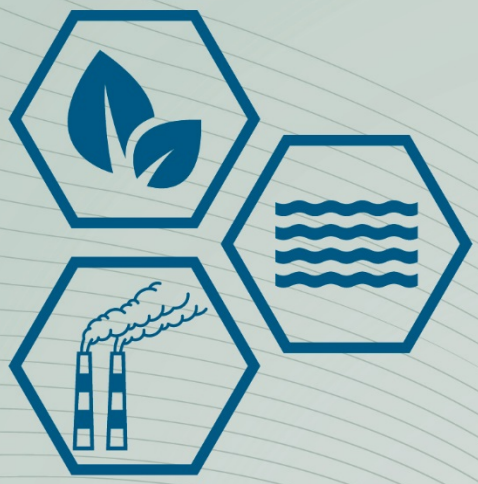

Toxicological Profile for Disulfoton

August 2022

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

FOREWORD

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

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

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. 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 the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;

(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, intermediate, and chronic health effects; and

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

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

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

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

Christopher M. Reh, Ph.D.
Associate Director
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

Date	Description
August 2022	Final toxicological profile released
July 2021	Draft for public comment toxicological profile released
September 2011	Addendum to the toxicological profile released
August 1995	Final toxicological profile released

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Melanie Buser, M.P.H. (Lead)
Nickolette Roney, M.P.H.
ATSDR, Office of Innovation and Analytics,
Toxicology Section, Atlanta, GA

Adriana Antezana, M.P.H.
Hannah Derrick, B.S.
Andrea Chiger, M.P.H.
Lauren Brown, M.S., DABT
Kaley Beins, M.P.H.
Abt Associates, Rockville, MD

Bob Sonawane, Ph.D.
Bruce Fowler, Ph.D.
Toxicology and Risk Assessment
Consulting Services, Maryland
(subcontractor to Abt Associates)

Kimberly Zaccaria, Ph.D., D.A.B.T.
Jenny Crisman, B.S.
SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:
Includes ATSDR; National Center for Environmental Health (NCEH); National Institute for Occupational Safety and Health (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

Additional reviews for science and/or policy:
ATSDR, Office of Community Health and Hazard Assessment; ATSDR, Office of Capacity Development and Applied Prevention Science; ATSDR, Office of Science; NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice; EPA.

PEER REVIEWERS

1. Dr. Xiaozhong Yu, MD, MPH, Ph.D., Associate Professor, Environmental Health Science, College of Public Health, University of Georgia, Athens, Georgia
2. Dr. Lucio G. Costa, PharmD, Professor, Environmental Health Director, Toxicology Program, University of Washington, Seattle, Washington
3. Dr. Dale Hattis, Professor, Ph.D., The George Perkins Marsh Institute, Clark University, Worcester, Massachusetts

These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Disulfoton (o,o-diethyl s-[2-eththioethyl] phosphorodithioate, Chemical Abstracts Service [CAS] Number 298-04-4, Di-syston) is a systemic organophosphate insecticide/acaricide. It is a manufactured substance and does not occur naturally. Disulfoton was cancelled by the U.S. Environmental Protection Agency (EPA) in 2009 for use as a pesticide, as a result of its toxicity (EPA 2010). Remaining stocks were permitted to be sold until 2011, and its use in U.S. agriculture has been reported as recently as 2016 (USGS 2021). Previously, disulfoton had been used to protect many field and vegetable crops from a variety of harmful insects. As a result of its cancelled use and rapid degradation in air, water, and soil, the potential for human exposure is low. Inhalation and dermal exposures to disulfoton are low for the general population, and exposure in drinking water is likely negligible. Levels of disulfoton in environmental media are also expected to be low. People who previously manufactured, handled, or applied disulfoton or who were involved in the disposal of disulfoton were at a higher risk of exposure than the general population. Occupational exposure is expected to be negligible in the United States since its cancellation. People who live near disulfoton manufacturing or processing sites, or hazardous waste sites containing disulfoton may be at higher risk of exposure.

Toxicokinetic data show that disulfoton is readily and extensively absorbed by the gastrointestinal tract. The urinary metabolites of disulfoton are diethyl phosphate (DEP), diethyl thiophosphate (DETP), diethyl dithiophosphate (DEDPT), and diethyl phosphorothiolate (DEPTh). 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.

1.2 SUMMARY OF HEALTH EFFECTS

Information on disulfoton toxicity comes primarily from oral studies on laboratory animals, followed by inhalation studies on laboratory animals and a few human case studies of oral ingestion of disulfoton. Toxicity studies on disulfoton have evaluated a variety of endpoints, primarily neurological, respiratory, endocrine, reproductive, and developmental. The genotoxicity of disulfoton has also been tested on a variety of species test systems.

1. RELEVANCE TO PUBLIC HEALTH

As displayed in Figures 1-1 and 1-2, the most sensitive endpoints for disulfoton toxicity appear to be neurological and developmental. A systematic review was conducted on these endpoints. Weight-of-evidence conclusions are defined in Appendix C. The review resulted in the following hazard identification conclusions.

- Developmental effects are a presumed health effect following oral exposure.
- Neurological effects are a presumed health effect following oral exposure.
- Neurological effects are a presumed health effect following inhalation exposure.
- Neurological effects are not classifiable (defined as a low level of evidence in human studies and a low level of evidence in animal studies) following dermal exposure.

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Disulfoton

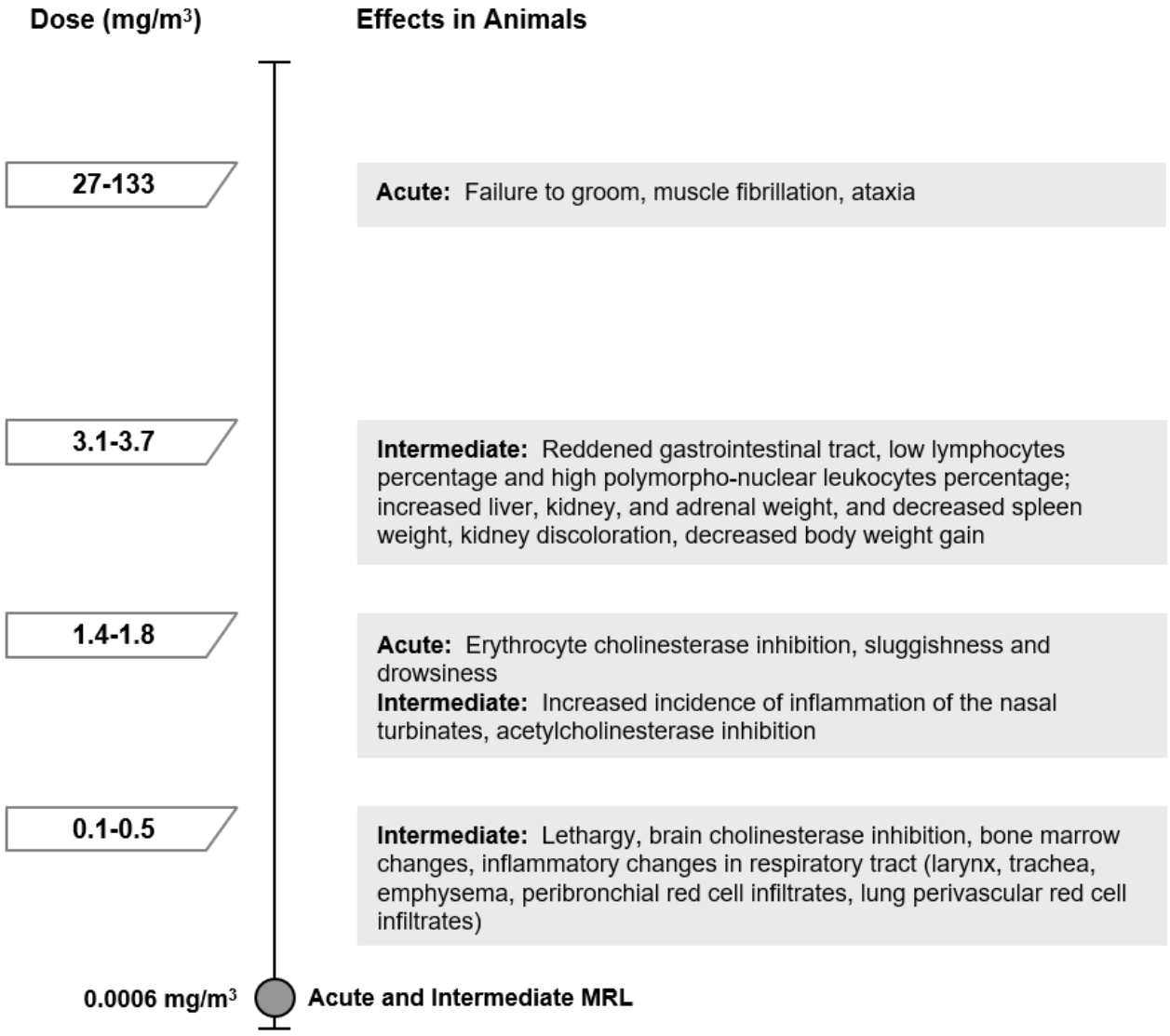
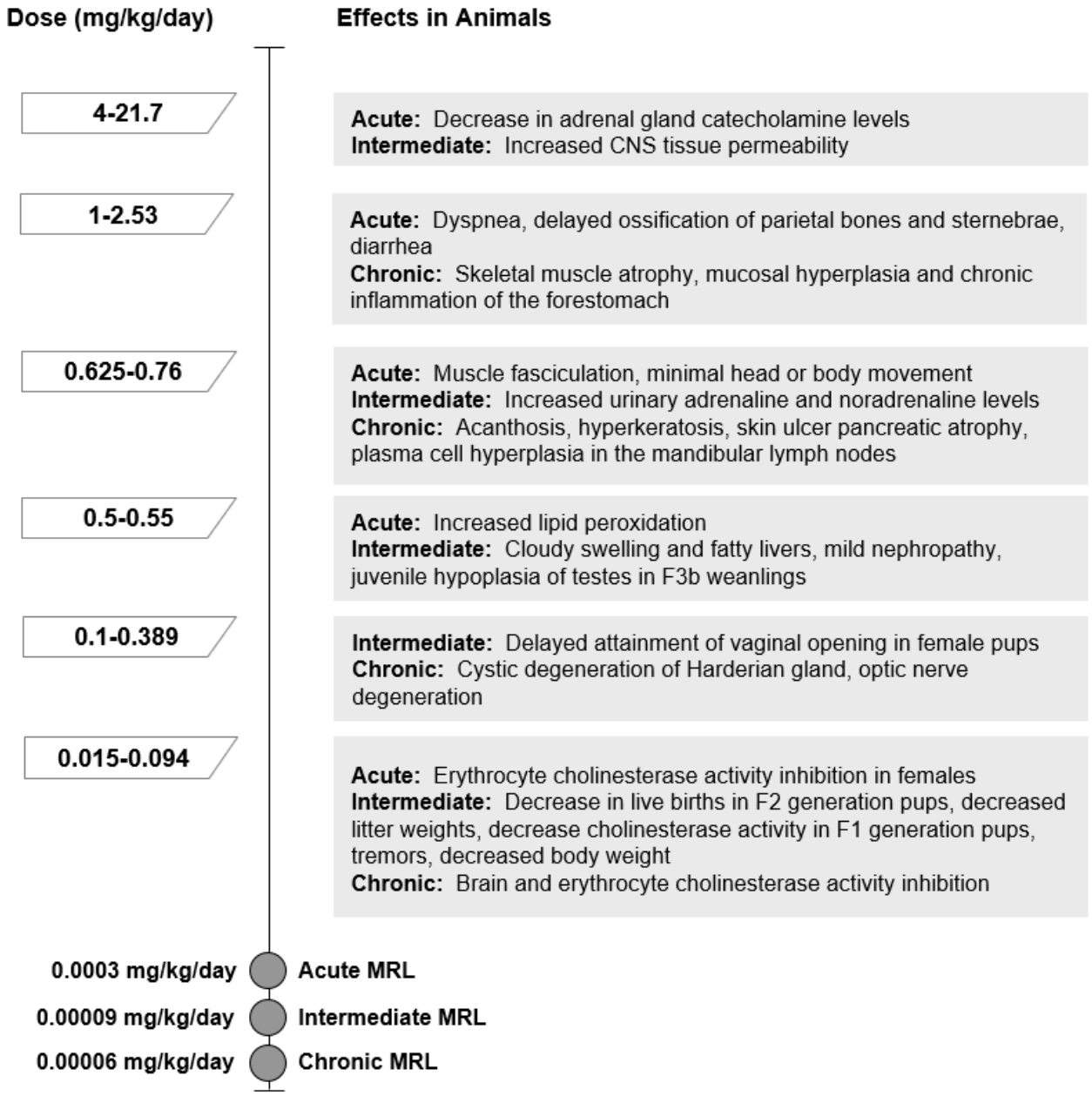


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Disulfoton



1. RELEVANCE TO PUBLIC HEALTH

Developmental Effects. Studies in laboratory animals support developmental toxicity as a sensitive endpoint following oral exposure to disulfoton. Following oral exposure of both parents, or maternal only, to disulfoton, rat offspring showed significant inhibition of brain or red blood cell acetylcholinesterase (AChE) activity (Hixson and Hathaway 1986; Klaus 2006c; Ryan et al. 1970; Sheets 2005; Taylor 1965a). No cholinergic signs of toxicity were noted at the doses tested in these studies, and no treatment-related effects were seen in a functional observational assessment performed in one study (Sheets 2005). Female pups exposed *in utero* and during lactation had delayed vaginal opening, a developmental milestone (Sheets 2005). Additionally, in a multi-generational exposure study, third-generation offspring had significantly depressed red blood cell AChE activities (Taylor 1965a). Swelling of the liver, mild nephropathy, and juvenile hypoplasia of the testes were also observed, likely resulting from exposure during gestation (Taylor 1965a). These findings are consistent with significant cholinesterase inhibition and related cholinergic toxicity observed in animals and humans following oral exposure to disulfoton.

Neurological Effects. Numerous inhalation and oral studies in laboratory animals and a few human studies strongly support nervous system effects as the most sensitive endpoint following exposure to disulfoton. Cholinesterase inhibition results in the accumulation of acetylcholine at synapses and neuromuscular junctions. This accumulation overstimulates the cholinergic systems, which can result in various adverse neurological outcomes such as headache, vertigo, and confusion. Human occupational studies have shown significant depression of AChE activity following oral and dermal exposure (Wolfe et al. 1978) and neurological symptoms including headaches, nausea, weakness, and fatigue (Gómez-Arroyo et al. 2000). These findings are further corroborated by findings in numerous human case studies where clinical findings have measured severely depressed cholinesterase activity and muscarinic effects alongside signs of intoxication including confusion, vomiting, masseter muscle spasms, and other symptoms (Futagami et al. 1995; Hattori et al. 1982; Savage et al. 1971; Yashiki et al. 1990). These studies are limited as levels of exposure associated with these effects could not be measured. Additionally, lifestyle factors, such as smoking, for individuals were not sufficiently assessed; this limitation increases the risk of bias (Futagami et al. 1995; Gómez-Arroyo et al. 2000; Hattori et al. 1982; Wolfe et al. 1978; Yashiki et al. 1990). In animal studies, excessive accumulation of acetylcholine and catecholamines has been observed after dosing with disulfoton. Significant AChE inhibition is the primary neurological effect observed in rats across a wide range of oral doses and inhalation concentrations (Costa and Murphy 1983a; Costa et al. 1986; EPA 2007; Hayes 1983, 1985; Klaus 2006a, 2006b; 2006c; Matsuda et al. 2000; Sheets 1993a, 1993b; Shiotsuka 1989; Schwab and Murphy 1981; Schwab et al. 1983; Stavinoha et al. 1969; Su et al. 1971; Thyssen 1978, 1980; Yagle and Costa 1996).

Among these studies, many have observed inhibition to be dose-dependent. In addition to these studies, typical clinical signs of cholinergic toxicity and depression have been observed in mice and rats, including sluggishness, muscle twitching, ataxia, tremors, dyspnea, and convulsions (Crawford and Anderson 1974; Doull 1957; Flucke 1986; Mihail 1978). Neurotoxic signs have occurred in pregnant laboratory animals, including muscular tremors and severe inhibition of cholinesterase activity (Hixson and Hathaway 1986; Klaus 2006c; Lamb and Hixson 1983; Tesh et al. 1982). Additionally, female animals across multiple studies have been found to be more susceptible than male rats to cholinergic effects of disulfoton (Carpy et al. 1975; Jones et al. 1999; Klaus 2006b; Rivett et al. 1972; Thyssen 1978); however, the cause of this observation was not further examined. Studies are inconclusive on the whether disulfoton alters behavior or functional task performance in animals (Clark and Pearson 1973; Clark et al. 1971; Flucke 1986; Jones et al. 1999; Sheets 1993a).

1.3 MINIMAL RISK LEVELS (MRLs)

As presented in Figure 1-3, following inhalation exposure, the neurologic system is the most sensitive target with the highest level of evidence associated with disulfoton exposure. The inhalation database was considered adequate for derivation of an intermediate-duration MRL for disulfoton. Additionally, the intermediate-duration MRL was adopted as the as the acute-duration inhalation MRL as it is considered protective of acute-duration inhalation exposure to disulfoton. However, a chronic-duration inhalation MRL was not developed as the database was inadequate. For oral exposure (Figure 1-4), the available data suggest that neurological, reproductive, developmental, and ocular endpoints are sensitive targets in animals. The oral database was considered adequate for the derivation of acute-, intermediate-, and chronic-duration oral MRLs for disulfoton. MRLs derived for the inhalation and oral-exposure routes for disulfoton are summarized in Table 1-1, and are discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Disulfoton – Inhalation

The neurological endpoint is the most sensitive target of disulfoton inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

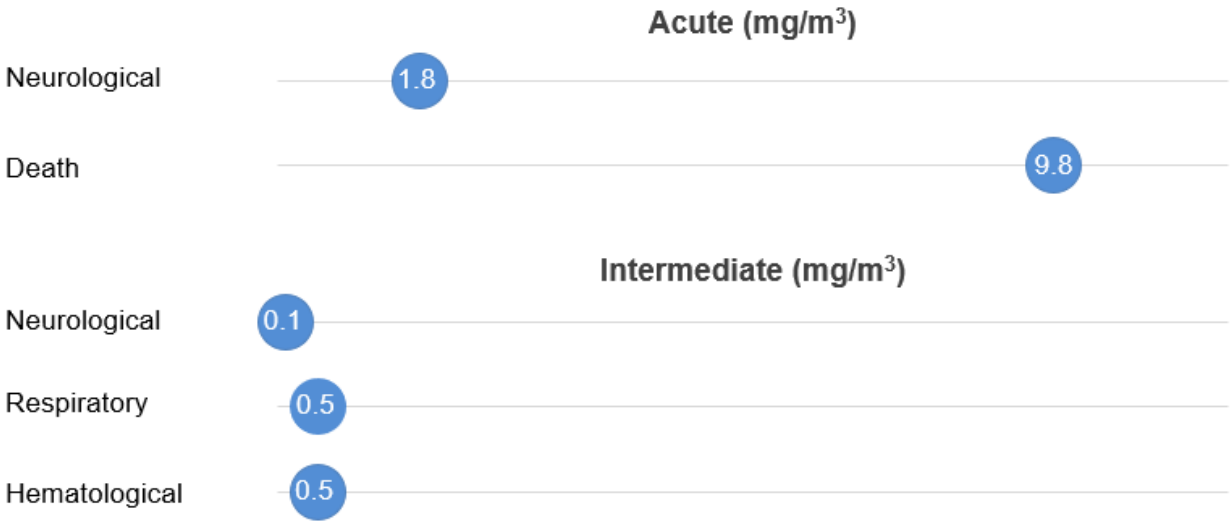


Figure 1-4. Summary of Sensitive Targets of Disulfoton – Oral

The neurological and developmental endpoints are the most sensitive targets of disulfoton oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

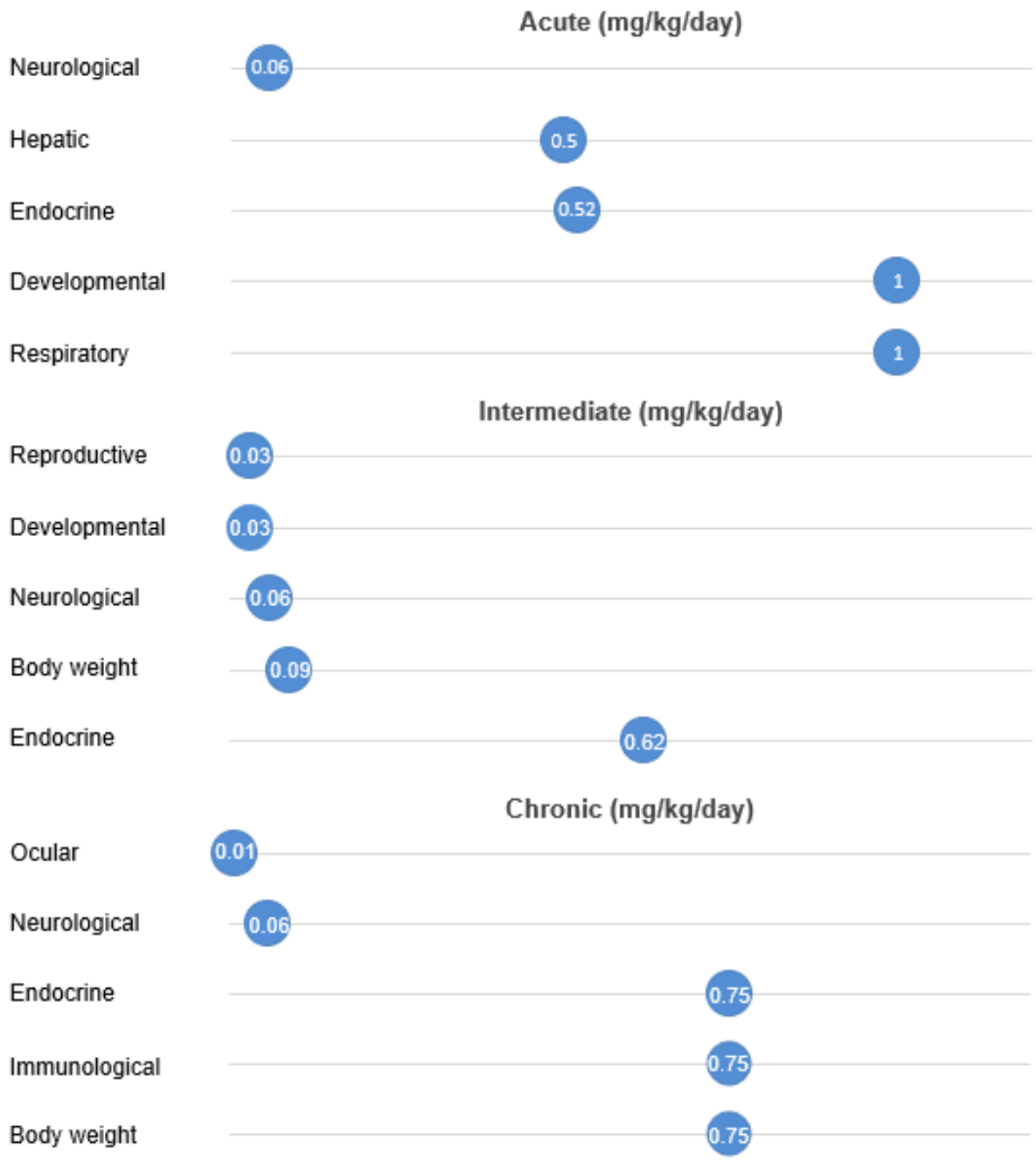


Table 1-1. Minimal Risk Levels (MRLs) for Disulfoton[a]

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty factor	Reference
Inhalation exposure (mg/m^3)					
Acute	The intermediate-duration inhalation MRL of **0.0006 mg/m^3 (0.6 µg/m^3)** is adopted as the acute-duration inhalation MRL				
Intermediate	**0.0006 (0.6 µg/m^3)**	Decreased brain AChE activity	NOAEL: 0.1 ($NOAEL_{HEC}$: 0.018)	30	Thyssen 1980
Chronic	Insufficient data for derivation of an MRL				
Oral exposure (mg/kg/day)					
Acute	**0.0003 (0.3 µg/kg/day)**	Decreased red blood cell AChE activity	$BMDL_{20RD}$: 0.028	100	Klaus 2006b
Intermediate	**0.00009 (0.09 µg/kg/day)**	Decreased brain AChE activity	NOAEL: 0.009	100	Hixson and Hathaway 1986
Chronic	**0.00006 (0.06 µg/kg/day)**	Decreased red blood cell AChE activity	LOAEL: 0.06	1,000	Hayes 1985

[a]See Appendix A for additional information.

AChE = acetylcholinesterase; $BMDL_{20RD}$ = benchmark dose lower bound with 20% relative deviation; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 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. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

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 by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to disulfoton, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to substance x was also conducted; the results of this review are presented in Appendix C.

Animal inhalation studies are presented in Table 2-1 and Figure 2-2, and animal oral studies are presented in Table 2-2 and Figure 2-3; animal dermal data are presented in Table 2-3.

Levels of significant exposure (LSEs) 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 (SLOAELs) 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

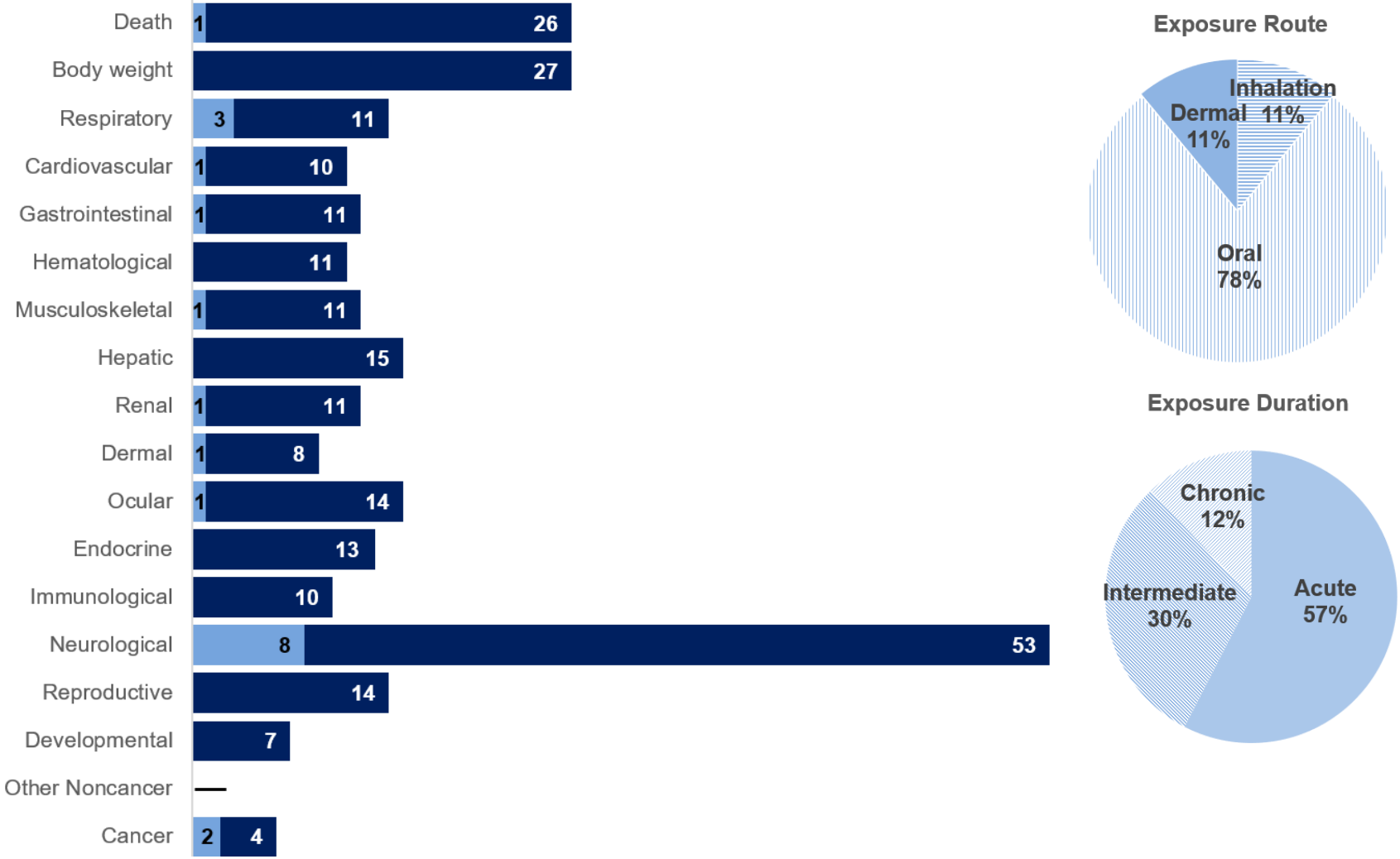
dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there 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 endpoints. 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.

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

The health effects of disulfoton have been evaluated in experimental animal studies and a few human occupational studies and case studies. As illustrated in Figure 2-1, most of the health effects data come from oral and inhalation studies in animals. Animal data are available for each exposure route and exposure duration category. Multiple studies evaluating the toxicity of disulfoton have evaluated a suite of endpoints. Neurological effects are the most examined in the literature, followed by death and body weight effects. The most common neurological effect noted is altered AChE activity; typically, ATSDR classifies AChE inhibition between 20 and 59% as a less serious LOAEL and >59% as a serious LOAEL. Cholinesterase inhibition classified as a less serious LOAEL and accompanied by clinical symptoms of cholinergic toxicity may be classified as a serious LOAEL. Human case reports and occupational studies have evaluated and reported the effect of disulfoton exposure on the central nervous system. The genotoxicity of disulfoton has also been examined.

Figure 2-1. Overview of the Number of Studies Examining Disulfoton Health Effects*

Most studies examined the potential neurological and body weight effects of disulfoton, in addition to mortality.
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 112 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
ACUTE EXPOSURE									
Doull 1957									
1	Rat (Sprague-Dawley) 5 M	0.5–1 hour	65.1, 121.1, 195.1, 202.2, 279.5, 416.0, 433.4	CS LE	Death			202.2	3/5 died
					Neuro			65.1	Muscle twitching and fibrillation, ataxia, salivation, urination, defecation, lacrimation
DuBois and Kinoshita 1971									
2	Rat (Holtzman) 3 F	10 days 1 hour/day	0, 0.14, 0.35, 0.7	BI CS	Neuro	0.7			
DuBois and Kinoshita 1971									
3	Rat (Holtzman) 3 F	5 days 1 hour/day	0, 0.14, 0.35, 0.7	BI CS	Neuro	0.7			
Thyssen 1978									
4	Rat (Wistar) 10–20 M 10–20 F	1 hour	M: 133, 196, 256, 322, 660 F: 27, 33, 46, 58, 80, 133	BC BW CS LE	Death			63 F 290 M	Computed LC_{50}
					Neuro		27 F 133 M		Sluggishness, failure to groom, typical signs of cholinesterase inhibition, not otherwise described
Thyssen 1978									
5	Rat (Wistar) 10–20 M 20–40 F	4 hours	M: 34, 48, 51, 64, 78, 96 F: 3.4, 5, 7, 10, 13, 20	BC BW CS LE	Death			15 F 60 M	Computed LC_{50}
					Neuro	51 M	3.4 F 64 M		Sluggishness, failure to groom, typical signs of cholinesterase inhibition, not otherwise described

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
Thyssen 1978									
6	Rat (Wistar) 10 M, 10 F	5 days 4 hours/day	0, 0.5, 1.8, 9.8	BI BW GN LE	Death			9.8 F	9/10 died
					Bd wt	9.8			
					Neuro	0.5		1.8	19–26% depression in RBC AChE activity; unspecified behavioral disorders, sluggish, drowsy
Doull 1957									
7	Mouse (Carworth Farms) 10 F	1 hour	53.4, 58.2, 65.1, 121.1, 195.1	CS LE	Death			53.4	1/10 died
					Neuro			53.4	Muscular twitches and fibrillations, ataxia; salivation, urination, defecation, lacrimation
INTERMEDIATE EXPOSURE									
Shiotsuka 1988									
8	Rat (Fischer-344) 9–10 M, 10 F	3 weeks 5 days/week 6 hours/day	0, 0.006, 0.07, 0.7	BI BW CS LE	Bd wt	0.7			
					Neuro	0.7			
Shiotsuka 1989									
9	Rat (Fischer-344) 12 M, 12 F	13 weeks 5 days/week 6 hours/day	0, 0.018, 0.16, 1.4	BC BI BW CS FI GN HP LE HE OP OW UR	Bd wt	1.4			
					Resp	1.4 F			
						0.16 M	1.4 M		50% increased incidence of inflammation of the nasal turbinates
					Cardio	1.4			
					Gastro	1.4			
					Hemato	1.4			
					Musc/skel	1.4			
					Hepatic	1.4			
					Renal	1.4			
					Dermal	1.4			
					Ocular	1.4			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Endocr	1.4			
					Immuno	1.4			
					Neuro	0.16	1.4		14–31% inhibition of plasma AChE, 22–34% inhibition of RBC AChE, 28–29% inhibition of brain ChE
Thyssen 1980									
10	Rat (Wistar TNO/W 74) 10 M	3 weeks 5 days/week 6 hours/day	0, 0.02	BC BI BW CS GN HE HP OW UR	Bd wt	0.02			
					Resp	0.02			
					Cardio	0.02			
					Gastro	0.02			
					Hemato	0.02			
					Hepatic	0.02			
					Renal	0.02			
					Endocr	0.02			
					Immuno	0.02			
					Neuro	0.02			
					Repro	0.02			
Thyssen 1980									
11	Rat (Wistar TNO/W 74) 10 M, 10 F	3 weeks 5 days/week 6 hours/day	0, 0.1, 0.5, 3.7		Death			3.7 F	5/10 died
					Bd wt	0.5 F	3.7 F		11–12% decreased body weight gain
						3.7 M			
					Resp	0.1 F	0.5 F	3.7 F	LOAEL: inflammatory changes in respiratory tract (larynx, trachea, emphysema, peribronchial red cell infiltrates, lungs perivascular red cell infiltrated); serious LOAEL: mottled distended lungs in the rats that died
						3.7 M			
					Cardio	3.7			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Gastro	0.5		3.7 F	Bloated gastrointestinal tract and ulcer-like foci in the glandular mucosa in rats that died
					Hemato	0.1	0.5		Minimal to definite bone marrow changes concurrent with respiratory inflammatory changes
					Hepatic	3.7			
					Renal	0.5 F	3.7 F		Pale discoloration of kidneys in dead rats
					Endocr	0.5 F	3.7 F		Increased absolute (14%) and relative (21%) adrenal weight
						3.7 M			
					Immuno	3.7			
					Neuro	0.1 F[b]	0.5 F		30% inhibition of brain AChE, lethargy by day 15
						0.5 M	3.7 M		24% inhibition of RBC AChE, 48% inhibition of brain AChE
					Repro	3.7			
Thyssen 1980									
12	Rat (Wistar TNO/W 74) 10–20 F	6 hours/day 5 days/week 3 weeks	0, 0.02, 3.1	BC BI BW CS GN HE HP OW UR	Death			3.1	3/20 died
					Bd wt	3.1			
					Resp	0.02		3.1	Increased inflammatory changes in the respiratory tract (larynx, trachea, emphysema, peribronchial red cell infiltrates, lungs perivascular red cell infiltrated); distended and dark discoloration in lungs of dead rats
					Cardio	3.1			
					Gastro	0.02	3.1		Reddened gastrointestinal tract in dead rat

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Hemato	0.02	3.1		Low lymphocytes percentage (35–60%) and high polymorpho-nuclear leukocytes percentage (40–62%) in 2/5 rats; reactive bone marrow changes accompanied by inflammatory changes in the respiratory tract
					Hepatic	0.02	3.1		Increased absolute (13%) and relative (20%) liver weight
					Renal	0.02	3.1		Increased relative kidney weight (14%)
					Endocr	0.02	3.1		Increased absolute (10%) and relative (18%) adrenal weight
					Immuno	0.02	3.1		Decreased absolute (18%) and relative (14%) spleen weight
					Neuro	0.02		3.1	Muscle tremors, convulsions, increased salivation, difficulty breathing
					Repro	3.1			

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate-duration inhalation MRL of 0.0006 mg/m^3; concentration adjusted for intermittent exposure, converted to a human equivalent concentration of 0.018 mg/m^3 and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability). This MRL was also adopted for the acute-duration inhalation MRL; see Appendix A for more detailed information regarding the MRL.

RBC and brain AChE activity are assessed by comparing the activity of exposed groups to study controls and assessing whether AChE was inhibited by the chemical of interest. ATSDR classifies a NOAEL as <20% inhibition; a LOAEL is classified as 20–59% inhibition; and a SLOAEL is classified as >59% inhibition. If AChE activity is inhibited by 20–59% but is accompanied with clinical signs of cholinergic toxicity, it may be classified as a SLOAEL.
Highlighted rows indicate an MRL principal study.

