokopp et al. 1983). Due to the unavailability of data regarding disulfoton concentrations in tissues and body fluids of the background population, it is not known if the available analytical methods will be sensitive enough to determine these concentrations. Analytical methods are available for the detection of 4-hydroxy-3-methoxymandelic (HMMA), the major metabolite of catecholamine metabolism and a possible biomarker to characterize effects by disulfoton (Wysocka-Paruszewska 1971). It would be helpful to determine if the available analytical methods can measure disulfoton levels in body tissues and fluids of the background population. This will permit assessment of the severity of exposure of a highly exposed population.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Several methods are available for determining disulfoton and its degradation products in environmental samples such as contaminated water, food, and soil (Edge11 et al. 1991; EPA 1988c; Grant et al. 1969; Ruzicka et al. 1968; Szeto and Brown 1982; Zweig and Devine 1969). The specificity and accuracy of the methods are generally well established (see Table 6-2). In spiked water samples, the mean recoveries of disulfoton, disulfoton sulfone, and disulfoton sulfoxide were in the range of 86.5-104.0% (Edge11 et al. 1991). The recoveries of disulfoton and its metabolites in soil and asparagus tissue ranged from 83.5% to 110% (Szeto and Brown 1982). Consumption of contaminated food is probably the most important route of disulfoton exposure for the general population. Disulfoton has been found at much lower concentrations than the AD1 value (Winter 1992; Yess 1991). Developing sensitive methods for determining disulfoton in ambient air and for establishing background levels of disulfoton in environmental samples would be desirable.

6.3.2 Ongoing Studies

Drs. Singmaster and Acin-Diaz of the University of Puerto Rico are developing methods for determining disulfoton residue levels in food commodities. No other ongoing studies regarding the determination of disulfoton and its metabolite and degradation products in biological or environmental media were found.

7. REGULATIONS AND ADVISORIES

International, national, and state regulations and guidelines for disulfoton are listed in Table 7- 1.

An acute-duration inhalation MRL for disulfoton of 0.006 mg/ m^3 was derived. The MRL is based on a NOAEL of 0.5 mg/ m^3 for lethargy and decreased cholinesterase activity in rats exposed for 4 hours/day, 5 days/week (Thyssen 1978).

An intermediate-duration inhalation MRL for disulfoton of $2x10^{-4}$ mg/ m^3 was derived. The MRL is based on a NOAEL of 0.02 mg/ m^3 for decreased cholinesterase activity in rats exposed for 6 hours/day, 5 days/week for 3 weeks (Thyssen 1980).

An acute-duration oral MRL for disulfoton of 0.001 mg/kg/day was derived. The MRL is based on a NOAEL value of 0.1 mg/kg/day for decreased cholinesterase activity in rats treated by gavage on gestation days 6-15 (Lamb and Hixson 1983).

An intermediate-duration oral MRL for disulfoton of $9x10^{-5}$ mg/kg/day was derived. The MRL is based on a NOAEL value of 0.009 mg/kg/day for decreased cholinesterase activity in rat pups in a multigeneration feeding study in rats (Hixson and Hathaway 1986).

A chronic-duration oral MRL for disulfoton of 6 $x10^{-5}$ mg/kg/day was derived. The MRL is based on a LOAEL value of 0.06 mg/kg/day for decreased cholinesterase activity in female rats in a chronic feeding study (Hayes 1985).

EPA has verified a chronic oral reference dose (RfD) for disulfoton of 4 $x10^{-5}$ mg/kg/day (IRIS 1994). The RfD is based on the LOAEL of 0.04 mg/kg/day for cholinesterase inhibition in rats treated with disulfoton in the diet for 2 years (Hayes 1985).

The chronic-duration oral MRL for disulfoton is 6 $x10^{-5}$ mg/kg/day, and the EPA chronic oral RfD is 4 $x10^{-5}$ mg/kg/day (IRIS 1994). Both of these values are based on the same study (Hayes 1985) and the identical end point. Even though the MRL and the RfD are essentially the same, they have minor differences due to the manner in which the exposure doses were calculated. The LOAEL of 0.04 mg/kg/day used by EPA was calculated by multiplying the analytical dietary concentration of

0.8 ppm (nominal concentration of 1 ppm) by the reference rat food consumption factor of 0.05. However, Hayes (1985) provided an equivalent dose of 0.08 mg/kg/day for the nominal concentration of 1 ppm, based on actual food consumption and body weight data. The LOAEL of 0.06 mg/kg/day used in deriving the chronic oral MRL was obtained by multiplying the 0.08 mg/kg/day dose, corresponding to the nominal concentration of 1 ppm, by the analytical concentration of 0.8 ppm.

Disulfoton is on the list of chemicals appearing in "The Emergency Planning and Community Rightto-Know Act of 1986" (EPCRA) (EPA 1988d). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media.

An Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for disulfoton does not exist. A U.S. Court of Appeals decision rescinded the 1989 PELs promulgated by OSHA (OSHA 1989), which included a PEL for disulfoton. Only PELs in place prior to the 1989 are now allowed. Disulfoton had no PEL prior to 1989; therefore, it currently has no PEL.

Disulfoton is regulated by the Clean Water Effluent Guidelines as state in Title 40, Sections 400-475, of the Code of Federal Regulations. The point source category for which disulfoton has a specific Regulatory Limitation is the organic pesticide chemicals industry (EPA 1978a).

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), disulfoton is classified for restrictive use (EPA 1978b).

Under the Resource Conservation and Recovery Act (RCRA), disulfoton is listed as a hazardous waste when it is a discarded commercial chemical product, off-specification species (e.g., a product that does not meet purity or property specifications), container residue, and spill residue (EPA 1980c).

Table 7-1. Regulations and Guidelines Applicable to Disulfoton

Agency	Description	Information	References
INTERNATIONAL			
WHO	ADI	0.002 mg/kg	WHO 1976
	Temporary ADI established at 0.001 mg/kg		
	Guidelines in specific foods:		
	Alfalfa (hay, clover (hay)	10 mg/kg	
	Forage crops (green)	5 mg/kg	
	Vegetables including beans, broccoli, brussel sprouts, cabbage, cauliflower, celery, lettuce, maize, potatoes, peanut shells, peas (including pods), rice (in husk), spinich, sugar beets (roots), tomatoes		
	Raw grain (except rice and maize)	0.5 mg/kg	
	Coffee beans, pecans, peanuts (kernels), pineapple, soybeans	0.2 mg/kg	
		0.1 mg/kg	
NATIONAL			
Regulations:			
a. Water			
EPA OWRS	Priority pollutants regulated in pesticide active ingredient manufacturing wastewater	Yes	40 CFR 455 EPA 1992a
	Priority pollutant effluent limitation for BAT and PSES	Yes	
	Maximum for any 1 day	7.33×10^{-3} kg/kkg[a]	
	Monthly average shall not exceed	3.79×10^{-3} kg/kkg	
	Priority pollutant effluent limitation for NSPS and PSNS		
	Maximum for any 1 day	5.28×10^{-3} kg/kkg	
	Monthly average shall not exceed	2.72×10^{-3} kg/kkg	
EPA OW	App. D - NPDES Permit Application Testing Requirement, Table V: Toxic and Hazardous Substances	Yes	40 CFR 122 EPA 1983
	Form 2D - NPDES Permits	Yes	40 CFR 122 EPA 1983
	Form 2C - Criteria and Standards for NPDES	Yes	40 CFR 125 EPA 1989e
	Guidelines for Testing Pollutants Under CWA	Yes	40 CFR 136.3 EPA 1973
	Substances Prohibited from Underground Injection Control	Yes	40 CFR 148 EPA 1989a
	Calculating Effluent Limits for Organic Pesticides	Yes	40 CFR 455.20 EPA 1978a
	Test Methods for Pesticides	Yes	40 CFR 455.50 EPA 1992b
b. Other:			
EPA OERR	Reportable Quantity	1 pound	40 CFR 117.3 EPA 1985
	App. B - Extremely Hazardous Substance TPQ	500 pounds	40 CFR 355 EPA 1987a
EPA OPP	Intent to Cancel or Restrict Registration of Pesticide Products Containing Disulfoton	No	
EPA OPTS	Pesticides Classified for Restrictive Use	Yes	40 CFR 152.175 EPA 1978b

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

Agency	Description	Information	References
NATIONAL (cont.)			
	LDR for Newly Identified and Listed Hazardous Wastes and Hazardous Soil	Yes	58 FR 48092 EPA 1993
EPA OSW	Designation of Hazardous Substance	Yes	40 CFR 116.4 EPA 1978c
	Listing as Hazardous Waste: Discarded commercial chemical products off-specification species, container residues, and spill residues thereof	Yes	40 CFR 261.33 EPA 1980b
	App. VIII - Listing as Hazardous Waste Constituent	Yes	40 CFR 261 EPA 1988a
	App. II - List of Hazardous and Organic Constituents	Yes	40 CFR 258 EPA 1991
	Hazardous Wastes from Specific Sources	Yes	40 CFR 261.32 EPA 1981c
	App. IX - Hazardous Wastes Excluded from Non-specific Sources	3.34 ppm	40 CFR 261 EPA 1984c
	App. IX - Groundwater Monitoring List	Yes	40 CFR 264 EPA 1987b
	LDR - Identification of Waste to be Evaluated by August 8, 1988	Yes	40 CFR 268.10 EPA 1986b
	LDR - Treatment Standards Expressed as Waste Concentrations	P039 = 0.017 mg/L (ww) P039 = 0.1 mg/kg (nonww) K037 = 0.025 mg/L (ww) K037 = 0.1 mg/kg (nonww)	40 CFR 268.43 EPA 1988b
	Reportable Quantity	1 lb.	40 CFR 302.4 EPA 1989d
Guidelines:			
a. Air			
ACGIH	TLV TWA	0.1 mg/m^3	ACGIH 1994
NIOSH	REL TWA	0. 1 mg/m^3 (skin)	NIOSH 1992
b. Water			
EPA ODW	One-day health advisory (10 kg child)	0.01 mg/L	EPA 1994
	10-day health advisory (10 kg child)	0.01 mg/L	
	Longer-term health advisory (10 kg child)	0.003 mg/L	
	Longer-term health advisory (adult)	0.009 mg/L	
	DWEL	0.001 mg/L	
	Lifetime health advisory (adult)	0.0003 mg/L	
c. Other			
EPA	RfD (oral)	$4x10^{-5}$ mg/kg/day	IRIS 1994