AChE = acetylcholinesterase; BC = blood chemistry; Bd wt or BW = body weight; BH = behavioral; BI = biochemical indices; Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathological; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; LC_{50} = concentration producing 50% death; M = male(s); MRL = Minimal Risk Level; Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; OP = ophthalmology; OW = organ weight; RBC = red blood cell; Repro = reproductive; Resp = respiratory; SLOAEL = serious LOAEL; UR = urinalysis

Figure 2-2. Levels of Significant Exposure to Disulfoton – Inhalation
Acute (≤14 days)

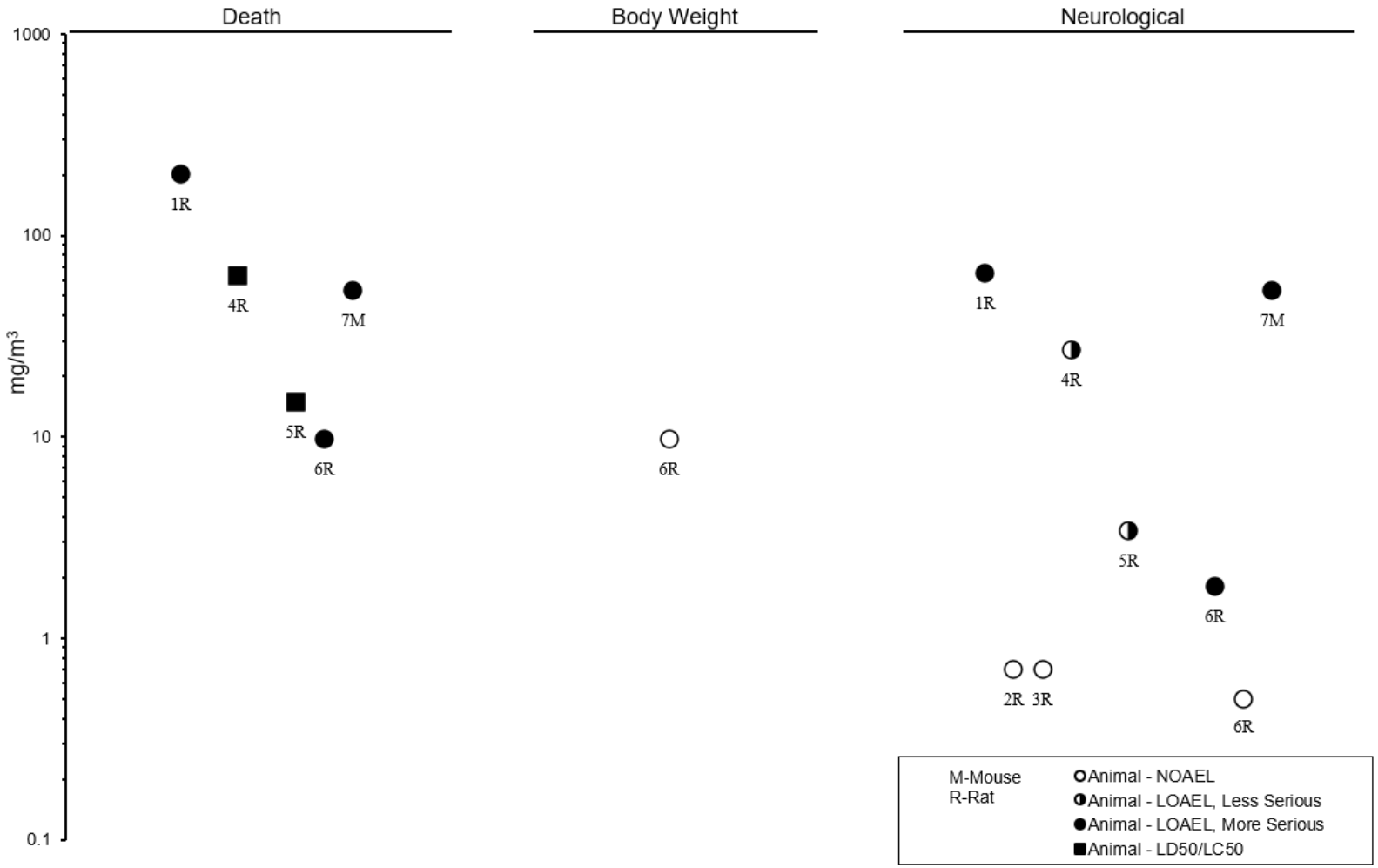


Figure 2-2. Levels of Significant Exposure to Disulfoton– Inhalation
Intermediate (15–364 days)

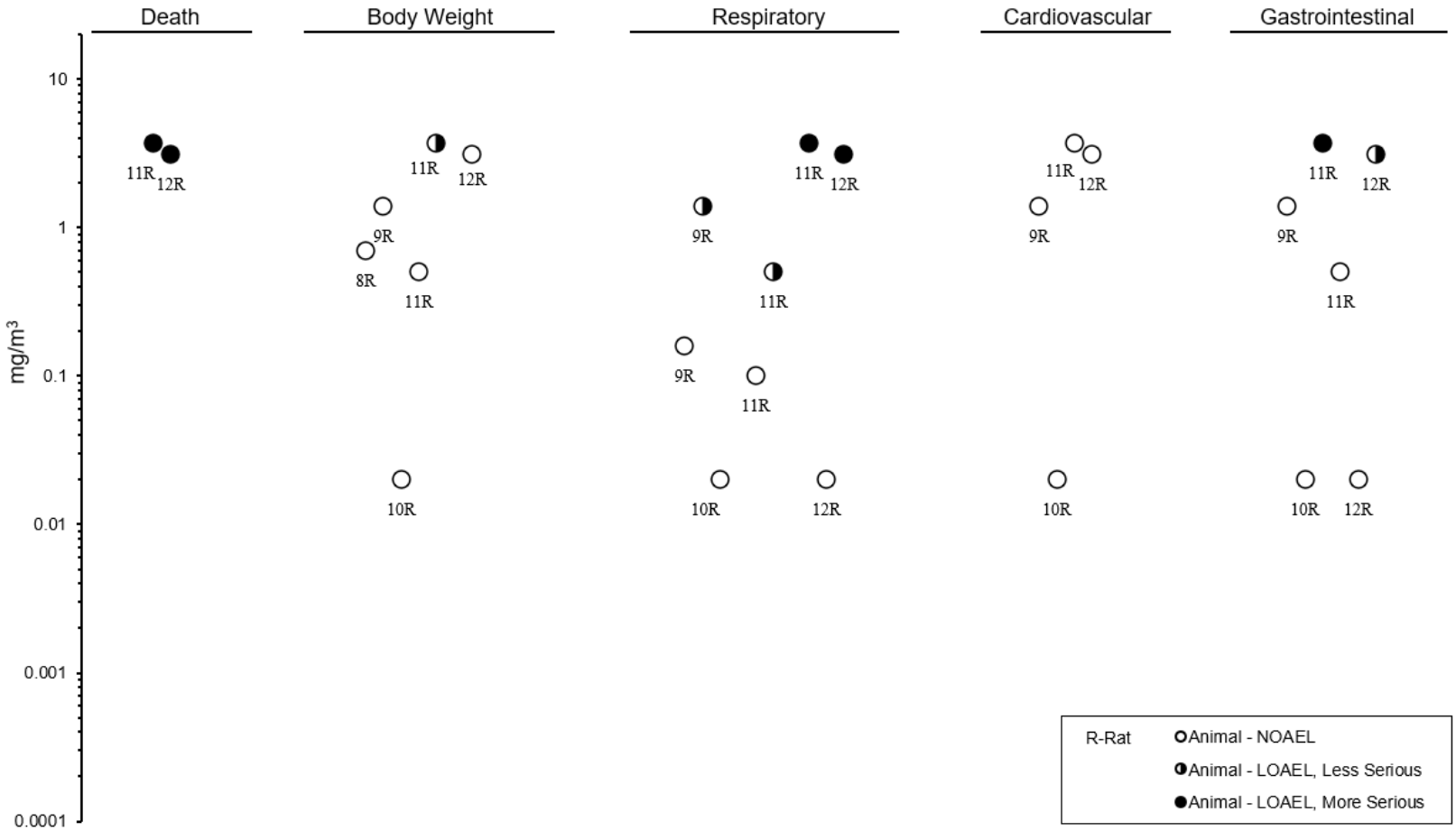


Figure 2-2. Levels of Significant Exposure to Disulfoton– Inhalation
Intermediate (15–364 days)

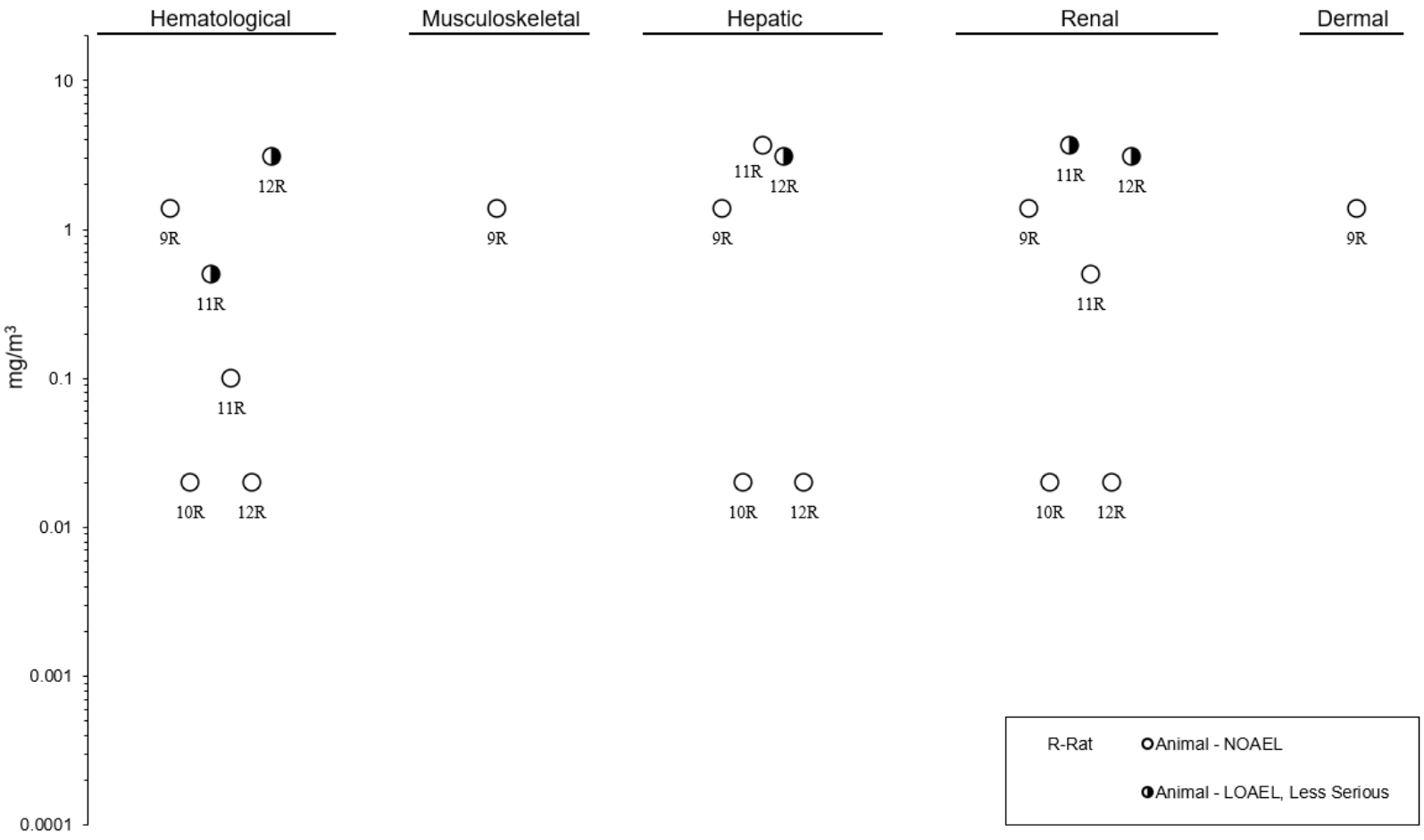


Figure 2-2. Levels of Significant Exposure to Disulfoton– Inhalation

Intermediate (15–364 days)

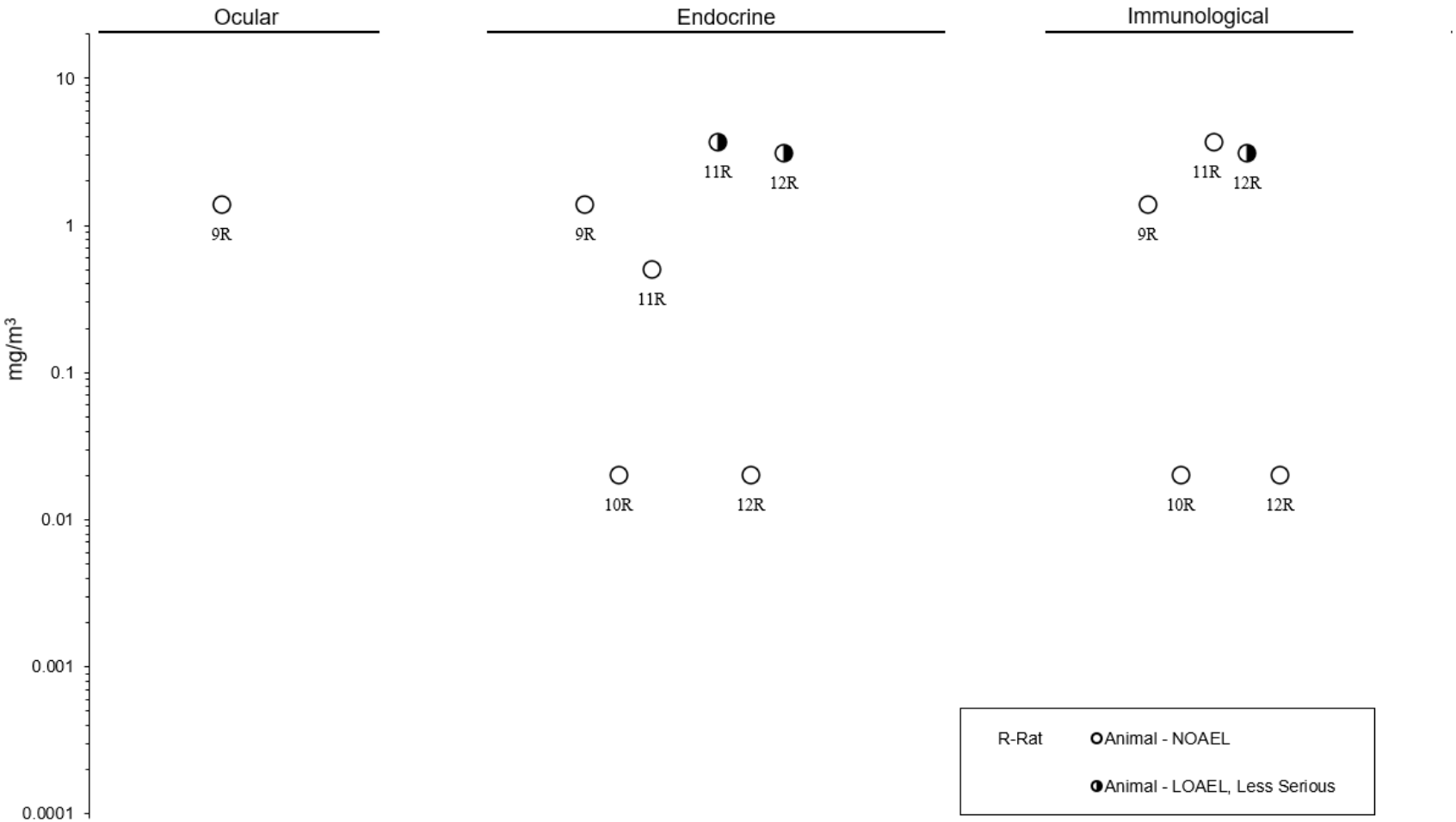


Figure 2-2. Levels of Significant Exposure to Disulfoton– Inhalation
Intermediate (15–364 days)

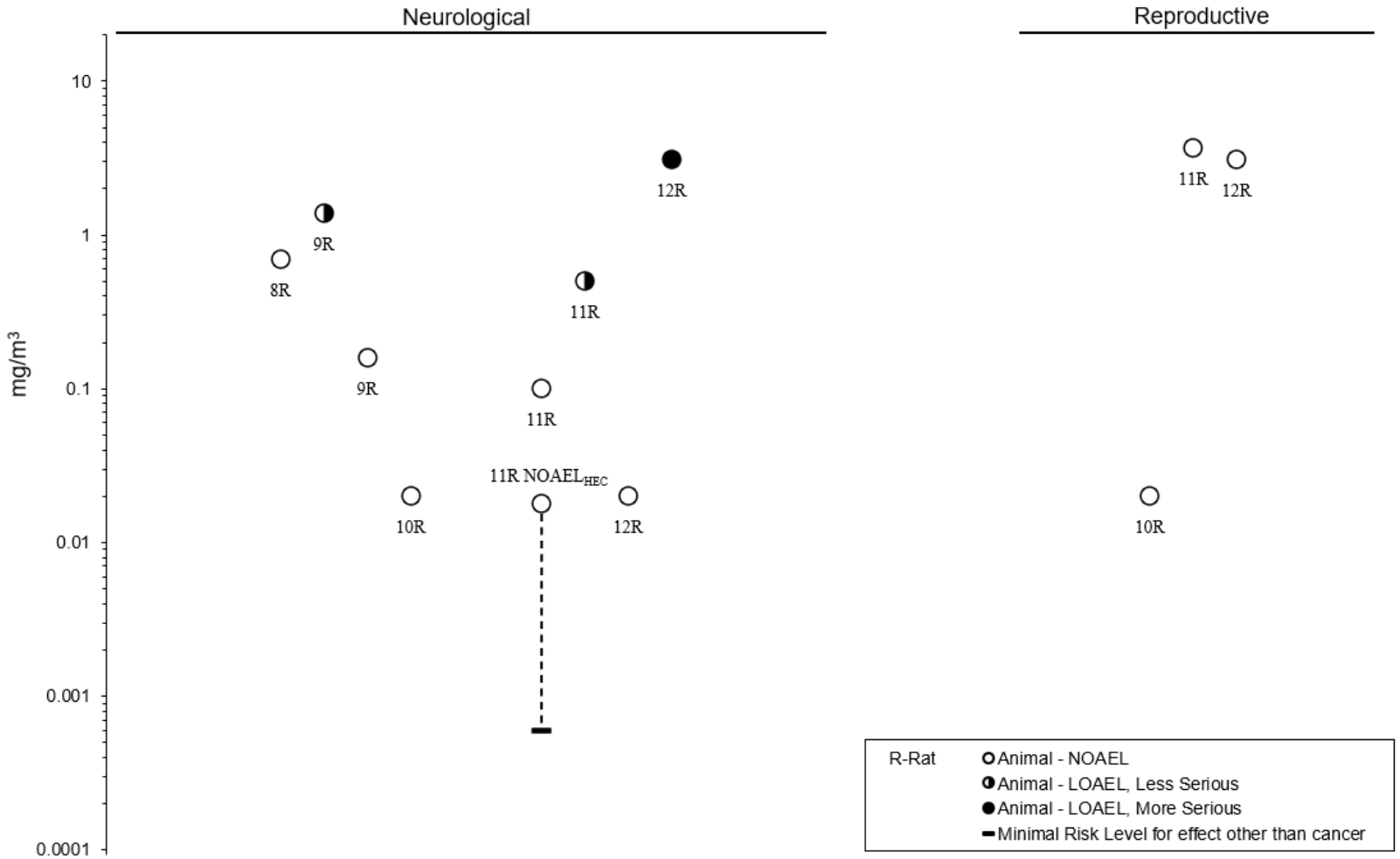


Table 2-2. Levels of Significant Exposure to Disulfoton – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
Brzezinski 1969									
1	Rat (Wistar) 5 B	Once (GO)	0, 6.25	BI	Endocr			6.25 F	173 and 313% increase in urinary noradrenaline and adrenaline levels, respectively
Brzezinski 1973									
2	Rat (Wistar) 14–25 M	Once (GO)	0, 5	BI	Endocr			5	Increase in urinary adrenaline (238%) and noradrenaline (61%) 1 day after exposure
Costa and Murphy 1983a									
3	Rat (Sprague-Dawley) 5–14 M	10 days (GO)	0, 2	BI	Neuro			2	89% inhibition of brain AChE activity
Costa et al. 1984									
4	Rat (Sprague-Dawley) 3–10 M	10 days (GO)	0, 2	BI BW CS OW	Bd wt			2	32% reduction in weight gain
					Neuro			2	50% reduction in pancreatic AChE activity, salivation, lacrimation, diarrhea
Costa et al. 1986									
5	Rat (Sprague-Dawley) 10 M	10 days (GO)	0, 2	BI BW	Bd wt			2	50% reduced body weight gain
					Neuro			2	Decreased density of muscarinic receptors in cerebral cortex; 84% inhibition of brain AChE
Crawford and Anderson 1974									
6	Rat (NS) 4 M, 4 F	Once (GW)	M: 2.0 F: 0.5, 1.0, 2.0, 4.0	CS LE	Death			2 F	2/4 died
					Neuro			0.5 F	Tremors

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
EPA 2007									
7	Rat (Wistar) 6 M, 6 F	Once (G)	M: 1.5 F: 0, 0.75	CS LE NX	Neuro			0.75 F	65% inhibition of RBC AChE 8 hours post-dosing
							1.5 M		40–51% inhibition of RBC AChE and 27–42% inhibition of brain AChE 4, 6, and 8 hours post-dosing
EPA 2007									
8	Rat (Wistar) 10 M, 10 F	Once (G)	0, 0.5	CS LE NX	Neuro		0.5		50–56% inhibition of RBC AChE and 26–56% inhibition of brain AChE activity 24 hours post-dosing
EPA 2007									
9	Rat (Wistar) 6 M, 6 F	Once (G)	0, 0.25, 0.75, 1.5 (M) 0, 0.25, 0.5, 0.75 (F)	CS LE NX	Neuro	0.25 F	0.5 F	0.75 F	34% inhibition RBC AChE activity at 0.5 mg/kg/day; 70% inhibition of RBC AChE activity at 0.75 mg/kg/day
						0.75 M	1.5 M		46% inhibition of RBC AChE activity and 32% inhibition of brain AChE activity
EPA 2007									
10	Rat (Wistar) 10 F, 10 M	Once (G)	0, 0.125, 0.25, 0.5	CS LE NX	Neuro	0.125 F	0.25 F		22% inhibition of RBC AChE activity and 19% inhibition of brain AChE
						0.25 M	0.5 M		53% inhibition of RBC AChE activity and 39% inhibition of brain AChE
Fawade and Pawar 1983									
11	Rat (Hindustan antibiotics) 8 M	Once (GO)	0, 2	BI	Hepatic		2		Increased lipid peroxidation (20–32%)

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Fitzgerald and Costa 1992									
12	Rat (Long-Evans) 4 M	14 days (GO)	0, 2	BW CS	Bd wt		2		Temporary but significant (p<0.025) decreased body weight gain at day 3 with recovery by days 5–6
					Neuro			2	Decrease in muscarinic cholinergic receptors in cortex (22%), medulla pons (11%), hippocampus (17%), striatum (30%)
Fitzgerald and Costa 1993									
13	Rat (Long-Evans) 4–7 M	1–2 weeks 7 days/week (GO)	0, 2	BI BW CS	Bd wt		2		Significantly (p<0.025) reduced body weight gain beginning at day 3 with recovery by days 5–6
					Neuro			2	60–84% decrease in brain AChE activity, diarrhea, flaccidity, malaise
Klaus 2006a									
14	Rat (Wistar) 6 M, 6 F	11 days (G)	0, 0.25, 0.5, 1.0 (M); 0, 0.125, 0.25, 0.5 (F)	BX BW CS LE NX	Bd wt	0.5 F 1 M			
					Neuro	0.125 F	0.25 F	0.5 F	28% inhibition of RBC AChE activity and 33% inhibition of brain AChE activity at 0.25 mg/kg/day; 63% inhibition of RBC AChE activity and 70% inhibition of brain AChE activity at 0.5 mg/kg/day
						0.25 M	0.5 M	1 M	38% inhibition of RBC AChE activity and 39% inhibition of brain AChE activity at 0.5 mg/kg/day; 72% inhibition of RBC AChE activity and 70% inhibition of brain AChE activity at 1 mg/kg/day

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Klaus 2006b									
15	Rat (Wistar) 10 M, 10 F	11 days PNDs 11–21 (G)	0, 0.06, 0.125, 0.25	CS LE NX	Neuro		0.06 F[b]		29% inhibition of RBC AChE activity ($BMDL_{20RD}$=0.028 mg/kg/day)
						0.06 M	0.125 M		23% inhibition of brain AChE activity, 19% of RBC AChE activity
Lamb and Hixson 1983									
16	Rat (CD) 25 F	10 days GDs 6–15 (G)	0, 0.1, 0.3, 1.0	CS BI DX FX	Neuro	0.1	0.3	1	41% inhibition of plasma and RBC AChE activity in dams at 0.3 mg/kg/day; 82–90% inhibition of plasma and RBC AChE activity in dams at 1 mg/kg/day
					Develop	0.3	1		Delayed ossification of parietal bones and sternebrae
Matsuda et al. 2000									
17	Rat (Wistar albino) NR/M	Once (GO)	6	BC HP	Neuro			6	75 and 69% inhibition of AChE in whole blood and skeletal muscle, respectively
Mihail 1978									
18	Rat (Wistar) 15 M,15 F	Once (GO)	M: 1, 4, 4.5, 5, 6, 7.5, 9, 10 F: 0.5, 1, 1.25, 1.5, 2, 2.5, 5	CS GN LE	Death			1.9 F 6.2 M	Computed LD_{50}
					Resp	0.5 F	1		Dyspnea up to 8 days post-treatment
					Neuro	0.5 F 1 M		1 F 4 M	Muscle twitching cramps, salivation
Pawar and Fawade 1978									
19	Rat (Hindustan antibiotics) NS B	Once (G)	0, 1-12.3	CS LE	Death			3.2 F 7.2 M	LD_{50}

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Schwab and Murphy 1981									
20	Rat (Holtzman) 50 F	9 days (F)	0, 0.38, 1.0	BI BW CS	Bd wt	0.38	1		10–12% reduced body weight gain at all weighing times
					Neuro			0.38	60–65% inhibition of brain AChE after <15-day exposure
Schwab et al. 1981									
21	Rat (Sprague-Dawley) 5–10 M	3 days a time for 1–23 days (GO)	0, 2, 2.5, 3, 3.5	BI BW CS LE	Death			3.5	Three of five unpretreated rats died after three doses
					Bd wt			2	21% reduced body weight
					Neuro			2	Exophthalmia, salivation, excessive urination and defecation, tremors
Schwab et al. 1983									
22	Rat (Sprague-Dawley) 3–5 M	1–10 days (GO)	0, 2.0	BI BW CS	Bd wt		2		Weight loss not otherwise specified
					Neuro			2	Salivation, lacrimation, excessive urination and diarrhea, fasciculations, tremors, 15–51% inhibition of ileal AChE activity
Sheets 1993a									
23	Rat (Sprague-Dawley) 10 M, 9–10 F	Once (GO)	M: 0,0.24, 1.5, 5.2 F: 0, 0.24, 0.76, 1.5	BI BW CS GN HP LE OW	Death			1.5 F	1/10 died from acute cholinergic intoxication
					Musc/skel	5.2			
					Ocular	5.2			
					Neuro	0.24 F		0.76 F	Muscle fasciculations, decreased vocalization, minimal head or body movement, 53% decrease in RBC AChE activity
						0.24 M		1.5 M	Muscle fasciculations, tremors, minimal head or body movement

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Su et al. 1971									
24	Rat (Holtzman) 6–12 F	1 week (F)	0, 0.05, 0.25, 1.25	BI	Neuro	0.05	0.25		50% inhibition of brain AChE activity
Wysocka- Paruszewska 1971									
25	Rat (Wistar) 4 M, 4 F	Once (GO)	M: 0, 1.25, 2.5, 3.75, 5 F: 0, 0.26, 0.52, 0.78, 1.04	BI	Endocr	0.26 F	0.52 F		Increased excretion of 4-hydroxy-3-methoxy-mandelic acid in urine (27.8–32%)
							1.25 M		Increased excretion of 4-hydroxy-3-methoxy-mandelic acid in urine (51% after 2 days)
Yagle and Costa 1996									
26	Rat (Sprague-Dawley) 34 M	14 days (GO)	0, 2	BC BW CS HP	Bd wt		2		3-8% lower body weight
					Gastro		2		Diarrhea in 5/34 rats
					Neuro			2	81% decrease in AChE activity
Fawade and Pawar 1978									
27	Mouse (Hindustan antibiotics) 8 M	2–4 days (GO)	0, 0.5, 1, 1.5, 2	BI	Hepatic		0.5		Increased lipid peroxidation (9%)
Fawade and Pawar 1980									
28	Mouse (Hindustan antibiotics) 8 M	Daily 3 days (GO)	0, 1	BI	Hepatic		1		Increased lipid peroxidation (34–58%)
Herbold 1980									
29	Mouse (NMRI/ ORIG) 50 M	Once (GO)	0, 5	CS RX	Repro	5			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Mihail 1978									
30	Mouse (MMRI) 15 M,1 5F	Once (GO)	M: 2.5, 5, 6, 7, 8, 10; F: 2.5, 5, 6.5, 7.5, 10, 11	CS LE	Death			8.2 F 7 M	Computed LD_{50}
					Resp	2.5	5		Acute dyspnea
					Neuro	2.5		5	Muscle twitches, clonic cramps, salivation
Pawar and Fawade 1978									
31	Mouse (Hindustan antibiotics) NS B	Once (G)	0, 1–10	CS LE	Death			2.7 F 5.8 M	LD_{50}
Schafer and Bowles 1985									
32	Mouse (wild deer mouse) 1–6 NS	Once (G)	NR	CS LE	Death			18	Mortality of an unspecified number of mice
Stevens et al. 1972a									
33	Mouse (Swiss-Webster) NS M	Once (GO)	19.3	CS LE	Death			19.3	LD_{50}
Stevens et al. 1972b									
34	Mouse (Swiss) 6–20 M	1–10 days (GO)	0, 2.4, 4.9, 9.6	LE	Death			9.6	2/8 died
					Hepatic	4.9	9.6		Significant shortening of the hexobarbital sleeping time
Crawford and Anderson 1973									
35	Guinea pig (NS) 3M, 3F	Once (GW)	M: 2.5, 5, 10, 20; F: 4,0, 8, 16, 32	CS LE	Death			12.7 F 8.9 M	LD_{50}
Mihail 1978									
36	Dog (Beagle) 1–2 F	Once (GO)	1, 2, 5, 10	CS LE	Death			5	Computed LD_{50}

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Tesh et al. 1982									
37	Rabbit (New Zealand) 14–22 F	13 days GDs 6–18 (G)	0, 0.3, 1, 1.5, 2, 3	BW DX	Bd wt	3			
					Develop	1.5			
INTERMEDIATE EXPOSURE									
Christenson and Wahle 1993									
38	Rat (Fischer-344) 35 M, 35 F	6 months (F)	M: 0, 0.02, 0.03, 0.06 F: 0, 0.02, 0.03, 0.07	BI BW CS FI LE	Bd wt	0.07			
					Neuro	0.03 F	0.07 F		22–29% inhibition in RBC AChE activity
						0.06 M			
Clark and Pearson 1973									
39	Rat (Charles River) 10 M	3 months (F)	0, 0.5, 1.25, 2.5	CS NX	Neuro		0.5		59% inhibition of brain AChE activity
Clark and Stavinoha 1971									
40	Rat (NS) NS	2 months (F)	0, 2.5	HP	Neuro		2.5		Increased permeability of CNS tissue
Hayes 1985									
41	Rat (Fischer 344) 50 M, 50 F	3-6 months (F)	M: 0, 0.05, 0.18, 0.75; F: 0, 0.06, 0.21, 1.02	BC BI BW CS FI GN HE HP OW UR	Neuro		0.06 F	0.21 F	14–22% inhibition of RBC AChE at 0.06 mg/kg/day; 68–69% inhibition of RBC AChE at 0.21 mg/kg/day
						0.05 M	0.18 M	0.75 M	14–22% inhibition of RBC AChE at 0.18 mg/kg/day; 68–69% inhibition of RBC AChE at 0.75 mg/kg/day
Hixson and Hathaway 1986									
42	Rat (Sprague-Dawley) 26 M, 26 F	F0: 15 weeks premating; F1b: 13 weeks premating and through pregnancy (F)	0, 0.009, 0.03, 0.09	CS BI BW FI DX GN HP	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
					Neuro	0.03 F		0.09 F	Tremor in the F0 females during the production of the F1 generation
						0.03 M			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Repro	0.009	0.03	0.09	Decreased F2b litter live births (25%) compared to control and decreased litter weights through GD 21 (30% change, compared to control at 8%) at 0.03 mg/kg/day; decreased sperm-positive F0 (21–33%) and F1 females (22-33%); decreased maternal F1 weight during gestation (8–12%) and lactation (10–12%), and maternal F0 weight during lactation (4–8%) compared to control; decreased litter counts, viability and lactation indices and increased stillbirths among all litters at 0.09 mg/kg/day
					Develop	0.009[c]	0.03		24–32% inhibition of brain AChE activity in F1 generation pups
Klaus 2006c									
43	Rat (Wistar) 13 F	21 days GDs 0–20 (F)	0, 0.042, 0.168, 0.694	BC BW CS FI LE NX	Bd wt	0.694			
					Neuro	0.042	0.168	0.694	44% inhibition RBC AChE activity and 32% inhibition of brain AChE activity at 0.0168 mg/kg/day; 90% inhibition of RBC AChE activity and 85% inhibition of brain AChE activity at 0.694 mg/kg/day
Klaus 2006c									
44	Rat (Wistar) NS	Maternal exposure on GDs 0–20	0, 0.042, 0.168, 0.694	BC	Develop	0.042	0.168	0.694	20% inhibition of RBC AChE activity in pups at 0.168 mg/kg/day; 83% inhibition of RBC AChE activity in pups at 0.694 mg/kg/day

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Klotzsche 1972									
45	Rat (Wistar) 25 M, 25 F	90 days (F)	M:0, 0.01, 0.07, 0.34 F: 0, 0.02, 0.11, 0.55	BC BI BW CS FI GN HE HP UR	Bd wt	0.55 F			
						0.34 M			
					Resp	0.55 F			
						0.34 M			
					Cardio	0.55 F			
						0.34 M			
					Gastro	0.55 F			
						0.34 M			
					Hemato	0.55 F			
						0.34 M			
					Musc/skel	0.55 F			
						0.34 M			
					Hepatic	0.55 F			
						0.34 M			
					Renal	0.55 F			
						0.34 M			
					Dermal	0.55 F			
						0.34 M			
					Ocular	0.55 F			
						0.34 M			
					Endocr	0.55 F			
						0.34 M			
					Immuno	0.55 F			
						0.34 M			
					Neuro	0.11 F 0.07 M	0.55 F 0.34 M		30–40% inhibition of plasma AChE and RBC AChE

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Robinson et al. 1978									
46	Rat (Albino) 71–72 M	30 days (F)	0, 2.5	BI BW	Death			2.5	4/71 died
					Bd wt			2.5	29% reduced body weight gain
					Neuro			2.5	Inhibition of AChE activity of 77.2% in brain, 81.9% in the stomach, 70.3% in the diaphragm
Ryan et al. 1970									
47	Rat (Albino) 5 M, 5 F	60–95 days (F)	0, 0.5	BI CS DX NX RX	Neuro		0.5		48% and 18% inhibition of brain AChE in males and females, respectively
					Repro			0.5	2/5 females failed to become pregnant
					Develop		0.5		32.1% inhibition of fetal brain AChE activity
Schwab and Murphy 1981									
48	Rat (Holtzman) 50 F	30–62 days (F)	0, 0.38, 1	BI BW CS	Bd wt	0.38	1		10–12% reduced body weight gain at all weighing times
					Neuro			0.38	75–80% inhibition of brain AChE
Sheets 1993b									
49	Rat (Fischer-344) 12 M, 12 F	13 weeks (F)	M: 0, 0.063, 0.27, 1.08 F: 0, 0.071, 0.315, 1.31	BI BW CS FI GN HP LE OP	Death			1.31 F	1/12 died on day 48
					Bd wt	1.31 F			
						1.08 M			
					Musc/skel	1.31 F			
						1.08 M			
					Ocular	1.31 F			
						1.08 M			
					Neuro	0.071 F		0.315 F	Muscle fasciculations, urine stain, 79–80% inhibition of RBC AChE activity, 64% inhibition of brain AChE activity

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
						0.063 M		0.27 M	61–67% inhibition of RBC AChE activity; 35% inhibition of brain AChE activity
Sheets 2005									
50	Rat (Wistar) 19–30 F	6 weeks GDs 0–21 and LDs 0–21 (F)	0, 0.038, 0.156, 0.670 during gestation; 0, 0.102, 0.389, 1.714 during lactation	BW CS DX FI GN LE NX	Bd wt		1.714		8–9% body weight decrease on LDs 14–21 compared to controls
					Neuro		0.102	0.389	27% inhibition of RBC AChE activity at 0.102 mg/kg/day; 73% inhibition of RBC AChE activity and 65% inhibition of brain AChE activity at 0.389 mg/kg/day
					Repro	1.714			
Sheets 2005									
51	Rat (Wistar) 5–20 B	Maternal generational exposure	0, 0.038, 0.156, 0.670 during gestation; 0, 0.102, 0.389, 1.714 during lactation	BW CS DX FI GN LE NX OP RX	Ocular	1.714			
					Neuro	0.389	1.714		53-56% inhibition of RBC AChE activity and 30% inhibition of brain AChE
					Develop		0.389 F		Delayed mean age for attainment of vaginal opening
						0.389 M	1.714 M		16% decrease in pup weight by PND 21 compared to controls; 18% depressed body weight gain from birth to PND 21
Stavinoha et al. 1969									
52	Rat (Holtzman or Charles River) 4–5 F	141–178 days (F)	0, 0.5, 1.25, 2.5	BI BW	Bd wt	0.5		1.25	40% reduced body weight gain
					Neuro			0.5	72% inhibition of brain AChE activity

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Taylor 1965a									
53	Rat (Holtzman) 10 M, 20 F	3 generations (F)	0, 0.1, 0.25, 0.5	BI CS DX HP	Develop		0.1	0.5	30–40% inhibition of RBC AChE in F3b weanlings at 0.1 mg/kg/day; cloudy swelling and fatty livers, mild nephropathy, juvenile hypoplasia of testes in F3b weanlings at 0.5 mg/kg/day
Clark and Stavinoha 1971									
54	Mouse (NS) NS	2 months (F)	0, 19.5	HP	Neuro		19.5		Increased permeability of central nervous system tissue
Clark et al. 1971									
55	Mouse (Charles River) 40–48 B	4 weeks (F)	0, 26	CS	Death			26 F	5/25 died
Clark et al. 1971									
56	Mouse (Charles River) 80–96 B	4-12 weeks (F)	0, 21.7, 26	CS	Neuro		21.7		Increased exploratory behavior
Rivett et al. 1972									
57	Mouse (CF-LP) 12 M, 12 F	13 weeks (F)	M: 0, 0.02, 0.12, 0.63 F: 0, 0.03, 0.14, 0.71	BC BI BW CS FI GN HE HP UR	Bd wt	0.71			
					Resp	0.71			
					Cardio	0.71			
					Gastro	0.71			
					Hemato	0.71			
					Hepatic	0.71			
					Renal	0.71			
					Ocular	0.71			
					Endocr	0.71			
					Immuno	0.71			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro	0.14 F	0.71 F		27–37% inhibition of RBC AChE and plasma AChE activity
						0.63 M			
Hikita et al. 1973									
58	Dog (Beagle) 2–4 NS	5 months 5 days/week 1 time/day (C)	0, 0.5, 1.0, 1.5	BC BI CS	Neuro			0.5	80% inhibition of RBC AChE
Hoffman and Welscher1975									
59	Dog (Beagle) 4 M, 4 F	40 weeks (F)	0, 0.06	BI	Neuro		0.06		22–50% inhibition of RBC AChE; 33–36% inhibition of plasma AChE
CHRONIC EXPOSURE									
Carpy et al. 1975									
60	Rat (Sprague-Dawley) 60 M, 60 F	1.5–2 years (F)	M: 0, 0.05, 0.06, 0.1 F: 0, 0.04, 0.09, 0.1	BC BI BW CS FI GN HE HP OW UR	Immuno	0.1			
					Neuro	0.09 F	0.1 F		21% inhibition of brain AChE
						0.05 M	0.06 M		26–37% inhibition of brain AChE
Carpy et al. 1975									
61	Rat (Sprague-Dawley) 60 M, 60 F	1.5–2 years (F)	M: 0, 0.05, 0.06, 0.1 F: 0, 0.04, 0.09, 0.1	BC BI BW CS FI GN HE HP OW UR	Bd wt	0.1			
					Resp	0.1			
					Cardio	0.1			
					Gastro	0.1			
					Hemato	0.1			
					Musc/skel	0.1			
					Hepatic	0.1			
					Renal	0.1			
					Dermal	0.1			
					Ocular	0.1			
					Endocr	0.1			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Hayes 1985									
62	Rat (Fischer 344) 50 M, 50 F	104–106 weeks (F)	M: 0, 0.05, 0.18, 0.75; F: 0, 0.06, 0.21, 1.02	BC BI BW CS FI GN HE HP OW UR	Death			1.02 F	20/50 died; increase in mortality compared to control
					Bd wt	0.21 F	1.02 F		11–19% decrease in body weight gain
						0.18 M	0.75 M		
					Resp	0.21 F	1.02 F		Granulomatous and suppurative inflammation of the lungs
						0.18 M	0.75 M		
					Cardio	1.02 F			
					Gastro	0.21 F	1.02 F		Mucosal hyperplasia and chronic inflammation of the forestomach
						0.75 M			
					Hemato	1.02 F			
					Musc/skel	0.21 F		1.02 F	Skeletal muscle atrophy corresponded to generalized debilitation at this dose
						0.75 M			
					Hepatic	1.02 F			
					Renal	1.02 F			
					Dermal	0.21 F	1.02 F		Acanthosis, hyperkeratosis, ulcer of the skin
						0.18 M	0.75 M		
					Ocular	0.06 F	0.21 F	1.02 F	Cystic degeneration of Harderian gland at 0.21 mg/kg/day; corneal neovascularization at 1.02 mg/kg/day
						0.18 M		0.75 M	Corneal neovascularization; inflammation of the eye (cornea)
					Endocr	1.02 F			
						0.18 M	0.75 M		Pancreatic atrophy
					Immuno	0.21 F	1.02 F		Splenic lymphoid follicle depletion

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
						0.18 M	0.75 M		Plasma cell hyperplasia in the mandibular lymph nodes
					Neuro		0.06 F[d]	0.21 F	24% inhibition of RBC AChE at 0.06 mg/kg/day; 57–77% inhibition of RBC AChE, 53% inhibition of brain AChE, optic nerve degeneration, rough fur coat at 0.21 mg/kg/day
						0.05 M		0.18 M	46–67% inhibition of RBC AChE, 53% inhibition of brain AChE, optic nerve degeneration
					Repro	0.21 F	1.02 F		Uterine cystic hyperplasia
						0.75 M			
Hayes 1983									
63	Mouse (CD-1) 50 M, 50 F	23 months (F)	M: 0, 0.11, 0.5, 2.13 F: 0, 0.14, 0.65, 2.53	BC BI BW CS FI HE OW	Bd wt	2.53 F			
						2.13 M			
					Resp	2.53 F			
						2.13 M			
					Cardio	2.53 F			
						2.13 M			
					Gastro	2.53 F			
						2.13 M			
					Hemato	2.53 F			
					Musc/skel	2.53 F			
					Hepatic	2.53 F			
					Renal	2.53 F			
					Dermal	2.53 F			
					Ocular	2.53 F			
					Endocr	2.53 F			
					Immuno	2.53 F			
						2.13 M			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro	0.65 F		2.53 F	Significant inhibition of RBC AChE and brain AChE by 82 and 46%, respectively
						0.5 M	2.13 M		Significant inhibition of RBC AChE and brain AChE by 56 and 44%, respectively
Hoffman and Welscher 1975									
64	Dog (Beagle) 4 M, 4 F	2 years (F)	0, 0.02, 0.03, 0.14	BC BI BW CS FI GN HE HP OP OW	Bd wt	0.14			
					Resp	0.14			
					Cardio	0.14			
					Gastro	0.14			
					Hemato	0.14			
					Musc/skel	0.14			
					Hepatic	0.14			
					Renal	0.14			
					Ocular	0.14			
					Endocr	0.14			
					Immuno	0.14			
					Neuro	0.03	0.14		46–53% inhibition of RBC AChE; 34.4% inhibition of brain AChE in males

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Ishikawa and Miyata 1980									
65	Dog (Beagle) 1–10 NS	2 years 5 days/week 1 time/day (C)	0, 0.63, 1.25, 1.89	BI CS HP OP	Ocular			0.63	Myopia, astigmatism, severe degeneration of ciliary muscle cells
Jones et al. 1999									
66	Dog (Beagle) 4 M, 4 F	12 months (F)	M: 0, 0.015, 0.121, 0.321 F: 0, 0.013, 0.094, 0.283	BC CS HE NX OP UR	Hemato	0.013 F 0.015 M			
					Ocular	0.013 F		0.094 F	60% inhibition of cornea ChE
							0.015 M	0.321 M	33% inhibition of cornea ChE at 0.015 mg/kg/day; 67% inhibition of retina and cornea ChE at 0.321 mg/kg/day
					Neuro	0.013 F	0.094 F	0.283 F	22% inhibition of brain AChE at 0.094 mg/kg/day; >60% inhibition of RBC AChE at day 91 of exposure at 0.283 mg/kg/day
						0.015 M		0.321 M	>80% inhibition of RBC AChE on day 91 of exposure

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Uga et al. 1977									
67	Dog (Beagle) 1–2 NS	2 years 5 days/week 1 time/day (C)	0, 0.5, 1.0, 1.5	HP	Neuro			0.5	Necrosis and atrophy of optic nerve and retina

[a]The number corresponds to entries in Figure 2-3.
[b]Used to derive an acute oral MRL of 0.0003 mg/kg/day; the $BMDL_{20RD}$ of 0.028 mg/kg/day was 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 oral MRL of 0.00009 mg/kg/day; the NOAEL of 0.009 mg/kg/day was 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 oral MRL of 0.00006 mg/kg/day; the LOAEL of 0.06 mg/kg/day was divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability). See Appendix A for details.

RBC and brain AChE activity are assessed by comparing the activity of exposed groups to study controls and assessing whether AChE was inhibited by the chemical of interest. ATSDR classifies a NOAEL as <20% inhibition; a LOAEL is classified as 20–59% inhibition; and SLOAEL is classified as >59% inhibition. If AChE activity is inhibited by 20–59% but is accompanied with clinical signs of cholinergic toxicity, it may be classified as a SLOAEL.
Highlighted rows indicate an MRL principal study.

AChE = acetylcholinesterase; B = both male(s) and female(s); BC = blood chemistry; Bd wt or BW = body weight; BH = behavioral; BI = biochemical indices; (C) = capsule; Cardio = cardiovascular; ChE = cholinesterase; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; FX = fetotoxicity; (G) = gavage; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil vehicle; HE = hematology; Hemato = hematological; HP = histopathological; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; LD = lactation day; LD_{50} = lethal dose, 50% kill; M = male(s); MRL = Minimal Risk Level; Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OP = ophthalmology; OW = organ weight; RBC = red blood cell; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity; SLOAEL = serious LOAEL; UR = urinalysis

Figure 2-3. Levels of Significant Exposure to Disulfoton – Oral Acute (≤14 days)

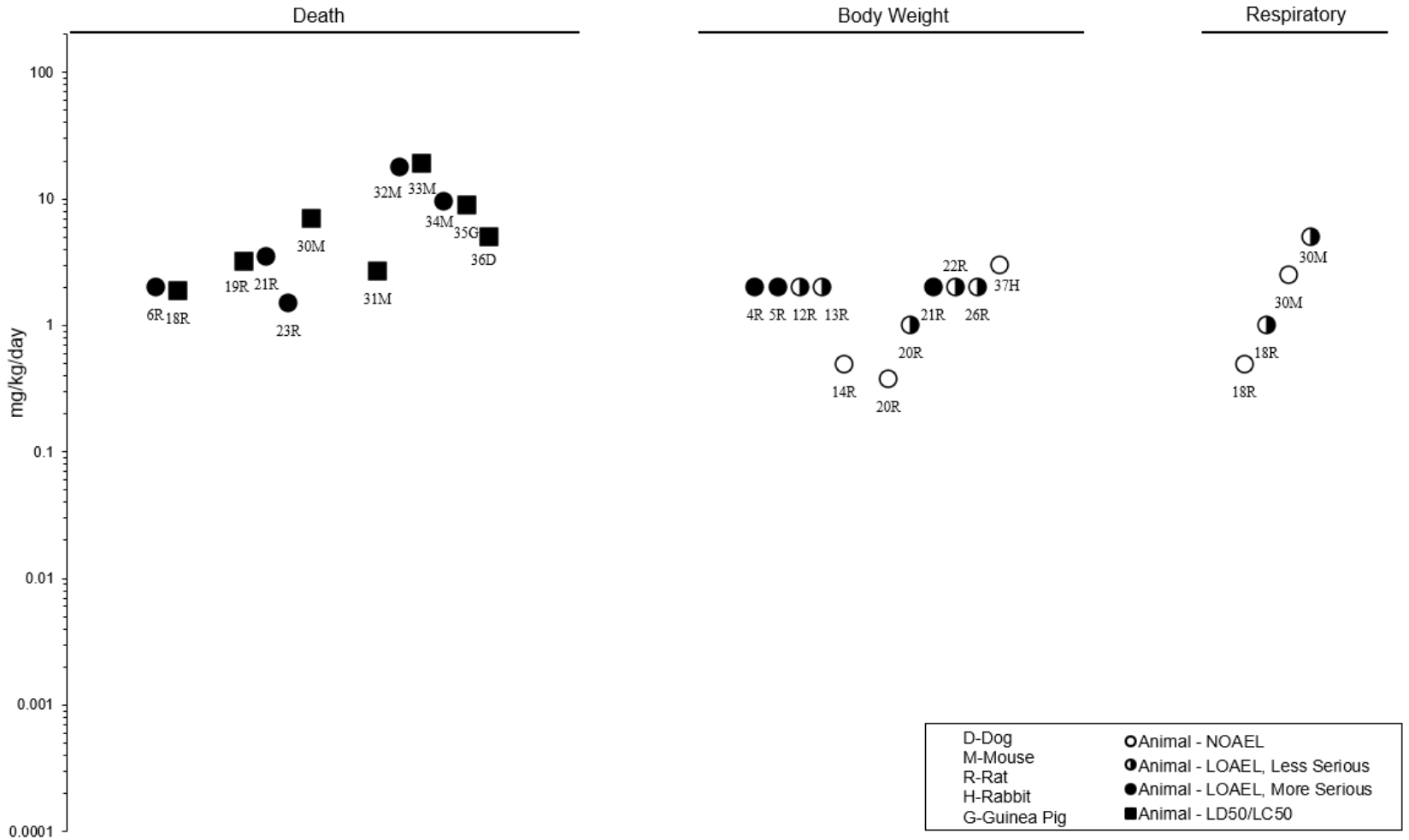


Figure 2-3. Levels of Significant Exposure to Disulfoton–Oral
Acute (≤14 days)

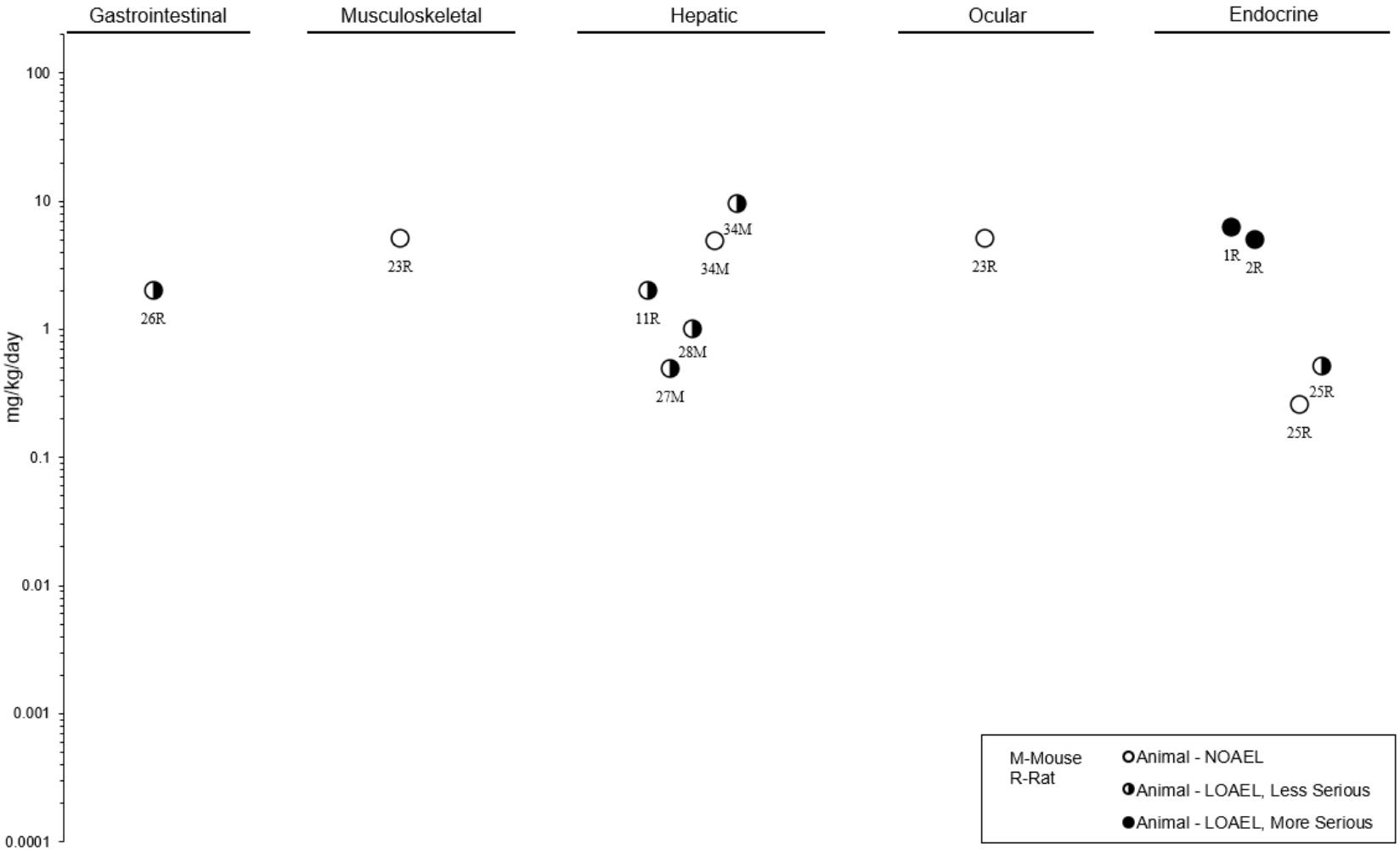


Figure 2-3. Levels of Significant Exposure to Disulfoton–Oral
Acute (≤14 days)

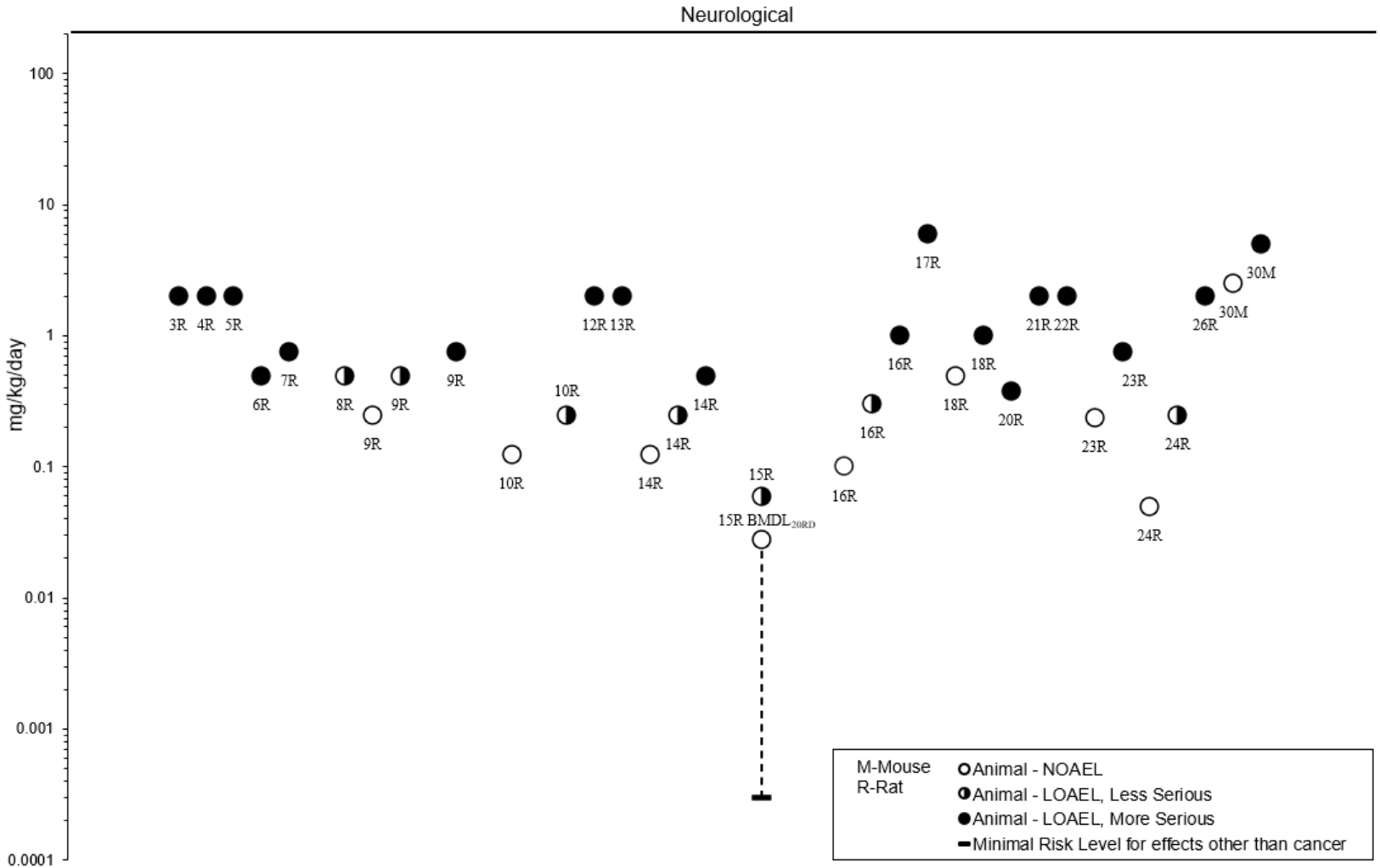


Figure 2-3. Levels of Significant Exposure to Disulfoton–Oral
Acute (≤14 days)

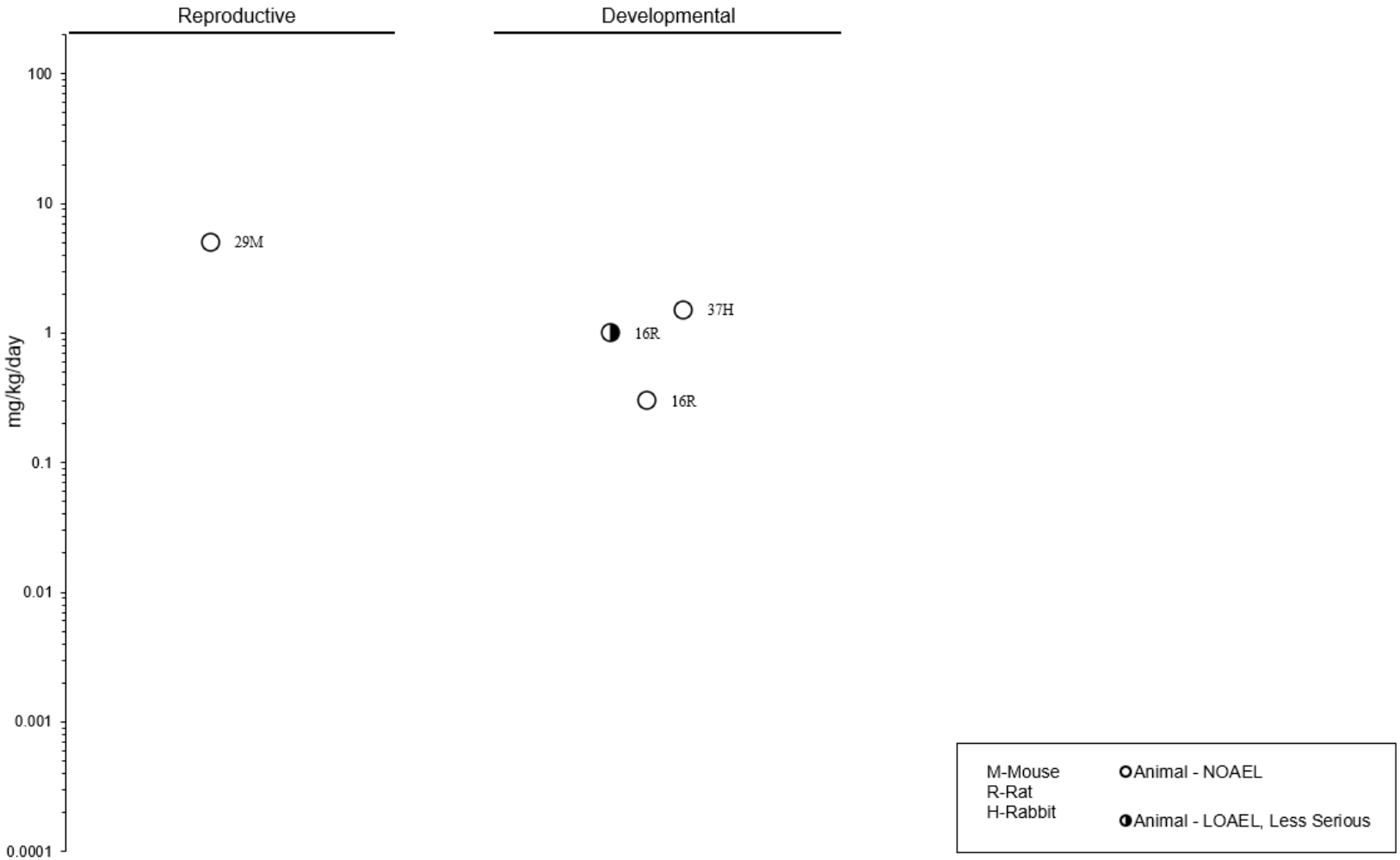


Figure 2-3. Levels of Significant Exposure to Disulfoton–Oral
Intermediate (15–364 days)

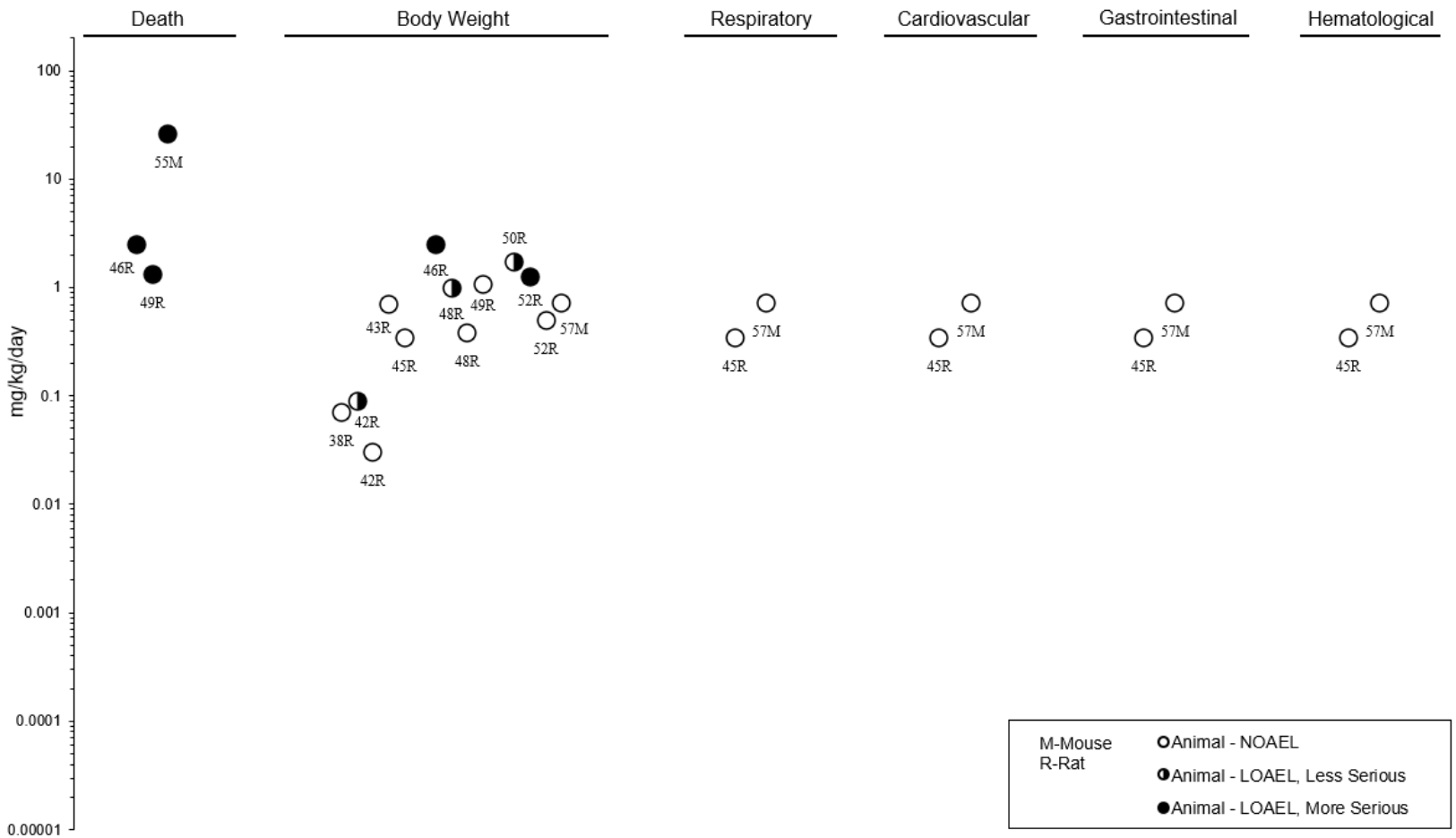


Figure 2-3. Levels of Significant Exposure to Disulfoton–Oral
Intermediate (15–364 days)

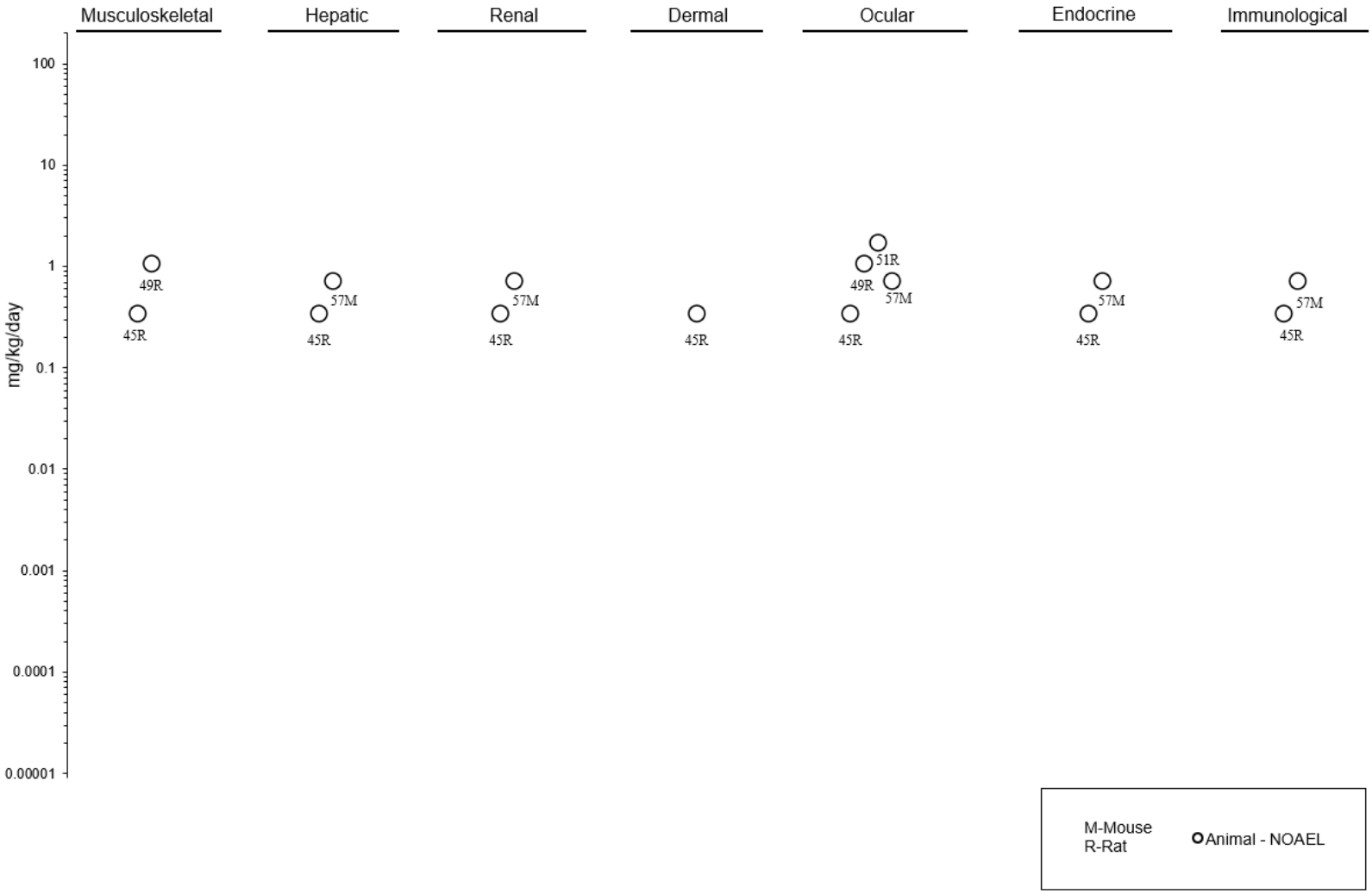


Figure 2-3. Levels of Significant Exposure to Disulfoton–Oral
Intermediate (15–364 days)

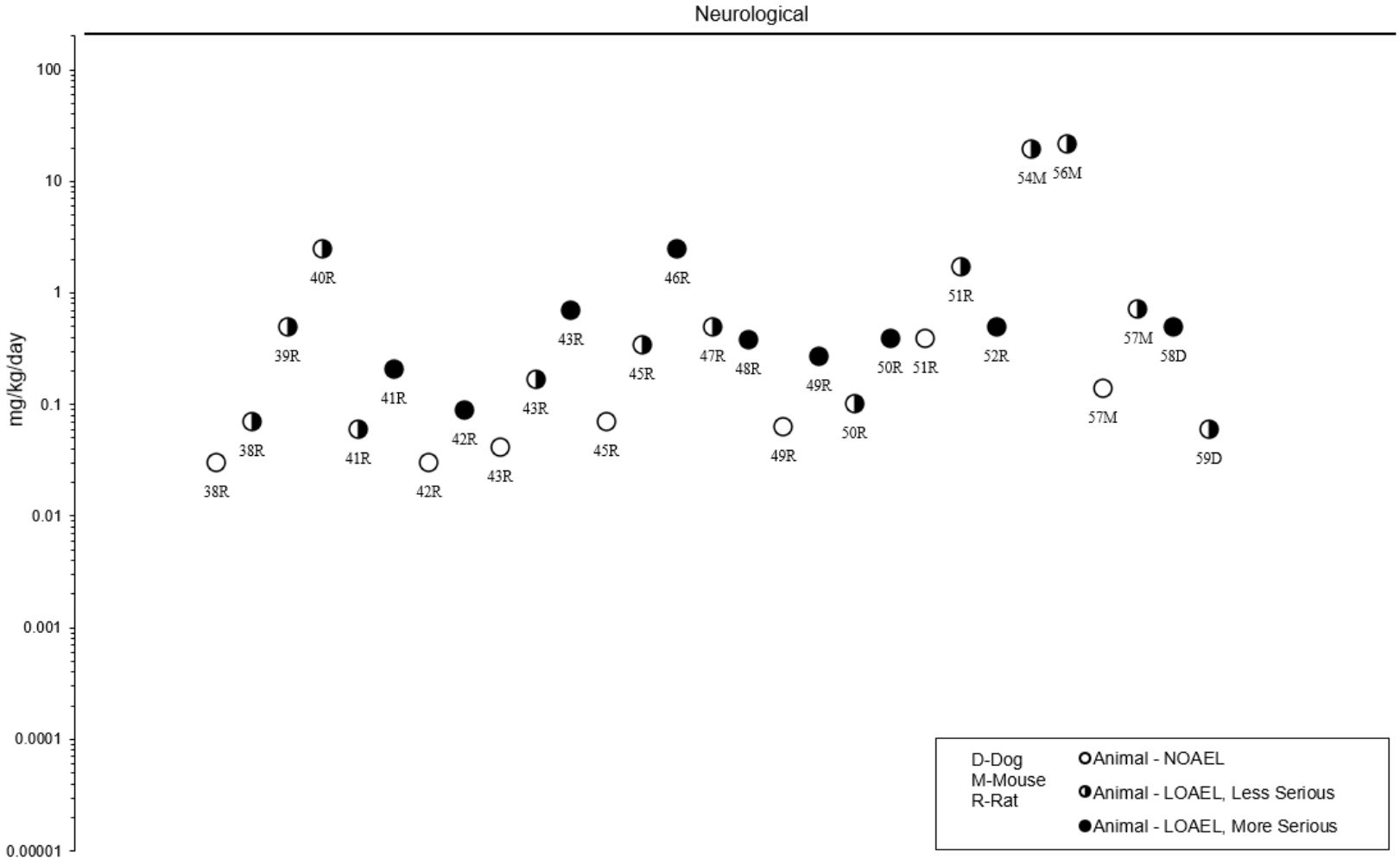


Figure 2-3. Levels of Significant Exposure to Disulfoton–Oral
Intermediate (15–364 days)

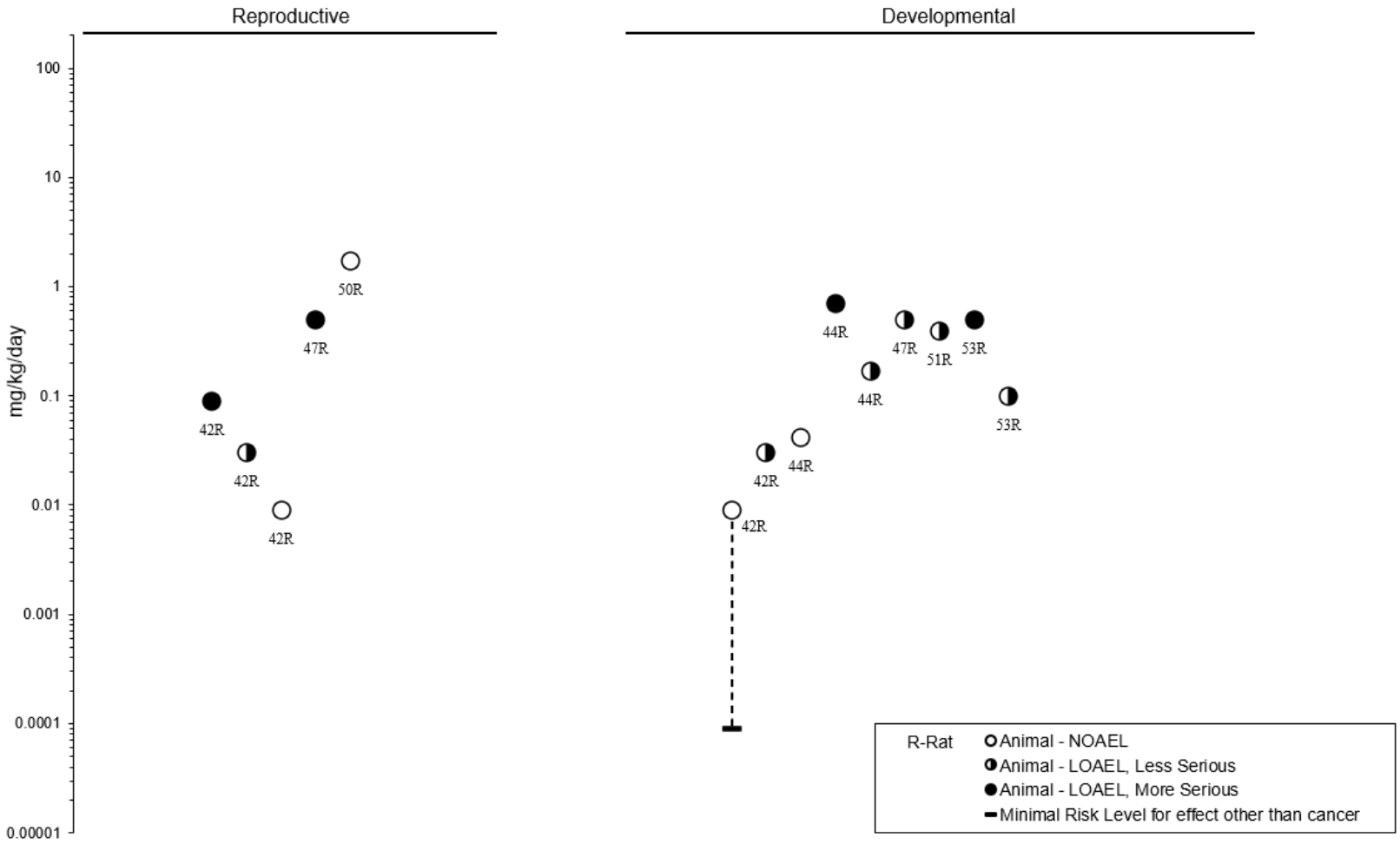


Figure 2-3. Levels of Significant Exposure to Disulfoton–Oral
Chronic (≥365 days)

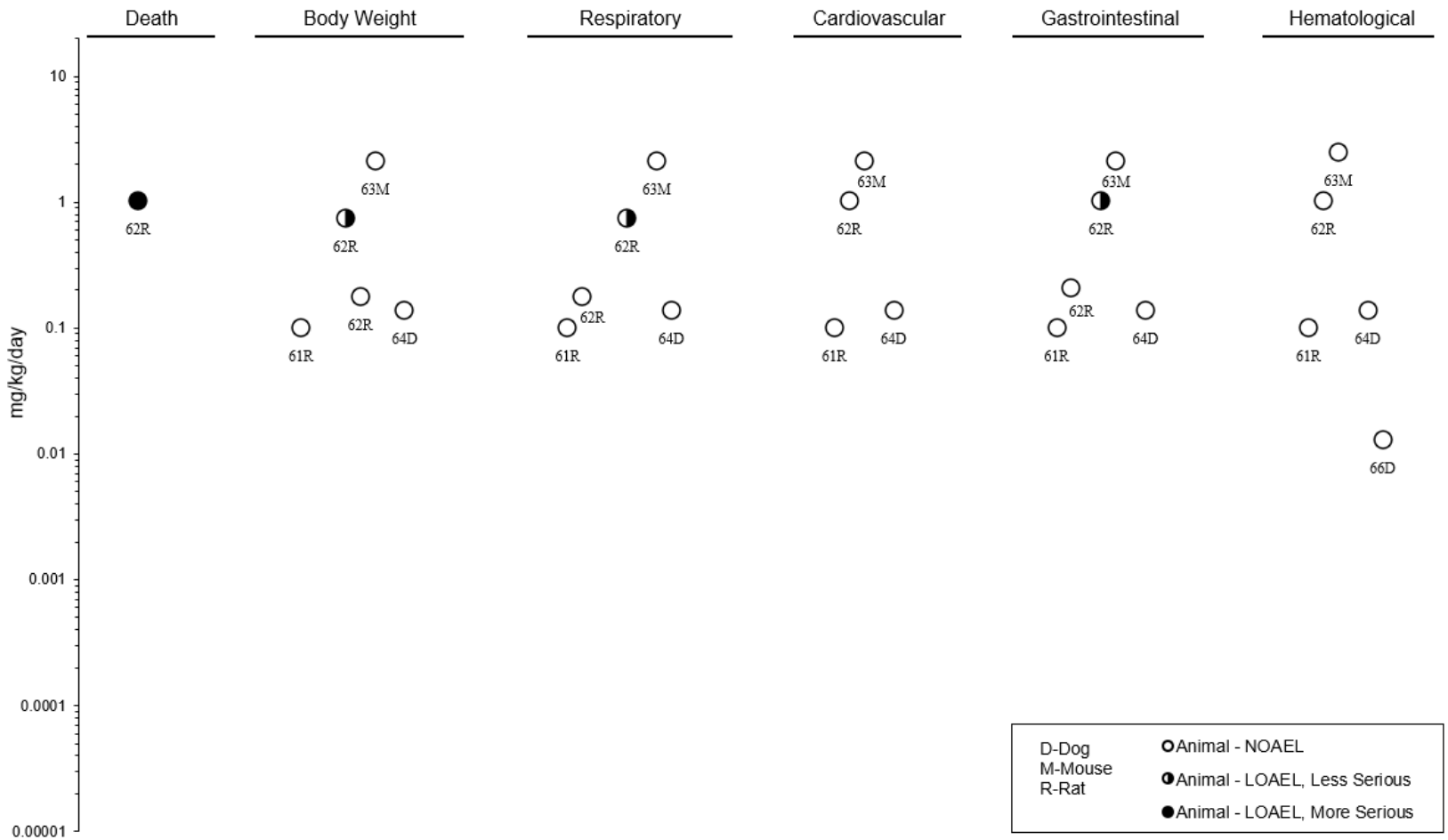


Figure 2-3. Levels of Significant Exposure to Disulfoton–Oral
Chronic (≥365 days)