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

Agency	Description	Information	References
STATE			
Regulations and Guidelines:			
a. Air:			
	Acceptable ambient air concentrations		NATICH 1992
CT	8 hr avg. time	2 $\mu g/m^3$	
FL- Pinella	8 hr avg. time	1 $\mu g/m^3$	
FL-Pinella[b]	24 hr avg. time	$2.40x10^{-1}$ $\mu g/m^3$	
ND	8 hr avg. time	$1x10^{-3}$ mg/m^3	
NV	8 hr avg. time	$2x10^{-3}$ mg/m^3	
TX	30 min avg. time	1 $\mu g/m^3$	
TX	Annual avg. time	$1x10^{-1}$ $\mu g/m^3$	
VA	24 hr avg. time	1.7 $\mu g/m^3$	
WA-SWEST	24 hr avg. time	$3x10^{-1}$ $\mu g/m^3$	
	Air toxics emissions inventory data		
MO		1.45 mT/year (state-wide)	
b. Water:			
	Drinking Water Guidelines		FSTRAC 1990
AZ		0.3 µg/L	
ME		0.3 µg/L	
MN		0.3 µg/L	
RI		0.3 µg/L	
VT		0.3 µg/L	
	Water Quality Criteria: Human Health		CELDs 1994
NY		No detect	
	Groundwater Quality Standards		CELDs 1994
NY		No detect	
	Groundwater Quality Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	

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

Agency	Description	Information	References
STATE (Cont.)			
CA		Yes	
IL		Yes	
KY		Yes	
MN		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WV		Yes	
WI		Yes	
	Hazardous Waste Constituents		CELDs 1994
AL		Yes	
CA		Yes	
CO		Yes	
IL		Yes	
KY		Yes	
LA		Yes	
MD		Yes	
MN		Yes	
MT		Yes	
NE		Yes	
NH		Yes	
NJ		Yes	
NY		Yes	
ND		Yes	
OH		Yes	
SC		Yes	
SD		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	

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

Agency	Description	Information	References
STATE (Cont.)			
	Maximum Leachable Concentration		CELDs 1994
TX		0.1 mg/L	
	Restricted Pesticides		CELDs 1994
AL		Yes	
CA		Yes	
FL		Yes	
ME		Yes	
MI		Yes	
OR		All formulations >2%	
WA		Yes	

[a]EPA limits a facility's effluent to contain the designated kilograms of the sum of all organic pesticide active ingredients (listed in 40 CFR 455.20(b) which includes disulfoton) per 1000 kg of the sum of all active ingredients manufactured at a facility.

ACGIH = American Conference of Governmental and Industrial Hygienists; ADI = Acceptable Daily Intake; BAT = Available Technology; CELDs = Computer-aided Environmental Legislative Data System; DWEL = Drinking Water Exposure Level; EPA = Environmental Protection Agency; FSTRAC = Federal-State Toxicology and Regulatory Alliance Committee; mT = metric ton; NATICH = National Air Toxics Clearinghouse; NIOSH = National Institute of Occupational Safety and Health; NSPS = New Source Performance Standards; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OPP = Office of Pesticide Programs; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; PSNS = Pretreatment Standards for New Sources; REL = Recommended Exposure Level; RfD = Reference Dose; TLV = Threshold Limit Value; TPQ = Threshold Planning Quantity; TWA = Time- Weighted Average; WHO = World Health Organization

8. REFERENCES

*ACGIH. 1994. 1993-1994 Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental and Industrial Hygienists. Cincinnati, OH, 20.

*Aoki Y, Takeda M, Uchiyama M. 1975. Comparative study of methods for the extraction of eleven organophosphorus pesticide residues in rice. J Assoc Off Anal Chem 58:1286-1293.

*Atkinson R. 1988. Estimation of gas-phase hydroxyl radical rate constants for organic chemicals. Environ Toxicol Chem 7:435-442.

*ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles. Agency for Toxic Substances and Disease Registry, Atlanta, GA.

Balcomb R, Stevens R, Bowen C. 1984. Toxicity of 16 granular insecticides to wild-caught songbirds. Bull Environ Contam Toxicol 33:302-307.

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

*Belanger A, Hamilton HA. 1979. Determination of disulfoton and permethrin residues in an organic soil and their translocation into lettuce, onion and carrot. J Environ Sci Health [B] 14:213-226.

*Belisle AA, Swineford DM. 1988. Simple specific analysis of organophosphorus and carbamate pesticides in sediments using column extraction and gas chromatography. Environ Toxicol Chemistry 7:749-752.

*Berlow JR, Cunningham M. 1989. Proposed amendment to final best demonstrated available technology (BDAT) background document for organophosphorus wastes (KO36 nonwastewaters). Vol. 14. NTIS/PB90-166521.

*Betowski LD, Jones TL. 1988. Analysis of organophosphorus pesticide samples by high-performance liquid chromatography/mass spectrometry and high-performance liquid chromatography/mass spectrometry/mass spectrometry. Environ Sci Technol 22:1230-1434.

*Bhaskaran R, Kandasawy D, Oblisami G, et al. 1973. Utilization of disulfoton as carbon and phosphorus sources by soil microflora. Cm-r Sci 42:835-836.

*Bombinski, TJ, DuBois KP. 1958. Toxicity and mechanism of action of Di-Syston. Arch Ind Health 17:192-199.

*Borburgh HJ, Hammers WE. 1992. Extraction of organophosphorous pesticides from water samples on Bakerbond SPE octadecyl cartridges at the ng/L level. Toxicol Environ Chem 35(1):79-86.

*Cited in text

*Bourgeois D, Gaudet J, Deveau P, et al. 1993. Microextraction of organophosphorous pesticides from environmental water and analysis by gas chromatography. Bull Environ Contam Toxicol 50(3):433-440.

*Bowman BT, Sans WW. 1983. Determination of octanol-water partitioning coefficients (Kow) of 61 organophosphorus and carbamate insecticides and their relationship to respective water solubility (S) values. J Environ Sci Health [B] 13:667-633.

*Bowman MC, Beroza M. 1969. Rapid GLC method for determining residues for fenthion, disulfoton and phorate in corn, milk, grass and feces. J Assoc Off Anal Chem 52:1231-1239.

*Bowman MC, Beroza M, Gentry CR. 1969. GLC determination of residues of disulfoton, oxydemetonmethyl, and their metabolites in tobacco plants. J Assoc Off Anal Chem 52: 157- 162.

*Bradway DE, Moseman R, May R. 1981. Analysis of alkyl phosphates by extractive alkylation. Bull Environ Contam Toxicol 26:520-523.

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

*Brodeur J, DuBois KP. 1963. Comparison of acute toxicity of anticholinesterase insecticides to weanling and adult male rats. In: Proceedings of the Society for Experimental Biology and Medicine, Vol. 114. New York, NY: Academic Press, 509-511.

*Brodeur J, DuBois KP. 1964. Studies on the mechanism of acquired tolerance by O,O-diethyl S-2 (ethylthio) phosphorodithioate (Di-Syston). Arch Int Pharmacodyn Ther 149:560-570.

*Brokopp CD, Wyatt JL, Gabica J. 1981. Dialkyl phosphates in urine samples from pesticide formulators exposed to disulfoton and phorate. Bull Environ Contam Toxicol 26:524-529.

*Brusick DJ. 1981. Mutagenic evaluation of S76 in the mitotic non-disjunction in Saccharomyces cerevisiae strain D6. Study No. T3003064. Litton Bionetics Inc., Kensington, MD.

*Brzezinski J. 1969. Catecholamines in urine of rats intoxicated with phosphororganic insecticides. Dissertationes Pharmaceuticae et Pharmacologicae 21:381-385.

*Brzezinski J. 1972. Effect of poisoning with phosphorus organic insecticides on the catechol amine levels in rat plasma, brain, and adrenals. Dissertationes Pharmaceuticae et Pharmacologicae 24:217-220.

*Brzezinski J. 1973. The effect of atropine on the levels of adrenaline and noradrenaline changed by acute poisoning with Di-Syston in rats. Pol J Pharmacol Pharm 25:611-615.

*Brzezinski J, Ludwicki K. 1973. The interrelationship of the changes of acetylcholine esterase and catecholamines blood and urine levels in rats poisoned with Disyston. Pol J Pharmacol Pharm 25:313-316.

*Brzezinski J, Rusiecki W. 1970. The excretion of catecholamines in rat urine related to Disyston poisoning. Dissertationes Pharmaceuticae et Pharmacologicae 22:507-511.

8. REFERENCES

*Bull DL. 1965. Metabolism of Di-Syston by insects, isolated cotton leaves, and rats. J Econ Entomol 58:249-254.

*Cape1 PD, Gig er W, Reichert P, et al. 1988. Accidental input of pesticides into Rhine River. Environ Sci Technol 22:705-717.

*Carey AE, Kutz FW. 1985. Trends in ambient concentrations of agrochemicals in humans and the environment of the United States. Environmental Monitoring Assessment 5:155-163.

*Carpy S, Klotzsch C, Cerioli A. 1975. Disulfoton: 2-Year feeding study in rats. Study no. 47069. Sandoz Inc., Switzerland.

*CDC/ATSDR. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary and immune systems. Atlanta, GA: CDC/ATSDR Subcommittee on Biomarkers of Organ Damage and Dysfunction, Centers for Disease Control, Agency for Toxic Substances and Disease Registry. Summary report, August 27, 1990.

*CELDS. 1992. Computer-aided Environmental Legislative Design System. University of Illinois, Urbana, IL. December 2, 1992.

*CELDs. 1994. Computer-assisted Environmental Legislative Database. University of Illinois, Urbana, IL. September 17, 1994.

*Cetinkaya M. 1993. Gas chromatographic determination of pesticide residues in hair dyes. Pa&em Kosmet 74(1):23-25.

*Chapman RA, Harris CR, Tolman JH, et al. 1993. Further comparison of the persistence in clay loam of single and repeated annual applications of some granular insecticides. J Environ Sci Health Part B: Pest Food Contamin Agric 28(2):151-170.

*Chapman RA, Harris CR, Tolman JH, et al. 1994b. The persistence of insecticidal chemicals in soils treated with granular formulations of disulfoton and their uptake by potato plants. J Environ Sci Health Part B: Pest Food Contamin Agric 29(2):233-245.

*Chapman RA, Tolman JH, Cole C. 1994a. The effect of multiple soil applications of disulfoton on enhanced microbial degradation in soil and subsequent uptake of insecticidal chemicals by potato plants. J Environ Sci Health Part B: Pest Food Contamin Agric 29(3):485-506.

*Chen HH, Hsueh JL, Sirianni SR, et al. 1981. Induction of sister-chromatid exchanges and cell cycle delay in cultured mammalian cells treated with eight organophosphorus pesticides. Mutat Res 88:307-316.

*Chen HH, Sirianni SR, Huang CC. 1982. Sister chromatid exchanges in Chinese hamster cells treated with seventeen organophosphorus compounds in the presence of a metabolic activation system. Environ Mutagen 4:621-624.

*Christenson WR, Wahle BS. 1993. Technical grade disulfoton (DI-SYSTON) : a special 6-month feeding study to determine a cholinesterase no-observed-effect level in the rat. Study No. 91-972-IR, Report No. 106336. Miles Inc. Agriculture Division, Toxicology, Stilwell, Kansas.

*Clapp DW, Naylor DV, Lewis GC. 1976. The fate of disulfoton in Portneuf silt loam soil. J Environ Qua1 5:207-10.

*Clark G, Koester AG, Pearson DW. 1971. Exploratory behavior in chronic disulfoton poisoning in mice. Psychopharmacologia 20:169-171.

*Clark G, Pearson DW. 1973. Learning in chronic disulfoton poisoning. J Gen Psycho1 89:305-311.

*Clark G, Stavinoha WB. 1969. Alterations in liver RNA induced by atropine and disulfoton. Toxicol Appl Pharmacol 14:376-379.

*Clark G, Stavinoha WB. 1971. A permeability change in CNS tissue in chronic poisoning with disulfoton. Life Sci [I] 10:421-423.

*Cohen DB. 1986. Groundwater contamination by toxic substances: A California assessment. ACS Symposium Series 315. Washington, DC: American Chemical Society, 499-529.

*Comeliussen PE. 1970. Pesticide residues in total diet samples, V. Pestic Monit J 4:89-105.

*Costa LG, Kaylor G, Murphy SD. 1986. Carbachol- and norepinephrine-stimulated phosphoinositide metabolism in rat brains: Effect of chronic cholinesterase inhibition. J Pharmacol Exp Ther 239:32-37.

*Costa LG, Kaylor G, Murphy SD. 1990. In vitro and in vivo modulation of cholinergic muscarinic receptors in rat lymphocytes and brain by cholinergic agents. Int J Immunopharmacol 12:67-75.

*Costa LG, Murphy SD. 1982. Passive avoidance retention in mice tolerant to the organophosphorus insecticide disulfoton. Toxicol Appl Pharmacol 65:451-458.

*Costa LG, Murphy SD. 1983a. [3H]Nicotine binding in rat brain: Alterations after chronic acetylcholinesterase inhibition. J Pharmacol Exp Ther 226:392-397.

*Costa LG, Murphy SD. 1983b. Unidirectional cross-tolerance between the carbamate insecticide propoxur and the organophosphate disulfoton in mice. Fundam Appl Toxicol 3:483-486.

*Costa LG, Murphy SD. 1986. Cholinergic and opiate involvement in the antinociceptive effect of diisopropylfluorophosphate. Pharmacol Biochem Behav 24:733-736.

*Costa LG, Schwab BW, Hand H, et al. 1981. Reduced [3H]quinuclidinyl benzilate binding to muscarinic receptors in disulfoton-tolerant mice. Toxicol Appl Pharmacol 60:441-450.

*Costa LG, Schwab BW, Murphy SD. 1982a. Differential alterations of cholinergic muscarinic receptors during chronic and acute tolerance to organophosphoms insecticides. Biochem Pharmacol 31:3407-3413.

*Costa LG, Schwab BW, Murphy SD. 1982b. Tolerance to anticholinesterase compounds in mammals. Toxicology 25:79-97.

8. REFERENCES

*Costa LG, Shao M, Basker K, et al. 1984. Chronic administration of an organophosphorus insecticide to rats alters cholinergic muscarinic receptors in the pancreas. Chem Biol Interact 48:261-269.

*CPCR. 1992. Crop protection chemicals reference. Di-Syston. 8th ed. New York, NY: Chemical and Pharmaceutical Press, 1160- 117 1.

*Crawford LS, Anderson CA. 1973. Acute oral toxicity of Di-Syston technical to guinea pigs Report no. 39113, Mobay Chemical Corporation, Environmental Health Research Institute, Stilwell, Kansas.

*Crawford LS, Anderson CA. 1974. Acute oral toxicity of several Di-Syston metabolites to female and male rats. Report no. 39687, Mobay Chemical Corporation, Environmental Health Research s Institute, Stilwell, Kansas.

*CRISP Database. 1994. U.S Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute for Environmental Health Science. August 14, 1994.

*Daughton CG, Crosby DG, Gamas RL, et al. 1976. Analysis of phosphorus-containing hydrolytic products of organophosphorus pesticides in water. J Agric Food Chem 24:236-241.

*Dementi B. 1994. Ocular effects of organophosphates: a historical perspective of Saku disease. J Appl Toxicol 14: 119- 129

*Di Corcia A, Marchetti M. 1992. Method development for monitoring pesticides in environmental waters: liquid-solid extraction followed by liquid chromatography. Environ Sci Technol 26(1):66-74.

*Dillon AP. 1981. Disposal of selected pesticides. In: Pesticide disposal and detoxification: processes and techniques. Noyes Data Corporation, Park Ridge, NJ.

*Domine D, Devilliers J, Chastrette M, Karcher W. 1992. Multivariate structure-property relationships (MSPR) of pesticides. J Pest Sci 35:73-82.

*Doull J. 1957. The acute inhalation toxicity of Di-Syston to rats. Report no. 1802. University of Chicago, Department of Pharmacology, Chicago, IL.

*Doull J, Vaughn G. 1958. The effects of diets containing Di-Syston. University of Chicago, Department of Pharmacology, Chicago, IL. (Unpublished study cited in EPA 1987 and WHO 1974).

*Dragan D, Carpov A. 1987. Microencapsulated organophosphorous insecticides. III. Some aspects on the volatilization of malathion and disulfoton from aqueous suspensions of microcapsules. J Microencapsul4:97-105.

*Draper WM, Crosby DG. 1984. Solar photooxidation of pesticides in dilute hydrogen peroxide. J Agric Food Chem 32:231-237.

*DuBois KP. 1957. The dermal toxicity of Di-Syston to rats. Report no. 2063. University of Chicago, Toxicity Laboratory, Chicago, IL.

*DuBois KP. 1971. The acute inhalation of DI-SYSTON to rats. Report No. 31029. University of Chicago, Toxicology Laboratory, Chicago, IL.

*DuBois KP, Kinoshita FK. 1968. Influence of induction of hepatic microsomal enzymes by phenobarbital on toxicity of organic phosphate insecticides. Proc Sot Exp Biol Med 129:699-702.

*DuBois KP, Kinoshita FK. 1971. Effect of repeated inhalation exposure of female rats to Di-Syston. University of Chicago, Chicago, IL. Report No. 30571. MRID 87935.

*Duggan RE, Corneliussen PE. 1972. Dietary intake of pesticide chemicals in the United States (III): June 196%April 1970. Pestic Monit J 5:331-341.

*Duggan RE, Corneliussen PE, Duggan MB, et al. 1983. Pesticide residue levels in foods in the United States from June 1, 1969 to June 30, 1976. Washington, DC: Food and Drug Administration, Division of Chemical Technology, 15, 22, 27, 30, 32, 33.

*Ecobichon DJ. 1990. Toxic effects of pesticides. In: Klaasen CD, Amdur MO, Doull J, eds. Casarett and Doull's toxicology. 4th ed. New York, NY: Macmillan Publishing <0., 565-622.

*Edge11 KW, Jenkins EL, Lopez-Avila V, et al. 199 1. Capillary column gas chromatography with nitrogen-phosphorus detection for determination of nitrogen- and phosphorus-containing pesticides in finished drinking waters: Collaborative study. J Assoc Off Anal Chem 74:295-309.

*Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environmental Science and Technology 15:30-38.

*Ellenhorn MJ, Barceloux DG. 1988. Medical toxicology. Diagnosis and treatment of human poisoning. New York, NY: Elsevier, 1075-1076.

*Ellington JJ, Stancil FE, Payne WD, et al. 1988. Measurement of hydrolysis rate constants for evaluation of hazardous waste land disposal: Vol. 3. Data on 70 chemicals. Engineering Research Laboratory, U.S. Environmental Protection Agency, Athens, GA. EPA/600/S3-88-028. NTIS PB38-234842/AS.

*EPA. 1973. Environmental Protection Agency. Code of Federal Regulations 40 CFR 136.3.

*EPA. 1978a. Environmental Protection Agency. Code of Federal Regulations 40 CFR 455.20.

*EPA. 1978b. Environmental Protection Agency. Code of Federal Regulations 40 CFR 152.175.

*EPA. 1978c. Environmental Protection Agency. Code of Federal Regulations 40 CFR 116.4.

*EPA. 1980a. Environmental Protection Agency. In vitro microbiological mutagenicity and unscheduled DNA synthesis studies of eighteen pesticides. Research Triangle Park, NC: Health Effects Research Laboratory, U.S. Environmental Protection Agency. EPA-600/l-79-0441. PB80-133226.

*EPA. 1980b. Environmental Protection Agency. Code of Federal Regulations 40 CFR 261.33.

*EPA. 1980c. Resource Conservation and Recovery Act (RCRA). U.S. Environmental Protection Agency,Washington, DC.

*EPA. 1981a. Environmental Protection Agency. Mutagenesis screening of pesticides: "Drosophila." Research Triangle Park, NC: Health Effects Research Laboratory, U.S. Environmental Protection Agency. EPA-600/l-81-017. PB81-160848.

*EPA. 1981b. Environmental Protection Agency. Code of Federal Regulations 40 CFR 261.32.

*EPA. 1981c. Environmental Protection Agency. Code of Federal Regulations 40 CFR 261.33.

*EPA. 1983. Environmental Protection Agency. Code of Federal Regulations 40 CFR 122.

*EPA. 1984a. In vitro and in vivo mutagenicity studies on environmental chemicals. Research Triangle Park, NC: Health Effects Research Laboratory, U.S. Environmental Protection Agency. EPA-600/l-84-003. PB84-138973.

*EPA. 1984b. Pesticide fact sheet: Disulfoton. Washington, DC: Office of Pesticide and Toxic Substances, Offices of Pesticide Programs.

*EPA. 1984c. Environmental Protection Agency. Code of Federal Regulations 40 CFR 261.

*EPA. 1985. Environmental Protection Agency. Code of Federal Regulations 40 CFR 117.3.

*EPA. 1986a. Test methods for evaluating solid wastes (SW-846). 3rd ed. Washington, DC: Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency.