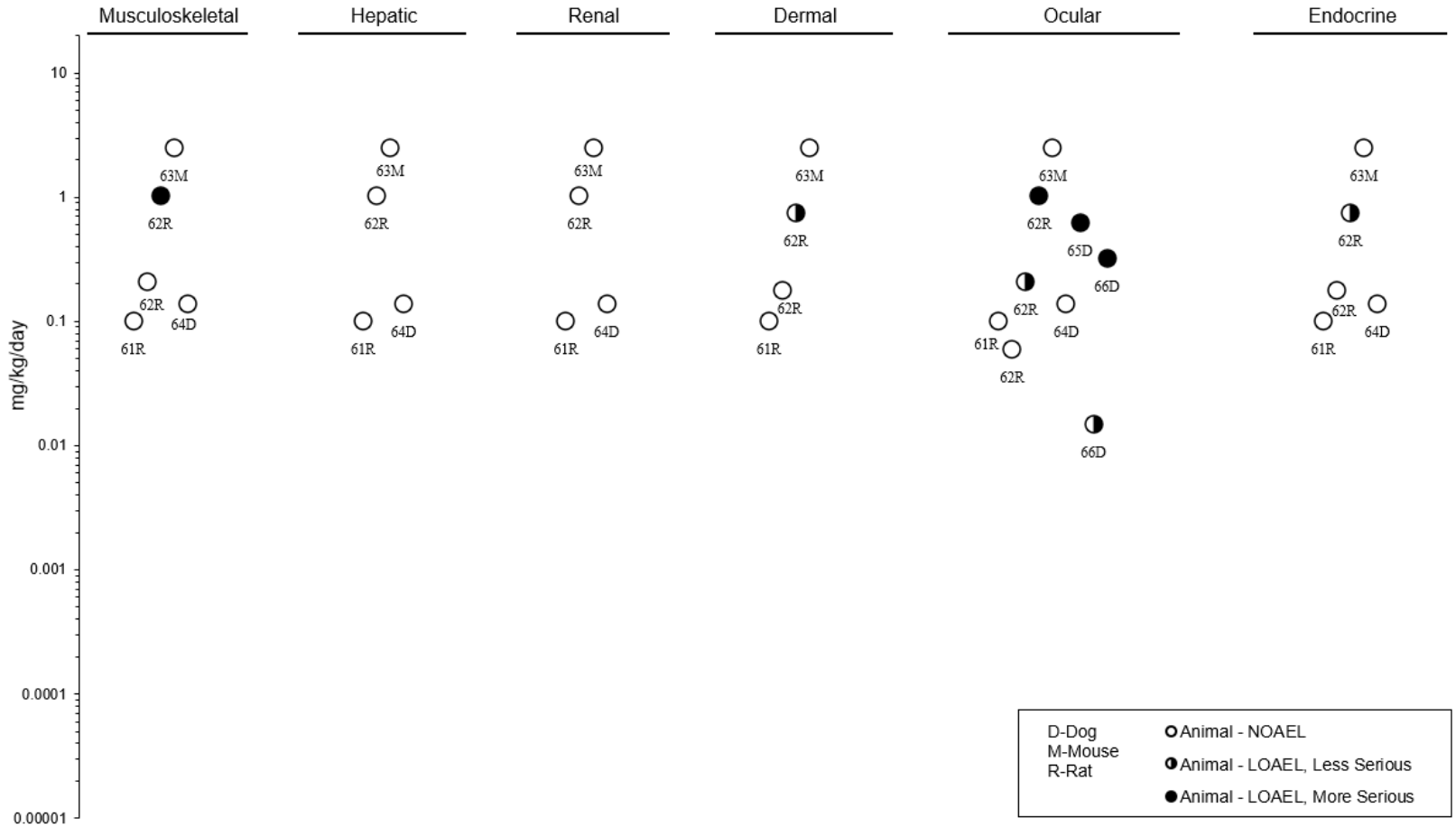


Figure 2-3. Levels of Significant Exposure to Disulfoton–Oral
Chronic (≥365 days)

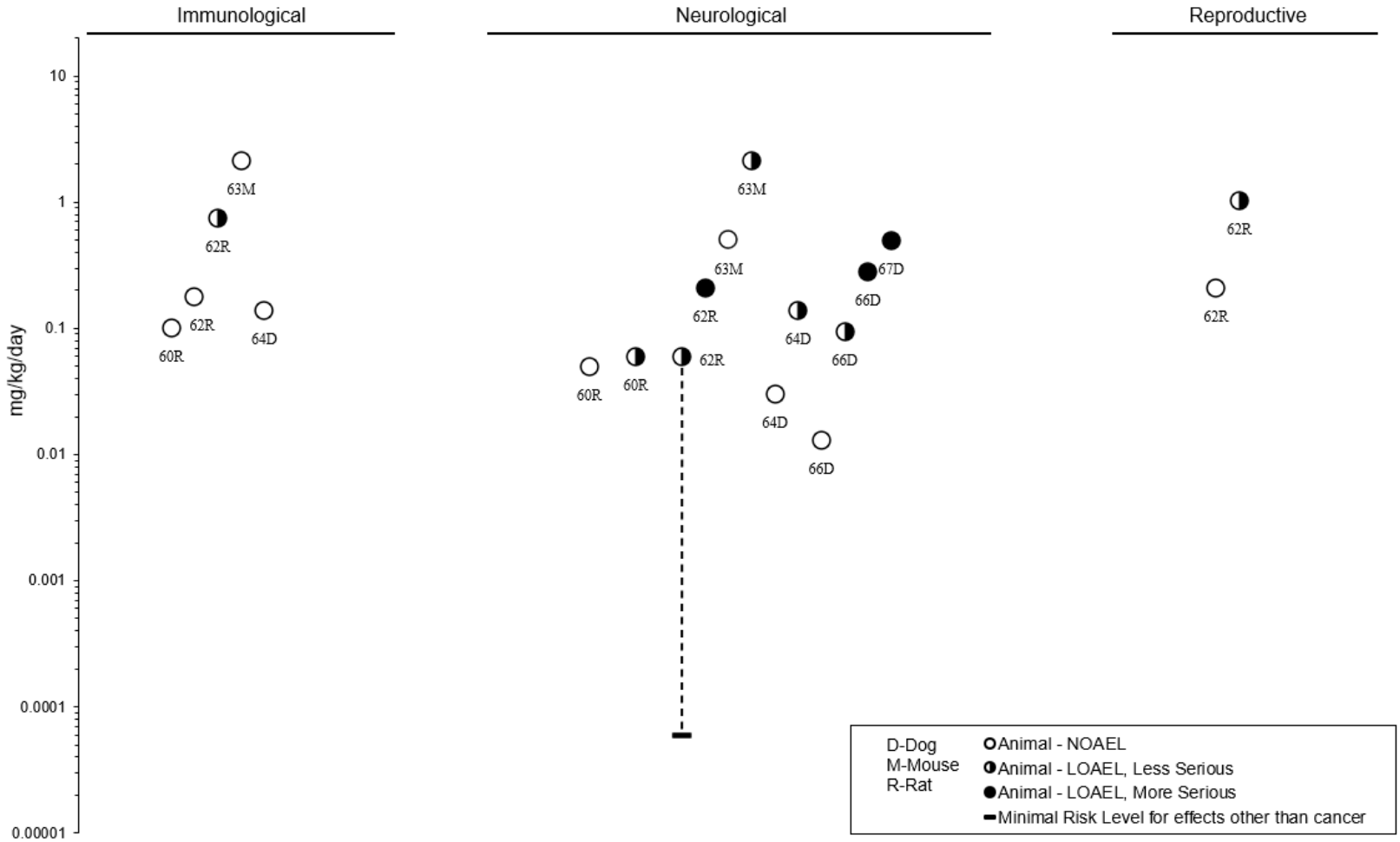


Table 2-3. Levels of Significant Exposure to Disulfoton – Dermal

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
Croutch and Sheets 2000									
1	Rat (Wistar) 5 M, 5 F	3 days	0, 50, 100, 200, 500	BW CS NX	Bd wt	500			
					Dermal	500			
					Neuro		50 F	200 F	39% inhibition of RBC AChE activity 24 hours after the third dose at 50 mg/kg/day; 62% inhibition of RBC AChE activity 24 hours after the third dose at 200 mg/kg/day
						100 M	200 M		21% inhibition of RBC AChE and brain AChE activity 24 hours after the third dose
DuBois 1957									
2	Rat (Sprague-Dawley) 35 M	Once	NR	LE	Death			20	LD_{50}
Mihail 1978									
3	Rat (Wistar) 5–10 M, 5–10 F	Once	M: 5, 10, 15, 17.5, 20 F: 2.5, 3, 3.5, 5, 10	LE	Death			3.6 F 15.9 M	Computed LD_{50}
Flucke 1986									
4	Rabbit (New Zealand) 2 NS	1–2 days 6 hours/day	0, 0.4, 2, 10	BI CS LE	Death			10	2/2 died
Flucke 1986									
5	Rabbit (New Zealand) 2 NS	1-5 days 6 hours/day	0, 0.4, 2, 10	BI CS LE	Neuro	2		10	2/2 rabbits exhibited unspecified cholinergic signs and died after one or two doses

Table 2-3. Levels of Significant Exposure to Disulfoton – Dermal

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Flucke 1986									
6	Rabbit (New Zealand) 5 M, 5 F	1–2 weeks 5 days/week 6 hours/day	0, 6.5	CS LE	Death			6.5	10/10 died
					Bd wt			6.5	Little or no feed intake and distinct weight loss up to time of death
					Resp			6.5	Distended, pale, mottled, fluid containing lungs in rabbits that died
					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
					Dermal	6.5			
					Immuno			6.5	Small pale spleen in rabbits that died
					Neuro			6.5	Muscle spasms, dyspnea, salivation after 1–2 days of exposure
INTERMEDIATE EXPOSURE									
Flucke 1986									
7	Rabbit (New Zealand) 5 M, 5 F	3 weeks 5 days/week 6 hours/day	0, 0.4, 1.6, 6.5	BI BC BW CS FI GN HE HP LE OW UR OW	Death			6.5	Females died after 1–6 treatments, males died after 3–10 treatments
					Bd wt	1.6			
					Resp	1.6			
					Cardio	1.6			
					Hemato	1.6			
					Hepatic	1.6			

Table 2-3. Levels of Significant Exposure to Disulfoton – Dermal

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal	1.6			
					Dermal	1.6			
					Endocr	1.6			
					Neuro	0.4			
							1.6 F		21–33% inhibition of RBC AChE activity
					Repro	1.6			
Flucke 1988									
8	Rabbit (New Zealand White) 5 M, 5 F	21 days 5 days/week 6 hours/day	0, 0.8, 1, 3	BC BW CS FI HE HP LE NX OW UR	Bd wt	1 F	3 F		Statistically significant 3% decrease in body weight
						3 M			
					Resp	1	3		Difficulty breathing observed in rabbits on days 17 and 21
					Gastro	1	3		Diarrhea observed in two rabbits on days 16 and 17
					Hemato	3			
					Neuro		0.8 F		20% inhibition of RBC AChE activity on day 21
						1 M		3 M	62% inhibition of RBC AChE activity on day 21

Red blood cell and brain AChE activity are assessed by comparing the activity of exposed groups to study controls and assessing whether AChE was inhibited by the chemical of interest. ATSDR classifies a NOAEL as <20% inhibition; a LOAEL is classified as 20–59% inhibition; and a SLOAEL is classified as >59% inhibition. If AChE activity is inhibited by 20–59% but is accompanied with clinical signs of cholinergic toxicity, it may be classified as a SLOAEL.

AChE = acetylcholinesterase; BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical indices; Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathological; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; LD_{50} = lethal dose, 50% kill; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NR = not reported; NS = not specified; OW = organ weight; RBC = red blood cell; Resp = respiratory; SLOAEL = serious LOAEL; UR = urinalysis

2.2 DEATH

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

In an acute inhalation study, 1-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 1-hour exposure resulted in death of three of six males at 180.1 mg/m^3 and two of six females at 87.6 mg/m^3 (DuBois and Kinoshita 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 1–8 days after exposure. No deaths occurred in either sex at ≤1.8 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 disulfoton 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. Additionally, female rats may be more susceptible to the lethality of disulfoton than male rats. In female mice, a 1-hour exposure 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.

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 and 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 glomerulus, and congestion of most organs. Analysis of urine and blood samples confirmed that disulfoton was responsible for the death (Hattori et al. 1982).

The dose of disulfoton associated with death following acute oral exposure in animals depends on the sex, species, and duration of exposure. Female rats and mice are generally more sensitive than male rats and mice, and rats generally appear to be more sensitive than mice following oral exposure to disulfoton. LD_{50} values are 1.9–3.2 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 an 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 1974), 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 four of six female rats given a dose of 2.5 mg/kg by gavage and in one of nine 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), one of five male rats died after receiving one dose of 3.5 mg/kg disulfoton, while two more rats died after receiving the same dose for 3 consecutive days (Schwab et al. 1981). In the same study, one of eight rats died after receiving either 2.5 or 3.5 mg/kg/day 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 of 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 1.31 mg/kg/day disulfoton in the diet was found dead on day 48 due to cholinergic effects (tremor, muscle fasciculations) (Sheets 1993b). In addition, 4 of 71 male rats died when given a diet providing 2.5 mg/kg/day disulfoton 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).

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 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.

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 likely related to the different formulations of disulfoton. In a range-finding study, two of two 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 five of five females after 1–6 treatments and of five of five 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 (Flucke 1986). The rabbits that died in these experiments exhibited persistent cholinergic signs of intoxication (muscle spasms, dyspnea, and salivation) before death. One of five male rabbits exposed to 3 mg/kg/day of disulfoton died after 17 days of exposure with clinical signs of cholinesterase depression (Flucke 1988).

2.3 BODY WEIGHT

No studies were located regarding effects on body weight in humans after inhalation, oral, or dermal exposure to disulfoton.

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).

Weight loss or decreased body weight gain is commonly observed in animals after acute exposure to disulfoton following oral exposure and is one of the typical signs of cholinergic toxicity of cholinesterase inhibitors (see Section 2.15). 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 et al. 1981; Schwab and Murphy 1981). Rats treated with 2.0 or 2.5 mg/kg/day disulfoton by gavage for 1–10 days initially exhibited a 20–50% reduction in weight gain (Costa et al. 1984, 1986; Schwab et al. 1981; Schwab et al. 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). Similarly, rats exhibited significantly lower body weight, 92–97% of control animals, on the third day of exposure to 2 mg/kg/day disulfoton; the difference was no longer significant after a 28 day recovery period (Yagle and Costa 1996). However, no treatment-related effects on body weight were seen in rats given ≤0.5 mg/kg/day (female) or ≤1 mg/kg/day (males) for 11 days (Klaus 2006a). When effects were seen, 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 acute exposure 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 exposure studies. Rats given 2.5 mg/kg/day disulfoton for 30 days gained 29% less body weight 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. 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 F1 parental females and 9–11% in F1 parental males receiving 0.09 mg/kg/day disulfoton in the diet during the premating period of 13 weeks (Hixson and Hathaway 1986). In a developmental study, body weight gain was depressed by 17–18% in offspring of dams exposed to 8 ppm in feed (0.67 mg/kg/day during gestation; 1.714 mg/kg/day during lactation), compared to controls by postnatal day (PND) 21 (Sheets 2005). In other intermediate-duration dietary studies, no effects on body weight gain were observed in rats given ≤1.31 mg/kg/day (Christenson and Wahle 1993; Klaus 2006c; Klotzsche 1972; Sheets 1993b, 2005) or in mice given ≤0.71 mg/kg/day (Rivett et al. 1972).

Hayes (1985) reported that in rats given disulfoton in the diet for 2 years, body weight gain was decreased by 11–19% 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. 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 and Welscher 1975).

In a 3-day study, disulfoton was applied to shaved skin of rats, occupying 10% of body surface and left for 6 hours, 5 days/week (Croutch and Sheets 2000). No effects on body weight were observed in rats treated with ≤500 mg/kg/day (5 mg a.i./kg/day). 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 and treated with the highest dose of 6.5 mg/kg/day (Flucke 1986). No effects on body weight were found in rabbits treated with ≤1.6 mg/kg/day for 3 weeks. In a similar study, significantly decreased body weight was reported for female rabbits exposed to 3 mg/kg/day for 3 weeks; however, the difference was only 3% from controls (Flucke 1988). At this dose, slight, but nonsignificant, decreases in body weight were seen in male rabbits, and decreased body weight gain was seen in both sexes.

2.4 RESPIRATORY

One study examined the association of pesticide use among male farm workers and both non-allergic and allergic wheeze (Hoppin et al. 2017). Current use of disulfoton was inversely associated with non-allergic wheeze (odds ratio [OR] 0.63; 95% confidence interval [CI] 0.42, 0.95), and no association was found with allergic wheeze (OR1.17; 95% CI 0.73, 1.87). No possible explanation for the inverse association was provided, and the study was limited, as the use of pesticide and symptoms were self-reported and no exposure levels were measured (Hoppin et al. 2017). Another study of 22 female and 8 male floriculturists who sprayed a mixture of pesticides including di-syxtox (containing disulfoton) for 10 and 1.5 years, respectively, found no respiratory disturbances following medical examination (Gómez-Arroyo et al. 2000). Among females exposed to the mixture of pesticides, occasional nasal mucosa irritations, along with headache and skin irritations, were reported; however, exposure levels, including specific to disulfoton were not measured.

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 2.14), which were minimal in male rats and

significant 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.

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. Moreover, no lesions were found in the lungs of 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 and Welscher 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.

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 rabbits treated with the high dose 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. Two of ten rabbits exposed to 3 mg/kg/day of disulfoton for 3 weeks showed difficulty breathing, with one rabbit dying after 17 days of exposure (Flucke 1988).

2.5 CARDIOVASCULAR

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

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).

Following ingestion of Di-Syston granules (5% disulfoton), a 75-year-old woman developed cardiac arrhythmias along with confusion and severe miosis approximately 5 hours after ingestion (Futagami et al. 1995). Cholinesterase activity was also inhibited in this patient (see Section 2.15). Inhibition of cholinesterase activity (and associated clinical symptoms) persisted for 19 days, but the patient showed almost complete recovery 28 days after hospital admission (no further details regarding recovery were reported).

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 and Welscher 1975) in the diet for up to 2 years.

No studies were located regarding cardiovascular 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 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).

2.6 GASTROINTESTINAL

No gastrointestinal disturbances were noted upon medical examination of 30 pesticide workers who worked with mixtures of several chemicals, including disulfoton (Gómez-Arroyo et al. 2000). Among the

22 female workers, nausea was reported when in contact with pesticides; however, this effect cannot be solely attributed to disulfoton exposure.

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 observed 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 observed. Likewise, no gastrointestinal tract lesions were seen in male or female rats exposed intermittently to ≤1.4 mg/m^3 for 13 weeks (Shiotsuka 1989).

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 and Welscher 1975) in the diet for up to 2 years. However, Hayes (1985) reported increased incidences of mucosal hyperplasia and chronic inflammation of the forestomach in female rats given 1.02 mg/kg/day disulfoton in the diet for 2 years. It was also noted that mucosal hyperplasia was usually diffuse; sometimes more locally severe; and accompanied by inflammation, fibrosis, and ulceration. Forestomach lesions were not observed in male rats at 0.75 mg/kg/day or in females at 0.21 mg/kg/day (Hayes 1985). Diarrhea was reported in 5 of 34 rats given a single oral dose of 2 mg/kg/day but only lasted 3–4 days after exposure, which indicated the development of tolerance (Yagle and Costa 1996).

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 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 (when one part of the intestine slides inside another part) 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. Diarrhea was seen in 2 of 10 rabbits treated with 3 mg/kg/day, with 1 rabbit dying after 17 days of exposure (Flucke 1988).

2.7 HEMATOLOGICAL

No studies were located regarding hematological effects in humans after inhalation, oral, or dermal exposure to disulfoton.

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 reported. 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 2.14). 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).

Limited information from animal studies suggests that intermediate- or chronic-duration exposure to disulfoton was 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 and Welscher 1975). No hematological effects were observed in female and male dogs following 1-year exposure to 0.013–0.321 mg/kg/day disulfoton in feed (Jones et al. 1999).

No hematological effects were found in two 3-week studies of rabbits exposed to ≤3 mg/kg/day of disulfoton, applied to the shorn, unabraded skin of rabbits and left for 6 hours, 5 days/week (Flucke 1986, 1988).

2.8 MUSCULOSKELETAL

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

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).

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 Section 2.12) 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 observed 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 and Welscher 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.

2.9 HEPATIC

No studies were located regarding hepatic effects in humans after inhalation, oral, or dermal exposure to disulfoton.

Clinical chemistry tests and histological examination of livers revealed no 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).

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, duration of dosing, and time between dosing and enzyme assays. Microsomal enzyme induction was considered not to be adverse

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 P450 content, was observed in mice given 9.6 mg/kg/day disulfoton for 3 days and sacrificed 24 hours later for 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 1–4 days (Fawade and Pawar 1978, 1980, 1983). Fawade and Pawar (1978) noted disulfoton significantly increased ascorbate-promoted lipid peroxidation and NADPH-driven lipid peroxidation by 13 and 14%, respectively, in mice orally dosed with 0.5, 1, 1.5, or 2 mg/kg/day for 2 days, then all to 1 mg/kg/day for 2 additional days. The study authors suggested that disulfoton or its oxygenated metabolite may have changed the conformation of heme protein thus enhancing lipid peroxidation. Fawade and Pawar (1978) also reported that "hepatic microsomal electron transport elements," defined as cytochrome P450 and cytochrome b_5, decreased as dose decreased (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 et 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 and Welscher 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.

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 exposed to the highest dose (6.5 mg/kg/day) died within 2 weeks during treatment. Necropsy of these rabbits revealed an enhanced lobular pattern in the liver; however, the study authors did not conclude whether this observation is associated with potential health effects (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 (Flucke 1986).

2.10 RENAL

No studies were located regarding renal effects in humans after inhalation or dermal exposure to disulfoton.

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).

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. Urinary stains (indicative of urine leakage) were observed in female rats fed 0.32 mg/kg/day disulfoton for 13 weeks (Sheets 1993b). No further renal effects were recorded. 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 and Welscher 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 female 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. The number of kidneys with malignant lymphoma among exposed mice did not significantly differ from controls, indicating they were not related to disulfoton exposure; the toxicological significance of the increased kidney weight is not clear.

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 exposed to the highest dose (6.5 mg/kg/day) died within 2 weeks during treatment. Necropsy of these rabbits 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.

2.11 DERMAL

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

Skin irritations were reported by 22 female floriculturist workers with occupational exposure to a mixture of sprayed pesticides, including disulfoton (Gómez-Arroyo et al. 2000). No further information was provided on dermal effects, and this effect cannot be directly attributed to disulfoton exposure.

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).

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.

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 (Flucke 1986). No treatment-related skin changes were seen in male and female rabbits treated with ≤3 mg/kg/day of disulfoton left on skin for 6 hours/day, 5 days/week for 21 days (Flucke 1988).

2.12 OCULAR

No studies were located regarding ocular effects in humans after inhalation or dermal exposure to disulfoton.

No ophthalmological evidence of ocular effects was 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).

The only information regarding ocular effects in humans comes from an epidemiological study in which a marked increase of myopia was observed in children aged 4–16 years living in areas where insecticides were used on a large-scale when compared with a control group of children. This observation coincided with an increased use of disulfoton in combination with other organophosphates to treat food crops (Ishikawa and Miyata 1980). 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 offspring of rat dams exposed to ≤1.174 mg/kg/day through gestation and 21 days of lactation, no treatment-related ocular effects were seen, including pupil constriction (Sheets 2005). 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 and Welscher 1975) in the diet for up to 2 years.

In Beagle dogs fed 0.015, 0.121, 0.321 mg/kg/day (males) or 0.013, 0.094, 0.283 mg/kg/day (females) disulfoton in the diet for 1 year, there was no significant inhibition of cholinesterase levels in lateral or dorsal rectus muscles (Jones et al. 1999). In male dogs, 33% inhibition of cornea cholinesterase was observed at 0.5 ppm. Cornea cholinesterase was 50–67% inhibited in female and male dogs exposed to 4 and 12 ppm, respectively. In both sexes, retina cholinesterase inhibition was 25–67% in both the 4 and 12 ppm exposure groups and ciliary body cholinesterase inhibition was 18–54% (Jones et al. 1999). Tissue cholinesterase inhibition did not appear to cause histological changes, gross pathology changes, nor alter ocular physiologic function. Additionally, no other findings, including tracking, refractivity, intraocular pressure, and pachymetry, indicated adverse ophthalmologic effects in dogs following chronic exposure to disulfoton (Jones et al. 1999).

2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans after inhalation, oral, or dermal exposure to disulfoton.

No histological lesions were found in the thyroid or adrenal glands of male rats exposed intermittently 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 thyroid, parathyroids, pituitary, or pancreas were observed in rats exposed intermittently to ≤1.4 mg/m^3 for 13 weeks (Shiotsuka 1989).

Disulfoton exposure altered catecholamine levels in animals, and this hormonal imbalance may be associated with elevated acetylcholine levels (Brzezinski 1969, 1973; 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.

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 doses ≤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 was observed in females at doses ≤1.02 mg/kg/day, and no histopathological lesions in the adrenal, pituitary, thyroid, or parathyroids 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, parathyroids, 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 and Welscher 1975). The Hoffman study also found no changes or histopathological lesions in the parotid glands in dogs.

In a 3-week study in which disulfoton was applied to the shorn, unabraded skin of rabbits and left for 6 hours/day, 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).

2.14 IMMUNOLOGICAL

No studies were located regarding immunological effects in humans after inhalation, oral, or dermal 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, 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 treatment-related 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).

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 study 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 nodes or thymus revealed no treatment-related lesions in either sex at any dose. In other chronic dietary studies, no treatment-related 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 and Welscher 1975).

Down-regulation of cholinergic muscarinic receptors in T-lymphocytes and significantly inhibited AChE activity in T-lymphocytes were found in rats given 2 mg/kg/day disulfoton by gavage for 1–2 weeks (Fitzgerald and Costa 1993). The inhibition of T-lymphocyte AChE activity paralleled that in the brain. The immunological significance of these neurological effects (see Section 2.15) is not known.

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 exposed to the highest dose (6.5 mg/kg/day) died within 2 weeks during treatment. Necropsy of these rabbits 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.

2.15 NEUROLOGICAL

The neurologic system is the most sensitive target with the highest level of evidence associated with disulfoton exposure. AChE inhibition is the most sensitive neurological endpoint following exposure to disulfoton via inhalation or oral exposure, and acetylcholine is the primary neurotransmitter of the parasympathetic nervous systems. Brain AChE inhibition is the more toxicologically significant endpoint; however, since it can only be measured post-mortem, red blood cell AChE activity is used as a surrogate, as it is expected to correlate with brain AChE activity (EPA 2000). Disulfoton exposure results in inhibition of cholinesterase activity in blood and at nerve synapses of muscles, secretory organs, and nervous tissues such as the brain and spinal cord (Murphy 1986). The resulting acetylcholine accumulation results in central nervous system, nicotinic, and muscarinic effects. Brain and red blood cell AChE are considered significant if activity is inhibited by ≥20% following exposure, when compared to study controls.

The highest NOAEL values and all the LOAEL values for neurological effects in rats and mice for each duration category are recorded in Tables 2-1, 2-2, and 2-3, and plotted in Figures 2-2 and 2-3. Typically, ATSDR classifies AChE inhibition between 20–59% as a less serious LOAEL, and >59% as a serious LOAEL. Cholinesterase inhibition classified as a less serious LOAEL and accompanied by clinical symptoms of cholinergic toxicity may be classified as a serious LOAEL.

Nervous system effects may occur in humans after occupational exposure to disulfoton (Wolfe et al. 1978). Workers at a three pesticide-fertilizer mixing operations were exposed to mean disulfoton concentrations of 0.06–0.633 mg/m^3 in air, in addition to dermal exposure. Following 9 weeks of exposure, workers of dry mixing operations had a 22.8% depression in red blood cell AChE activity, but there were no reports of adverse clinical signs due to disulfoton exposure. The study was limited in that

baseline blood AChE activities were measured 2 weeks after the initial exposure and were compared with cholinesterase activities at 9 weeks, and it is unclear if workers were wearing respirators or not (Wolfe et al. 1978). Occasional headaches and nausea were reported by 22 female floriculturists following occupational exposure to a mixture of pesticides, including disulfoton, when spraying in greenhouses without any protection over a 10-year period (Gómez-Arroyo et al. 2000). Hearing loss has been associated with use of some organophosphate pesticides in agricultural workers (Crawford et al. 2008); however, data regarding potential associations between hearing loss and disulfoton exposure were not identified.

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 disulfoton 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) (Thyssen 1978). These effects were transient, lasting for about 24 hours after exposure. In an experiment designed to measure cholinesterase activity in rats exposed to 0.5, 1.8, or 9.8 mg/m^3 for 4 hours/day for 5 days, red blood cell AChE 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 (Thyssen 1978). In addition, all rats were reported to display unspecified behavioral disorders at 1.8 mg/m^3 and also unspecified signs of cholinergic toxicity at 9.8 mg/m^3. No inhibition of red blood cell AChE activity and no signs of cholinergic toxicity were observed at 0.5 mg/m^3 (Thyssen 1978). 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). Red blood cell AChE activity was inhibited in males by 24–28% and in females by 27–32% at 3.7 mg/m^3. Brain AChE 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 in Wistar male and female rats, no clinical signs of neurological effects and no effects on plasma, red blood cell, or brain AChE were observed at 0.02 mg/m^3 (Thyssen 1980). Female rats exposed to 3.1 mg/m^3 had muscle tremors, convulsions, increased salivation, and dyspnea, confirming the results of the first experiment. Male rats were not exposed to 3.1 mg/m^3 in the second experiment (Thyssen 1980). In Fischer rats exposed intermittently to 1.4 mg/m^3 for 13 weeks, red blood cell AChE activity was inhibited by 22–28% in males and 26–34% in females, and brain AChE activity was inhibited by 29% in males and 28% in females (Shiotsuka 1989). Cholinesterase activities were not affected at ≤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 AChE activities were found at 0.006–0.7 mg/m^3 disulfoton (Shiotsuka 1988). Red blood cell AChE activity was statistically consistently decreased at 0.7 mg/m^3, but the decrease was never greater than 17% of control levels.

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 (Hattori et al. 1982). Severe signs and symptoms of disulfoton toxicosis (miosis, salivation, masseter muscle spasms, and monoplegia) were observed in a 75-year old man within 2–3 hours of consuming 3 to 4 heaping tablespoons of Di-Syston (Yashiki et al. 1990). Serum cholinesterase activity was depressed below 10 IU for 5 days after admission, and below 40 IU at 8 days following admission (normal activity range is 175–440 IU). The occurrence of severe clinical signs and the measured concentrations of disulfoton in the patient's blood suggests a severe level of disulfoton intoxication occurred, but the patient recovered with medical intervention (Yashiki et al. 1990). A case-study of a non-occupationally exposed 75-year-old female, who ingested a "large quantity of Di-Syston granules," had markedly depressed red blood cell and plasma AChE activity 3.5 hours after ingestion (Futagami et al. 1995). Vomiting, nausea, and muscle fasciculations were also observed, and 5 hours after ingestion, confusion, miosis, and cardiac arrhythmias were noted. Twenty-four hours after ingestion, red blood cell AChE activity recovered from 3,524 IU/L to 8,688 IU/L (normal range considered 10,000–14,000 IU/L). By the next day red blood cell AChE activity depressed again, and remained low for 19 days after ingestion, which the study authors attributed

to absorption from residual Di-Syston and/or the more toxic compounds metabolized in the liver (Futagami et al. 1995). The patient showed almost complete recovery 28 days after hospital admission (no further details regarding recovery were reported).

Several studies in rats observed significant depression of brain AChE activity following oral exposure to disulfoton for 7–10 days (Costa and Murphy 1983a; Costa et al. 1986; Schwab and Murphy 1981; Su et al. 1971). Signs of cholinergic toxicity like 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 rat pups of both sexes, peak time of effect (red blood cell and brain AChE activity inhibition) was estimated at 24 hours post-dosing of 0.5 mg/kg (EPA 2007). A follow-up study tested multiple doses in both sexes and at the peak time of effect, red blood cell AChE activity was inhibited by 22–53%, and brain AChE by 19–39% in both sexes; cholinesterase inhibition increased with dose (EPA 2007). In a similarly designed study, the peak time of effects (cholinesterase inhibition) was estimated at 8 hours in females and 6 hours in males, after a single oral dose of 0.75 or 1.5 mg/kg in females and males, respectively (EPA 2007). When exposed to single varying doses and observed at the peak time of effect, females exhibited >34% red blood cell AChE inhibition at >0.5 mg/kg, and males exhibited 32 and 46% red blood cell and brain AChE activity inhibition, respectively, at 1.5 mg/kg (EPA 2007). In an extensive neurotoxicity screening study, rats were given single gavage doses of disulfoton (0.24, 1.5, and 5.2 mg/kg for males; 0.24, 0.76, and 1.5 mg/kg for females) (Sheets 1993a). The study reported clinical signs of cholinergic intoxication including muscle fasciculations, tremors, ataxia, oral stain (drooling), urine leakage, diarrhea, and decreased activity in the high-dose males (5.2 mg/kg) and high-dose females (1.5 mg/kg), and muscle fasciculations 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 (Sheets 1993a). These effects included muscle fasciculations, 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 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. Red blood cell AChE activity was inhibited by 21% in high-dose males, 75% in high-dose females, and 53% in mid-dose females (Sheets 1993a). 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 a separate study, AChE mRNA levels in

soleus muscle and sciatic nerve of male rats significantly decreased by 53% (compare to controls) 12 hours after administration of a single 6 mg/kg dose of disulfoton by gavage (Matsuda et al. 2000). This down-regulation persisted 30 days after the dose suggesting alterations at the transcriptional level. The nicotinic acetylcholine receptor in the soleus muscle also decreased 6 hours after the dose but recovered to control levels after 30 days. Gamma-enolase mRNA in sciatic nerve increased by 200% 2 hours after the dose and exceeded a 250% increase after 30 days; up-regulation of gamma-enolase mRNA was suggested as a marker of nervous system abnormality following disulfoton exposure, although the function of this gamma-enolase mRNA is not clear (Matsuda et al. 2000). Additionally, 75 and 69% inhibition of AChE was seen in whole blood and skeletal muscles of rats, respectively, 12 hours after the dose, but activity recovered for both, though more slowly in whole blood (30 days). The study authors suggested that down-regulation of AChE in skeletal muscle is associated with structural and functional alterations of the neuromuscular junction (Matsuda et al. 2000). No clinical observations were made as part of the study protocol.

Animals exposed to disulfoton develop typical signs of cholinergic toxicity associated with inhibition of brain AChE 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 diminished, while cholinesterase remained inhibited, indicating a tolerance to disulfoton developed. 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; Yagle and Costa 1996). Similar effects were also observed in female rats after 3 days on a diet that was mixed with 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 AChE 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 AChE 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 AChE 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(s) associated with disulfoton toxicity

was not impaired, despite the disappearance of overt neurological signs of toxicity following repeated doses of disulfoton. Cholinesterase activity depression has been seen in acute oral studies where clinical signs of cholinergic toxicity were absent (Klaus 2006a, 2006b). Klaus (2006a) treated Wistar rats by gavage for 11 days, and cholinesterase activity inhibition was dose-dependent in both sexes. Red blood cell and brain AChE were both significantly inhibited 1 hour after final dosing in males exposed to ≥0.5 mg/kg/day and in females exposed to ≥0.25 mg/kg/day (Klaus 2006a). Lower doses were tested in rat pups exposed to 0, 0.06, 0.125, or 0.25 mg/kg/day for 11 days beginning on PND 11 (Klaus 2006b). Significant red blood cell AChE inhibition began at ≥0.25 mg/kg/day in male pups. Female pups were more sensitive as significant red blood cell AChE depression (29% inhibition) began at 0.06 mg/kg/day and was dose-dependent (Klaus 2006b).

In rats given 2 mg/kg/day disulfoton for 14 days, there was 81 and 28% inhibition of AChE and [^{3}H] quinuclidinyl benzilate binding in the cerebral cortex, respectively (Yagle and Costa 1996). After a 28-day recovery period, activity and binding restored to nearly that of controls. The study primarily examined the loss of muscarinic receptors (MR) corresponding to changes in mRNA levels, focusing on m1, m2, and m3 subtypes (Yagle and Costa 1996). The m1 and m3 subtypes activate phosphoinositide hydrolysis, and the m2 subtype is negatively coupled to adenylyl cyclase. In the hippocampus, m1 mRNA and m2 RNA levels decreased by 23 and 24%, respectively; m2 mRNA decreased by 19% in the medulla, and m3 mRNA levels in the cortex lowered by 10%. All decreases were significant, but all m1 and m3 mRNA levels recovered in all tissues following a 4 week recovery, while m2 RNA in the hippocampus remained decreased. The study concluded that disulfoton may lead to protein and mRNA down-regulation in only certain brain tissues that express a particular combination of MR subtypes (Yagle and Costa 1996).

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) F0 female rats, but not the mid-dose (0.03 mg/kg/day) F0 females, during the production of the F1 generation (Hixson and Hathaway 1986). Pregnant rats given disulfoton during gestation had significantly inhibited plasma and red blood cell AChE 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).

An intermediate-duration extensive neurotoxicity screening was conducted for 13 weeks in rats fed disulfoton in the diet that provided doses of 0.06, 0.27, or 1.08 mg/kg/day for males and 0.07, 0.32, or

1.3 mg/kg/day for females (Sheets 1993b). Clinical signs of cholinergic intoxication seen in males exposed to 1.08 mg/kg/day included muscle fasciculations, diarrhea, tremors, ataxia, urine stain (urine leakage), oral stain (indicating excess salivation), and red nasal stain (known as red tears), and females exposed to 1.3 mg/kg/day showed similar signs and decreased movement. Mid-dose females (0.27 mg/kg/day) showed muscle fasciculations only. A battery of functional observational tests revealed effects in high-dose males and mid and high-dose females, and these effects included tremors, increased defecation, decreased forelimb grip strength, and decreased movement. 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. Red blood cell AChE activity was inhibited by 95–100% in high-dose rats and 67–80% in mid-dose rats. Brain AChE 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.

Neurotoxicity has been observed in pregnant female rats exposed to disulfoton in feed (Klaus 2006c; Sheets 2005). In an extensive study, females were exposed on gestation days (GDs) 0–21 to 0, 0.038, 0.156, or 0.67 mg/kg/day, and then exposed to corresponding doses of 0, 0.102, 0.389, or 1.714 mg/kg/day on lactation days 0–21 (Sheets 2005). Red blood cell AChE was inhibited by 27% in the lowest dose group, and significantly inhibited by 73% in the mid-dose groups, which also showed a 65% inhibition of brain AChE. Clinical signs suggesting neurotoxicity were only seen in the highest dose group during lactation, including repetitive chewing movements, muscle fasciculations, and jerking movements (Sheets 2005). In a separate study, pregnant female rats were continuously exposed to 0, 0.042, 0.168, or 0.694 mg/kg/day from GD 0 to 20 (Klaus 2006c). While no clinical signs of neurotoxicity were observed, at 0.168 mg/kg/day, red blood cell AChE activity was inhibited by 44% and brain AChE activity was inhibited by 32%; inhibition was dose-dependent (Klaus 2006c).

Intermediate-duration studies in animals indicate tolerance to disulfoton is developed over time. Clinical signs of cholinergic toxicity appear initially and diminish while cholinesterase activity remains inhibited, which is characteristically observed in organophosphate pesticides (Costa and Murphy 1982). 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 diminished 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 AChE 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 red blood cells 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; 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, red blood cell AChE 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 red blood cell AChE activity and a 33–36% inhibition of plasma AChE activity was found in dogs given diets containing disulfoton at a dose of 0.06 mg/kg/day for 40 weeks (Hoffman and Welscher 1975). In Beagle dogs given disulfoton in feed for 1 year, there was 31–65% inhibition of plasma AChE beginning 1 week after exposure to 0.12 mg/kg/day (males) and 0.09 mg/kg/day (females) (Jones et al. 1999). In the same study, red blood cell AChE in both sexes exposed to ≥09 mg/kg/day was inhibited by 48–90% at 3 months of exposure and continued to decrease to 40–85% by the end of the study period. Additionally, significant brain AChE inhibition of 22–33% was observed in female Beagle dogs, and overall cholinesterase inhibition was more marked in female dogs compared to males in the lowest dose group (Jones et al. 1999). Neural examination of the dogs did not find any functional abnormalities in reflexes or task performance and no clinical neurological findings related to disulfoton administration.

Disulfoton has also been studied for behavioral effects. Rats fed ≥0.5 mg/kg/day disulfoton for 90 days had significantly depressed brain AChE 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 result (improved learning) at reduced brain AChE 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). This was

evaluated by the permeability of stained brain tissue slices to copper ferricyanide complex. 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 are not clear. In the same study, plasma, red blood cell, and brain AChE activity were significantly inhibited in both male and female rats. A dose of 0.1 mg/kg/day resulted in a 21% inhibition of brain AChE activity in female rats. At 0.05 mg/kg/day, brain AChE 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, red blood cell AChE 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 AChE 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. Significant depression of red blood cell, plasma, and brain AChE 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 and Welscher 1975). However, significant depression of plasma, red blood cell, and brain AChE activity occurred at 0.14 mg/kg/day 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 were observed in dogs given disulfoton (0.5–1.5 mg/kg/day) for 2 years (Uga et al. 1977). The study authors regarded the pathological changes in the retina as mild; however, the nerve fibers in the optic nerve were reduced in number.

A farmer who had worn disulfoton contaminated 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 AChE activity was severely depressed, it was 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, red blood cell AChE 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 AChE activity was observed in workers involved with wet mix operations (0.013 mg/kg/day) (Wolfe et al. 1978). No significant reductions in plasma or red blood cell AChE 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 a 39% inhibition of red blood cell AChE in female rats applied 50 mg/kg (0.5 mg a.i./kg) of disulfoton on 10% of body surface and left for 6 hours/day for 3 days (Croutch and Sheets 2000). Inhibition was less significant at 100 mg/kg (0.1 mg a.i./kg). Brain and red blood cell AChE increased dose dependently starting at 100 mg/kg in both male and female rats. Cholinesterase activity was measured 24 hours after the final third day exposure was applied. Females were more sensitive to disulfoton exposure, as maximum brain and red blood cell AChE inhibition were 72–74%, while only 32–42% in males (Croutch and Sheets 2000). No clinical signs of cholinesterase depression were seen at any dose. 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. In a range-finding study, two of two 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 five of five females after 1–6 treatments and five of five males after 3–10 treatments with 6.5 mg/kg/day (Flucke 1986). Persistent cholinergic signs (muscle spasm, dyspnea, and salivation) were observed in the high-dose females after 1 or two treatments and in high-dose males after two treatments. No clinical signs of cholinergic intoxication were seen in the rabbits treated with 0.4 or 1.6 mg/kg/day, but red blood cell AChE activity was inhibited by 21–33% in the female rabbits treated with 1.6 mg/kg/day (Flucke 1986). In a similar study, one male rabbit died exhibiting clinical signs of cholinesterase depression following exposure to 3 mg/kg/day disulfoton 6 hours/day, 5 days/weeks for 3 weeks (Flucke 1988). In male and female rabbits, red blood cell AChE inhibition increased dose-dependently after day 21, and was significant in males at 3 mg/kg/day (62% inhibition) and in females at ≥0.8 mg/kg/day (20–51%). Brain AChE activity

was measured at study terminations and was only significant for males and females exposed to 3 mg/kg/day, with 55% and 27% inhibition, respectively (Flucke 1988).

In a study investigating the mechanism of neurological effects, disulfoton was added to the brain tissue of Wistar rats (Smulders et al. 2004). Competition binding experiments showed that disulfoton resulted in inhibitory effects on nicotinic acetylcholine receptors, which may account for neurotoxic signs not explained by AChE inhibition. Disulfoton did not bind to agonist-recognition sites of rat neuronal α4β2 nicotinic acetylcholine receptors indicating a noncompetitive two-step mechanism. Inhibition may result from rapidly reversible association and dissociation of disulfoton binding to a separate binding site, followed by receptor desensitization (Smulders et al. 2004).

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal 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 the epididymides, prostate, seminal vesicles, testicles, cervix, mammary glands, ovaries, or uterus were found in rats exposed intermittently to ≤1.4 mg/m3 for 13 weeks (Shiotsuka 1989).

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 multi-generation study was conducted in male and female rats exposed to disulfoton in the diet at doses of 0.009, 0.03, and 0.09 mg/kg/day (Hixson and Hathaway 1986). At the 0.09 mg/kg/day dose, decreased reproductive performance occurred, evidenced by a decreased percentage of females placed for mating and decreased percentage of sperm-positive F0 and F1 parental females. In addition, decreased maternal weight of F0 and F1 dams during gestation and lactation, decreased litter counts, viability index, and lactation index, and increased stillbirths and percentage of stillbirths occurred in both generations at 0.09 mg/kg/day. A decrease in F2b litter counts and litter weights occurred at 0.03 mg/kg/day. Gross and

histological examination of the ovaries, vagina, uterus, testes, epididymides, seminal vesicles, and prostate of the F0 and F1 parents revealed no treatment-related lesions. In an intermediate-duration study, male and female rats given 0.5 mg/kg/day disulfoton in their diets 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). In pregnant rats exposed during GDs 0–21 and then lactation days 0–21, no treatment-related effects on fertility, gestation indices, or gestation length were observed at exposures to ≤1.714 mg/kg/day of disulfoton in feed (Sheets 2005). 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 and Welscher 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 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. Effects on reproductive function was not evaluated.

2.17 DEVELOPMENTAL

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

Pregnant rats given disulfoton on GDs 6–15 had decreased plasma and red blood cell AChE activity at ≥0.3 mg/kg/day (Lamb and Hixson 1983). Fetotoxic effects included increased incidences of incomplete ossified parietal bones and sternebrae 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, no effects on fetal survival, growth, or development were reported in this study. 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 given 0.5 mg/kg/day disulfoton in the diet for 60 days prior to mating and/or during mating resulted in a 32.1% depression in fetal brain AChE activity (Ryan et al. 1970).

There were no treatment-related effects on number of litters, live births, stillbirths, or viability in pregnant rats after exposure to 0, 0.038, 0.156, or 0.67 mg/kg/day during gestation days 0–21 (corresponding to doses of 0, 0.102, 0.389, or 1.714 mg/kg/day) during lactation (Sheets 2005). Additionally, offspring showed no treatment-related effects in the functional observational battery assessment or in learning and memory testing. In female offspring from mid- and high-dose dams, delayed vaginal opening was observed, and in high-dose female offspring, 56% inhibition of red blood cell AChE and 30% inhibition of brain AChE activity were noted (Sheets 2005). Similarly, in male offspring, significant inhibition was seen in the high-dose group, with red blood cell and brain AChE activity inhibited by 53 and 30%, respectively. A 17–18% depression in body weight gain was also seen in both sexes of offspring born to dams in the high-dose group, when compared to controls (Sheets 2005). In a 3-generation reproductive study in rats, cloudy swelling and fatty infiltration of the liver, mild nephropathy (females), and juvenile hypoplasia of the testes were observed in F3b litters (Taylor 1965a). These litters also had significantly depressed red blood cell AChE activities. In another multi-generation study in rats, brain AChE activity was inhibited by 24 and 32% in male and female F1a pups, respectively, at 0.03 mg/kg/day, and by 50% and 59% in male and female F1a pups, respectively, at 0.09 mg/kg/day (Hixson and Hathaway 1986). No inhibition of brain AChE was found in the F1a pups at 0.009 mg/kg/day, and no grossly observable developmental abnormalities were observed in any pups in the F1 or F2 generation. In offspring of dams exposed to 0, 0.042, 0.168, or 0.694 mg/kg/day in feed, red blood cell AChE inhibition was inhibited by 20% for mid-dose offspring, and by 83% in high-dose offspring; no clinical signs were noted (Klaus 2006c).

2.18 OTHER NONCANCER

No studies were located regarding other cancer effects in humans or animals after oral, inhalation, or dermal exposure to disulfoton.

2.19 CANCER

No studies were located regarding cancer effects in humans after oral exposure to disulfoton, and no studies were located regarding cancer effects in humans or experimental animals after dermal exposure to disulfoton. The EPA has classified disulfoton in Group E, indicating evidence of noncarcinogenicity for humans (EPA 2021). The National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC) have not assessed the carcinogenicity of disulfoton (IARC 2018; NTP 2016).

Two occupational exposure studies have not observed associations between occupational exposure to disulfoton and cancer in pesticide applicators; exposure in these studies assumed to be primarily inhalation. One study evaluated the risk of aggressive prostate cancer in a cohort of 20,923 licensed private pesticide applicators in Iowa and North Carolina from the Agricultural Health Study cohort (Pardo et al. 2020). In this cohort, the risk of aggressive prostate cancer was not increased in subjects previously exposed to disulfoton ("ever used;" n=1,776) compared to unexposed subjects ("never used;" n=19,147); hazard ratio (HR) 0.96, 95% CI 0.74–1.26. Major limitations of this study include self-reported historical use of pesticides and lack of measured exposure levels. In a much smaller study, medical examination of 30 floriculturist workers occupationally exposed to various pesticides, including disulfoton, found no evidence of increased cancer (Gómez-Arroyo et al. 2000). Female workers had been occupationally exposed for 10 years, and males for 1.5 years; however, exposure to disulfoton was not measured. Given the small sample size, these results cannot be generalized to other populations.

In a 13-week study in rats exposed intermittently to ≤1.4 mg/m^3, Shiotsuka (1989) reported that comprehensive histological examination of organs and tissues revealed no treatment-related neoplastic lesions. Chronic-duration inhalation studies, which would be more appropriate to assess possible carcinogenicity, were not located for disulfoton.

No histological evidence of a carcinogenic effect was observed in Sprague-Dawley rats fed ≤0.1 mg/kg/day disulfoton for 1.5–2.0 years (Carpy et al. 1975), in F344 rats fed ≤1.02 mg/kg/day disulfoton for 2 years (Hayes 1985), or in CD-1 mice fed in diet ≤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 and Welscher 1975). No further carcinogenicity studies were located.

2.20 GENOTOXICITY

No studies were located regarding genotoxicity of disulfoton in humans after oral or dermal exposure or in experimental animals after inhalation or dermal exposure.

Cytogenetic testing in epithelial cells found significant differences between 30 floriculturist workers (8 men exposed for 1.5 years and 22 women exposed for 10 years) reportedly occupationally exposed to disulfoton and other pesticides (organochlorines, carbamates and other organophosphates) compared to control workers (Gómez-Arroyo et al. 2000). The study showed that pesticide exposure induced alterations on cell proliferation kinetics as M2 cells decreased and M3 cells increased significantly compared to controls suggesting acceleration of the cell cycle. Additionally, the mitotic index was significantly higher in the exposed group. Higher frequency of micronuclei/100 cells in the exposed group (1.01; 0.38 in controls) suggested that pesticide exposure increased genetic damage (Gómez-Arroyo et al. 2000). The study authors reasoned that tissue is damaged at the chromosomal level and also underwent nuclear abnormalities of pyknosis (shrunken nuclei), karyolysis (nuclear dissolution), and karyorrhexis (nuclei disintegrated), which were confirmed in the study. In the same study, higher sister chromatid exchange (SCE) frequency in lymphocytes of peripheral blood was observed among exposed workers (mean SCE 7.1±0.17) compared to controls (mean SCE 4.0±0.1); no significant difference was seen between exposed males and females. Study results were concluded to not be affected by alcohol consumption or smoking status. However, the study was limited due to differential exposure between males and females in years of exposure and nature of agricultural work (Gómez-Arroyo et al. 2000). Additionally, workers were exposed to complex mixtures of chemicals; thus, it is not clear that study findings can be attributed to disulfoton exposure alone.

The results of *in vivo* studies are summarized in Table 2-4. Disulfoton did not induce micronuclei in the red blood cells 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 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 melanogaster* (EPA 1981; Sandhu et al. 1985; Waters et al. 1981, 1982).

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

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

– = negative results

Disulfoton has been tested in numerous types of *in vitro* assays mainly with negative results; all results are summarized in Table 2-5. Disulfoton was negative in most assays for reverse mutation in most strains of *Salmonella typhimurium* with or without metabolic activation (EPA 1980; 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 1980, 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 1980; Herbold 1983; Inukai and Iyatomi 1976; Sandhu et al. 1985; Waters et al. 1981, 1982).

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

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Prokaryotic organisms				
Salmonella typhimurium LT-2 strains	Reverse mutation	No data	+	Hanna and Dyer 1975
S. typhimurium TA 1535	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, EPA 1984a; Waters et al. 1981, 1982
TA1535		–	–	
TA1537		–	–	
TA1538		–	–	
TA98		–	–	
TA100		–	–	
S. typhimurium	Reverse mutation			Inukai and Iyatomi 1976
TA1535		–	–	
TA1537		–	–	
TA98		–	–	
TA100		–	–	
Escherichia coli WP2 strains	Reverse mutation	No data	+	Hanna and Dyer 1975
E. coli WP2 uvrA	Reverse mutation	–	–	EPA 1980, EPA 1984a; Sandhu et al. 1985; Waters et al. 1981, 1982
S. typhimurium SL4525(rec+)/ SL4700(rec–)	Differential toxicity	No data	–	EPA 1984a; 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

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

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Eukaryotic organisms				
Fungi:				
Saccharomyces cerevisiae D7	Reverse mutation	–	–	EPA 1984a; Sandhu et al. 1985; Waters et al. 1981, 1982
S. cerevisiae S138 S211	Reverse mutation	–	–	Jagannath 1981
S. cerevisiae D7	Gene conversion and mitotic crossing-over	–	–	Sandhu et al. 1985; Waters et al. 1981, 1982
S. cerevisiae D3	Induction of mitotic recombinants	–	–	EPA 1980; Sandhu et al. 1985
S. cerevisiae D3	Primary DNA damage	No data	–	Waters et al. 1981, 1982
S. cerevisiae D3	Mitotic non-disjunction	–	–	Brusick 1981
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	Chromosomal aberrations	+	–	Lynch et al. 2008
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 lymphoma cells L5T	Forward mutation	No data	–	Waters et al. 1981, 1982

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

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Human lung fibroblasts WI-38 cells	Unscheduled DNA synthesis	–	+	EPA 1980, EPA 1984a; Sandhu et al. 1985
Human hematopoietic cells 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

– = negative result; + = positive results; (+) = weakly positive result; DNA = deoxyribonucleic acid; HGPRT = hypoxanthine-guanine phosphoribosyl transferase; RNA = ribonucleic acid

Negative results were obtained in assays for reverse mutation, gene conversion, mitotic crossing over and recombinants, and primary deoxyribonucleic acid (DNA) damage in eukaryotic yeast, *Saccharomyces cerevisiae*, with and without activation (Brusick 1981; EPA 1984a; Jagannath 1981; Sandhu et al. 1985; Waters et al. 1981, 1982). On the other hand, 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. Chromosomal aberrations were positive in Chinese hamster ovary cells with metabolic activation; however, they were negative without activation (Lynch et al. 2008). Positive or weakly positive results were obtained for SCEs 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 SCEs 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, unscheduled DNA synthesis in human lung fibroblasts (EPA 1984a; Sandhu et al. 1985; Waters et al. 1981, 1982), and 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 alterations of DNA or ribonucleic acid (RNA) synthesis in human HeLa cells (Litterst et al. 1969).

The genotoxicity of disulfoton has been reviewed (Brusick 1981; EPA 1980, 1984a; Herbold 1983; Inukai and Iyatomi 1976; Jagannath 1981; Moriya et al. 1983; Sandhu et al. 1985; Waters et al. 1981, 1982), and results are primarily negative in numerous tests for reverse mutation, and differential toxicity in bacteria, with or without activation, assays for mutagenic activity, gene conversion, mitotic crossing, and DNA damage in the yeast were also negative with or without activation. There is no evidence of chromosomal aberrations in different human cell lines. In mammalian cells, the test results were mixed; forward mutations for mouse lymphoma cells without but not with activation. Overall, the current database suggests that disulfoton has little to no genotoxicity potency.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Information on the toxicokinetics of disulfoton comes from studies in humans and animals. These data are summarized below.

- Disulfoton is readily and extensively absorbed by the gastrointestinal tract following oral exposure. It has been measured in the gastrointestinal tract up to 3 days after exposure in humans; however, the extent or rate of absorption in humans is unknown.
- Absorbed disulfoton is primarily distributed to the liver. It is also distributed to the kidneys, whole blood, red blood cells, plasma, fat, skin, muscles, brain, small intestine, pancreas, and bile.
- 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.
- The major route of excretion of disulfoton is through urine, with smaller amounts being excreted in feces and expired air.

3.1.1 Absorption

Disulfoton and/or its metabolites have been detected in the blood and urine of humans who consumed unknown amounts of disulfoton (Futagami et al. 1995; Hattori et al. 1982; Yashiki et al. 1990). Di-Syston is a disulfoton mixture that is coated with surfactant and has a sandy and granular texture that may be easily absorbed into the gastric mucosa (Futagami et al. 1995). 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, about 2 hours after ingestion of Di-Syston (Yashiki et al. 1990). The 4.92 nmol/g blood concentration corresponded to 1.35 µg/g. Gastrointestinal absorption was not yet complete, since 3.3 mg of disulfoton was recovered from the stomach contents, which was collected about 2 hours after ingestion (Yashiki et al. 1990). In another case, total plasma phosphorodithioate sulfone (disulfoton and its metabolites, phosphorodithioate sulfoxide and its sulfone) in a patient who ingested an unknown amount of Di-Syston (5% disulfoton) was 1,095 ng/mL upon admission, and decreased to 505 ng/mL 20 hours after admission; however, there was a rebound increase on day 2 to 1,322 ng/mL (Futagami et al. 1995). Futagami et al. (1995) noted that the concentration at admission was about twice as high as reported in Yashiki et al. (1990). On day 2 the observed “rebound phenomenon” of the concentration in plasma was

partially attributed to the delayed, but prolonged absorption, of Di-Syston in the gastrointestinal tract. An odor of aspirated stomach fluid was also noted, suggesting the presence of Di-Syston in the gastrointestinal tract, up to day 3 of admission (Futagami et al. 1995). Contents from the stomach decreased following repeated gastrointestinal lavage. The concentration of metabolites in the urine was not quantitated in either the Yashiki et al. (1990) or Futagami et al. (1995) study. While these data indicate that 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 10-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. Female rats were given a lower dose than male rats, as they are more sensitive to the toxic effects of disulfoton. 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 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.

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).

Zenzdian (2000) developed standard protocols for evaluating dermal penetration of pesticides in rats. The rate of dermal absorption for disulfoton at a dose of 3.1 nM/cm^2 ranged from 15.9% of the administered dose at 1 hour to 42.0% at 168 hours. Initially, absorption at higher doses was lower but it approached the same maximum after 168 hours.

3.1.2 Distribution

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 (kidneys, plasma, fat, whole blood, skin, muscles, 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 0.5–1.5 mg/kg/day disulfoton in capsules for 2 years, disulfoton was detected in the kidneys (0.06 ppm), urine (0.06 ppm), liver (0.02 ppm), serum (0.04 ppm), and 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 tissues, thymus, spleen, red blood cells, extraocular muscles, and muscles of the extremities and torso.

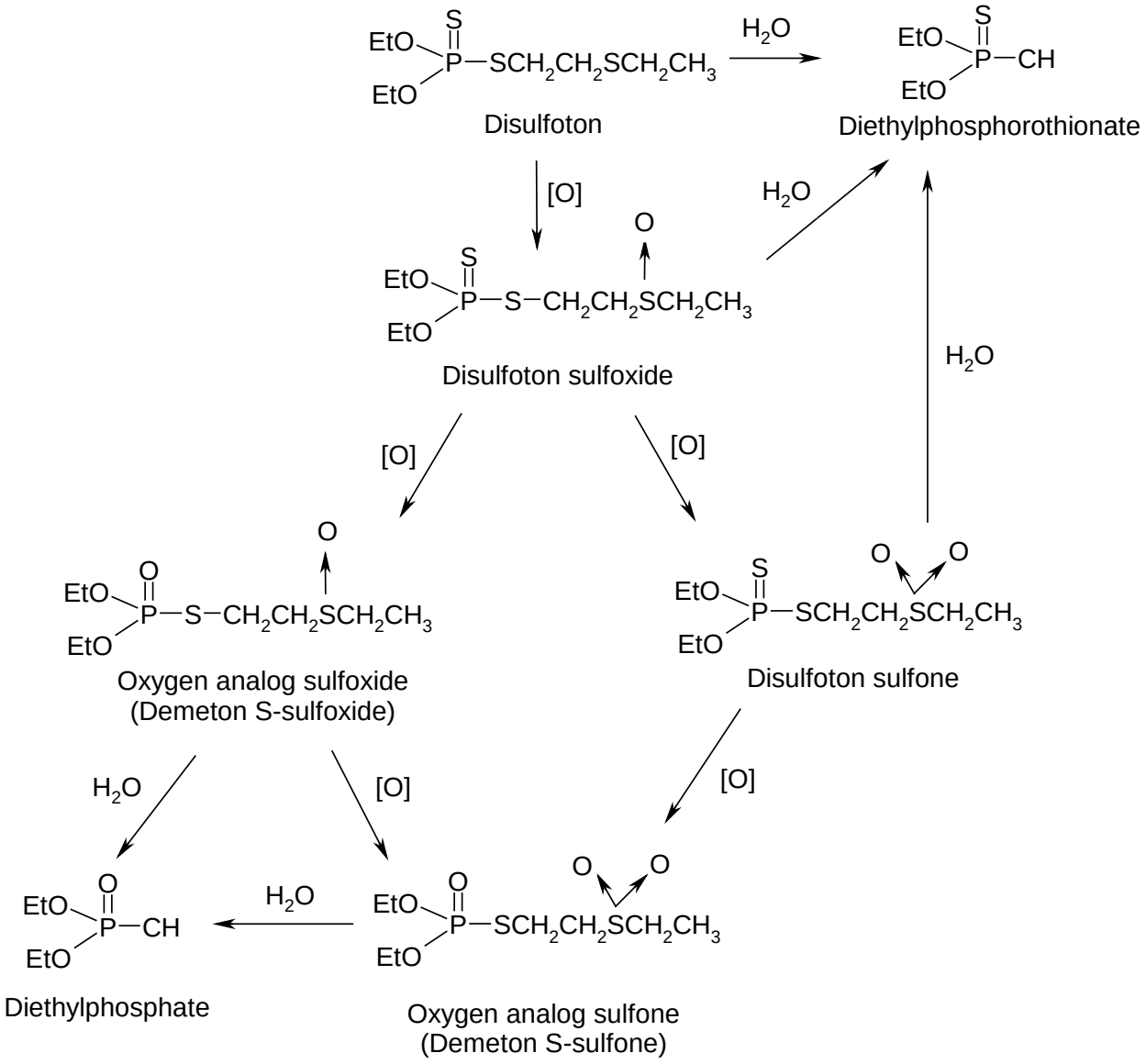
In rats, after 1 hour of dermal exposure to 3.1 nM/cm^2, the systemic distribution of disulfoton was 0.48% of the administered dose in the blood, and 4.84% in the carcass (Zenzdian 2000). These values reduced to 0.01 and 0.09% respectively, at 168 hours.

3.1.3 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 3-1). 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.

Figure 3-1. Metabolic Pathways for Disulfoton



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, DEP,

DETP, and 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 (Yashiki et al. 1990). In a 75-year-old woman who ingested Di-Syston granules, disulfoton and its metabolites phosphorodithioate sulfoxide and phosphorodithioate sulfone were detected in plasma (Futagami et al. 1995). Workers exposed mainly to disulfoton at a pesticide formulating plant excreted the metabolites DEP, DETP, DEDPT, and DEPTh in urine after dermal and possibly inhalation exposure to disulfoton (Brokopp et al. 1981).

Studies in rats and mice indicate pathways similar to humans. Unidentified urinary metabolites in mice injected intraperitoneally with 32-ρ disulfoton were described as hydrolysis 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 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. 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 3-1, 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 pathway, however, cannot be deduced from relative percentages of metabolites formed because the final urinary metabolites are common products of several of the intermediate metabolites. 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 male rats, while only demeton S-sulfone was apparent in the urine of female rats (Lee et al. 1985). However, after dosing with 0.2 mg/kg/day for 14 days, the pattern in both sexes 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 demeton S-sulfone.

The studies described above support the accepted theory 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 (Eto 1974). These active metabolites bind to ubiquitous AChE 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 P450 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 P450 mixed-function oxidase (MFO) system. The components of the MFO system include cytochrome P450, the terminal oxidase, and NADPH, and NADPH-dependent cytochrome c reductase (Stevens and Greene 1974). Generally, anticholinesterase insecticides such as disulfoton bind to oxidized cytochrome P450 to form a disulfoton:cytochrome P450 complex (Stevens et al. 1973). An electron is then transferred from cytochrome c reductase to cytochrome P450 (Gillette et al. 1972), thereby reducing the disulfoton:cytochrome P450 complex. Molecular oxygen then binds to this complex to form a disulfoton:reduced cytochrome P450:02 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 P450 (Hildebrandt and Estabrook 1971).

Flavin monooxygenase specifically oxidizes sulfides to (R)-(+)-sulfoxide enantiomers, while cytochrome P450-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 P450) may be required to form sulfones (Tynes and Hodgson 1985). Disulfoton interacted with cytochrome P450 to markedly inhibit the metabolism of p-nitroanisole and parathion, both of which have rather high affinities for cytochrome P450. These findings underscore the fact that cytochrome P450 and flavin monooxygenase both have the potential to participate in the oxidation of disulfoton (Tynes and Hodgson 1985).

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 mammalian species studied. 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). Flavin monooxygenase in pig liver also had a higher affinity (lower Km) 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.

3.1.4 Excretion

No studies were located regarding the rate or extent of excretion in humans after 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. 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 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. 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.

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 hydrolytic metabolites 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).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK

models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

No chemical-specific PBPK models have been developed for disulfoton.

3.1.6 Animal-to-Human Extrapolations

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 animal studies, females appear more sensitive to toxic effects of disulfoton following inhalation, oral, or dermal exposure (Bombinski and DuBois 1958; Crawford and Anderson 1974; Gaines 1969; Klaus 2006b; Mihail 1978; Pawar and Fawade 1978; Thyssen 1978). Males appear to excrete disulfoton faster (Lee et al. 1985; Puhl and Fredrickson 1975). It is unknown if these differences between the sexes are seen in humans.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic

makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to disulfoton are discussed in Section 5.7, Populations with Potentially High Exposures.

No data were located that identify subpopulations of humans more susceptible to the toxic effects of disulfoton or data specific to children. Since significant cholinesterase activity inhibition has been seen in animals and humans following exposure to disulfoton (see Section 2.15), populations taking AChE inhibitors (anticholinesterases) may be further susceptible to toxic effects of disulfoton. Anticholinesterases, such as Galantamine and Donepezil, are used as pharmaceuticals most commonly to treat neurodegenerative disease such as Parkinson's disease, Alzheimer's disease, dementia, glaucoma, and myasthenia gravis (Khan et al. 2018; Knight et al. 2018; Moss 2020). Anticholinesterases are also used to reverse the effects of nondepolarizing muscle agents used during intubation in general anesthesia (Shaydenfish et al. 2020). Plasma cholinesterase activity may be lowered by liver disease, malnutrition, infection, and renal failure (Anderson et al. 2019).

Plasma cholinesterase is more often reduced by the present of certain genetic variants (Anderson et al. 2019). It is estimated that between 1:3000 and 1:10,000 individuals are homozygous for the genetic enzyme variant allele code for decreased cholinesterase activity or quantity (Anderson et al. 2019). Lockridge et al. (2016) also describes a genetic variant associated with decreased plasma butyrylcholinesterase activity and reduced enzyme concentration. Based on occupational and case studies, the study authors suspect that individuals with this genetic variant may likely be susceptible to further cholinesterase inhibition from exposure to organophosphates pesticides including disulfoton (Lockridge et al. 2016).

Depressed serum cholinesterase has been routinely reported in agricultural workers who are likely exposed to various carbamates and organophosphates in agropesticides (Ames et al. 1989; Neupane et al. 2014; Shentema et al. 2020; Thetkathuek et al. 2017). It is expected that workers with inhibited cholinesterase activity from previous or current exposures to other pesticides may be susceptible to further cholinesterase inhibition from exposure to disulfoton.

There is insufficient information to determine if effects in children would be similar to effects seen in adults after acute exposure or long-term, low-level exposure to disulfoton. It is unknown if disulfoton

affects the developing human fetus or the development of children, and if disulfoton or its metabolites cross the placental barrier. Animal studies suggest that younger animals are more susceptible to disulfoton toxicosis than older animals as mortality in weanling rats was seen at lower levels when compared to adult rats (Brodeur and Dubois 1963). The study 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. Also, 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).

Animals and humans are expected to have similar metabolic pathways of disulfoton (see Section 3.1.3), and these are expected to be similar in children. However, there is insufficient information on the movement of disulfoton into the developing fetus or breast milk. There are no child, adult, or laboratory animal PBPK models, nor are there children-specific biomarkers.

Limited information is available from animal studies on potential effects of oral disulfoton exposure in the developing young, as discussed in Section 2.17. When pregnant rats were given disulfoton at 1.0 mg/kg/day, there were increased incidences of incomplete ossified parietal bones and sternebrae; however, no soft tissue, external, or skeletal malformations were observed in pups (Lamb and Hixson 1983). The authors considered this evidence of growth retardation due to maternal toxicity rather than specific fetotoxic effects. In another study, prior to mating, rats were given 0.5 mg/kg/day disulfoton in diet for 60 days, resulting in marked depression of fetal brain AChE activity (Ryan et al. 1970). In multi-generational exposure studies, third generation litters had cloudy swelling and fatty infiltration of the liver, mild nephropathy, juvenile hypoplasia of the testes in males, and depressed red blood cell AChE activity (Taylor 1965a). In a similar study, depressed brain AChE activity was seen in first generation litters in the mid- and high-dose exposure groups, 0.03 and 0.09 mg/kg/day, respectively (Hixson and Hathaway 1986).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers 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, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to disulfoton are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for disulfoton from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by disulfoton are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Disulfoton and its metabolites have been measured in various human or animals tissues and body fluids (blood, urine, feces, liver, kidneys, and body fat) following disulfoton exposure (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. About 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). A total disulfoton and metabolite level of 1,095 ng/mL was measured in the blood of a woman 3.5 hours after ingestion of disulfoton (Futagami et al. 1995). In all cases, the ingested 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 could result in detectable levels in the liver (Bull 1965; Puhl and Fredrickson 1975), but monitoring of liver levels in humans would require biopsy. Dialkyl phosphate metabolites are used as biomarkers of exposure to multiple organophosphate insecticides and thus cannot be solely used to identify disulfoton exposure. Additionally, the measurement of these metabolites primarily reflects recent exposure to organophosphates. Specimens of urine collected from 31 locations across the United States, comprising the sample areas of the National Health and Nutrition Examination Survey (NHANES) from 2011–2012, reported detection (detection limit 0.1 ng/mL) of DETP at a frequency of 71% and DEDPT at a frequency of 5.4% of those tested (CDC 2019). 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 post-exposure (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). Disulfoton sulfoxide and disulfoton sulfone are specific to disulfoton but are only reported in this one study. 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. One animal study demonstrated that a greater percentage of the disulfoton dose was eliminated as DEP (Bull 1965). This provides limited evidence that DEP is a more sensitive urinary biomarker than the other metabolites discussed.

Urine catecholamines may also serve as biomarkers of disulfoton exposure as evidenced by limited animal data, since no human data are available. 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). Organophosphates and carbamates are known to inhibit AChE, which can cause an accumulation of acetylcholine at the nerve synapses (King and Aaron 2015), and since the secretion of catecholamines is influenced by acetylcholine (Norman and Henry 2015), it is likely that other organophosphates can 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; however, no effect on NADPH cytochrome c reductase was observed. 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.

3.3.2 Biomarkers of Effect

Disulfoton toxicity manifests as cholinergic toxicity symptoms such as salivation, diarrhea, pupil constriction, muscle tremors, nausea, and weight loss. These symptoms have been observed in humans accidentally exposed to disulfoton (Futagami et al. 1995; Yashiki et al. 1990) and in animals given disulfoton (Schwab et al. 1981). Ataxia, convulsions, coma, respiratory distress, and death are common signs associated with a more severe toxicosis. Nervous tissue is the most sensitive target organ.

Cholinesterase inhibition is a biomarker for other organophosphates and thus not always conclusive evidence of disulfoton toxicity (Osweiler et al. 1985). Organophosphates share a common mechanism of cholinesterase inhibition and similar adverse effects and symptoms have been observed (Robert and Reigart 2013). Depression of cholinesterase activity can indicate the possibility of more serious neurological effects, but the severity of the signs and symptoms and the degree of cholinesterase depression are not always correlated. Employees occupationally exposed to disulfoton for 9 weeks had marked depression of red blood cell AChE activity, but no clinical signs of toxicity (Wolfe et al. 1978).

Animal studies have demonstrated that brain AChE 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). Inhibition of red blood cell AChE activity or serum cholinesterase activity with or without concomitant neurological signs is a common indicator of organophosphate exposure. Red blood cell AChE 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 a 14-day rat study, while T-lymphocyte AChE correlated better with brain AChE activity than did red blood cell AChE, the recovery of T-lymphocyte activity recovered faster; therefore, red blood cell activity correlated better with brain AChE (Fitzgerald and Costa 1993).

AChE (also known as red blood cell cholinesterase, erythrocyte cholinesterase, or true cholinesterase) activity is typically used as a biomarker of effect for organophosphate toxicity, including disulfoton. Specifically, a reduction of an individual's activity relative to their baseline activity indicates a toxic effect; ATSDR considers a ≥20% decrease in an individual's cholinesterase activity a toxic effect. The normal range of AChE activity can be wide due to the variation in the human population; therefore, the percentage change is used instead of activity levels. In a case study, a woman had depressed red blood cell AChE activity of 3,524 IU/L at admission and 3,122 IU/L 19 days after exposure (reference range: 10,000–14,000 IU/L); observed cholinergic signs of toxicity gradually decreased over the 19-day period despite continued depression of AChE activity (Futagami et al. 1995). Cholinesterase depression was not observed in 11 employees exposed to disulfoton for ≤2.5 weeks, but the presence of urinary metabolites of disulfoton (a biomarker of exposure) indicated exposure (Brokopp et al. 1981).

Plasma cholinesterase (also known as serum cholinesterase, pseudocholinesterase, or butyryl-cholinesterase) is used to support acetylcholinesertase and clinical manifestations to diagnose organophosphate toxicity (Moon and Chun 2014; Strelitz et al. 2014; Worek et al. 2005). Experimental studies of animals exposed to disulfoton have observed that plasma cholinesterase activity decreases more rapidly than AChE but recovers to baseline more quickly (Klaus 2006a, 2006b; Sheets 2005). In one clinical case, a man who showed severe signs of cholinergic toxicity after accidentally ingesting disulfoton had depressed serum cholinesterase activity up to 8 days after exposure (Yashiki et al. 1990). A relationship between plasma cholinesterase and clinical symptoms of organophosphate poisoning has been observed (Prasad et al. 2013; Worek et al. 2005) and plasma cholinesterase appears to be most accurate for acute prognosis of organophosphate poisoning (Aygun et al. 2002). However, use of plasma cholinesterase on its own as a diagnostic tool is not agreed upon because: (1) it is most often used as a biomarker of liver function; (2) it can be altered with pregnancy, infection, and various medical illnesses;

and (3) levels can vary widely in an individual with repeat sampling (Katz and Brooks 2020; Zivkovic et al. 2014). Therefore, while assaying plasma cholinesterase activity is easier, red blood cell AChE is considered to be a more accurate biomarker for nervous system toxicity (Katz and Brooks 2020).

As previously stated, cholinesterase activity and neurological symptoms are used as biomarkers of effect for disulfoton, other organophosphates, and carbamate pesticides which may affect the toxicity of disulfoton. Furthermore, liver disease, malnutrition, infection, renal failure, and anticholinesterase pharmaceuticals, which are used to treat neurodegenerative diseases, may also lower AChE activity (Anderson et al. 2019; Khan et al. 2018; Knight et al. 2018; Moss 2020). 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.

Increased levels of urinary catecholamines may also be associated with accumulation of acetylcholine that resulted from AChE 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).

In rats given a single oral dose of disulfoton, gamma-enolase mRNA in sciatic nerve increased by 200% two hours after the exposure and exceeded 250% 30 days after exposure (Matsuda et al. 2000). In the same study, depressed AChE mRNA levels in soleus muscle and sciatic nerve indicated disulfoton exposure 12 hours after exposure. Since gamma-enolase mRNA levels remained high for over 4 weeks following exposure, study authors suggested up-regulation of gamma-enolase mRNA as a marker of nervous system abnormality. However how an increase in gamma-enolase mRNA indicates toxicity is unclear (Matsuda et al. 2000). No additional studies were located that examined the up-regulation of gamma-enolase mRNA following organophosphate exposure. A more detailed discussion of the health effects caused by disulfoton can be found in Chapter 2.

3.4 INTERACTIONS WITH OTHER CHEMICALS

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 Greene 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 P450 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 P450 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 P450, or the 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 P450 activity (Sipes and Gandolfi 1986). Therefore, pretreatment with phenobarbital will not result in flavin monooxygenase-mediated activation of disulfoton to its active metabolite. Cytochrome P450 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 P450 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_{50} 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. 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 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). The levels of electron transport chain components (cytochrome b, cytochrome c reductase, and total heme) in rats were lowered by administration of metabolic inhibitors, nickel chloride, cobalt chloride, or cycloheximide (Fawade and Pawar 1983). When given a single dose of disulfoton, the electron transport components were further decreased in rats pretreated with nickel chloride or cobalt chloride. Data from this study suggests an additive effect by disulfoton (Fawade and Pawar 1983). In a separate experiment, an additive effect between disulfoton and the tested 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, the inhibitors decreased the activity of delta-aminolevulinic acid synthetase, but this decrease was reversed when disulfoton was administered (Fawade and Pawar 1983).

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. 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.