*EPA. 1986b. Environmental Protection Agency. Code of Federal Regulations 40 CFR 268.10.

*EPA. 1987a. Environmental Protection Agency. Code of Federal Regulations 40 CFR 355.

*EPA. 1987b. Environmental Protection Agency. Code of Federal Regulations 40 CFR 264.

*EPA. 1987c. Environmental Protection Agency. Hazardous substances; reportable quantity adjustments; proposed rules. 40 CFR 117 and 302. Federal Register 52:8169.

*EPA. 1988a. Environmental Protection Agency. Code of Federal Regulations 40 CFR 261.

*EPA. 1988b. Environmental Protection Agency. Code of Federal Regulations 40 CFR 268.43.

*EPA. 1988c. Method for the determination of organic compounds in drinking water. Cincinnati, OH: Environmental Monitoring Systems Laboratory, Office of Research and Development, U.S. Environmental Protection Agency. EPA 600/4-88-039.

*EPA. 1988d. The Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA). Section 313 of Title III. U.S. Environmental Protection Agency, Washington, DC.

*EPA. 1989a. Environmental Protection Agency. Code of Federal Regulations 40 CFR 148.

*EPA. 1989b. Drinking water health advisory: Pesticides. U.S. Environmental Protection Agency, Office of Drinking Water Health Advisory. Chelsea, MI: Lewis Publishers, 345-362.

*EPA. 1989c. Interim methods for development of inhalation reference doses. U.S. Environmental Protection Agency. EPA/600/890/066F.

*EPA. 1989d. Environmental Protection Agency. Code of Federal Regulations 40 CFR 302.4.

*EPA. 1989e. Environmental Protection Agency. Code of Federal Regulations 40 CFR 125.

*EPA. 1990. Health and environmental effects document for disulfoton. (Final draft). Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, U.S. EPA, Cincinnati, OH.

*EPA. 1991. Environmental Protection Agency. Code of Federal Regulations 40 CFR 258.

*EPA. 1992a. Environmental Protection Agency. Pesticide chemicals manufacturing category effluent limitations guidelines, pretreatment standards, and new source performance standards. 40 CFR 455. Federal Register 57:12560-12601.

*EPA. 1992b. Environmental Protection Agency. Code of Federal Regulations 40 CFR 455.50.

*EPA. 1992c. EPA Method 1657. Methods for the determination of nonconventional pesticides in municipal and industrial wastewater. U.S. Environmental Protection Agency.

*EPA. 1993. Environmental Protection Agency. Federal Register 58 FR 48092 .

*EPA. 1994. Drinking water regulations and health advisories. Office of Drinking Water, U.S. Environmental Protection Agency, Washington, DC.

*Eta, M. 1974. Organophosphorus pesticides: Organic and biological chemistry. Cleveland, OH: CRC Press, 123-321.

*FAO/WHO. 1991. Pesticide residues in food-Disulfoton. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues. Food and Agriculture Organization of the United Nations and the World Health Organization, Rome, Italy. Pp. 151-172.

*Farm Chemicals Handbook. 1993. Farm Chemicals Handbook. 1993 ed. Meister Publishing Company, Willoughby OH.

*Fawade MM, Pawar SS. 1978. Alterations in mixed function oxidase system during thiodemeton (o-o diethyl S-2(ethylthio) ethyl phosphorothioate) toxicity. Indian J Exp Biol 16:481-484.

*Fawade MM, Pawar SS. 1980. Effect of phenobarbital pretreatment on mixed function oxidase and lipid peroxidation during thiodemeton toxicity. Indian J Exp Biol 18:645-647.

*Fawade MM, Pawar SS. 1983. Effect of NlC12 and cycloheximide on microsomal drug metabolism and ALA-synthetase during thiodemeton toxicity. Indian J Exp Biol 21:343-346.

*FDA. 1988. Food and Drug Administration Pesticide Program - Residues in Foods - 1987. J Assoc Off Anal Chem 7 1: 122A- 163A.

*FDA. 1990. Residues in foods, 1989 (3rd annual FDA pesticide residue monitoring program report). J Assoc Off Anal Chem 73(5):127A-146A.

*FDA. 1991. Residues in foods, 1990 (4th annual FDA pesticide residue monitoring program report). J Assoc Off Anal Chem 74(5):121A-140A.

*FDA. 1992. Residue monitoring, 1991 (5th annual FDA pesticide residue monitoring program report). J Assoc Off Anal Chem 75(5):135A-157A.

*FDA. 1993. FDA monitoring program, 1992 (6th annual FDA pesticide residue monitoring program report). J Assoc Off Anal Chem 76:127A-148A.

*Fitzgerald BB, Costa LG. 1992. Modulation of Ml and M2 muscarinic receptor subtypes following repeated organophosphate exposure in rats. Toxicol Appl Pharmacol 117:112-125.

*Fitzgerald BB, Costa LG. 1993. Modulation of muscarinic receptors and acetylcholinesterase activity in lymphocytes and in brain areas following repeated organophosphate exposure in rats. Fundam Appl Toxicol 20:210-216.

*Flucke W. 1986. S 276 Technical - Study of subacute dermal toxicity to rabbits. Unpublished Report 14747 from Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany.

*Foley DJ, McPhillips JJ. 1973. Response of the rat ileum, uterus and vas deferens to carbachol and acetylcholine following repeated daily administration of a cholinesterase inhibitor. Br J Pharmacol 48:418-425.

*Foley DJ, Stitzel RE, McPhillips JJ. 1973. The relationship between inhibition of acetylcholinesterase and sensitivity of the rat ileum to carbachol. Pharmacology 10:298-305.

Frank R, Braun HE, Wilkie I, et al. 1991. A review of insecticide poisonings among domestic livestock in southern Ontario, Canada, 1982-1989. Can Vet J 32:219-226.

*Frank R, Logan L. 1988. Pesticide and industrial chemical residues at the mouth of the Grand Saugeen and Thames rivers Ontario Canada 1981-1985. Arch Environ Contam Toxicol 17:741-754.

*FSTRAC. 1990. Summary of state and federal drinking water standards and guidelines. Washington, D.C.: Federal-State Toxicology and Regulatory Alliance Committee, Chemical Communication Subcommittee, February 1990.

*Gaines TB. 1969. Acute toxicity of pesticides. Toxicol Appl Pharmacol 14:515-534.

*Garg AK, Sethi GR. 1980. Persistence of insecticide residues in paddy soil. Ind J Plant Protect 8:157-163.

*Gelardi RC, Mountford MK. 1993. Infant formulas evidence of the absence of pesticide residues. Meeting of the American Industrial Health Council on the Domestic Agenda for Risk Assessment, Washington D.C., USA, December 1, 1992. Regul Toxicol Pharmacol 17(2 Part 1):181-192.

*Gianessi LP. 1986. A national pesticide usage data base, summary of report submitted to the office of standards and regulations, U.S. EPA under cooperative agreement CR 811858-01-0 by Resources for the Future, Washington, DC.

*Gianessi LP, Puffer CA. 1992. Insecticide use in U.S. crop production. Resources for the Future, Washington, DC.

*Gigon PL, Gram TE, Gillette JR. 1969. Studies on the rate of reduction of hepatic microsomal cytochrome P-450 by reduced nicotinamide adenine dinucleotide phosphate: Effect of drug substrates. Mol Pharmacol 5:109-122.

Gillette JR, Brodie BB, LaDue BN. 1957. The oxidation of drugs by liver microsomes: On the role of TPHN and oxygen. J Pharmacol Exp Ther 119:532-540.

*Gillette JR, Davis DC, Sesame HA. 1972. Cytochrome P-450 and its role in drug metabolism. Ann Rev Pharmacol 57-84.

*Glooschenko WA, Sirachan WMJ, Sarnpson RCJ. 1976. Distribution of pesticides and polychlorinated biphenyls in water, sediments, and seston of the upper Great Lakes-1974. Pestic Monit J 10:61-67.

*Gohre K, Miller GC. 1986. Photooxidation of thioether pesticides on soil surfaces. J Agric Food Chem 34:709-713.

*Goldfrank LR, Flomenbaum NE, Lewin NA, et al. 1990. Goldfrank’s toxicologic emergencies. 4th ed. Norwalk, CT: Appleton and Lange, 684-692.

*Goodrich JA, Lykins BW Jr, Clark RM. 1991. Drinking water from agriculturally contaminated groundwater. J Environ Qua1 20:707-717.

Gopal PK, Ahuja SP. 1979. Lipid and growth changes in organs of chicks (Gallus domesticus) during acute and chronic toxicity with disyston and folithion. Indian J Exp Biol 17:1153-l 154.

*Grant DL, Sherwood CR, McCully KA. 1969. Gas-liquid and thin-layer chromatography of phorate, disulfoton and five of their oxidation products. J Chromatogr 44:67-74.

*Greenhalgh R. 1978. Terminal residues of organophosphorus pesticides. Pure Appl Chem 50:513-518.

*Gunderson EL. 1988. FDA total diet study, April 1982-April 1984, dietary intakes of pesticides, selected elements and other chemicals. J Assoc Off Anal Chem 71:1200-1209.

*Haddad LM, Winchester JF. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: W.B. Saunders Co., 1079-1081.

8. REFERENCES

*Hajjar NP, Hodg son E. 1980. Flavin adenine dinucleotide monooxygenase: Its role in the sulfoxidation of pesticides in mammals. Science 209:1134-l 136.

*Hajjar NP, Hodgson E. 1982. Sulfoxidation of thioether-containing pesticides by the flavin-adenine dinucleotide-dependent monooxygenase of pig liver microsomes. Biochem Pharmacol 31:745-752.

*Hallberg GR. 1989. Pesticide pollution of groundwater in the humid USA. Agric, Ecosys Environ 26:299-368.

*Hanna PJ, Dyer KP. 1975. Mutagenicity of organophosphorus compounds in bacteria and Drosophila. Mutat Res 28:405-420.

*Harris CI. 1969. Movement of pesticides in soil. J Agric Food Chem 17:88-82.

*Harris CK, Chapman RA, Tolman JH, et al. 1988. A comparison of the persistence in a clay loam of single and repeated annual applications of seven granular insecticides used for corn rootworm control. J Environ Sci Health [B] 23:1-32.

*Hattori H, Suzuki U, Yasuoka T, et al. 1982. Identification and quantitation of disulfoton in urine and blood of a cadaver by gas chromatography/mass spectrometry. Nippon Hoigaku Zasshi 36:411-413.

*Hayes RH. 1983. Oncogenicity study of disulfoton technical on mice. Study no. 80-271-04. Mobay Chemical Corporation, Corporate Toxicology Department, Stilwell, Kansas.