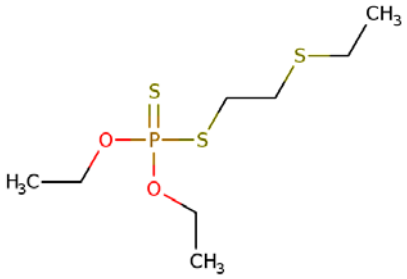
Cross-tolerance between disulfoton and another organophosphate, chlorpyrifos, was observed in mice (Costa and Murphy 1983b). In the same study, propoxur-tolerant mice were tolerant to disulfoton but not vice versa. Propoxur (a carbamate) is metabolized by carboxylesterases, and these enzymes are inhibited in disulfoton-tolerant animals; disulfoton-tolerant animals are more susceptible to propoxur and/or carbamate insecticides than are non-pretreated animals. In another study, disulfoton-tolerant rats were tolerant to the cholinergic effects of octamethyl pyrophosphoramide (OMPA) but not parathion (McPhillips 1969a, 1969b). The study authors were unable to explain why the insecticides OMPA and parathion caused different effects. Additionally, when two or more organophosphates are absorbed, additive toxicity is likely to occur due to similarities in their mechanism of toxicity (Robert and Reigart 2013). Among studies that examined, additive effects of exposure to organophosphates and carbamates, none examining disulfoton were located. An assay study on organophosphate and carbamate pesticides (carbaryl, carbofuran, parathion, demeton-S-methyl, and aldicarb) with similar mechanisms demonstrated an additive inhibitory effect on cholinesterase activity (Mwila et al. 2013).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Disulfoton is a systemic insecticide/acaricide that belongs to the organophosphate class of pesticides. Disulfoton does not occur naturally. Table 4-1 lists common synonyms, trade names, and other pertinent identification information for disulfoton.

Table 4-1. Chemical Identity of Disulfoton

Characteristic	Information	Reference
Chemical name	Disulfoton	NLM 2021
Synonym(s) and Registered trade name(s)	o,o-Diethyl s-(2-eththioethyl) phosphorodithioate; Ethylthiodemeton; M-74; thiodemeton; Di-Syston; Dithiosystox; Solvirex; ENT 23347; Frumin AL	NLM 2021
Chemical formula	$C_8H_{19}O_2PS_3$	Lide 2005
Chemical structure		NLM 2021
CAS registry number	298-04-4	Lide 2005
EPA hazardous waste	P039	EPA 2019a

CAS = Chemical Abstracts Service; EPA = Environmental Protection Agency; NLM = National Library of Medicine; UNII = Unique Ingredient Identifier

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Pure disulfoton is a colorless oil with low volatility and water solubility, but is readily soluble in most organic solvents and fatty oils (Bowman and Sans 1983; EPA 1978). The half-life of disulfoton suggests that it is short-lived in the atmosphere. Table 4-2 lists important physical and chemical properties of disulfoton.

Table 4-2. Physical and Chemical Properties of Disulfoton

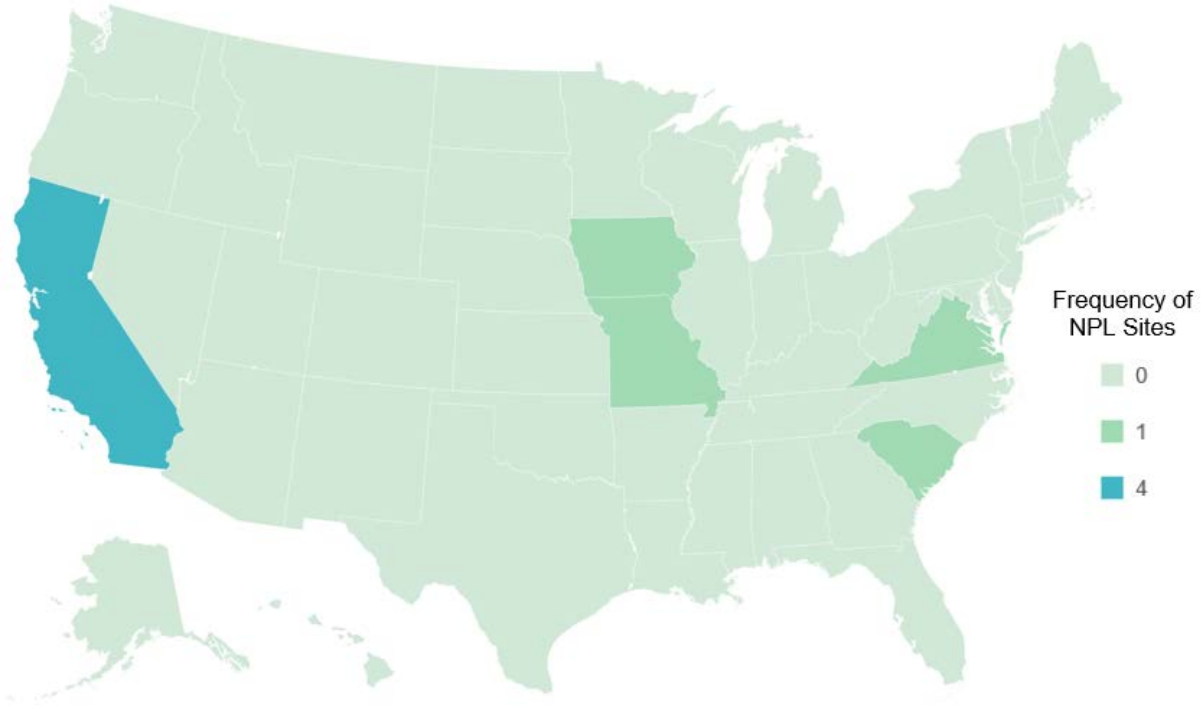
Property	Information	Reference
Molecular weight	274.405 g/mol	Lide 2005
Color	Colorless to yellow	Sanborn et al. 1977
Physical state	Liquid	Muir et al. 2004
Melting point(s)	-25.0°C	Lide 2005
Boiling point(s)	108°C at 0.01 mm Hg 128°C at 1.0 mm Hg	Lide 2005
Density: at 20°C	1.144 g/cm^3	Lide 2005
Odor	Sulfur	NLM 2021
Odor threshold:		NLM 2021
Water	No data	
Air	No data	
Solubility:		
Water at 20°C	25 mg/L	NLM 2021
Organic solvent(s)	Readily soluble in most	EPA 1978
Partition coefficients:		
Log K_{ow}	4.02	NIOSH 2017
Log K_{oc}	3.2–3.3	Wauchope et al. 2002
Vapor pressure at 25°C	9.75x10^{-5} mm Hg	NLM 2021
Henry's law constant at 25°C	2.2x10^{-6} atm-m^3/mol	NLM 2021
Degradation half-life in air via reaction with OH radicals	≈3 hours	Meylan and Howard 1993
Dissociation constant	No data	NLM 2021
Heat of vaporization	76.7 kJ/mol at 25°C	NIST 2018
Autoignition temperature	No data	NLM 2021
Flashpoint	>180°F (>82°C)	NIOSH 2018
Flammability limits in air	No data	NIOSH 2018
Conversion factors	1 ppm=11.22 mg/m^3 1 mg/m^3=0.089 ppm	ACGIH 2002

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Disulfoton has been identified in at least 8 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites evaluated for disulfoton is not known. The number of sites in each state is shown in Figure 5-1.

Figure 5-1. Number of NPL Sites with Disulfoton Contamination



Source: ATSDR 2019

- Disulfoton was cancelled for use as a pesticide in the United States in 2009 by the EPA, and remaining stocks were permitted to be sold until 2011. Reported use of products containing disulfoton continued through 2016.
- The potential for human exposure to disulfoton is expected to be low for the general population.
- Disulfoton is a systemic organophosphate insecticide/acaricide used for agricultural purposes.
- Despite having a short predicted half-life in air (~3 hours), disulfoton may be transported long distances in the atmosphere; it has been detected in regions up to hundreds of kilometers away from countries where it is still is use as a pesticide.

- The detection of disulfoton in soil and the mobility of its degradation products suggest the potential for disulfoton to leach into groundwater.
- People who live near hazardous waste sites containing disulfoton may be at a higher risk of exposure than the general population, as are people who manufacture or handle disulfoton.

Disulfoton is not permitted for use as a pesticide in the United States as of 2009 following voluntary cancellation orders from a few companies that produce disulfoton-containing pesticides. Remaining stocks were permitted to be sold until 2011. Agricultural use of disulfoton-containing pesticides in the United States in 2016 was estimated by the U.S. Geological Survey in Virginia and North Carolina; no use of disulfoton-containing pesticides has been reported since 2016 (USGS 2021). Additionally, its use abroad may still continue. Historically, workers in industries that manufactured and formulated disulfoton, farm workers who entered treated fields after the insecticide was applied, and applicators of the insecticide were at a higher risk of exposure than the general population. However, this risk is no longer a concern in the United States given that production of disulfoton is no longer permitted and its current use is not likely. Due to the potential presence of disulfoton at hazardous waste sites, exposure may be possible for populations that live near these sites.

Disulfoton entered the environment primarily during its use as an insecticide/acaricide in crops and vegetables, and in home gardens. Other important pathways for disulfoton entry into the environment were the disposal of liquid disulfoton wastes into soil evaporation pits, ditches, ponds (Winterlin et al. 1989), and hazardous waste sites. Considering entry pathways and chemical and biological properties of disulfoton, soil is the environmental medium most likely to have been 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; Sanborn 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 (Capel 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 10ºC river water was 7–41 days (Wanner et al. 1989). The measured whole-body bioconcentration factor (BCF) 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; Greenhalgh 1978; Harris et al. 1988; Jury et al. 1987a; Menzie 1972).

In the past, when it was still in use, 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 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.

According to the Pesticide Residue Monitoring Program reports, disulfoton has not been detected in food in the United States in recent years (FDA 2017a, 2017b, 2018, 2019, 2022). The USGS estimated use of disulfoton on agriculture in the United States including vegetables and fruit up until 2016; no use has been reported since 2016 (USGS 2021). In the past, the Food and Drug Administration (FDA) estimated the average dietary intake of disulfoton for 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 1993; FAO/WHO 1991; Winter 1992; Yess 1991).

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Disulfoton production in the United States is expected to have ceased due to its cancellation for use as a pesticide by EPA in 2009. Disulfoton can be produced commercially by a reaction of the sodium salt of O,O'-diethylhydrogen phosphorodithioate with 2-chloroethylthioethyl ether (VonRumker et al. 1974). No information is available in the Toxics Release Inventory (TRI) database on facilities that manufacture or process disulfoton because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005). Information on current production volume is also not available in EPA's Chemical Data Reporting database (CDR 2016). Following its cancellation by the

EPA in 2009, remaining stock was allowed to be sold and distributed by registrants until 2011 (EPA 2010). Disulfoton is listed as available for purchase through various chemical vendors, likely for laboratory use; however, there is insufficient information to determine where it is being produced (NLM 2021). According to the National Pesticide Information Retrieval System, there are currently no products containing disulfoton manufactured, sold, or used in the United States (NPIRS 2021).

5.2.2 Import/Export

Import and export data for disulfoton in recent years were not located, likely because disulfoton use was cancelled by EPA in 2009 (EPA 2010). An analysis of shipping records from 2001 to 2003 indicated that U.S. exports of disulfoton in that time period ranged from 118,573 to 288,054 pounds (Smith et al. 2008).

5.2.3 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. Use of disulfoton products in the United States has likely ceased since its 2009 cancellation by EPA; however, EPA registrants were allowed to sell and distribute remaining stock until 2011, and non-registrants were allowed to use, sell, and distribute disulfoton products until they ran out (EPA 2010). As emulsifiable concentrates and in granular or pelleted/tableted forms, disulfoton was previously used to treat seeds and was applied to soils or plants. Disulfoton was also available in a ready-to-use liquid formulation (EPA 1984b). Historically, disulfoton was used to protect small grains, sugar cane, sorghum, Brazilian coffee crops, 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 (de Faria et al. 2016; EPA 1984b; VonRumker et al. 1974). Agricultural uses accounted for most of its consumption; small quantities were used on home and garden plants and for other purposes, such as mosquito abatement (VonRumker et al. 1974; Warnick and Eldredge 1972).

5.2.4 Disposal

The two preferable methods for disposing of wastes containing disulfoton are incineration and alkaline hydrolysis (NLM 2021). For disposal of low-viscosity wastes (permitting atomization in the combustion chamber) containing disulfoton, liquid injection incineration at 650–1,600°C 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°C and a residence time of seconds to hours, or fluidized bed incineration at 450–980°C 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 (NLM 2021). Alkaline hydrolysis leads to the complete degradation of disulfoton to non-toxic end products (alkaline salts of O,O-dimethylphosphorothioic acid and ethylthioethyl mercaptan). Acid hydrolysis produces essentially the same end products; however, the reaction rate is much slower (IRPTC 1985; Sittig 1980). Fifty percent hydrolysis at 70°C 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 proposed incineration as the best demonstrated available technology (BDAT) for treating organophosphorus non-wastewaters (waste containing >1% by weight total suspended solids and >1% by weight total organic carbon). EPA 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 non-wastewaters (EPA 1989).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5.3.1 Air

There is no information on releases of disulfoton to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Disulfoton was cancelled for use in 2009, and it is unlikely to be released to the air in the United States (EPA 2010). Previously, disulfoton entered the atmosphere during its production and application as an insecticide (CPCR 1992).

5.3.2 Water

There is no information on releases of disulfoton to water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Disulfoton was cancelled in 2009, and it is unlikely to be currently released to surface water or groundwater in the United States (EPA 2010). In the past, potential sources of release into surface water include wastewater discharge and runoff presumably from facilities involved in disulfoton manufacturing, formulation, and packaging (EPA 2008). Also, when disulfoton was still in use, leaching and runoff from treated fields and pesticide disposal pits had the potential to contaminate groundwater and surface water with disulfoton.

5.3.3 Soil

There is no information on releases of disulfoton to soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Disulfoton was cancelled in 2009, and it is unlikely to be released to soil in the United States (EPA 2010). Previously, disulfoton was 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 (Kadoum and Mock 1978).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. There is a paucity of experimental data regarding the transport and partitioning of disulfoton in air. Given the vapor pressure of $9.75x10^{-5}$ mm Hg at 25°C (NLM 2021), disulfoton should exist almost entirely in the vapor phase in the atmosphere (Eisenreich et al. 1981). Due to this, as well as its low particle diameter, the removal rate by dry deposition is expected to be low (Schroeder et al. 1987). Therefore, despite a short predicted half-life of 3 hours in the atmosphere (Atkinson 1988), vapor-phase disulfoton may travel long distances in the air depending on its reactivity characteristics. The detection of disulfoton in regions where it is not used suggests that its presence is due to atmospheric transport and deposition (Asman et al. 2005; Muir et al. 2004). Muir et al. (2004) estimated an empirical half-distance of 949 km for disulfoton. Asman et al. (2005) concluded that disulfoton may have been transported at least 500 km in order to be detected in rainwater in Denmark, where it is no longer sold. Muir et al. (2004) also calculated characteristic travel distance (CTD) and spatial range in air (SR_{air}) as values of indicators of long-range transport potential (LRTP) using three model scenarios: default conditions, [OH] reduced 10-fold, and intermittent precipitation. Under default conditions according to the model, the CTD of disulfoton is 20–21 km, and the SR_{air} is 2% of the earth's circumference. When atmospheric degradation rates are lowered by a factor of 10, CTD increases to 188–199 km, and SR_{air} increases to 7%. When accounting for intermittent precipitation, CTD increases to 193–206 km, and SR_{air} remains at 7% (Muir et al. 2004). Hayward et al. (2010) studied concentrations of disulfoton in Egbert, Ontario and calculated the CDT of disulfoton as 207 km. Muir et al. (2004) notes that the uncertainty in atmospheric degradation rates is large enough to account for the discrepancy in estimated and observed long-range transport of the pesticide.

The solubility of 25 mg/L (NLM 2021) ensures that at least partial removal of atmospheric disulfoton will occur by wet deposition. Disulfoton has been detected in precipitation (Asman et al. 2005; Kurt-Karakus et al. 2011).

Water. The transport of disulfoton from water to air can occur due to volatilization. Volatilization from water is slow to negligible for compounds with a Henry's law constant of $<10^{-5}$ atm-m^3/mol (Thomas 1990). Therefore, disulfoton, with a Henry's law constant value of $2.2x10^{-6}$ atm-m^3/mol (NLM 2021), will volatilize slowly from water. The rate of volatilization increases as the water temperature and ambient air flow rate (wind) 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 m at 11°C was 900 days (Wanner et al. 1989). The estimated volatilization half-life of an aqueous suspension of microcapsules containing disulfoton at 20°C with still air was >90 days (Dragan and Carpov 1987).

Sediment and Soil. Adsorption to particulate matter will transport disulfoton from water to suspended solids and sediment in water. The organic carbon-adjusted soil sorption coefficient (K_{oc}) for disulfoton varies between 600 and 2,612 (Gawlik et al. 2000; Gramatica et al. 2000; Wauchope et al. 1992). This range of K_{oc} values suggests that disulfoton in water adsorbs moderately to strongly to suspended solids and sediments (Swann et al. 1983), and this process may facilitate transport of disulfoton.

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 600–2,612 suggest that the adsorption of disulfoton to soil is moderate to 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 (de Faria et al. 2016; 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 1989). 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 leach through certain soils into groundwater. Disulfoton sulfone and an oxygen analogue of disulfoton sulfone, degradation products of disulfoton with comparable toxicity and higher solubility, were observed moving into deeper soil layers, suggesting that disulfoton and its potential metabolites can reach groundwater even if the sorption is significant or even dominant (de Faria et al. 2016).

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 (NLM 2021), 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 (Sanborn et al. 1977). 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.

Other Media. The bioconcentration of disulfoton and its oxidation products (sulfoxide and sulfone) in carp (*Cyprinus carpio*) was investigated in a continuous flow water system for ≤56 days (Takase and Oyama 1985). The whole-body BCF values in carp were ≈450 for disulfoton, <1 for the sulfoxide, and <6 for the sulfone. Disulfoton disappeared rapidly from fish tissues when the fish were transferred to

uncontaminated fresh water. BCFs of disulfoton in fish based on concentrations at 168 hours were 261 (female guppy), 482 (male guppy), 202 (killifish), 96.7 (goldfish), and 127 (white cloud mountain fish) (Tsuda et al. 1997). Since estimated BCF values for disulfoton are below 1,000, disulfoton is not considered to be bioaccumulative. 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.

5.4.2 Transformation and Degradation

Air. One of the important reactions for most organic pollutants in the atmosphere is with hydroxyl radicals. Using an estimation method (Meylan and Howard 1993), the estimated rate constant for the vapor-phase reaction of disulfoton with hydroxyl radicals is 13.2×10^{-11} cm^3/molecule-second. At 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 about 3 hours. 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.

Water. The three processes responsible for the transformation and degradation of disulfoton in water are abiotic hydrolysis, photosensitized oxidation, and biodegradation. Estimated hydrolysis half-lives were 103 days at 25°C and pH 7 (EPA 1988) and 170 days at 11°C 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 matter (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 m 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 µm solution of disulfoton was exposed to October sunlight (Davis, California) in the presence of 100 µm hydrogen peroxide, 49% of the insecticide disappeared in 10.2 days due to reaction with hydroxyl radicals (Draper and Crosby 1984). Since eutrophic water samples of the same type studied generate hydrogen peroxide levels 30 µM or lower, the rate of this reaction will be slower in natural surface 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°C (Wanner et al. 1989). Therefore, biodegradation of disulfoton in water is expected to be important, 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 accidental spill incident (Mossman et al. 1988); however, the removal of disulfoton by chemical processes was much slower than by biodegradation (Capel et al. 1988).

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, 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 (Bhaskahan et al. 1973). In flooded soil under anaerobic conditions, the reduction of

disulfoton to disulfoton sulfoxide or disulfoton sulfide was due to biological conversion (Tomizawa 1975). 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 (Capel 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 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, defined as the concentration of disulfoton remaining elevated or constant in soil, varied between 28 and >64 days (Belanger and Hamilton 1979; Clapp et al. 1976; Jury et al. 1987b; Kearney 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 metabolites isolated from disulfoton degradation in soil were the sulfoxide and sulfone (Chapman et al. 1994a, 1994b); minute amounts of oxons were found (Clapp et al. 1976; Greenhalgh 1978; Shaw 1975; 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).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to disulfoton depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of disulfoton in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on disulfoton levels monitored or estimated in the

environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-1 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-2.

Table 5-1. Lowest Limit of Detection for Disulfoton Based on Standards[a]

Media	Detection limit	Reference
Environmental media		
Wastewater	5.9 ng/L	Basheer et al. 2007
Surface water	0.0006 ng/L	Kurt-Karakus et al. 2011
Drinking water	0.3 µg/L	Edgell et al. 1991
Groundwater	1.9 ng/L	WQP 2021
Ambient air	5.7 pg/m^3	Kurt-Karakus et al. 2011
Sediment	≤0.1 mg/kg	Belisle and Swineford 1988
Food products and crops		
Soil, asparagus tissue	0.01 mg/kg	Szeto and Brown 1982
Cereal, maize, and wheat	0.55 µg/kg	Gonzalez-Curbelo et al. 2017
Strawberries	0.05 µg/g	Baldim et al. 2012
Rice, wheat, buckwheat, and dried beans	0.3 µg/kg	Aoki et al. 1975
Cow milk (disulfoton and five metabolites as total residue)	1 µg/kg	Bowman and Beroza 1969
Beverages	0.10 µg/L	dos Anjos and de Andrade 2014
Human serum		
Whole blood	0.90 ng/mL	Usui et al. 2012
Blood	0.01 µg/g	Musshoff et al. 2002
Urine	0.46 ng/mL	Usui et al. 2012

Table 5-2. Summary of Environmental Levels of Disulfoton

Media	Low	High	For more information
Outdoor air (pg/m^3)	<5.7	67.4	Table 5-3 or Section 5.5.1
Surface water (ng/L)	<2	3,300	Table 5-4 or Section 5.5.2
Ground water (ng/L)		<60	Section 5.5.2
Rain water (ng/L)	<1.2	<60	Section 5.5.2

Detections of disulfoton in air, water, and soil at NPL sites are summarized in Table 5-3.

Table 5-3. Disulfoton Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measures	NPL sites
Water (ppb)	NA	NA	NA	NA	NA
Soil (ppb)	430,000	383,000	17.5	7	4
Air (ppbv)	NA	NA	NA	NA	NA

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

No data were located measuring disulfoton in air after its cancellation in 2009 as the concentration in the United States is now expected to be lower compared to data from prior to 2009. In Egbert, Ontario where disulfoton was in use during the time of the study, disulfoton was detected in air at a mean concentration of 50.7 pg/m^3 (Hayward et al. 2010). Disulfoton concentrations in the air fell near or below quantitation limits during the winter, but were measured at much higher levels during the growing seasons between May and September (see Table 5-4) (Hayward et al. 2010). Disulfoton was not detected (detection limit 5.7 pg/m^3) in 11 passive air samples collected in 2004–2005 from five locations in the Great Lakes Region of Canada (Kurt-Karakus et al. 2011). Disulfoton was also not detected in 151 atmospheric samples collected April to September 1995 at seven locations across the Midwestern United States (Foreman et al. 2000). 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). Measured concentrations of disulfoton in air are presented in Table 5-4.

Table 5-4. Outdoor Air Monitoring Data for Disulfoton

Location	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Egbert, Ontario	Rural agricultural	March 2006–September 2007	27.5–67.4 pg/m^3	50.7 pg/m^3	Range and mean (arithmetic means of both active sampling techniques) is during growing periods (May–September)	Hayward et al. 2010
Ontario	Not specified	2004–2005	<5.7 pg/m^3			Kurt-Karakus et al. 2011
Mississippi, Iowa, Minnesota, Michigan	Urban and agricultural	1995 April–September	Not detected		Weekly samples (151 total); detection limit not reported	Foreman et al. 2000
10 U.S. locations[a]	Not specified	1980	≤4.7 ng/m^3	0.1 ng/m^3	1 out of 123 samples (0.8%) were positive for disulfoton	Carey and Kutz 1985; Kutz 1983; Kutz and Carey 1986

[a]Columbia, South Carolina; Lubbock, Houston, and Harlingen, Texas; Huntsville, Alabama; Pasadena and Fresno, California; Mississippi State, Mississippi; Helena, Montana; and Pekin, Illinois.

5.5.2 Water

Disulfoton was not reported above the lower quantification limit of 1.9–60 ng/L (ppt) in over 1,100 ambient surface water data points compiled for 2020–2021 from EPA STOrage and RETrieval (STORET) and National Water Information System (NWIS databases (WQP 2021). In a study of the Yakima River Basin, Washington, May 1999 through January 2000, disulfoton was detected in 4 of 98 river water samples (USGS 2002). The minimum concentration was <17 ng/L and the maximum concentration was estimated to be 3,300 ng/L. Estimated usage of disulfoton in Granger Drainage Basin, part of the Yakima River Basin, for 1999 was 6,100 pounds applied to asparagus (USGS 2002). Between 1998 and 2001, 30 lakes in Canada and the northeastern United States were sampled for current-use pesticides, including disulfoton, using a method with a much lower detection limit of 0.002 ng/L (Muir et al. 2004). Disulfoton was detected in lakes with agricultural inputs as well as remote lakes, with no distinct differences observed between agricultural input lakes and other lakes at mid-latitude. Disulfoton was detected in 40 of 164 surface water samples collected in 2003–2005 from 10 inland lakes located in Ontario, Canada at concentrations of <0.006–1.8 ng/L (Kurt-Karakus et al. 2011).

Disulfoton was not reported at or above the lower quantification limit of 60 ng/L (ppt) in over 600 groundwater data points compiled for 2020–2021 from EPA STORET and NWIS databases (WQP 2021). In a pesticide analysis study conducted from 2016 to 2018 of 54 shallow monitoring wells located in Nassau/Queens and Suffolk counties, Long Island, disulfoton was detected in 1 well (Fisher et al 2021). This well was located in a pesticide management area with mixed agriculture and horticulture crops; the concentration was not reported. In the past, 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) and in a 1985 survey of groundwater in the Nomini Creek Watershed in Virginia (range 0.39–2.87 µg/L) (Mostaghimi et al. 1993).

Disulfoton was not reported at or above the lower quantification limit of 60 ng/L (ppt) in 25 rainwater samples collected in Minnesota in 2020 from EPA STORET and NWIS databases (WQP 2021). Disulfoton was not detected (detection limit not reported) in 32 precipitation samples collected April to September 1995 at seven locations across the Midwestern United States (Coupe et al. 2000). Disulfoton was detected in 10 of 51 rainwater samples collected in 2003–2005 from the Great Lakes Region of Ontario, Canada at concentrations of <0.0012–3.8 ng/L (Kurt-Karakus et al. 2011). Between January 2000 and July 2001, disulfoton was detected, but not quantified, in rainwater in Roskilde, Denmark and in rainwater at concentrations up to 7 ng/L in Oure, Denmark, despite it being banned and not sold in the country. The sum deposition was calculated to be 0 ng/m/year in Roskilde and 1,169 ng/m/year in Oure (Asman et al. 2005). Surface water monitoring data for disulfoton are presented in Table 5-5.

5.5.3 Sediment and Soil

Only NPL data measured disulfoton in sediment and soils after 2009 and is reported in Table 5-2. All other located data are of samples taken prior to the cancellation of disulfoton and levels are expected to now be lower in the United States. 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). In the Salton Sea, a manmade lake in California designated by the state as an agricultural drainage reservoir, the concentration of disulfoton in sediment was less than the detection limit of 0.20 ng/g dry weight at all locations sampled in 2000 (Sapozhnikova et al. 2004). Concentrations were measured again in 2001 and disulfoton was found at less than the detection limit (0.20 ng/g dry weight) in four locations sampled and at 29.6 ng/g dry weight in a fifth location sampled where the concentration was previously below the detection limit (Sapozhnikova et al. 2004).

Table 5-5. Surface Water Monitoring Data for Disulfoton

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Turnbull, Wawanosh, Bells, Plastic, Opeongo, Wavy, Windy, Flack, Batchawana, Big Turkey Lakes	Ontario, Canada	2003–2005	<0.0006–1.8 ng/L	0.001	Disulfoton was detected in 24% of samples; detection limit: 0.0006 ng/L	Kurt-Karakus et al. 2011
Yakama River Basin: Moxee Drain; Granger Drain; Yakama River at Kiona	Washington	1999–2000	<17–3,300 ng/L	<17 ng/L	Disulfoton concentration at 90^{th} percentile: <17 ng/L	USGS 2002
C1, A, Ward Hunt, A-A, D-J, BK-Z Lakes	Arctic lakes in Canada and Northeastern United States	1998–2001	<0.002–0.06 ng/L	0.01 ng/L	Disulfoton was detected in one out of six lakes; detection limit: 0.002 ng/L	Muir et al. 2004
Mista, Merrick, Shipiskan, Wuchuska, Big Trout, Fourmont, and Minipi Lakes	Sub-Arctic lakes in Canada and Northeastern United States	1998–2001	<0.002–3.0 ng/L	1.2 ng/L	Disulfoton was detected in five out of seven lakes; detection limit: 0.002 ng/L	Muir et al. 2004
Nipigon, Paguchi, Eva, Thunder, Sandybeach, Dasserat, St. Jean, Britt Brook, Virgin, Opeongo, and Cromwell Lakes; Connery Pond, Moose Pond, and Bates Pond	Remote mid-latitude lakes in Canada and Northeastern United States	1998–2001	<0.002–4.9 ng/L	0.76 ng/L	Disulfoton was detected in 10 out of 11 lakes; detection limit: 0.002 ng/L	Muir et al. 2004
Simcoe, Seneca, and Cayuga Lakes	Agricultural input lakes in Canada and Northeastern United States	1998–2001	<0.002–0.44 ng/L	0.23 ng/L	Disulfoton was detected in two out of three lakes; detection limit: 0.002 ng/L	Muir et al. 2004

Table 5-5. Surface Water Monitoring Data for Disulfoton

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Grand River Basin, Saugeen River Basin, and Thames River Basin; Ontario, Canada	River surface water	January 1981–December 1985	Not detected	Not detected	Samples were collected year-round during storm runoff and base flow conditions; three to four samples were collected at the mouth of each river; detection limit: <0.1 µg/L	Frank and Logan 1988
Lake Huron (9 sites), North Channel (2 sites), Georgian Bay (5 sites), and Lake Superior (17 sites)	Upper Great Lakes surface water	Summer of 1974	Not detected	Not detected	Sampling stations were chosen based on proximity to major rivers, industrial plants, and municipal areas but were at least 1 km from shore as not to be immediately influenced by these source areas; 1 sample was taken at each station for a total of 33 samples; quantification limit: 0.003 µg/L	Glooschenko et al. 1976

Disulfoton was detected in sediment samples in Kafue Town (0.067 µg/g) and Kitwe (0.041 µg/g) in a study to determine the types of pesticides and herbicides in the Kafue River in Zambia (Syakalima et al. 2006). In 1974, disulfoton was detected at concentrations up to 227.8 ppb in nine bottom soil samples from tail water pits used to collect irrigation runoff from corn and sorghum fields in Haskell County, Kansas (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). Disulfoton concentrations measured in soil and sediments are presented in Table 5-6.

Table 5-6. Concentrations of Disulfoton in Soil and Sediment

Location/date	Concentration	Reference
Salton Sea, California sediment		Sapozhnikova et al. 2004
May 2000		
Middle sampling location 1	<0.20 ng/g dry weight (<0.20 µg/kg)	
Southern sampling location 1	<0.20 ng/g dry weight (<0.20 µg/kg)	
Northern sampling location 1	<0.20 ng/g dry weight (<0.20 µg/kg)	
May 2001		
Middle sampling location 1	29.6 ng/g dry weight	
Southern sampling location 2	<0.20 ng/g dry weight (<0.20 µg/kg)	
Southern sampling location 3	<0.20 ng/g dry weight (<0.20 µg/kg)	
Northern sampling location 1	<0.20 ng/g dry weight (<0.20 µg/kg)	
Northern sampling location 2	<0.20 ng/g dry weight (<0.20 µg/kg)	
Haskell County, Kansas		Kadoum and Mock 1978
1974		
Pit bottom soil from samples serving corn fields		
Median	11.4 µg/kg	
Mean	13.8 µg/kg	
Maximum	32.7 µg/kg	
Bottom soil from samples serving corn and sorghum fields		
Mean	11.0 µg/kg	
Bottom soil from samples serving sorghum fields		
Median	117.2 µg/kg	
Mean	117.2 µg/kg	
Maximum	227.8 µg/kg	

5.5.4 Other Media

Under the National Lake Fish Tissue Study, the EPA estimated the concentration of selected persistent, bio accumulative, and toxic chemical residues in fish tissue from 500 sampling locations in the United States (EPA 2009b). Disulfoton was not detected in any of the samples (detection limit 161 µg/kg) from years 2000–2003. Disulfoton concentrations were measured in fish tissues from the Salton Sea, a manmade lake designated by the state as an agricultural drainage reservoir in California (Sapozhnikova et al. 2004). Mean disulfoton concentrations and standard deviations were 20±17 ng/g in liver, 17±16 ng/g in gonads, 7±8 ng/g in muscle, and 7±4 ng/g in gills. Disulfoton was observed in all tissues from Tilapia and Corvina in elevated concentrations compared to other studies, as noted by Sapozhnikova et al. (2004), and disulfoton was one of the most abundant pesticides observed. In Zambia, disulfoton was detected in fish muscle at mean concentrations of 0.020 µg/g in Chingola, 0.46 µg/g in Kitwe, and 0.034 µg/g in Kafue National Park (Syakalima et al. 2006). Results from these studies are further summarized in Table 5-7.

Table 5-7. Concentrations of Disulfoton in Fish Tissues

Location	Date(s)	Species/ tissue	Mean concentration	Range	Number of Samples	Reference
Salton Sea, California	May 2001	Corvina species				
		Muscle	6.7 ng/g wet weight	0.5–23.7 ng/g wet weight	6	
		Liver	19.7 ng/g wet weight	8.5–54.6 ng/g wet weight	6	
		Gonads	16.5 ng/g wet weight	2.3–46.9 ng/g wet weight	6	
		Gills	6.7 ng/g wet weight	3.5–15.3 ng/g wet weight	6	
Salton Sea, California	May 2001	Tilapia species				Sapozhnikova et al. 2004
		Muscle	7.8 ng/g wet weight	1.8–17.6 ng/g wet weight	9	
		Liver	31.0 ng/g wet weight	4.6–80.3 ng/g wet weight	9	
		Gonads	29.3 ng/g wet weight	5.0–52.3 ng/g wet weight	9	
		Gills	12.2 ng/g wet weight	0.9–34.2 ng/g wet weight	9	

Table 5-7. Concentrations of Disulfoton in Fish Tissues

Location	Date(s)	Species/ tissue	Mean concentration	Range	Number of Samples	Reference
Kafue River in Chingola, Zambia	2003–2005 (March–November of each year)	*Serranochromis angusticeps* Muscle	0.020 µg/g	Not reported	10	Syakalima et al. 2006
Kafue River in Kitwe, Zambia	2003–2005 (March–November of each year)	*S. angusticeps* Muscle	0.046 µg/g	Not reported	10	Syakalima et al. 2006
Kafue River in Kafue National Park, Zambia	2003–2005 (March–November of each year)	*S. angusticeps* Muscle	0.034 µg/g	Not reported	10	Syakalima et al. 2006
500 sampling locations in lakes and reservoirs in the U.S. lower 48 states	2000–2003	Predator composites	0 µg/kg	Not applicable	486	EPA 2009b
		Bottom-dweller composites	0 µg/kg	Not applicable	395	

In 2009, the EPA cancelled disulfoton as a pesticide, and it is no longer used on crops in the United States (EPA 2009b). However, use as a pesticide may continue abroad. The FDA's Pesticide Monitoring Program for domestic and imported foods reports that disulfoton residues have not been detected in recent years (FDA 2017a, 2017b, 2018, 2019, 2021b). Previously, 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 detected disulfoton sulfone 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 (Luke et al. 1988). Disulfoton was not detected in various domestic food commodities by state regulatory monitoring activities during fiscal year 1988–1989 (Minyard and Roberts 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) (Schattenberg and Hsu 1992). In a 1993 study of pesticide residue contamination of processed infant formula, disulfoton was not detected (detection limit <0.02 µg/g [ppm]) in 32 milk-based and 25 soy-based infant formulas (Gelardi and Mountford 1993).

Disulfoton has been detected in beverages. Disulfoton was detected below the limit of quantification (2.37 µg/L) in two brand names of coconut water, but was not detected in another brand name of coconut water or natural coconut tested by dos Anjos and de Andrade (2014). In a study of 15 white wine samples, disulfoton was detected in two samples at 3.53 and 5.78 µg/L; it was not found in any of four rose wine samples tested (dos Anjos and de Andrade 2015).

5.6 GENERAL POPULATION EXPOSURE

Since disulfoton was cancelled by the EPA in 2009 (EPA 2010), the general population in the United States is not likely to be exposed to disulfoton, although remaining stock was permitted to be sold until 2011 or until stock ran out, and agricultural use in the United States was estimated as recent as 2016 (USGS 2021). Its use abroad may continue, but it is unknown if uses abroad may lead to exposure of the general population as there is insufficient information to confirm its use. Disulfoton has been detected in soils at multiple hazardous waste sites in the United States, indicating populations living near these hazardous waste sites may be at risk of disulfoton exposure.

Disulfoton has been very infrequently detected in ambient air and at very low concentrations (see Section 5.5.1). 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 5.5.2). This is consistent with observations that it occurs at very low concentrations and has only infrequently been detected in groundwater (Fisher et al 2021; WQP 2021). Therefore, general population exposure to disulfoton from consumption of drinking water is likely to be negligible.

In the past, disulfoton was detected in some foods (see Section 5.5.4). However, the FDA has not detected disulfoton in the U.S. food supply in recent years (FDA 2017a, 2017b, 2018, 2019, 2022). The USGS estimated that <0.02 to 0.18 pounds of disulfoton per square mile were used on vegetable and fruit crops in two U.S. states in 2016 (USGS 2021). Use of disulfoton has substantially decreased since 2000, and no use of disulfoton on U.S. agriculture was reported after 2016, suggesting that use has ceased and it is not likely to be present in food grown in the United States.

Toxicokinetic data show that disulfoton is readily and extensively absorbed by the gastrointestinal tract. The urinary metabolites of disulfoton are DEP, DETP, DEDPT, and DEPTh. 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. Using NHANES data from 1999 to 2008, Gillezeau et al. (2019) found that average urinary levels of organophosphate metabolites have decreased over time, but levels appear to have plateaued in recent years and some highly exposed individuals remain. NHANES data for organophosphate metabolites (from 2007–2008) showed specimens of urine collected contained detectable levels of DEP (detection limit of 0.37 µg/L) at a frequency of 31.40%, of DETP (detection limit of 0.56 µg/L) at a frequency of 41.12%, and of DEDTP (detection limit of 0.39 µg/L) at a frequency of 0.63% (Gillezeau et al. 2019). More recently, analysis of urine from NHANES for 2011–2012 showed detection (detection limit 0.1 ng/mL) of DETP at a frequency of 71% and DEDPT at a frequency of 5.4% of those tested (CDC 2019). However, as previously stated, these metabolites are not specific for disulfoton and can be found after exposure to other organophosphates.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

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. NIOSH (2018) recommends that the exposure level to skin not exceed 0.1 mg/m^3 for a 10-hour time-weighted average workday. In a study conducted by Storm et al. (2000), toxicity and other relevant data for disulfoton and 29 other organophosphate pesticides were evaluated to determine inhalation occupational exposure limits (OELs) and to support development of a risk assessment strategy for organophosphates in general. Specifically, the study assessed the value of relative potency analysis and the predictability of inhalation OELs by acute toxicity measures and by repeated oral exposure at the NOAEL. The OELs were derived by use of the endpoint of prevention of red blood cell AChE inhibition and by use of a weight-of-evidence risk assessment approach. When red blood cell AChE activity decreased to 70% (30% inhibition) of an individuals' baseline, it was concluded that the potential for overexposure to organophosphates exists and adverse effects may occur. It was advised that in cases where organophosphate workers experiencing this degree of red blood cell AChE inhibition occurs, actions be taken to prevent exposure until red blood cell AChE activity returns to the individuals' baseline. Suggested OEL values for the entire group of organophosphates evaluated ranged from 0.002 to 2 mg/m^3. The suggested OEL for disulfoton specifically was 0.01 mg/m^3. The suggested OEL for disulfoton was less than the current threshold limit value (TLV) of 0.1 mg/m^3 (Storm et al. 2000).