*Hayes RH. 1985. Chronic feeding/oncogenicity study of technical disulfoton (Di-Syston) with rats. Study no. 82-271-01. Mobay Chemical Corporation, Corporate Toxicology Department, Stilwell, Kansas.

*HazDat. 1994. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA. September 8, 1994.

*Hebert VR, Miller GC. 1990. Depth dependence of direct and indirect photolysis on soil surfaces. J Agric Food Chem 38:913-918.

*Helling CS, Dennison DG, Kaufman DD. 1974. Fungicide movement in soils. Phytopathology 64:1091-1100.

*Herbold B. 1980. Dominant lethal test on male mouse to evaluate S276 for mutagenic potential. Report No. 9440. Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany.

*Herbold B. 1981. Micronucleus test on the mouse to evaluate for mutagenic effect. Report No. 10451. Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany.

*Herbold B. 1983. POL test on E. coli to evaluate for potential DNA damage. Report No. 12139. Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany.

*Hikita H, Miyata M, Ishikawa S. 1973. [Experimental study of chronic organophosphate (OP) insecticides in the beagle dog[2]activities of cholinesterases and residue of OP.] Nichi Gan Kaishi 77:1254-1265. (Japanese)

*Hildebrandt A., Estabrook RW. 1971. Evidence for the participation of cytochrome b5 in hepatic microsomal mixed-function oxidase reactions. Arch Biochem Biophys 143:66-79.

Hill EF, Camardese MD. 1984. Toxicity of anticholinesterase insecticides to birds: Technical grade versus granular formulations. Ecotoxicol Environ Safety 8:551-563.

Hixson EJ. 1982. Acute oral toxicity of Di-Syston technical in hens. Report no. 341. Mobay Chemical Corporation, Environmental Health Research Institute, Stilwell, Kansas.

*Hixson EJ. 1983. Acute delayed neurotoxicity study on disulfoton. Toxicology report no. 365 (Study no. 82-418-01). Mobay Chemical Corporation, Environmental Health Research Institute, Stilwell, Kansas.

*Hixson EJ, Hathaway. 1986. Effect of disulfoton (DI-SYSTON) on reproduction in rats. Study No. 82-67 l-02. Report No. 90965. Mobay Corporation, Corporate Toxicology Department, Stilwell, Kansas.

*Hodgson DW, J.F. Thompson, Watts, RR. 1982. Accuracy of pesticide reference standard solutions. Part II: Chemical stability under four storage conditions. J Assoc Off Anal Chem 65:94-102.

*Hoffman K, Weischer CH, Luckhaus G, et al. 1975. S 276 (disulfoton) chronic toxicity study on dogs (two-year feeding experiment). Report nos. 5618 and 45287. AG Bayer, West Germany.

*Holden PW. 1986. Pesticides and groundwater quality. Washington, DC: National Academy Press, 20-21, 44-45, 67, 69.

*Holstege DM, Scharberg DL, Richardson ER, et al. 1991. Multiresidue screen for organophosphorus insecticides using gel permeation chromatography-silica gel cleanup. J Assoc Off Anal Chem 741394-399.

Holt TM, Hawkins RK. 1978. Rat hippocampal norepinephrine response to cholinesterase inhibition. Res Commun Chem Path01 Pharmacol 20:239-251.

*HSDB. 1994. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda MD.

*Hsu JP, Schattenberg HJ, Garza MM. 1991. Fast turnaround multiresidue screen for pesticides in produce. J Assoc Off Anal Chem 74(5):886-892.

*Huang CC. 1973. Effect on growth but not on chromosomes of the mammalian cells after treatment with three organophosphorus insecticides. Proc Sot Exp Biol Med 142:36-40.

*Hundley HK, Cairns T, Luke MA, et al. 1988. Pesticide residue findings by the Luke method in domestic and imported foods and animal feeds for fiscal years 1982-1986. J Assoc Off Anal Chem 71(3):875-892.

*Inukai H, Iyatomi A. 1976. Disulfoton: mutagenicity test on bacterial systems. Report No. 29. Nitokuno, Agricultural Chemicals Institute, Laboratory of Toxicology, Japan.

*IRIS. 1994. Integrated Risk Information System. U.S. Environmental Protection Agency, Cincinnati, OH. August 1994.

*IRPTC. 1985. IRPTC data profile on: Disulfoton. International Register of Potentially Toxic Chemicals, United Nations Environment Programme, Geneva, Switzerland.

*Ishikawa S, Miyata M. 1980. Development of myopia following chronic organophosphate pesticide intoxication: An epidemiological and experimental study. In: Merigan WH, Weiss B, eds. Neurotoxicity of the visual system. New York, NY: Raven Press, 233-254.

*Iyaniwura TT. 1991. Relative inhibition of rat plasma and erythrocyte cholinesterases by pesticide combinations. Vet Hum Toxicol 33:166-168.

*Jagannath DR. 1981. Mutagenic evaluation of S276 in the Saccharomyces cerevisiae reverse mutation induction assay. Study No. T4003065. Litton Bionetics Inc., Kensington, MD.

*Jury WA, Focht DD, Farmer WJ. 1987a. Evaluation of pesticide groundwater pollution potential from standard indices of soil-chemical adsorption and biodegradation. J Environ Qua1 16:422-428.

*Jury WA, Winer AM, Spencer WF, et al. 1987b. Transport and transformation of organic chemicals in the soil-air-water. Ecosystem 99:119-164.

*Kadoum AM, Mock DE. 1978. Herbicide and insecticide residues in tailwater pits: Water and pit bottom soil from irrigated corn and sorghum fields. J Agric Food Chem 26(1):45-50.

*Kaloyanova FP, El Batawi MA. 1991. Organophosphorus compounds. In: Human toxicology of pesticides. Boca Raton, FL: CRC Press, 3-41.

*Kawasaki S, Ueda H, Itoh H, et al. 1992. Screening of organophosphorus pesticides using liquid chromatography-atmospheric pressure chemical ionization mass spectrometry. J Chromatogr 595:193-202.

*Kearney PC, Woolson EA, Plimmer JR, et al. 1969. Decontamination of pesticides in soil. Residue Rev 29:137.

*Kenaga EE. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol Environ Safety 4:26-38.

*Kenaga EE, Goring CAI. 1980. Relationship between water solubility, soil-sorbtion, octanol-water partitioning, and bioconcentration of chemicals in biota. ASTM Special Technical Publication (SIP) 707. American Society for the Testing of Materials, Philadelphia, PA.

*Kennedy ER, Abel1 MT, Reynolds J, et al. 1994. A sampling and analytical method for the simultaneous determination of multiple organophosphorus pesticides in air. ‘Am Ind Hyg Assoc J 55(12):1172-1177.

*Kikuchi H, Suzuki Y, Hashimoto Y. 1981. Increase of Beta-glucuronidase activity in the serum of rats administered organophosphate and carbamate insecticides. J Toxicol Sci 6:27-35.

*King PH, McCarty PL. 1968. A chromatographic model for predicting pesticide migration in soils. Soil Science 106:248-261.

*Kleinschmidt MG Jr. 1971. Fate of Di-Syston O,O-diethyl S-2-(ethylthio) ethyl phosphorodithioate in potatoes during processing. J Agric Food Chem 19: 1196-l 197.

*Klotzsche C. 1972. Disulfoton, 90 day feeding study in rats. Sandoz Agroforschung, Switzerland. Report No. 88585.

*Kordel W, Stutte J, Kotthoff G. 1993. HPLC-screening method for the determination of the adsorption-coefficient on soil: comparison of different stationary phases. Chemosphere 27(12):2341-2352.

*Krill RM, Sunzogni WC. 1986. Chemical monitoring of Wisconsin's groundwater. J Am Water Works Assoc 78:70-75.

*Kundiev YI, Rappoport MB. 1967. [Changes of the skin following application of organophosphorus insecticides.] Vrach Delo 5:106-109. (Russian).

*Kutz FW. 1983. Chemical exposure monitoring. Residue Rev 55:277-292.

*Kutz FW. 1983. Chemical exposure monitoring. Residue Rev 85:277-292.

*Kutz FW, Carey AE. 1986. Pesticides and toxic substances in the environment. J Arboriculture 12:92-95.

*Kutz FW, Yobs AR, Yang HSC. 1976. National pesticide monitoring program. In: R. E. Lee Jr., ed. Air Pollution from Pesticides and Agricultural Processes. Cleveland, OH, CRC press. Pp. 95-136.

*Lamb DW, Hixson EJ. 1983. Embryotoxic and teratogenic effects of disulfoton. Study no. 81-611-02. Mobay Chemical Corporation, Kansas City, MO.

*Lee SGK, Hanna LA, Johnston K, et al. 1985. Excretion and metabolism of Di-Syston in rats. Unpublished Report MR90946 from Mobay Corporation, USA.

*LeFever GS, Green RD. 1975. The effects of chronic ganglion blockade and chronic cholinesterase inhibition on the sensitivity of rabbit stomach muscularis to cholinergic and adrenergic agonists. J Pharmacol Exp Ther 193:739-747.

*Liao W, Joe T, Cusick WG. 1991. Multiresidue screening method for fresh fruits and vegetables with gas chromatographic/mass spectrometric detection. J Assoc Off Anal Chem 74:554-565.

*Light DR, Waxman DJ, Walsh C. 1982. Studies on the chirality of sulfoxidation catalyzed by bacterial flavoenzyme cyclohexanone monooxygenase and hog liver flavin adenine dinucleotide containing monooxygenase. Biochemistry 21:2490-2498.

*Litterst CL, Lichtenstein EP, Kajiwara K. 1969. Effects of insecticides on growth of HeLa cells. J Agric Food Chem 17:1199-1203.

*Llorens J, Crofton KM, Tilson HA, et al. 1993. Characterization of disulfoton-induced behavioral and neurochemical effects following repeated exposure. Fund Appl Toxicol 20:163-169.

*Lord KA, Burt PE. 1964. Effect of temperature on water solubility of phorate and disulfoton. Chem Ind 1262-1263.

*Lores EM, Bradway DE. 1977. Extraction and recovery of organophosphorus metabolites from urine using an anion exchange resin. J Agric Food Chem 25:75-79.

*Luke MA, Masumoto HT, Chims T, et al. 1988. Levels and incidences of pesticide residues in various foods and animal feeds analyzed by the luke multiresidue methodology for fiscal years 1982-1986. J Assoc Off Anal Chem 71:415-420.