Older occupational studies showed that when Di-Syston, containing 75% disulfoton on a pumice granule, was applied 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).

Children may receive higher disulfoton doses from ingestion or dermal exposures if they play in contaminated soils near hazardous waste sites or in soils where a disulfoton pesticide was applied; however, this is less likely as disulfoton pesticides were cancelled in the United States in 2009. Previously allowed pesticides containing disulfoton may still be in circulation.

CHAPTER 6. 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 NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of disulfoton.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk 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.

6.1 INFORMATION ON HEALTH EFFECTS

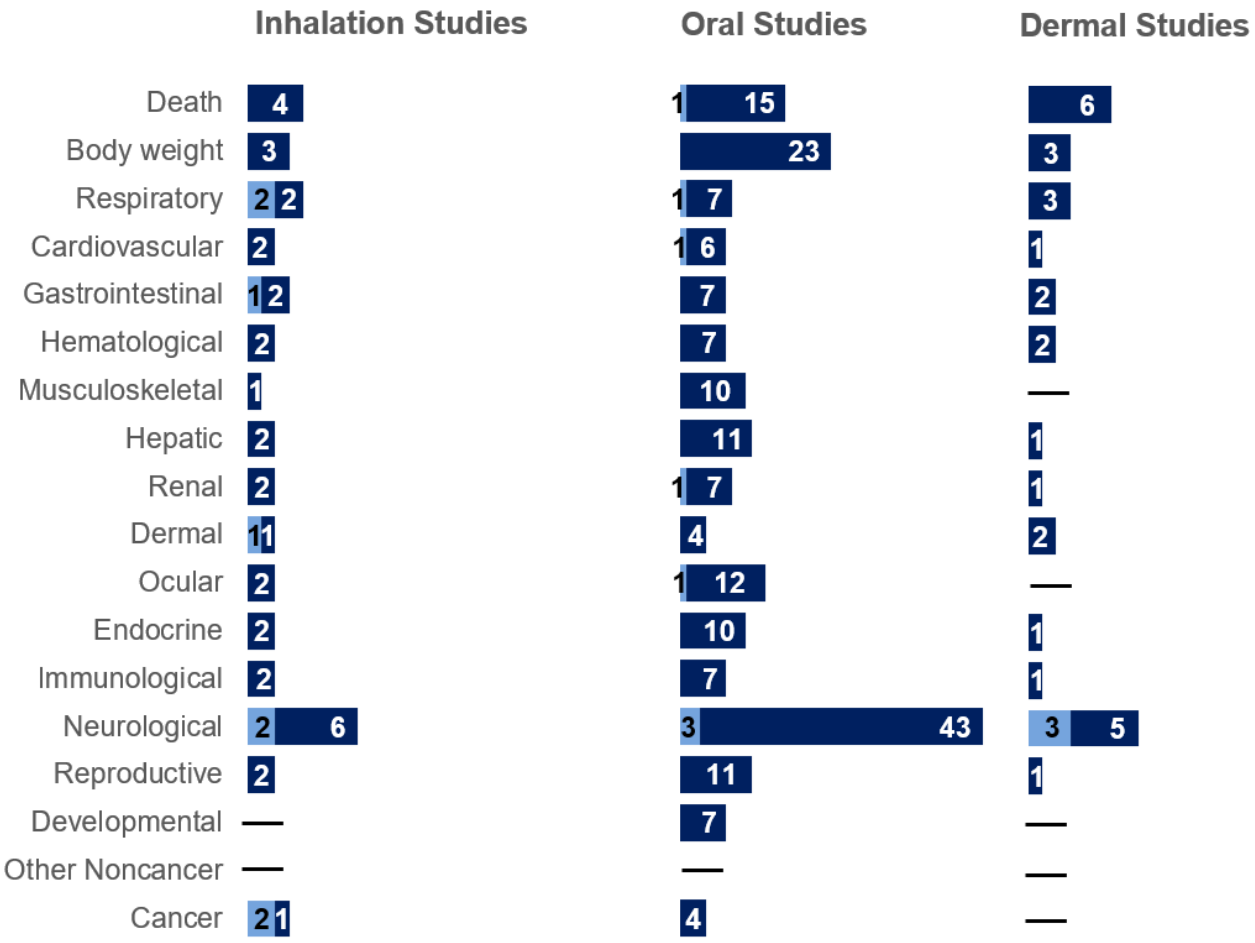
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to disulfoton that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of disulfoton. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

As Figure 6-1 shows, information on the health effects in humans exposed to disulfoton is limited and is primarily based on oral ingestion. In these studies, pesticide containing disulfoton was accidentally or purposefully ingested by an individual and primarily the neurological system was affected. A limited number of other endpoints were examined; death occurred in one case. Inhalation and dermal exposure human studies were primarily on workers occupationally exposed to disulfoton and various other chemicals. Neurological effects were primarily recorded in these studies, in addition to respiratory effects. There is a substantial number of studies on health effects in laboratory animals following oral exposure to disulfoton, followed by inhalation exposure studies, with a more limited number of dermal studies. Among all animal studies, neurological health effects were most often examined, followed by death and respiratory effects. Body weight effects were commonly reported in animal studies. Additionally, there were many studies that examined multiple endpoints including hepatic, endocrine, and hematological effects.

Figure 6-1. Summary of Existing Health Effects Studies on Disulfoton By Route and Endpoint*

Potential neurological and body weight effects were the most studied endpoints, in addition to mortality

The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Many studies examined more than one endpoint.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. The acute-duration oral and inhalation animal databases were adequate for the derivation of acute-duration oral and acute-duration inhalation MRL values. Neurological effects, primarily cholinesterase inhibition, are the most sensitive endpoint in both acute animal and human studies. In oral animal studies, significant cholinesterase inhibition and developmental effects have been reported after low-dose exposure (EPA 2007; Klaus 2006a, 2006b; Lamb and Hixson 1983; Schwab and Murphy 1981; Sheets 1993a; Su et al. 1971). Acute inhalation animal studies have primarily observed signs of cholinesterase inhibition (Doull 1957; Thyssen 1978). Acute-duration human studies are limited to cases of accidental or intentional ingestion of disulfoton and are consistent in neurological findings (Futagami et al. 1995; Hattori et al. 1982; Yashiki et al. 1990).

Intermediate-Duration MRLs. The intermediate-duration database was adequate for the derivation of oral and inhalation MRL values. Human studies of intermediate-duration are very limited; however, one human inhalation study observed cholinesterase depression (Wolfe et al. 1978) and supports findings in laboratory animals. Neurological, reproductive, and developmental oral toxicity have been studied in animals using low doses and have consistently observed cholinesterase inhibition (Hixson and Hathaway 1986; Hayes 1985; Hoffman and Welscher 1975; Klaus 2006c; Schwab and Murphy 1981; Sheets 1993b, 2005). Intermediate inhalation studies have examined a wide range of endpoints including neurological and respiratory (Shiotsuka 1989; Thyssen 1980).

Chronic-Duration MRLs. The chronic-inhalation database lacks toxicity data for both humans and animals. The chronic-duration oral database was considered adequate for the derivation of a chronic-oral MRL value. However, additional studies would be useful to establish sensitive doses for chronic-inhalation exposure since neurologic effects are established as a sensitive endpoint in acute and intermediate inhalation animal studies. It is likely that cholinesterase inhibition would be observed at low chronic inhalation doses, as neurological effects have been seen in one occupational study in workers exposed to a mixture of chemicals including disulfoton (Gómez-Arroyo et al. 2000). Additionally,

chronic-duration inhalation of disulfoton is possible for pesticide applicators/sprayers and pesticide manufacturing workers.

Health Effects.

Ocular. Additional oral-exposure disulfoton studies would be useful to establish dose-response relationships between disulfoton exposure and ocular effects. Myopia has been observed both in young children and in dogs, suggesting ocular toxicity as a sensitive endpoint to disulfoton exposure (Ishikawa and Miyata 1980; Suzuki and Ishikawa 1974). Depressed cornea cholinesterase has been observed in dogs at chronic low doses, 0.015 mg/kg/day (Jones et al. 1999), comparable to low doses where neurological effects were seen. However, no effects have been observed following ophthalmological and histological examinations in rats given 0.18 mg/kg/day chronically (Hayes 1985). Cystic degeneration of the Harderian gland and increased incidence of corneal neovascularization were seen in rats fed higher doses (Hayes 1985).

Immunological. Immune function tests would be useful to understand whether disulfoton is an immunotoxicant. 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 neuroimmune 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 and Welscher 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.

Neurological. Disulfoton is established as a neurotoxicant following inhalation, oral, or dermal exposure in humans and animals. Further studies examining sex differences in humans to the neurotoxic effects of disulfoton would elucidate findings in animals; female animals appear to be more sensitive than male animals (Klaus 2006a; Sheets 1993a, 1993b; Thyssen 1978, 1980). Gómez-Arroyo et al. (2000) reported clinical signs of headache and nausea in female workers but not in male workers; however, females were likely exposed for about 10 years, while males were likely exposed for 1.5 years. Disulfoton can cause red blood cell AChE depression in humans after inhalation exposure without other overt neurological effects (Wolfe et al. 1978). Overt neurological effects have been observed in humans after oral exposure to disulfoton including muscle tremors, increased salivation, and mortality (Futagami et al. 1995; Hattori et al. 1982; Yashiki et al. 1990). Weakness and fatigue (Savage et al. 1971) and depressed red blood cell AChE activity (Wolfe et al. 1978) were also observed in humans after dermal exposure to disulfoton.

Reproductive. More studies on reproductive function following inhalation and dermal routes to disulfoton are needed to establish if the male and/or female reproductive systems are affected. Disulfoton did not affect male fertility in mice in an oral dominant lethal study (Herbold 1980). Slightly reduced litter sizes in third generations were found in a 3-generation oral reproductive study in rats (Taylor 1965a). When males and females were exposed orally to disulfoton for 60 days prior to and/or during mating, two of five females failed to become pregnant (Ryan et al. 1970). A more extensive multigenerational feeding study in rats found decreased reproductive performance of males and females; decreased maternal weight of F0 and F1 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 F2b 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 and Welscher 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).

Developmental. Additional developmental studies involving inhalation or dermal exposure of animals to disulfoton might indicate whether fetotoxic effects are route-dependent. 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 red blood cell AChE depression and increased incidences of incomplete ossified parietal bones and sternebrae were observed in fetuses from rats fed disulfoton on GDs 6–15. However, the incomplete ossification was considered to be growth retardation due to maternal toxicity rather than specific fetotoxic effects (Lamb and Hixson 1983). Bone and soft tissue malformations were not observed. Female pups exposed *in utero* and during lactation had a delayed vaginal opening, a developmental milestone (Sheets 2005). Additionally, male and female pups showed significant red blood cell and brain AChE activity inhibition. In Klaus (2006c), significant red blood cell AChE inhibition was seen in offspring of dams exposed in feed during gestation. Effects in fetuses or pups, such as depressed brain AChE activity (Hixson and Hathaway 1986; Ryan et al. 1970), renal and hepatic pathology, and juvenile hypoplasia of testes (Taylor 1965a) were also observed in oral 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).

Epidemiology and Human Dosimetry Studies. Epidemiological studies are limited. An increase in the incidence of myopia was observed in young children thought to be orally exposed to disulfoton in combination with other organophosphates (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 AChE 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. Nausea and headaches were reported among pesticide applicators exposed to disulfoton and other pesticides simultaneously (Gómez-Arroyo et al. 2000). These studies are limited because it is not clear whether inhalation or dermal exposure contributed the most to the observed effects. One study derived an OEL for disulfoton based on decreased red blood cell AChE activity (Storm et al. 2000); however, further studies are needed to establish cause/effect relationships and for future monitoring of individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect. Disulfoton and its metabolites have been detected in the blood and 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). 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). However, some studies support use of urinary metabolites as nonspecific markers of occupational exposure to disulfoton (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 are an 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, and metabolites used to detect disulfoton exposure are not specific to the substance and are used to detect exposure to other organophosphate pesticides. Urinary metabolites are generally eliminated within 2 weeks after the last exposure and are not usually detected beyond this period; therefore, they are better indicators of recent or current 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 more useful and specific biomarkers.

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 serum cholinesterase and/or red blood cell AChE are usually reliable biomarkers of effect from exposure in humans (Storm et al. 2000, Wolfe et al. 1978; Yashiki et al. 1990), and inhibition of red blood cell AChE can indicate the possibility of more serious neurological effects. In rats, AChE levels in circulating lymphocytes correlated better with brain AChE activity than did red blood cell AChE activities during exposure, but not during recovery after exposure (Fitzgerald and Costa 1993). Thus, lymphocyte AChE activity may be a useful biomarker of effect during exposure, but red blood cell AChE likely remains the better sentinel for brain AChE activity after exposure has ceased. However, other organophosphates and carbamates can cause similar neurological effects. Although animal studies have demonstrated that brain AChE 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 effect in humans. There does not appear to be a need for additional studies on 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 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 there is 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, kidneys, fat, skin, muscles, 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). Data regarding toxicokinetics of disulfoton following dermal exposure are limited to a single study in rats, which reported a concentration-dependent skin absorption of approximately 3–40%; the predominant route of excretion was via the urine (Zenzdian 2000). 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.

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 were unknown, disulfoton was readily absorbed by two men who intentionally ingested disulfoton, 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, kidneys, adipose tissues, muscles, 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 animal studies 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.

Children's Susceptibility. One human study of young children showed myopia possibly resulting from increased exposure to disulfoton in combination with other organophosphates (Ishikawa and Miyata 1980). Animal studies suggest developmental effects occur following acute- and intermediate-duration oral exposure. Data needs related to both prenatal and childhood exposures, and developmental effects expressed whether prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above. Further data from animal studies would help investigate possible differences in susceptibility in human children, especially those living near hazardous waste sites. Toxicity of disulfoton metabolites has been established; however, it is unknown if these metabolites cross the placental barrier or can be excreted in breast milk. Animal studies suggesting developmental toxicity do not provide sufficient information on whether metabolism in the fetus or child differs from adults.

Physical and Chemical Properties. As seen in Tables 4-1 and 4-2, the relevant physical and chemical properties of disulfoton are known (Bowman and Sans 1983; EPA 1978; Lide 2005; Muir et al. 2004; Meylan and Howard 1993; NIOSH 2017, 2018; NLM 2021; Sanborn et al. 1977; Wauchope et al. 2002), and predicting the environmental fate and transport of disulfoton based on K_{ow}, K_{oc}, and Henry's law constant is possible.

Production, Import/Export, Use, Release, and Disposal. The most recent data indicated that the United States exported disulfoton from 2001 to 2003. However, disulfoton was cancelled for use as a pesticide in 2009 by the EPA. Therefore, recent data on its production, import/export volumes, release, and disposal are not expected.

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) and studies have attempted to quantify atmospheric transport (Asman et al. 2005; Muir et al. 2004), there is a discrepancy between observed transport and estimated long-range transport using models; 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 removal from water to sediment would be helpful (Wanner et al. 1989). There is conflicting evidence in the literature regarding disulfoton's mobility in soil. 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 Chapter 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 is not considered to be bioaccumulative in fish and has not been reported in fish. 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). However, disulfoton has not been detected in food in the United States in recent years, and is not likely to be found at levels significant to humans; therefore, there is not a data need for further information on its food chain bioaccumulation at this time.

Exposure Levels in Environmental Media. Disulfoton was cancelled for use in the United States in 2009; therefore, levels of disulfoton in environmental media are expected to be low, and the potential for human exposure is low. Ingestion of contaminated drinking water, inhalation exposure, and dermal exposure to disulfoton is expected to be low for the general population. In addition, disulfoton residues in foods have not been detected in recent years (FDA 2017a, 2017b, 2018, 2019). However, continued monitoring of disulfoton at hazardous waste sites may be helpful for further assessing the potential for human exposure.

Exposure Levels in Humans. No data on disulfoton (parent compound) levels in humans are available. Disulfoton metabolites have been measured in the blood and urine of humans exposed to disulfoton in clinical and occupational studies (Brokopp et al. 1981; Futagami et al. 1995; Yashiki et al. 1990). NHANES has also reported human urinary metabolite levels for diethyl phosphate (DEP), diethyl thiophosphate (DETP), and diethyl dithiophosphate (DEDTP); however, the presence of these metabolites cannot be attributed to disulfoton exposure alone since many other organophosphates have these same metabolites (Gillezeau et al. 2019).

Exposures of Children. No data on disulfoton levels in children are available. Adults and children are expected to have similar metabolic pathways of disulfoton. However, it is unknown if disulfoton or its metabolites cross the placental barrier. There is insufficient information on the movement of disulfoton into the developing fetus or into breast milk. Children may receive higher disulfoton doses from ingestion or dermal exposures if they play in soil contaminated with disulfoton; however, this is less likely as disulfoton pesticides were cancelled in the United States in 2009.

6.3 ONGOING STUDIES

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2021) database.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding disulfoton in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for disulfoton.

In 2009, disulfoton was cancelled for use in pesticide products in the United States (EPA 2010). Disulfoton is on the list of chemicals appearing in the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA); the Comprehensive Environmental Response, Compensation and Liability Act; and Section 112(r) of the Clean Air Act (EPA 2019a). Disulfoton is considered an extremely hazardous substance (EHS) under 40 CFR part 355, and facilities with disulfoton in quantities greater than or equal to 500 pounds must report (EPA 2018c). Disulfoton was not on the EPCRA Section 313 Chemical List for Reporting Year 2018, and was not reported to TRI (EPA 2019b). Under CERCLA, disulfoton is subject to reporting to the National Response Center in quantities greater than or equal to one pound (EPA 2018d).

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 2018b).

Table 7-1. Regulations and Guidelines Applicable to Disulfoton

Agency	Description	Information	Reference
	Air		
EPA	RfC	No data	IRIS 2002
WHO	Air quality guidelines	No data	WHO 2012

Table 7-1. Regulations and Guidelines Applicable to Disulfoton

Agency	Description	Information	Reference
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	1-Day health advisory (10-kg child)		
	10-Day health advisory (10-kg child)		
	DWEL		
	Lifetime health advisory		
	10^{-4} Cancer risk		
	National primary drinking water regulations	Not listed	EPA 2009a
	RfD	$4x10^{-5}$ mg/kg/day[a]	IRIS 2002
	Chronic dietary PAD	$1.3x10^{-4}$ mg/kg/day	EPA 2006
WHO	Drinking water quality guidelines	No data	WHO 2017
FDA	Substances added to food	Not listed	FDA 2021a
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2021
EPA	Carcinogenicity classification	Group E[b]	EPA 2021
IARC	Carcinogenicity classification	No data	IARC 2021
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	No data	OSHA 2021a, 2021b, 2022
NIOSH	REL (up to 10-hour TWA)	0.1 mg/m^3 [c]	NIOSH 2018
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2018e
DOE	PACs-air		DOE 2018a
	PAC-1[d]	0.18 mg/m^3	
	PAC-2[d]	2 mg/m^3	
	PAC-3[d]	8.8 mg/m^3	
	Miscellaneous Federal Guidelines		
EPA	Cancelled for use in pesticides	Cancelled	EPA 2010

[a]Based on the LOAEL of 0.04 mg/kg/day for decreased acetylcholinesterase activity in rat pups in a multigenerational feeding study in rats (Hixson and Hathaway 1986).
[b]Group E: evidence of noncarcinogenicity for humans.
[c]With skin designation, indicating the potential for dermal absorption.
[d]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

AEGL = acute exposure guideline levels; HHS = Department of Health and Human Services; DOE = Department of Energy; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PAD = Population Adjusted Dose; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Disulfoton
CAS Numbers: 298-04-4
Date: August 2022
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: The intermediate-duration inhalation MRL of 0.0006 mg/m^3 (0.6 µg/m^3) is adopted as the acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: A limited number of acute-duration inhalation animal studies were available evaluating the toxicity of disulfoton. These studies primarily evaluated neurological effects (Doull 1957; DuBois and Kinoshita 1971; Thyssen 1978). These studies also evaluated mortality (Doull 1957; Thyssen 1978), and one study evaluated body weight (Thyssen 1978) following acute inhalation exposure to disulfoton.

The available data suggest that neurological toxicity, particularly cholinesterase inhibition, is the most sensitive endpoint following acute-duration inhalation exposure to disulfoton. In human studies, mild depression of red blood cell AChE activity was reported in workers exposed by the inhalation and dermal routes (Wolfe et al. 1978). In an epidemiological study, headaches and nausea were reported by workers exposed to various pesticides including disulfoton (Gómez-Arroyo et al. 2000). Thyssen (1978) evaluated the acute-duration inhalation toxicity of disulfoton in three separate experiments using different durations: a single 1-hour exposure, single 4-hour exposure, or daily 4-hour exposure for 5 days. Exposure concentrations for male rats exposed to single 1-hour exposures were 133, 196, 256, 322, and 660 mg/m^3; for female rats, the exposure concentrations were 27, 33, 46, 58, 80, and 133 mg/m^3. For male rats exposed to single 4-hour exposures, exposure concentrations were 34, 48, 51, 64, 78, and 96 mg/m^3; for female rats, the exposure concentrations were 3.4, 5, 7, 10, 13, and 20 mg/m^3. For both male and female rats in the five day 4-hour exposure group, the exposure concentrations were 0, 0.5, 1.8, and 9.8 mg/m^3. These doses were adjusted for intermittent exposure, and are presented with relevant neurological NOAELs and LOAELs in Table A-1. Red blood cell and plasma AChE activity was measured from blood samples taken prior to exposure, and after the 1st, 3rd, and 5th days of exposure, and 72 hours after exposure termination (Thyssen 1978). At the lowest dose tested, 0.5 mg/m^3 ($NOAEL_{ADJ}$ 0.083 mg/m^3), no effects were seen in either sex. Significant inhibition of red blood cell AChE activity and unspecified behavioral disorder symptoms of poisoning were observed at 1.8 mg/m^3 ($LOAEL_{ADJ}$ 0.3 mg/m^3) in females. These results are consistent with plasma AChE observations, a more sensitive, but less toxicologically significant, indicator. Similar effects were observed in rats or mice exposed to higher concentrations for shorter durations (Doull 1957; Thyssen 1978). The lowest $LOAEL_{ADJ}$ for an acute-duration study is 1.8 mg/m^3 ($LOAEL_{ADJ}$ 0.3 mg/m^3). DuBois and Kinoshita (1971) identified a $NOAEL_{ADJ}$ of 0.029 mg/kg/day for brain AChE inhibition; however, higher doses were not tested to identify a LOAEL within this study.

Table A-1. Summary of Relevant Neurological NOAEL and LOAEL Values of Acute-Duration Inhalation Exposure to Disulfoton

Species (sex)	Frequency/ duration	NOAEL ($NOAEL_{ADJ}$) (mg/m^3)	LOAEL ($LOAEL_{ADJ}$) (mg/m^3)	Effect	Reference
Wistar rats (F)	4 hours/day 5 days	0.5 (0.083)	1.8 (0.3)	26% depression in red blood cell AChE activity; unspecified behavioral disorders, sluggishness, drowsiness	Thyssen 1978
Wistar rats (F)	4 hours		3.4 (0.5667)	Sluggishness, failure to groom, typical signs of cholinesterase inhibition not otherwise described	Thyssen 1978
Wistar rats (F)	1 hour		27 (4.5)	sluggishness, failure to groom, typical signs of cholinesterase inhibition not otherwise described	Thyssen 1978
Holtzman rats F)	1 hour/ day 5 days	0.7 (0.029)		No significant inhibition of brain AChE	DuBois and Kinoshita 1971
Holtzman rats (F)	1 hour/ day 10 days	0.7 (0.029)		No significant inhibition of brain AChE	DuBois and Kinoshita 1971

AChE = acetylcholinesterase; F = females; LOAEL = lowest-observed-adverse-effect level; $LOAEL_{ADJ}$ = LOAEL adjusted for intermittent exposure; dose was multiplied to represent a continuous 24-hour, 7-day exposure; NOAEL = no-observed-adverse-effect level; $NOAEL_{ADJ}$ = NOAEL adjusted for intermittent exposure; dose was multiplied to represent a continuous 24-hour, 7-day exposure

Among reliable animal study results, the $NOAEL_{ADJ}$ of 0.083 mg/m^3 for red blood cell AChE depression in female rats exposed via inhalation chamber for 4 hours/day for 5 days represents the most sensitive adverse effects from acute-duration inhalation exposure to disulfoton (Thyssen 1978). Using a $NOAEL_{ADJ}$ of 0.083 mg/m^3 as the point of departure (POD) and a total uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability) would result in an acute-duration inhalation MRL of 0.003 mg/m^3. However, this value is not proposed for the acute-duration MRL. ATSDR has instead opted to adopt the intermediate-duration inhalation MRL of 0.0006 mg/m^3 for the acute-duration MRL. The reasons for this include that Thyssen (1978) used red blood cell AChE as a surrogate for brain AChE. This is common practice when sufficient data on the latter are not available. However, the intermediate-duration inhalation MRL POD is based on brain AChE depression, a stronger indicator of the neurological effects of disulfoton. Additionally, the intermediate-duration MRL study exposed rats to 15 total exposures of disulfoton over a 21-day period and is not substantially longer than the threshold for acute-duration of 14 days. Therefore, the intermediate-duration inhalation MRL of 0.0006 mg/m^3 for disulfoton is adopted as the acute-duration inhalation MRL because it is protective of acute-duration inhalation exposure to disulfoton.

Agency Contact (Chemical Managers): Melanie Buser, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Disulfoton
CAS Numbers: 298-04-4
Date: August 2022
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.0006 mg/m^3 (0.6 µg/m^3) or 0.00006 ppm (0.06 ppb)
Critical Effect: Decreased brain AChE activity
Reference: Thyssen 1980
Point of Departure: NOAEL of 0.1 mg/m^3 ($NOAEL_{HEC}$ of 0.018 mg/m^3)
Uncertainty Factor: 30
LSE Graph Key: 11
Species: Rats

MRL Summary: An intermediate-duration inhalation MRL of 0.0006 mg/m^3 (0.6 µg/m^3) was derived for disulfoton based on inhibition of brain AChE activity in female rats exposed 6 hours/day for 5 days/week for 3 weeks (Thyssen 1980). The MRL is based on a NOAEL of 0.1 mg/m^3, which was adjusted for intermittent exposure, converted to a human equivalent concentration (HEC) of 0.018 mg/m^3, and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Toxicity following intermediate inhalation exposure to disulfoton has been examined across multiple endpoints, primarily neurological (Shiotsuka 1988, 1989; Thyssen 1980) and respiratory (Shiotsuka 1989; Thyssen 1980). Other effects of intermediate-inhalation exposure to disulfoton in rats include inflammatory changes in the respiratory tract associated with bone marrow changes at 20.5 mg/m^3, 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). The LOAELs and NOAELs (adjusted for intermittent exposure) considered for MRL derivation are presented in Table A-2.

Table A-2. Summary of Relevant Intermediate-Duration Inhalation NOAEL and LOAEL Values for Disulfoton

Species (sex)	Frequency/ duration	NOAEL ($NOAEL_{ADJ}$) (mg/m^3)	LOAEL ($LOAEL_{ADJ}$) (mg/m^3)	Effect	Reference
Neurological effects					
Wistar TNO/W 74 albino rats (M)	6 hours/day 5 days/week 3 weeks	0.02 (0.0036)		No depression of red blood cell AChE	Thyssen 1980
Wistar TNO/W 74 albino rats (F)	6 hours/day 5 days/week 3 weeks	0.02 (0.0036)	3.1 (0.55)	3/20 dead	Thyssen 1980

Table A-2. Summary of Relevant Intermediate-Duration Inhalation NOAEL and LOAEL Values for Disulfoton

Species (sex)	Frequency/ duration	NOAEL ($NOAEL_{ADJ}$) (mg/m^3)	LOAEL ($LOAEL_{ADJ}$) (mg/m^3)	Effect	Reference
Wistar TNO/W 74 albino rats (M)	6 hours/day 5 days/week 3 weeks	0.5 (0.089)	3.7 (0.66)	24% inhibition of red blood cell AChE, 48% inhibition of brain AChE	Thyssen 1980
Wistar TNO/W 74 albino rats (F)	6 hours/day 5 days/week 3 weeks	0.1 (0.018)	0.5 (0.089)	30% inhibition of brain AChE, lethargy by day 15	Thyssen 1980
Fischer-344 rats (M)	6 hour/day, 5 days/week, 13 weeks	0.16 (0.029)	1.4 (0.25)	22–34% inhibition of red blood cell AChE, 28–29% inhibition of brain AChE	Shiotsuka 1989
Respiratory effects					
Fischer-344 rats (M, F)	6 hour/day, 5 days/week, 13 weeks	0.16 (0.029)	1.4 (0.25)	50% increased incidence of inflammation of the nasal turbinates	Shiotsuka 1989

AChE = acetylcholinesterase; F = females; LOAEL = lowest-observed-adverse-effect level; $LOAEL_{ADJ}$ = LOAEL adjusted for intermittent exposure; dose was multiplied to represent a continuous 24-hour, 7-day exposure; M = males; NOAEL = no-observed-adverse-effect level; $NOAEL_{ADJ}$ = NOAEL adjusted for intermittent exposure; dose was multiplied to represent a continuous 24-hour, 7-day exposure

The available data suggest that neurological toxicity, particularly AChE inhibition, is the most sensitive endpoint following intermediate-duration inhalation exposure to disulfoton. In a 13-week study, inhibition of red blood cell and brain AChE 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). In male and female rats exposed to disulfoton 6 hours/day for a total of 15 days, inhibition of brain AChE was observed at 0.5 mg/m^3 (20–30%) accompanied with lethargy, and at 3.7 mg/m^3 (48–58%) accompanied with muscle tremors, convulsions, increased salivation, and difficulty breathing (Thyssen 1980). The NOAEL of this study was 0.1 mg/m^3. Thyssen (1980) conducted an additional study using a lower dose to establish a NOAEL of 0.02 mg/m^3 ($NOAEL_{ADJ}$=0.0036 mg/m^3) for no change in red blood cell AChE activity in male and female rats (Thyssen 1980). However, the cholinesterase activity of the control group in the second study differed from the primary study.

Selection of the Principal Study: Thyssen (1980) was selected as the principal study. The study conducted two studies evaluating AChE activity in rats, which demonstrated that AChE activity in female rats is sensitive to disulfoton exposure. The first study in Thyssen (1980) identified a NOAEL of 0.1 mg/m^3 and a LOAEL of 0.5 mg/m^3 for brain AChE inhibition, lethargy, and behavioral disturbances in female rats. There was not a clear dose-response relationship with either red blood cell or brain AChE inhibition in either sex (see Table A-3).While the second study in Thyssen (1980) identified a lower NOAEL than the first study, there was insufficient support to the toxicological significance of the findings. Only one other dose (3.1 mg/m^3) was tested in females to determine lethality. Additionally, the brain AChE activity of both sexes in the control group of the second study was 21–28% higher than that of the first study control group. Therefore, results from both studies could not be combined. AChE activity levels from the first Thyssen (1980) study are presented in Table A-3.

Table A-3. Percent Acetylcholinesterase Inhibition in Wistar Rats Exposed to Disulfoton via Inhalation for 15 Days

	Males (n=10/dose)		Females (n=10/dose)	
Dose (mg/m^3)	Brain u/g (% inhibition)	RBC u/mL (% inhibition)	Brain u/g (% inhibition)	RBC u/mL (% inhibition)
0 (control)	1.01	2.60	1.23	2.64
0.1	0.97 (4%)	2.61 (-0.4%)	1.28 (-4%)	2.50 (5%)
0.5	1.21 (-20%)	2.67 (-3%)	0.86 (30%)	2.64 (0%)
3.7	0.53 (48%)	1.98 (24%)	0.53 (57%)	1.79 (32%)

RBC = red blood cell

Source: Thyssen 1980

Summary of the Principal Study:

Thyssen JT. 1980. Disulfoton (S 276). The active ingredient of di-syston subacute inhalation study on rats. Wuppertal-Elberfeld, Germany: Bayer AG, Institute of Toxicology. 83-T-80. Bayer Report No. 9065. Mobay ACD Report No. 69361.

Thyssen (1980) conducted two separate 3-week experiments. In the first experiment, male and female Wistar TNO/W 74 albino rats were exposed to concentrations of 0, 0.1, 0.5, or 3.7 mg/m^3 in an inhalation chamber for 6 hours/day, 5 days/week for 3 weeks, totaling 15 exposures. There were 10 rats/sex/group. Endpoints monitored included body weight, behavior, blood chemistry, clinical signs, histopathology, organ weight, and urinalysis. Red blood cell and plasma AChE activity were measured via blood test prior to the start of the experiment and after the 5^{th}, 10^{th}, and 15^{th} exposures. Brain AChE was measured after the final exposure. The same methods were applied in the second experiment where 10 male and 10 female rats were exposed to 0 or 0.02 mg/m^3. Only 20 female rats were exposed to 3.1 mg/m^3 in order to determine if severe symptoms and mortality seen among females in the first study could be reproduced.

Rats showed concentration-related increased severity of AChE inhibition and cholinergic signs of toxicity. At the lowest exposure level of 0.1 mg/m^3, no significant changes in AChE activity were seen in either sex; however, lethargy was observed. At 0.5 mg/m^3, lethargy and failure to groom were observed during the 2^{nd} and 3^{rd} weeks; only significant inhibition of brain AChE was observed in female rats at this dose. At 3.7 mg/m^3, significant brain and red blood cell AChE inhibition was observed in both sexes, and signs of cholinergic toxicity included muscle tremors, convulsions, and death. A second experiment, using a different control group, was conducted to determine a lower NOAEL of AChE inhibition in rats. No AChE effects or signs of cholinergic toxicity were seen in either sex at 0.02 mg/m^3. At the exposure level of 3.1 mg/m^3 in females, the signs of cholinergic toxicity and mortality seen at 3.7 mg/m^3 in the first experiment were confirmed.

Selection of the Point of Departure for the MRL: Thyssen (1980) identified a NOAEL of 0.1 mg/m^3 ($NOAEL_{ADJ}$=0.018 mg/m^3) for AChE inhibition in female rats exposed to disulfoton for 6 hours/day, 5 days/week for 3 weeks. This is supported by the LOAEL of 0.5 mg/m^3 for brain AChE inhibition and lethargy seen in the same study. The available data in Thyssen (1980) are not amenable to benchmark dose (BMD) modeling as there is not a clear dose-response relationship with AChE inhibition. Therefore, the $NOAEL_{ADJ}$ 0.018 mg/m^3 was converted to a HEC.

Adjustment for Intermittent Exposure: Given that the exposure in Thyssen (1980) study was intermittent (6 hours/day for 5 days/week), the NOAEL was adjusted for intermittent exposure:

$$NOAEL_{ADJ} = 0.1\ mg/m^3\ \times \frac{6\ hrs}{24\ hrs} \times \frac{5\ days}{7\ days} = 0.01785\ mg/m^3$$

Conversion to Human Equivalent Concentration: The $NOAEL_{ADJ}$ was then adjusted to a HEC using the regional gas dose ratio ($RGDR_{ER}$) of 1.0. The methods for derivation of inhalation reference concentrations and application of inhalation dosimetry (EPA 1994) recommends the use of the default RGDR value of 1.0 when the blood:gas partition coefficient ($H_{b/g}$) is unknown.

$$NOAEL_{HEC} = NOAEL_{ADJ} \times RGDR_{ER}$$

$$NOAEL_{HEC} = 0.01785\ mg/m^3 \times 1.0 = 0.01785\ mg/m^3$$

Uncertainty Factor: The $NOAEL_{HEC,ADJ}$ was divided by a total uncertainty factor of 30:

- 3 for extrapolation from animals to humans after dosimetric adjustment
- 10 for human variability

$$MRL = \frac{NOAEL_{HEC}}{UFs} = \frac{0.01785\ mg/m^3}{30}$$

$$= 0.000595\ mg/m^3\ (Rounded\ to\ 0.0006\ mg/m^3)$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Wolfe et al. (1978) estimated mean disulfoton concentrations of 0.06–0.633 mg/m^3 in air for pesticide-fertilizer mixing operations workers who were exposed for 9 weeks. Among workers with the highest exposures, a 23% inhibition of red blood cell AChE activity was observed with no additional clinical signs. These effects in humans were observed at concentrations 300-fold higher than the MRL.

Agency Contact (Chemical Managers): Melanie Buser, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Disulfoton
CAS Numbers: 298-04-4
Date: August 2022
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL due to the lack of toxicity studies for any endpoint. No studies have been found on animal toxicity, and human studies have severe limitations.

Rationale for Not Deriving an MRL: Studies examining toxicity for chronic-duration inhalation of disulfoton are limited to observational human studies that do not provide sufficient toxicity data. Human studies have examined respiratory (Gómez-Arroyo et al. 2000; Hoppin et al. 2017), gastrointestinal, dermal, and neurological effects (Gómez-Arroyo et al. 2000). These studies lacked exposure data, and could not attribute findings solely to disulfoton exposure, as other pesticides were present.

Agency Contact (Chemical Managers): Melanie Buser, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Disulfoton
CAS Numbers: 298-04-4
Date: August 2022
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.0003 mg/kg/day (0.3 µg/kg/day)
Critical Effect: Decreased red blood cell AChE activity
Reference: Klaus 2006b
Point of Departure: $BMDL_{20RD}$ of 0.028 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 11
Species: Rats

MRL Summary: An acute-duration oral MRL of 0.0003 mg/kg/day (0.3 µg/kg/day) was derived for disulfoton based on decreased red blood cell AChE activity in female Wistar rat pups treated with disulfoton for 11 days daily by gavage beginning on PND 11 (Klaus 2006b). The MRL is based on a 20% relative deviation BMDL ($BMDL_{20RD}$) of 0.028 mg/kg/day, which was divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Numerous studies have evaluated the oral toxicity of disulfoton following acute-duration exposure across a wide range of endpoints. Neurotoxicity (Costa and Murphy 1983a; Costa et al. 1984, 1986; Crawford and Anderson 1974; EPA 2007; Fitzgerald and Costa 1992, 1993; Klaus 2006a, 2006b; Lamb and Hixson 1983; Matsuda et al. 2000; Mihail 1978; Schwab and Murphy 1981; Schwab et al. 1981, 1983; Sheets 1993a; Su et al. 1971; Yagle and Costa 1996), respiratory effects (Mihail 1978), hepatotoxicity (Fawade and Pawar 1978, 1980, 1983), endocrine effects (Brzezinski 1969; Wysocka-Paruszewska 1970, 1971), and developmental toxicity (Lamb and Hixson 1983) have been examined. The LOAELs for these studies range from 0.06 to 5 mg/kg/day; select LOAELs and NOAELs are presented in Table A-4.