*Maddy KT, Fong HR, Lowe JA, et al. 1982. A study of well water in selected California communities for residues of 1,3-dichloropropene, chlorallyl alcohol and 49 organophosphate or chlorinated hydrocarbon pesticides. Bull Environ Contam Toxicol 29:354-359.

*March RB, Fukuto TR, Metcalf RL. 1957. Metabolism of p32-dithio-systox in the white mouse and American cockroach. University of California, Citrus Experiment Station, Riverside, California. MRID 83215.

*McCarty PL, King PH. 1966. The movement of pesticides in soils. Purdue University, Engineering Bulletin Extension Series, 156-171.

*McCarty RT, Haufler M, Osbom MG, et al. 1969. Oral toxicity of four organophosphate insecticides to farm livestock. Am J Vet Res 1149-1153.

*McDonald Be, Costa LG, Murphy SD. 1988. Spatial memory impairment and central muscarinic receptor loss following prolonged treatment with organophosphates. Toxicol Lett 40:47-56.

*McPhillips JJ. 1969a. Altered sensitivity to drugs following repeated injections of cholinesterase inhibitor to rats. Toxicol Appl Pharmacol 14:67-73.

*McPhillips JJ. 1969b. Subsensitivity of the rat ileum to cholinergic drugs. J Pharmacol Exp Ther 166:249-254.

McPhillips JJ, Coon JM. 1966. Adaptation to octamethyl pyrophosphoramide in rats. Toxicol Appl Pharmacol 8:66-76.

*McPhillips JJ, Dar MS. 1967. Resistance to the effect of carbachol on the cardiovascular system and on the isolated ileum of rats after subacute administration of an organophosphorus cholinesterase inhibition. J Pharmacol Exp Ther 156:507-513.

*Melnikov NN. 1971. Chemistry of pesticides. New York, NY: Springer-Verlag, 368-369.

*Menzer RE, Fontanilla EL, Ditman LP. 1970. Degradation of disulfoton and phorate in soil influenced by environmental factors and soil type. Bull Environ Contam Toxicol 5:1-5.

*Menzie CM. 1972. Fate of pesticides in the environment. Ann Rev Entomol 17:199-222.

*Merck. 1989. Merck index: an encyclopedia of chemicals, drugs, and biologicals. 1 lth ed. Budavari S, ed. Rahway NJ: Merck & <0., Inc.

*Mihail F. 1978. S 276 (Disyston active ingredient) acute toxicity studies. Report no. 7602a. AG Bayer, Institut fur Toxicologic, West Germany.

*Miller GC, Hebert VR, Miller WW. 1989. Effect of sunlight on organic contaminants at the atmosphere-soil interface. In: Reactions and movement of organic chemicals in soils. SSSA Special Publication no. 22, 99-110.

*Miller H, Cramer P, Drinkwine A, et al. 1981. Development of methods for pesticides in wastewater: Applicability of a general approach. Advances in Identifying and Analyzing Organic Pollution in Water 1:115-138.

*Minyard JP Jr, Roberts WE. 1991. State findings on pesticide residues in foods:1988 and 1989 J Assoc Off Anal Chem 74:438-452.

*Mitchell TH, Ruzicka JH, Thomson J, et al. 1968. The chromatographic determination of organophosphorus pesticides. Part III. The effect of irradiation on the parent compounds. J Chromatogr 32: 17-23.

*Morgan DP. 1982. Recognition and management of pesticide poisonings. 3rd ed. EPA 540/9-80-005. Washington, DC: U.S. Government Printing Office, 2.

*Moriya M, Ohta T, Watanabe K, et al. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res 116:185-216.

*Mossman DJ, Schnoor JL, Stumm W. 1988. Predicting the effects of a pesticide release of the Rhine River. J Water Pollut Control Fed 60: 1806-1812.

*Mostaghimi S, McClellan PW, Cooke RA. 1993. Pesticide contamination of groundwater in Virginia: BMP impact assessment. Water Sci Technol 28(3):379-387.

Mount ME, Oehme FW. 1981. Brain cholinesterase activity in healthy cattle, swine and sheep and in cattle and sheep exposed to cholinesterase-inhibiting insecticides. Am J Vet Res 42:1345-1350.

*Muhlmann K, Schrader G. 1957. [Hydrolysis of phosphoric acid ester insecticides]. Z Naturforschg [B] 12:196-203. (German)

*Munch DJ, Frebis CP. 1992. Analyte stability studies conducted during the national pesticide survey. Environ Sci Technol 29:921-925.

*Murphy RS, Kutz FW, Strassman SC. 1983. Selected pesticide residues or metabolites in blood and urine specimens from a general population survey. Environ Health Perspect 48:81-86.

*Murphy SD. 1986. Toxic effects of pesticides. In: Klaasen CD, Amdur MO, Doull J, eds. Casarett and Doull's toxicology. 3rd ed. New York, NY: Macmillan Publishing Co., 519-581.

*Murphy SD, Costa LG, Wang C. 1984. Organophosphate insecticide interaction at primary and secondary receptors. In: Narahashi T, ed. Cellular and molecular neurotoxicology. New York, NY: Raven Press, 165-176.

*Murty KV, Raju DSS, Sharma CBSR. 1983. Cytogenetic hazards from agricultural chemicals: 7. Herbicides, fungicides and insecticides screened for effects on chiasmata in Hordeum vulgare. Biologisches Zentralblatt (Leipzig) 102:57 l-576.

*Myram C, Forrest JD. 1969. The application of pesticide granules from the air. Chem Ind, 1851.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

*Nash RG. 1974. Plant uptake of insecticides, fungicides and fumigants from soils. In: Guenzi WD, et al. eds. Pesticides in soil and water. Madison, WI: Soil Science of America Inc. Publishers, 257-313.

*NATICH. 1992. National Air Toxics Information Clearinghouse. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards.

*NIOSH. 1992. Recommendations for occupational safety and health compendium of policy documents and statements. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. DHHS (NIOSH) publication no. 92-100.

*NOES. 1990. National occupational exposure survey 1981 - 1983. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, Cincinnti, OH. July 1, 1990.

*OSHA. 1989. Air contaminants. Final rule. U.S. Department of Labor. Occupational Safety and Health Administration. Federal Register 54:2936.

*OSHA. 1992. Air contaminants. U.S. Department of Labor. Occupational Safety and Health Administration. Federal Register 57:26002.

*Osweiler GD, Carson TL, Buck WB, et al. 1985. Organophosphorous and carbamate insecticides. In: Clinical and diagnostic veterinary toxicology. 3rd ed. Dubuque, IA: Kendall/Hunt Publishing Co.., 298-317.

*OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment, U.S. Congress. OTA-BA-438. April 1990.

*Panda BB. 1983. Effect of the insecticides, oxydemeton, methyl and thiodemeton, on the mitotic and meiotic chromosomes of barley (Hordeum vulgare). Environ Exper Botany 23:293-296.

*Parker CE, Haney CA, Hass JR. 1982. High-performance liquid chromatography-negative chemical ionization mass spectrometry of organophosphorous pesticides. J Chromatogr 237:233-248.

*Pawar SS, Fawade MM. 1978. Alterations in the toxicity of thiodemeton due to the pretreatment of inducers, substrates and inhibitors of mixed function oxidase system. Bull Environ Contam Toxicol 20:805-810.

*Perrine SE, McPhillips JJ. 1970. Specific subsensitivity of the rat atrium to cholinergic drugs. J Pharmacol Exp Ther 175:496-502.

*Plumb RH Jr. 1991. The occurrence of Appendix IX organic constituents in disposal site ground water. Ground Water Monit Revue 11: 157-164.

*Paulsen LL. 1981. Organic sulfur substrates for the microsomal flavin-containing monooxygenase. Rev Biochem Toxicol 3:33-49.

*Puhl RJ, Fredrickson DR. 1975. The metabolism and excretion of Di-Syston by rats. Report no. 44261. Mobay Chemical Corporation, Chemagro Agricultural Division, Kansas, MO.

*Putman DL. 1987. Sister chromatid exchange in Chinese hamster ovary (CHO) cells. Study No. T51596.334. Microbiological Associates Inc., Bethesda, MD.

*Racke KD. 1992. Degradation of organophosphorus insecticides in environmental matrices. In: Chambers JE, Levi PE, eds. Organophosphates: Chemistry, fate, and effects. San Diego, CA: Academic Press, 47-78.

*Rae PSC, Davidson JM. 1982. Retention and transformation of selected pesticides and phosphorus in soil-water systems: A critical review. Engineering Research Laboratory, Office of Research and Development, Athens, GA. EPA-600/S3-82-060.

*Rae PSC, Homsby AG, Jessup RE. 1985. Indices for ranking the potential for pesticide contamination of groundwater. Proceedings of the Soil and Crop Science Society of Florida 44:1-8.

*Rae SLN, McKinley WP. 1969. Metabolism of organophosphorus insecticides by liver homogenates from different species. Can J Biochem 47:1155-l 159.

*Rivett KF, Bhatt A, Street AE, et al. 1972. Thio-demeton/oral toxicity to mice/dietary administration for three months. Huntington Research Centre, England. Report No. 5505/72/901.

*Robinson CP, Smith PW, Endecott BR. 1978. Depression of cholinesterase activity by ethylestrenol in organophosphorus-poisoned and normal rats. Toxicol Appl Pharmacol 44:207-211.

*Ruzicka JH, Thompson J, Wheals DD. 1967. The gas chromatographic determination of organophosphorus pesticides. Part II. A comparative study of hydrolysis rates. J Chromatogr 31:37.

*Ruzicka JH, Thomson J, Wheals BB. 1968. Gas-chromatographic determination of organophosphorus pesticides. Part V. Studies under field conditions. J Chromatogr 33:430-434.

*Ryan LC, Endecott BR, Hanneman GD, et al. 1970. Effects of an organophosphorus pesticide on reproduction in the rat. Department of Transportation, Federal Aviation Administration, Office of Aviation Medicine, AD 709327.

*Sanbom JK, Francis BM, Metcalf KL. 1977. The degradation of selected pesticides in soil: A review of published literature. Cincinnati, OH: U.S. Environmental Protection Agency. EPA 600/9-77-022.

*Sandhu SS, Waters MD, Simmon VP, et al. 1985. Evaluation of the genotoxic potential of certain pesticides used in Pakistan in basic and applied mutagenesis. Basic Life Sci 34:185-219.

*Savage EP, Bagby JR Jr, Mounce L, et al. 1971. Pesticide poisonings in rural Colorado. Rocky Mt Med J 6829-33.

*Schafer EW. 1972. Acute oral toxicity of 369 pesticidal, pharmaceutical, and other chemicals to wild birds. Toxicol Appl Pharmacol 21:315-330.

*Schafer EW Jr, Bowles WH Jr. 1985. Acute oral toxicity and repellency of 933 chemicals to house and deer mice. Arch Environ Contam Toxicol 14: 111-129.

*Schattenberg HJ III, Hsu J-P. 1992. Pesticide residue survey of produce from 1989 to 1991. J Assoc Off Anal Chem Int 75(5):925-933.

*Schroeder WH, Dobson M, Kane DM, et al. 1987. Toxic trace elements associated with airborne particulate matter: A review. J Air Pollut Control Assoc 37:1267-1285.

*Schwab BW, Costa LG, Murphy SD. 1983. Muscarinic receptor alterations as a mechanism of anticholinesterase (EC 3.1.1.7) tolerance. Toxicol Appl Pharmacol 71: 14-23.

*Schwab BW, Hand H, Costa LG, et al. 1981. Reduced muscarinic receptor binding in tissues of rats tolerant to the insecticide disulfoton. Neurotoxicology 2:635-647.

*Schwab BW, Murphy SD. 1981. Induction of anticholinesterase tolerance in rats with doses of disulfoton that produce no cholinergic signs. J Toxicol Environ Health 8:199-204.

*Shafik T, Bradway DE, Enos HF, et al. 1973. Human exposure to organophosphorus pesticides. A modified procedure for the gas-liquid chromatographic analysis of alkyl phosphate metabolites in urine. J Agric Food Chem 21:625-629.

*Shaw HR II. 1975. The metabolism of DI-SYSTON in soil. Research and Development Department, Chemagro Division of Baychem Corporation. Report No. 40234.

*Sheets LP. 1993a. An acute oral neurotoxicity screening study with technical grade disulfoton (DI-SYSTON) in rats. Study No. 92-412-OB, Report No. 103992. Miles Inc. Agriculture Division, Toxicology, Stilwell, Kansas.

*Sheets LP. 1993b. An subchronic dietary neurotoxicity screening study with technical grade disulfoton (DI-SYSTON) in Fischer 344 rats. Study No. 92-472-HS, Report No. 106332. Miles Inc. Agriculture Division, Toxicology, Stilwell, Kansas.

*Shiotsuka RN. 1988. Pilot assay to assess cholinesterase activity in rats exposed by inhalation to technical grade disulfoton. Study No. 88-941-AG. Report No. 98358. Mobay Corporation, Corporate Toxicology Department, Stilwell, Kansas.

*Shiotsuka RN. 1989. Subchronic inhalation toxicity study of technical grade disulfoton (DI-SYSTON) in rats. Study No. 88-141-UA. Report No. 99648. Mobay Corporation, Corporate Toxicology Department, Stilwell, Kansas.

*Shirasu Y, Moriya M, Tezuka H, et al. 1982. Mutagenicity screening studies on pesticides. In Proceedings of the 3rd Environmental Mutagens and Carcinogens International Conference, Sept. 21-27, 1981, Tokyo, 331-335.

*Shirasu Y, Moriya M, Tezuka H, et al. 1984. Mutagenicity of pesticides. Environ Sci Res 31:617-624.

*Singh AK, Hewetson DW, Jordon KC, et al. 1986. Analysis of organophosphorus insecticides in biological samples by selective ion monitoring gas chromatography-mass spectrometry. J Chromatogr 369:83-96.

*Singh BD, Singh Y, Sarma MDRK, et al. 1977. Cytogenetic aberrations and morphological changes induced by insecticide treatments of barley seed. Indian J Exp Biol 15:688-691.

*Sipes IG and Gandolfi AJ. 1986. Biotransformation of toxicants. In: Klaasen CD, Andur MO, Doull J, eds. Casarett and Doull's toxicology. 3rd ed. New York, NY: Macmillan Publishing Co., 64-98.

*Sittig M, ed. 1980. Pesticide manufacturing and toxic materials control encyclopedia. Park Ridge, NJ: Noyes Data Corporation, 366-373.

*Sittig M, ed. 1985. Handbook of toxic and hazardous chemicals and carcinogens, 2nd edition. M. Sittig, ed. Noyes Publications.

*Sittig M, ed. 1991. Disulfoton. In: Handbook of toxic and hazardous chemicals and carcinogens. 3rd ed. Park Ridge, NJ: Noyes Data Corporation, 695-696.

*Smith PW, Stavinoha WB, Ryan LC. 1968. Cholinesterase inhibition in relation to fitness to fly. Aerosp Med 39:754-758.

*Smyser BP, Sabourin PJ, Hodgson E. 1985. Oxidation of pesticides by purified microsomal FAD-containing monooxygenase from mouse and pig liver. Pest Biochem Physiol 24:368-374.

*Spalding RF, Snow DD. 1989. Stream levels of agrichemicals during a spring discharge event. Chemosphere 19:1129-l 140.

*SRI. 1994. 1994 Directory of chemical producers: United States of America. Menlo Park, CA: Stanford Research Institute International, 833.

*Stan HJ. 1989. Application of capillary gas chromatography with mass selective detection to pesticide residue analysis. J Chromatogr 467(1):85-98.

*Stan HJ, Mrowetz D. 1983. Residue analysis of organophosphoms pesticides in food with 2-dimensional gas chromatography using capillary columns and flame photometric detection. J High Res Chromatogr Chromatogr Corm-nun 6:255-263.

*Stavinoha WB, Ryan LC, Smith PW. 1969. Biochemical effects of an organophosphorus cholinesterase inhibitor on the rat brain. Ann N Y Acad Sci 160:378-382.

*Stevens JT, Greene FE. 1974. Alteration of hepatic microsomal metabolism of male mice by certain anticholinesterase insecticides. Bull Environ Contam Toxicol 11538544.

*Stevens JT, Greene FE, Stitzel RE, et al. 1973. Effects of anticholinesterase insecticides on mouse and rat liver microsomal mixed function oxidase. In: Deichmann W.B., Ed. Pesticides and the environment: A continuing controversy. Proceedings of the 8th Inter-American Conference on Toxicology and Occupational Medicine, University of Miami School of Medicine, 489-501.

*Stevens JT, Stitzel K, McPhillips JJ. 1972a. Effects of anticholinesterase insecticides on hepatic microsomal metabolism. J Pharmacol Exp Ther 181576-583.

*Stevens JT, Stitzel R, McPhillips JJ. 1972b. The effects of subacute administration of anticholinesterase insecticides on hepatic microsomal metabolism. Life Sci (II) 11:423-43 1.

*Su M, Kinoshita FK, Frawley JP, et al. 1971. Comparative inhibition of aliesterases and cholinesterase in rats fed eighteen organophosphorus insecticides. Toxicol Appl Pharmacol 20:241-249.

*Sundloff SF, Clemmons RM, Mayer DJ, et al. 1984. Cholinesterase activity in plasma, red blood cells, muscle, and brain of dogs following repeated exposure to Spotton (Fenthion). Vet Hum Toxicol 26:112-117.

*Suzuki H, Ishikawa S. 1974. Ultrastructure of the ciliary muscle treated by organophosphate pesticide in beagle dogs. Br J Ophthalmol 58:931-940.

*Swarm RL, Laskowski DA, McCall PJ, et al. 1983. A rapid method for the estimation of the environmental parameters, octanol/water partition coefficient, soil sorption constant, water to air ratio, and water solubility. Residue Rev 85:17-28.

*Szeto SY, Brown MJ. 1982. Gas-liquid chromatographic methods for determination of disulfoton, phorate, oxydemeton-methyl and their toxic metabolites in asparagus tissue and soil. J Agric Food Chem 30:1082-1086.

*Szeto SY, Mackenzie JR, Vernon RS, et al. 1983b. The degradation of disulfoton in lettuce after application for control of the lettuce aphid, Nasonovia ribisnigri (Mosley). J Environ Sci Health B18(6): 725-731.

*Szeto SY, Vernon RS, Brown MJ. 1983a. Degradation of disulfoton in soil and its translocation into asparagus. J Agric Food Chem 31:217-220.

Szutowski MM. 1975. Effect of carbon tetrachloride on activation and detoxification of organophosphorus insecticides in the rat. Toxicol Appl Pharmacol 33:350-355.

*Takase I, Oyama 0. 1985. Uptake and bioconcentration of disulfoton and its oxidation compounds in carp, Cyprinus carpio L. J Pest Sci 10:47-53.

*Taylor RE. 1965a. Di-Syston, three generation rat breeding studies. Harris Laboratories, Inc. Report No. 17164.

*Taylor RE. 1965b. Report on demyelination studies on hens. Report no. 15107. Harris Laboratories, Inc.

*Tesh JM, Ross FW, Secher RG, et al. 1982. S 276: Effects of oral administration upon pregnancy in the rabbit. Report no. R 2351. Life Science Research, Essex, England.

*Thomas RG. 1990. Volatilization from water. In: Lyman WS, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. Washington, DC: American Chemical Society, 15-16.

*Thornton JS, Anderson CA. 1968. Determination of residues of Di-Syston and metabolites by thermionic emission flame gas chromatography. J Agric Food Chem 16:895-898.

*Thornton JS, Hurley JB, Obrist JJ. 1976. Soil thin-layer mobility of twenty-four pesticides chemicals. Research and Development Department, Chemagro Agricultural Division, Mobay Chemical Corp. Report No. 51016.

*Thyssen JT. 1978. Acute inhalation toxicity. Report No. 7827. Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany.

*Thyssen JT. 1980. Subacute inhalation study on rats. Report No. 9065. Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany.

*Tomizawa L. 1975. Degradation of organophosphorus pesticides in soils with special reference to anaerobic soil conditions. Environ Qua1 Saf 4:117-127.

*Tomizawa L. 1980. Biological accumulation of pesticides in an ecosystem-evaluation of biodegradability and ecological magnification of rice pesticides by a model ecosystem. Japanese Agricultural Research Quarterly 14:143-149.

*Tynes RE, Hodgson E. 1985. Magnitude of involvement of the mammalian flavin-containing monooxygenase in the microsomal oxidation of pesticides. J Agric Food Chem 33:471-479.

*Uga S, Ishikawa S, Mukuno K. 1977. Histopathological study of canine optic nerve retina treated by organophosphate pesticide. Invest Ophthalmol Vis Sci 16:877-881.

*Uzokwu M. 1974. Comparative feto-toxicity of organophosphate insecticide in mice. Bull Epizoot Dis Afr 22:161-166.

*Vaughn G, Deiniger E, Doull J. 1958. Determination of a safe dietary level of Di-Syston for dogs. Department of Pharmacology, University of Chicago, Chicago, IL.

*Vaughn G, Deininger E, Doull J. 1958. Determination of a safe dietary level of Di-Syston for dogs. University of Chicago, Chicago, IL.

*VonRumker R, Lawless EW, Meiners AF. 1974. Production, distribution, use and environmental impact potential of selected pesticides. NTIS PB238 795.

*Wanner U, Egli, T., Fleischmann T, et al. 1989. Behavior of the insecticides disulfoton and thiometon in the Rhine River.A chemodynamic study. Environmental Science and Technology 23:1232-1242.

*Warnick SL, Eldredge JD. 1972. Human and environmental exposure to pesticides in Utah. Proceedings of the Utah Academy of Science Arts Letters 49:1972.

*Waters, MD, Nesnow S, Simmon VF, et al. 1981. Pesticides: Mutagenic and carcinogenic potential. ACS Symposium Series 160. Washington, DC: American Chemical Society, 89-113.

*Waters MD, Sandhu SS, Simmon VF, et al. 1982. Study of pesticide genotoxicity. Basic Life Sci 21:275-326.

Watson M Jr, Benson WW Jr, Gabica J Jr. 1971. Accidental organophosphate poisoning in cattle, two case histories. Arch Environ Health 22582-583.

*Wauchope RD, Buttler TM, Hornsby HG, et al. 1992. The SCS/ARS/CES pesticide properties database for environmental decision-making. Rev Environ Contam Toxicol 12:1-36.

*Waxman DJ, Light DR, Walsh C. 1982. Chiral sulfoxidations catalyzed by rat liver cytochromes P-450. Biochemistry 21:2499-2507.

*Weil CS, Condra NJ, Carpenter CP. 1971. Correlation of four hour vs. 24 hour contact skin penetration toxicity in the rat and rabbit and use of the former for prediction of relative hazard of pesticide formulations. Toxicol Appl Pharmacol 18:734-742.

*Westfall DP, McPhillips JJ, Foley DJ. 1974. Inhibition of cholinesterase activity after postganglionic denervation of the rat vas deferens: Evidence for prejunctional supersensitivity to acetylcholine. J Pharmacol Exp Ther 189:493-498.

White DH, Seginak JT. 1990. Brain cholinesterase inhibition in songbirds from pecan groves sprayed with phosalone and disulfoton. J Wild1 Dis 26:103-106.

*Whitmore RW, Kelly JE, Reading PL. 1992. National home and garden pesticide survey. Office of Pesticides and Toxic Substances, Biological and Economic Analysis Branch, U.S. Environmental Protection Agency, Washington, DC. NTIS PB92-174747.

WHO. 1974. 1973 Evaluations of some pesticide residues in food: The monographs. WHO Pesticide Residue Series no. 3. Geneva, Switzerland: World Health Organization.

*WHO. 1976. 1975 Evaluation of some pesticide residues in food: The monographs. WHO Pesticide Residue Series no. 5. Geneva, Switzerland: World Health Organization.

*Winter CK. 1992. Dietary pesticide risk assessment. Rev Environ Contam Toxicol 127:23-67.

*Winterlin W, Seiper JM, Craigmill A, et al. 1989. Degradation of pesticide waste taken from a highly contaminated soil evaporation pit in California USA. Arch Environ Contam Toxicol 18:734-747.

*Wolfe HR, Staiff DC, Armstrong JP, et al. 1978. Exposure of fertilizer mixing plant workers to disulfoton. Bull Environ Contam Toxicol 20:79-86.

*Worthing CR, ed. 1987. The pesticide manual: A world compendium. 8th ed. Lavenham, Suffolk, UK: The Lavenham Press, Ltd., 320-321.

*Wysocka-Paruszewska B. 1970. Urine level of 4-hydroxy-3-methoxymandelic acid in urine of rats poisoned with phosphorus organic insecticides. Dissertationes Pharmaceuticae et Pharmacologicae 22:485-489.

*Wysocka-Paruszewska B. 1971. Changes in the urine level of 4-hydroxy-3-methoxymandelic acid in rats related to the degree of intoxication with Di-Syston. Dissertationes Pharmaceuticae et Pharmacologicae 23:271-274.

*Yang LL. 1988. CHO/HGPRT mutation assay. Study No. T5196.332. Microbiological Associates Inc., Bethesda, MD.

*Yashiki M, Kojima T, Ohtani M, et al. 1990. Determination of disulfoton and its metabolites in the body fluids of a Di-Syston intoxication case. Forensic Sci Int 48145-154.

*Yess NJ. 1991. Food and Drug Administration pesticide program residues in food 1990. J Assoc Off Anal Chem 74:1-20.

*Yess NJ, Houston MG, Gunderson EL. 1991. Food and Drug Administration pesticide residue monitoring of foods: 1978-1982. J Assoc Off Anal Chem 74:265-272.

*Zepp RG, Baug hman GL. 1978. Prediction of photochemical transformation of pollutants in the aquatic environment. In: Hutzinger U, Van Lilyveld IH, Zoeteman BCJ, eds. Aquatic pollutants. Oxford: Pergamon Press.

*Zepp RG, Baughman GL, Schlotzhauer PF. 1981. Comparison of photochemical behavior of various humic substances in water. I. Sunlight induced reactions of aquatic pollutants photosensitized by human substances. Chemosphere 10:109-l 17.

*Zweig G, Devine JM. 1969. Determination of organophosphorous pesticides in water. Residue Rev 26: 17-36.

9. GLOSSARY

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

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.

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.

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.

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.

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.

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 occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

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.

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

Intermediate Exposure - Exposure to a chemical for a duration of 15364 days, as specified in the Toxicological Profiles.

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

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 is expected 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 dose 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.

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

Minimal Risk Level - An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen - A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

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

No-Observed-Adverse-Effect Level (NOAEL) - The dose of 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.

Permissible Exposure Limit (PEL) - An allowable exposure level in workplace air averaged over an 8-hour shift.

q1* - The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q1* 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 $\mu g/m^3$ for air).

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 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 CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 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.

Short-Term Exposure Limit (STEL) - The 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 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) - A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

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

Toxic Dose (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.

Uncertainty Factor (UF) - A factor used in operationally deriving the RfD 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 LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

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-l 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-l and Figure 2-l 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-l) 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-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.4, "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 (ql*).

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

SAMPLE

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

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
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

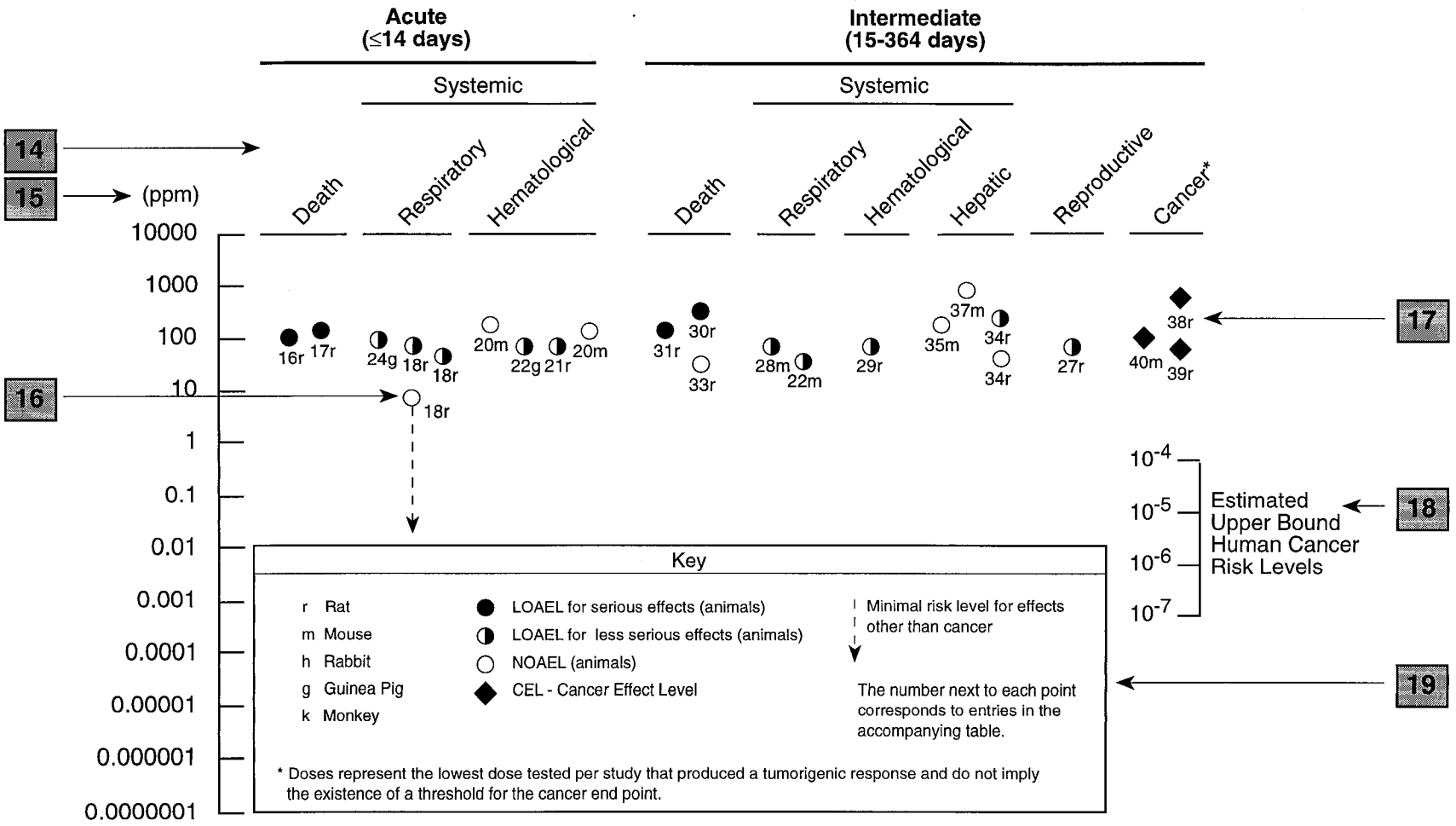
[a] The number corresponds to entries in Figure 2-1.

12 → [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).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

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



Chapter 2 (Section 2.4)

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 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Substances,” and 2.7, “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 B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

APPENDIX B

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
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
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
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
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
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

APPENDIX B

STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
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
δ	delta
γ	gamma
μm	micron
μg	microgram

*U.S. GOVERNMENT PRINTING OFFICE:1995-639-298