Table A-4. Summary of Relevant NOAEL and LOAEL Values Considered for Derivation of an Acute-Duration Oral MRL for Disulfoton

Species (sex)	Frequency/ duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
CD rats (F)	GDs 6–15	0.1	0.3	41% inhibition of red blood cell AChE activity in dams	Lamb and Hixson 1983
Holtzman rats (F)	Daily 7 days	0.05	0.25	50% inhibition of brain AChE activity	Su et al. 1971
CD rats (M, F)	Once	0.24		Non-significant cholinesterase activity inhibition	Sheets 1993a
Wistar rats (F)	Once	0.125	0.25	22% inhibition of red blood cell AChE activity	EPA 2007

Table A-4. Summary of Relevant NOAEL and LOAEL Values Considered for Derivation of an Acute-Duration Oral MRL for Disulfoton

Species (sex)	Frequency/ duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Wistar rats (F)	Daily 11 days	0.125	0.25	28% inhibition of red blood cell AChE activity and 33% inhibition of brain AChE	Klaus 2006a
Wistar rats (M)	Daily 11 days	0.25	0.5	38% inhibition of red blood cell AChE activity and 39% inhibition of brain AChE	Klaus 2006a
Developmental effects					
Wistar rats (pups, F)	Daily 11 days		0.06	29% inhibition of red blood cell AChE activity in pups	Klaus 2006b
Wistar rats (pups, M)	Daily 11 days	0.06	0.125	23% inhibition of brain AChE activity in pups	Klaus 2006b
Endocrine effects					
Wistar rats (F)	Once	0.26	0.52	Increased excretion of 4-hydroxy-3-methoxy-mandelic acid in urine (27.8–32%)	Wysocka-Paruszewska 1971

AChE = acetylcholinesterase; F = females; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level

The available data suggest that neurotoxicity, specifically AChE inhibition, is the most sensitive endpoint following acute-duration oral exposure to disulfoton. The lowest LOAEL identified for acute-oral exposure to disulfoton is 0.06 mg/kg/day for 29% inhibition of red blood cell AChE activity in female pups, and inhibition increased with dose (Klaus 2006b). In the same study, the NOAEL for male pups was 0.06 mg/kg/day accompanied by a LOAEL of 0.125 mg/kg/day. These findings are supported by the derived NOAEL of 0.05 mg/kg/day in female rats exposed to disulfoton daily for 7 days (Su et al. 1971). All other NOAELs for neurological effects were >0.1 mg/kg/day. Other effects of disulfoton exposure in acute-duration 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; Wysocka-Paruszewska 1970, 1971), and lipid peroxidation in the liver (Fawade and Pawar 1978, 1980, 1983). None of these effects occurred at doses lower than the acute-duration oral NOAELs for neurological effects.

Selection of the Principal Study: The Klaus (2006b) study in rat pups was selected as the principal study for deriving an acute-duration oral MRL for disulfoton because it identified the lowest LOAEL of 0.06 mg/kg/day for inhibited red blood cell AChE activity in female pups. A clear dose-response relationship is seen with disulfoton exposure and red blood cell AChE inhibition in female pups (see Table A-5). Female rats were chosen as they were more sensitive to the effects of disulfoton exposure and this higher sensitivity has been seen in several neurotoxicity studies. Male rat pups had a NOAEL of 0.06 mg/kg/day and a higher LOAEL of 0.125 mg/kg/day; therefore, the lower LOAEL in female rats was selected. Su et al. (1971) identified a derived NOAEL of 0.05 mg/kg/day, which is essentially equivalent to the lowest LOAEL; however, the next tested dose of 0.25 mg/kg/day is greater than the lowest LOAEL in Klaus (2006b).

Table A-5. Red Blood Cell and Brain AChE Activity in Male and Female Rat Pups Exposed to Disulfoton Daily via Gavage for 11 Consecutive Days

	Males (n=10/dose)				Females (n=10/dose)			
Dose (mg/kg)	Mean AChE activity (kU/L)± SD	% Inhibition	Mean brain AChE activity (U/g)±SD	% Inhibition	Mean AChE activity (kU/L)±SD	% Inhibition	Mean brain AChE activity (U/g)±SD	% Inhibition
0 (control)	1.99±0.36	–	9.47±0.34	–	2.02±0.19	–	9.50±0.37	–
0.06	2.14±0.20	-7.5%	8.81±0.41	7%	1.44±0.29	29%	8.64±0.24	9%
0.125	1.61±0.30	19%	7.29±0.46	23%	1.22±0.29	40%	7.22±0.33	24%
0.25	1.15±0.25	42%	5.58±0.20	41%	0.96±0.21	52%	5.36±0.27	44%

AChE = acetylcholinesterase; SD = standard deviation

Source: Klaus 2006b

Summary of the Principal Study:

Klaus AM. 2006b. Data evaluation record: Study type: Non-guideline: Cholinesterase inhibition in rat pups. MRID 46637102. Scientific data reviews: EPA series 361: Subject: 032501: 6(a)(2) data on disulfoton cholinesterase activity after acute dosing in young adults and 11-day old pups at peak time [MRID# 46589701-46589704], in maternal and fetal rats [MRID# 46635901], and in young adults dose 11 days [MRID# 46637101] and 11-day old pups dosed for 11 days [MRID# 46637101]. Washington, DC: U.S. Environmental Protection Agency.

Wistar rat pups were administered 0, 0.06, 0.125, or 0.250 mg/kg/day of disulfoton daily by gavage for 11 consecutive days, beginning on PND 11. Groups contained 10 pups/sex/dose. Pups were observed for clinical signs of toxicity and mortality. Plasma, red blood cell, and brain AChE activity in all rat pups was determined 1 hour after the final dose was administered. Plasma and red blood cell AChE activity were measured in blood following decapitation, and brain AChE was measured by whole-brain analysis.

Four pups (sex unreported) were found dead between PNDs 12 and 18, prior to scheduled sacrifice. However, all pups originated from the same litter and were in different dose groups; therefore, mortality was not likely treatment-related. No clinical signs of toxicity were observed at any dose. In male rat pups, brain and plasma AChE activity decreased with dose. Brain AChE inhibition was significant, with 23–41% inhibition at ≥0.125 mg/kg/day. Red blood cell AChE activity in male pups increased slightly by 7% in the 0.06 mg/kg/day dose group compared to controls, but then decreased dose-dependently by 19% at 0.125 mg/kg/day and 42% at 0.25 mg/kg/day. In female pups, red blood cell and brain AChE decreased dose dependently beginning at the lowest dose. Significant inhibition for red blood cell AChE began at 0.06 mg/kg/day (29% inhibition) and at 0.125 mg/kg/day for brain AChE (24% inhibition). These findings were supported by the dose-related inhibition of plasma AChE. No clinical signs of cholinesterase inhibition were observed in any of the dose groups.

Selection of the Point of Departure for the MRL: The $BMDL_{20RD}$ of 0.028 mg/kg/day for red blood cell AChE activity inhibition in female rat pups was selected as the basis for the oral acute MRL. Red blood

cell and brain AChE activity data for male and female rats were fit to all continuous models in EPA's Benchmark Dose Software (BMDS; version 3.1.2) using a benchmark response (BMR) of 20% relative deviation. The data did not require an adjustment for intermittent exposure. Red blood cell AChE activity data for male rat pups was not selected, as female pups appeared more sensitive to the effects of disulfoton exposure. The data were fit to all available continuous models in EPA's BMDS (version 3.1.2) using a BMR of 20% relative deviation. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Brain AChE activity data of both sexes did not produce adequate model fit. Using these criteria on red blood cell AChE data, the Exponential 4, Exponential 5, and Hill models provided adequate model fit. Generally, the number of parameters in a model cannot exceed the number of dose groups in the data. For the Hill model specifically, the number of dose groups should exceed the number of parameters by at least one in order to be selected as the POD due to the instability in the model. The Hill model uses five parameters and the Klaus (2006b) study only has four dose levels; therefore, the Hill model was not chosen for the POD. Among the two remaining models providing adequate fit to the data, the Akaike Information Criterion (AIC), BMD, and BMDL values were the same. Therefore, the model with the lower number of parameters (least complex) was selected. Table A-6 presents BMD_{20RD}/$BMDL_{20RD}$ values considered for MRL derivation. Therefore the frequentist, restricted Exponential 4 model (Figure A-1) for red blood cell AChE activity in female rat pups was selected for the POD for MRL derivation as it was the least complex.

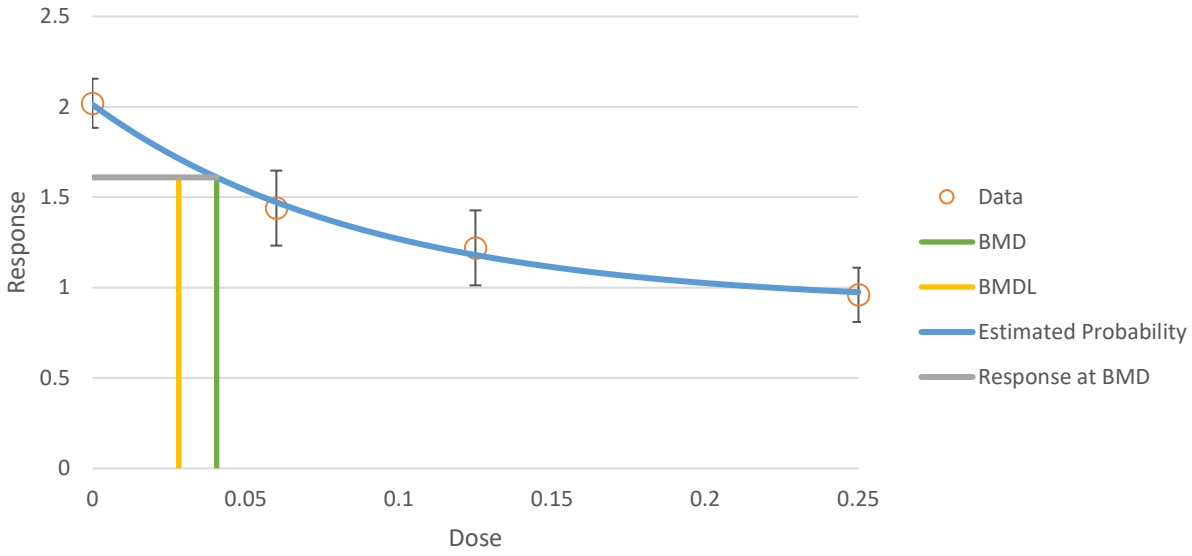
Table A-6. Results from BMD Analysis of Red Blood Cell AChE Activity in Female Wistar Rat Pups Administered Daily via Gavage for 11 Consecutive Days to Disulfoton

					Scaled residuals[c]	
Model	BMD_{20RD}[a] (mg/kg/day)	$BMDL_{20RD}$[a] (mg/kg/day)	p-Value[b]	AIC	Dose below BMD	Dose above BMD
Exponential 2	0.069	0.057	0.026	11.42	-1.68	1.29
Exponential 3	0.069	0.057	0.026	11.42	-1.68	1.29
Exponential 4[d]	**0.041**	**0.028**	**0.47**	**6.65**	**-0.43**	**0.10**
Exponential 5	0.041	0.028	0.47	6.65	-0.43	0.10
Hill	0.037	0.022	0.67	6.32	-0.22	0.03
Polynomial Degree 3	0.094	0.081	0.001	17.21	-1.44	2.10
Polynomial Degree 2	0.094	0.081	0.001	17.21	-1.44	2.10
Power	0.094	0.081	0.001	17.21	-1.44	2.10
Linear	0.094	0.081	0.001	17.21	-1.44	2.10

[a]BMDLs <10 times the lowest non-zero dose and their corresponding BMDs are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Selected model. The Exponential 4, Exponential 5, and Hill models provided adequate fit to the data. The Hill model was excluded as the number of model parameters exceeded the number of dose groups. Among the remaining models, the BMDL for the model with lowest number of parameters was selected (Exponential 4).

AChE = acetylcholine; AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{20RD}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{20RD}$ = dose associated with 20% relative deviation)

Figure A-1. Predicted (Frequentist Exponential Degree 4 Model with Constant Variance and 20% Relative Deviation) and Observed Red Blood Cell Acetylcholinesterase Activity in Female Rats



Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The $BMDL_{20RD}$ is divided by a total uncertainty factor of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

$$MRL = \frac{BMDL_{20RD}}{UFs} = \frac{0.028\ mg/kg/day}{10 \times 10}$$

$$= 0.00028\ mg/kg/day\ (Rounded\ to\ 0.0003\ mg/kg/day)$$

Agency Contact (Chemical Managers): Melanie Buser, MPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Disulfoton
CAS Numbers: 298-04-4
Date: August 2022
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.00009 mg/kg/day (0.09 µg/kg/day)
Critical Effect: Decreased brain AChE activity in offspring
Reference: Hixson and Hathaway 1986
Point of Departure: NOAEL of 0.009 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 42
Species: Rats

MRL Summary: An intermediate-duration oral MRL of 0.00009 mg/kg/day (0.09 µg/kg/day) was derived for disulfoton based on decreased brain AChE activity in F1a pups in a multi-generation feeding study in rats (Hixson and Hathaway 1986). The MRL is based on a NOAEL of 0.009 mg/kg/day, which was divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Numerous studies have examined the neurological (Christenson and Wahle 1993; Hayes 1985; Klaus 2006c; Sheets 1993b, 2005), developmental (Hixson and Hathaway 1986; Klaus 2006c; Ryan et al. 1970; Sheets 2005; Taylor 1965a), and reproductive (Hixson and Hathaway 1986; Ryan et al. 1970) toxicity of disulfoton following intermediate-duration oral exposure. The LOAELs for studies examining these endpoints range from 0.03 to 21.7 mg/kg/day. Select LOAELs from these studies are presented in Table A-7.

Table A-7. Summary of Relevant Neurological NOAEL and LOAEL Values Considered for Derivation of an Intermediate-Duration Oral MRL for Disulfoton

Species (sex)	Frequency/ duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Developmental effects					
Sprague-Dawley rats (M, F)	F0: 15 weeks premating; F1b: 13 weeks premating and through pregnancy	0.009	0.03	24–32% inhibition of brain AChE activity in F1a pups	Hixson and Hathaway 1986
Wistar rats (NS)	Maternal exposure on GD 0 through 20	0.042	0.168	20% inhibition of red blood cell AChE inhibition in fetal rats	Klaus 2006c

Table A-7. Summary of Relevant Neurological NOAEL and LOAEL Values Considered for Derivation of an Intermediate-Duration Oral MRL for Disulfoton

Species (sex)	Frequency/ duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
Fischer 344 rats (F)	Daily for 3–6 months		0.06	14–22% inhibition of red blood cell AChE	Hayes 1985
Wistar rats (pregnant F)	Continuous on GDs 0–20	0.042	0.168	44% inhibition red blood cell AChE activity and 32% inhibition of brain AChE activity	Klaus 2006c
Fischer 344 rats (F)	6 months *ad libitum*	0.03	0.07	22–29% inhibition in red blood cell AChE activity	Christenson and Wahle 1993
Reproductive effects					
Rats (M, F)	F0: 15 weeks premating; F1b: 13 weeks premating and through pregnancy	0.009	0.03	Decreased live births in F2b generation, decreased litter weights through gestation	Hixson and Hathaway 1986

AChE = acetylcholinesterase; F = females; LOAEL = lowest-observed-adverse-effect level; M = males; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level

The available data suggest that neurotoxicity, especially AChE inhibition, is the most sensitive endpoint following intermediate-duration oral exposure to disulfoton. Numerous intermediate-duration oral studies in rats, mice, and dogs have found significantly depressed brain or other tissue cholinesterase activities (Clark and Pearson 1973; Hayes 1985; Hoffman and Welscher 1975; Klaus 2006c; Klotzsche 1972; Rivett et al. 1972; Robinson et al. 1978; Ryan et al. 1970; Schwab and Murphy 1981; Sheets 1993b, 2005; Stavinoha et al. 1969; Vaughn et al. 1958). Additionally, signs of cholinergic toxicity were seen in rats including tremors and muscle fasciculations (Hixson and Hathaway 1986; Sheets 1993b) in addition to increased permeability of the central nervous system and increased exploratory behavior (Clark and Stavinoha 1971; Clark et al. 1971). Developmental and reproductive studies in animals reported depression of brain or red blood cell AChE activity in the offspring of rats and reduced litter sizes or failure to produce litters at doses of 0.03–0.5 mg/kg/day (Hixson and Hathaway 1986; Klaus 2006c; Ryan et al. 1970; Taylor 1965a). In addition, cloudy swelling or fatty livers, mild nephropathy, and juvenile hypoplasia of the testes occurred in F3 litters (Taylor 1965a) in fetal rats (Lamb and Hixson 1983). At the lowest LOAEL of 0.03 mg/kg/day, brain AChE activity was inhibited 24–32% in the F1a pups, and litter counts and litter weights were decreased in F2b litters (Hixson and Hathaway 1986). At the SLOAEL of 0.09 mg/kg/day in the same study, effects included tremors in the F0 females during the production of the F1 generation, decreased reproductive performance, decreased maternal F0 and F1 weight during gestation and lactation, decreased litter counts and viability and lactation indices, and increased stillbirth.

Selection of the Principal Study: Both the Hixson and Hathaway (1986) and Klaus (2006c) studies were considered for MRL derivation. Hixson and Hathaway (1986) evaluated developmental neurotoxicity in a multi-generation rat study and observed that mean brain AChE activity of F1 pups was dose-dependent with maternal exposure to disulfoton. This study identified the lowest LOAEL of 0.03 mg/kg/day for brain AChE inhibition, and corresponding NOAEL of 0.009 mg/kg/day. The Klaus (2006c) study also evaluated neurological and developmental toxicity in dams and offspring and demonstrated a dose-

response relationship of red blood cell AChE activity and disulfoton exposure. While these data were amenable to dose-response modeling, the resulting $BMDL_{20RD}$ was higher than the lowest LOAEL identified in Hixson and Hathaway (1986); therefore, the latter study was selected for MRL derivation. Mean brain AChE activity of F1a pups from Hixson and Hathaway (1986) is presented in Table A-8.

Table A-8. Mean Brain AChE Activity in F1a Pups in a Multi-Generation Intermediate-Duration Exposure Study

	Male pups (n=10/dose)		Female pups (n=10/dose)	
Dose (mg/kg/day)	Mean±standard deviation (IU/g)	% Inhibition	Mean±standard deviation (IU/g)	% Inhibition
0 (control)	11.9±0.7	–	12.3±0.9	–
0.009	12.0±0.6	-1	12.1±1.2	2
0.03	9.0±0.6	24	8.4±1.0	32
0.09	5.9±1.9	50	5.0±1.2	59

Source: Hixson and Hathaway 1986

Summary of the Principal Study:

Hixson EJ; Hathaway TR. 1986. Effect of disulfoton (Di-syston) on reproduction in rats. Mobay Chemical Corporation, Study Number 82-671-02.

Male and female Sprague-Dawley rats were orally administered disulfoton in feed for 15 weeks at daily doses of either 0, 0.009, 0.03, or 0.09 mg/kg/day; 26 rats/sex/dose all formed the F0 generation. Following the exposure period, 26 female rats and 13 males were mated to produce F1a litters. After 1 month, F0 rats were mated again to produce F1b litters. Pups from the F1b litters were randomly selected, 26 rats/sex/dose except the highest dose where only 22 females were available, and placed into generation F1. F1 rats were given treated feed for 13 weeks at the same doses as F0 rats. They were then mated to produce F2a litters. After 1 month, F1 rats were mated again to produce F2b pups. Toxicological signs were recorded daily and body weight and feed consumption were measured weekly prior to mating. Upon birth, the number of live and stillborn births were recorded. Litter observations (counts, weight, and viability) were recorded at birth and on days 1, 4, 7, 14 and 21. All animals were sacrificed for gross necropsy, and from each generation 10 rats/sex/dose were selected for additional tissue collection for histopathology. One hemisphere of the brain of 10 F1a pups/sex/dose was assayed to measure brain AChE activity.

Signs of AChE inhibition were only seen in F0 adults at the highest dose level, including differences in behavior, appearance, and tremor during gestation and lactation, primarily in dams. F1 rats at the highest dose showed significant decreases in body weights (6–11%) during the pre-mating feeding period and continued through gestation and lactation for F1 dams. At the highest dose level, reproductive performance and litter observations were adversely affected. Effects included decreases in sperm-positive mated F0 and F1 females (an indicator of male reproductive performance), decreased F1 maternal weight during gestation and lactation (including F0 dams), and increased stillbirths. At 0.03 mg/kg/day, F2b litters showed adverse effects including a 25% decrease in live births, and decreased litter weights through the 21-day gestation period. F1a litters did not show similar effects at this level, but upon examination, significantly decreased brain AChE activity (>24% inhibition) was noted in both sexes and was further inhibited in pups at the highest dose (50–59% inhibition).

Selection of the Point of Departure for the MRL: The NOAEL of 0.009 mg/kg/day for brain AChE inhibition in F1a pups in a multi-generation disulfoton exposure study was selected as the basis of the MRL. This NOAEL is also protective against reproductive effects, as demonstrated in Table A-7. These data were fit to all continuous models in EPA's BMDS (version 3.1.2) using a BMR of 20% relative deviation. For all model tests, the BMDS recommendation was "Questionable," indicating that none of the models provided an adequate fit for the data. The goodness-of-fit p-values were either <0.1 or the goodness-of-fit test could not be calculated. Therefore, the POD was defined as the NOAEL of 0.009 mg/kg/day.

Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The NOAEL is divided by a total uncertainty factor of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

$$MRL = \frac{NOAEL}{UFs} = \frac{0.009\ mg/kg/day}{10 \times 10} = 0.00009\ mg/kg/day$$

Agency Contact (Chemical Managers): Melanie Buser, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Disulfoton
CAS Numbers: 298-04-4
Date: August 2022
Profile Status: Final
Route: Oral
Duration: Chronic
MRL: 0.00006 mg/kg/day (0.06 µg/kg/day)
Critical Effect: Decreased red blood cell AChE activity
Reference: Hayes 1985
Point of Departure: LOAEL of 0.06 mg/kg/day
Uncertainty Factor: 1,000
LSE Graph Key: 62
Species: Rats

MRL Summary: A chronic-duration oral MRL of 0.00006 mg/kg/day (0.06 µg/kg/day) was derived for disulfoton based on red blood cell AChE inhibition in female rats exposed to disulfoton in the diet for 2 years (Hayes 1985). The MRL is based on a LOAEL of 0.06 mg/kg/day, which was divided by a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Disulfoton toxicity from chronic-duration exposure to disulfoton has been examined for various endpoints, most notably for the neurological (Carpy et al. 1975; Hayes 1983, 1985; Hoffman and Welscher 1975; Jones et al. 1999) and ocular (Hayes 1985; Ishikawa and Miyata 1980; Jones et al. 1999) endpoints. The LOAELs for studies range from 0.015 to 2.13 mg/kg/day. Select LOAELs are presented in Table A-9.

Table A-9. Summary of Relevant Neurological NOAEL and LOAEL Values Considered for Derivation of a Chronic-Duration Oral MRL for Disulfoton

Species (sex)	Frequency/ duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological					
F-344 rats (M)	Daily 104–106 weeks	0.05	0.18	Depressed red blood cell and brain AChE, optic nerve degeneration	Hayes 1985
F-344 rats (F)	Daily 104–106 weeks		0.06	24% inhibition of red blood cell AChE after 53 weeks of exposure	Hayes 1985
Sprague-Dawley rats (M)	Daily 1.5–2 years	0.05	0.06	26–37% inhibition of brain AChE	Carpy et al. 1975
Sprague-Dawley rats (F)	Daily 1.5–2 years	0.09	0.1	21% inhibition of brain AChE	Carpy et al. 1975
Beagle dogs (F)	Daily 12 months	0.013	0.09	22% inhibition of brain AChE	Jones et al. 1999

Table A-9. Summary of Relevant Neurological NOAEL and LOAEL Values Considered for Derivation of a Chronic-Duration Oral MRL for Disulfoton

Species (sex)	Frequency/ duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Beagle dogs (M, F)	Daily 2 years	0.03	0.14	46–53% inhibition of red blood cell AChE; 34.4% inhibition of brain AChE in males	Hoffman and Welscher 1975
Ocular					
Beagle dogs (M)	Daily 12 months		0.015	33% inhibition of cornea cholinesterase	Jones et al. 1999
F-344 rats (F)	Daily 104–106 weeks	0.06	0.21	cystic degeneration of Harderian gland	Hayes 1985

AChE = acetylcholinesterase; F = female; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level

Brain and red blood cell AChE inhibition appears to be the primary critical effect following chronic-duration oral exposure to disulfoton. As presented in Table A-9, inhibition of brain and red blood cell AChE was found in rats given 0.06 mg/kg/day, but not in rats given 0.05 mg/kg/day, of disulfoton in the diet for 1.5–2 years (Carpy et al. 1975; Hayes 1985). The same effect was seen 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). In a 1-year feeding study in dogs given 0.09 mg/kg/day, brain AChE was inhibited by 22% but no significant inhibition was noted at 0.013 mg/kg/day (Jones et al. 1999). This is consistent with another 1-year feeding study in dogs where red blood cell and plasma AChE 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 and Welscher 1975).

Ocular effects (degeneration of ciliary muscles cells, myopia, and astigmatism) were seen in dogs at 0.63 mg/kg/day (Ishikawa and Miyata 1980), cystic degeneration of the Harderian gland at 0.21 mg/kg/day, and corneal neovascularization at 0.75 mg/kg/day in rats (Hayes 1985). No ocular effects were seen at 0.06 mg/kg/day (Hayes 1985). However, female dogs treated with 0.015 mg/kg/day in the diet for 1 year had a 33% decrease of corneal cholinesterase activity, but no effects were seen in male dogs given 0.013 mg/kg/day (Jones et al. 1999). 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. 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.

Selection of the Principal Study: Although NOAEL values of 0.03 mg/kg/day (Hoffman and Welscher 1975) and 0.01 mg/kg/day (Jones et al. 1999) were found in dogs, the associated LOAELs, 0.14 and 0.09 mg/kg/day, respectively, are higher than the lowest LOAEL of 0.06 mg/kg/day for neurological effects in rats (Carpy et al. 1975; Hayes 1985). While Carpy et al. (1975) found a NOAEL and corresponding LOAEL for brain AChE inhibition, the study reported high mortality among controls, as mortality was higher in control females than in any of the female exposure groups. Additionally, the dose for the lowest exposure group, 0.5 ppm was changed to 5 ppm after 80 weeks to purposefully produce an adverse effect. In Hayes (1985), a NOAEL of 0.05 mg/kg/day was found for male rats, which is similar

to the LOAEL of 0.06 mg/kg/day for female rats in the same study. Use of the LOAEL, instead of the NOAEL, results in a more protective MRL given the lower dose at which the effects were observed. Since neurological effects are a critical endpoint for disulfoton in both animals and humans, the Agency opted to select the study that would result in the most health-protective MRL, which is Hayes (1985). Table A-10 presents the dose-response relationship of red blood cell AChE activity and disulfoton in female rats over 53, 79, and 105 weeks, in Hayes (1985). Hayes (1985) was selected as the principal study for the development of a chronic-duration oral MRL.

Table A-10. Red Blood Cell AChE Activity in Female Rats in an Oral Chronic-Duration Study

	53 weeks (n=60)		79 weeks (n=60)		105 weeks (n=60)	
Dose (mg/kg/day)	Mean activity (IU/ml)	Inhibition (%)	Mean activity (IU/ml)	Inhibition (%)	Mean activity (IU/ml)	Inhibition (%)
0 (control)	1.55	–	1.50	–	1.48	–
0.06	1.18	23.9	1.21	19.3	1.31	11.5
0.21	0.44	71.6	0.35	76.6	0.63	57.4
1.02	0.31	80.0	0.27	82.0	0.36	75.7

Source: Hayes 1985

Summary of the Principal Study:

Hayes RH 1985. Chronic feeding/oncogenicity study of technical disulfoton (Di-Syston) with rats. Mobay Chemical Corporation, Study Number 82-271-01.

Male and female Fischer-344 rats were fed disulfoton in the diet for 2 years at nominal concentrations of 0, 1, 4, or 16 ppm with 60 rats/sex/dietary level, resulting in mean concentrations of 0, 0.87, 3.6, and 14 ppm, respectively. Using gas chromatographic analysis, mean effective dose concentrations of 0.8, 3.3, and 13 ppm were calculated. Based on body weight and food consumption data supplied by the study investigators, these concentrations were equivalent to 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. Rats were observed for toxic effects, tumors, mortality, feed consumption, body weight, blood chemistry, hematology, urinalysis, organ weight, gross necropsy, and histopathology. Plasma and red blood cell AChE activities were analyzed at study initiation, and at months 3, 6, 12, 18, and 24 of the study. Brain AChE was analyzed from blood at the orbital plexus at study termination.

At the highest dose for females, a high mortality of 40% was observed. At the same dose level in females, effects among multiple endpoints were observed including acanthosis, hyperkeratosis, ulcer of the skin, chronic inflammation of the forestomach, and mucosal hyperplasia. Additionally, an 11–19% decrease in body weight, splenic lymphoid follicle depletion, skeletal muscle atrophy, corneal neovascularization, uterine cystic hyperplasia, and lung inflammation were seen at 1.02 mg/kg/day. Similar effects were observed in male rats at the highest dose level of 0.75 mg/kg/day, including decreases in body weight, skin ulceration, and corneal neovascularization, in addition to pancreatic atrophy, plasma cell hyperplasia in the mandibular lymph nodes, and eye inflammation. Depressed brain and red blood cell AChE activities were the most sensitive endpoint observed in the study. At 0.06 mg/kg/day, red blood cell AChE activity was inhibited by 24%, and at 0.18 mg/kg/day red blood cell and brain AChE activities were inhibited by 46–67% and 53%, respectively, in addition to optic nerve degeneration. These effects were also seen at higher doses in both sexes.

Selection of the Point of Departure for the MRL: The LOAEL of 0.06 mg/kg/day for red blood cell AChE inhibition in females rats chronically exposed to disulfoton for 53 weeks was selected as the basis of the MRL. At 79 weeks, red blood cell AChE inhibition at 0.06 mg/kg/day was 19.3%, and is biologically similar to the technical threshold of significant inhibition (20%), to support the LOAEL seen at 53 weeks. Additionally, a similar dose-response relationship was observed at weeks 53 and 79 in males. Red blood cell AChE inhibition at 105 weeks was not significant at 0.06 mg/kg/day; however, the study reported unusually low mortality rates among female controls by week 104, and high-dose females had high mortality by week 105. No AChE inhibition was seen in male rats exposed to the same nominal concentration of disulfoton, but the analytical concentration was 0.05 mg/kg/day. The available data in Hayes (1985) are not amenable to BMD modeling as neither standard deviation nor standard error values were provided for AChE levels presented in Table A-10.

Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The LOAEL is divided by a total uncertainty factor of 1,000:

- 10 for extrapolation from animals to humans
- 10 for human variability
- 10 for use of a LOAEL

$$MRL = \frac{LOAEL}{UFs} = \frac{0.06\ mg/kg/day}{10 \times 10 \times 10} = 0.00006\ mg/kg/day$$

Other Additional Studies of Pertinent Information that Lend Support to this MRL: The EPA Integrated Risk Information System (IRIS) Assessment (IRIS 2002) used the same study to calculate an oral reference dose (RfD) of $4x10^{-5}$ mg/kg/day. This oral RfD was based on a LOAEL of 0.04 mg/kg/day for cholinesterase inhibition and optic nerve degeneration. This value is different from the value used in this chronic-duration oral MRL, as the LOAEL used by EPA was calculated by multiplying the analytical dietary concentration of 0.8 ppm by the reference rat food consumption of 0.05 mg/kg/day. The LOAEL of 0.06 mg/kg/day used to derive the MRL was calculated using the body weight and food consumption data provided in Hayes (1985). In 2004, EPA announced that the IRIS program would no longer evaluate or update pesticide chemicals but that these chemicals would instead be evaluated by EPA's Office of Pesticide Programs (OPP) (EPA 2004). In 2006, EPA's OPP evaluated the data on disulfoton. In EPA's Reregistration Eligibility Decision for disulfoton, a chronic dietary population adjusted dose (PAD) of 0.00013 mg/kg/day using the NOAEL of 0.013 mg/kg/day from the Jones et al. (1999) study in dogs was developed. The chronic-duration oral MRL for disulfoton developed by ATSDR is more protective than EPA's chronic dietary PAD.

Agency Contact (Chemical Managers): Melanie Buser, MPH

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR DISULFOTON

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to disulfoton.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for disulfoton. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of disulfoton have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of disulfoton are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects
    - Developmental effects
    - Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for disulfoton released for public comment in 2021; thus, the literature search was restricted to studies published between January 2021 and November 2021. The following main databases were searched in November 2021:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for disulfoton. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures

and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to disulfoton were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
11/2021	("Disulfoton"[mh] OR "BAY 19639"[tw] OR "Bayer 19639"[tw] OR "Di-syston"[tw] OR "Di-Syston 8"[tw] OR "Di-Syston G"[tw] OR "Disulfoton"[tw] OR "Dithiodemeton"[tw] OR "Dithiosystox"[tw] OR "Dution"[tw] OR "Ekatin TD"[tw] OR "Ekatine"[tw] OR "Ethyl thiometon"[tw] OR "Ethylthiometon B"[tw] OR "Frumin"[tw] OR "Glebofos"[tw] OR "Insyst-D"[tw] OR "O,O-Diethyl 2-ethylthioethyl phosphorodithioate"[tw] OR "O,O-Diethyl S-(2-(ethylthio)ethyl) dithiophosphate"[tw] OR "O,O-Diethyl S-(2-(ethylthio)ethyl)phosphorodithioate"[tw] OR "O,O-Diethyl S-(2-ehthioethyl) phosphorodithioate"[tw] OR "O,O-Diethyl S-(2-ehthioethyl) thiothionophosphate"[tw] OR "O,O-Diethyl S-(2-ethylmercaptoethyl) dithiophosphate"[tw] OR "O,O-Diethyl S-2-(ethylthio)ethyl phosphorodithioate"[tw] OR "O,O-Diethyl S-[2-(ethylsulfanyl)ethyl] phosphorodithioate"[tw] OR "O,O-Diethyl S-[2-(ethylthio)ethyl] dithiophosphate"[tw] OR "O,O-Diethyl S-[2-(ethylthio)ethyl] phosphorodithioate"[tw] OR "O,O-Diethyl-S-ethylmercapto-ethyl dithiophosphate"[tw] OR "Phosphorodithioic acid, O,O-diethyl S-(2-(ethylthio)ethyl) ester"[tw] OR "Phosphorodithioic acid, O,O-diethyl S-[2-(ethylthio)ethyl] ester"[tw] OR "Phosphorodithioic acid, O,O-diethylS-[2-(ethylthio)ethyl] ester"[tw] OR "S 276"[tw] OR "S-2-(Ethylthio)ethyl O,O-diethyl ester of phosphorodithioic acid"[tw] OR "Solvigran"[tw] OR "Solvirex"[tw] OR "Thiodemeton"[tw] OR "Vuagt 1-4"[tw] OR "Vuagt 1964"[tw] OR (("m 74"[tw] OR "m 74"[tw]) AND pesticide)) AND (2018/01/01:3000[dp] OR 2019/06/01:3000[mhda] OR 2019/06/01:3000[crdat] OR 2019/06/01:3000[edat]) ("Demeton"[tw] OR "Di Syston"[tw] OR "Dimaz"[tw] OR "Disulfaton"[tw] OR "Disyston"[tw] OR "Disystox"[tw] OR "Ethylthiodemeton"[tw] OR "O,O-DIETHYL S-(2-(ETHYLTHIO)ETHYL)) DITHIOPHOSPHATE"[tw] OR "O,O-Diethyl S-2-ethylthioethyl phosphorodithioate"[tw] OR "O,O-diethyl-S-ethylmercapto-ethyl dithiophosphate"[tw] OR "O,O-ETHYL S-2(ETHYLTHIO)ETHYL PHOSPHORODITHIOATE"[tw] OR "O,O-DIETHYL S-(2-ETHTHIOETHYL) THIOTHIONOPHOSPHATE"[tw] OR "Phosphorodithioic acid O,O-diethyl S-[2-(ethylthio)ethyl] ester"[tw] OR "PHOSPHORODITHIONIC ACID, S2-(ETHYLTHIO)ETHYL-O,O-DIETHYL ESTER"[tw]) AND (2018/01/01:3000[dp] OR 2019/06/01:3000[mhda] OR 2019/06/01:3000[crdat] OR 2019/06/01:3000[edat])
NTRL	
11/2021	Limited 2018-present Di-syston Disulfoton Dithiodemeton Dithiosystox Dution Ethyl thiometon Ethylthiometon B

Table B-2. Database Query Strings

Database search date	Query string
	O,O-Diethyl 2-ethylthioethyl phosphorodithioate O,O-Diethyl S-(2-(ethylthio)ethyl) dithiophosphate O,O-Diethyl S-(2-(ethylthio)ethyl)phosphorodithioate O,O-Diethyl S-(2-ethhioethyl) phosphorodithioate O,O-Diethyl S-(2-ethhioethyl) thiothionophosphate O,O-Diethyl S-(2-ethylmercaptoethyl) dithiophosphate O,O-Diethyl S-2-(ethylthio)ethyl phosphorodithioate O,O-Diethyl S-[2-(ethylsulfanyl)ethyl] phosphorodithioate O,O-Diethyl S-[2-(ethylthio)ethyl] dithiophosphate O,O-Diethyl S-[2-(ethylthio)ethyl] phosphorodithioate O,O-Diethyl-S-ethylmercapto-ethyl dithiophosphate S-2-(Ethylthio)ethyl O,O-diethyl ester of phosphorodithioic acid Solvigran Solvirex Thiodemeton Demeton Di Syston Disyston Disystox Ethylthiodemeton O,O-DIETHYL S-(2-(ETHYLTHIO)ETHYL)) DITHIOPHOSPHATE O,O-Diethyl S-2-ethylthioethyl phosphorodithioate O,O-diethyl-S-ethylmercapto-ethyl dithiophosphate O,O-ETHYL S-2(ETHYLTHIO)ETHYL PHOSPHORODITHIOATE O,O-DIETHYL S-(2-ETHTHIOETHYL) THIOTHIONOPHOSPHATE Phosphorodithioic acid O,O-diethyl S-[2-(ethylthio)ethyl] ester PHOSPHORODITHIONIC ACID, S2-(ETHYLTHIO)ETHYL-O,O-DIETHYL ESTER
Toxcenter	
11/2021	FILE 'TOXCENTER' ENTERED AT 15:28:18 ON 23 NOV 2021 CHARGED TO COST=EH038.13.06.LB.04 L1 2702 SEA FILE=TOXCENTER 298-04-4 L2 2700 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 2441 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 99 SEA FILE=TOXCENTER L3 AND PY>2017 ACT TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)

Table B-2. Database Query Strings

Database search date	Query string
	L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L35 QUE L33 OR L34

Table B-2. Database Query Strings

Database search date	Query string
	L36 66 SEA FILE=TOXCENTER L4 AND L35 L37 2 SEA FILE=TOXCENTER L36 AND MEDLINE/FS L38 65 DUP REM L36 (1 DUPLICATE REMOVED) ANSWERS '1-65' FROM FILE TOXCENTER D SCAN L38

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
11/2021	Compound searched: 298-04-4
NTP	
11/2021	298-04-4 "Di-syston" "Disulfoton" "Dithiodemeton" "Dithiosystox" "Dution" "Ethyl thiometon" "Ethylthiometon B" "O,O-Diethyl 2-ethylthioethyl phosphorodithioate" "O,O-Diethyl S-(2-(ethylthio)ethyl) dithiophosphate" "O,O-Diethyl S-(2-(ethylthio)ethyl)phosphorodithioate" "O,O-Diethyl S-(2-ehthioethyl) phosphorodithioate" "O,O-Diethyl S-(2-ehthioethyl) thiothionophosphate" "O,O-Diethyl S-(2-ethylmercaptoethyl) dithiophosphate" "O,O-Diethyl S-2-(ethylthio)ethyl phosphorodithioate" "O,O-Diethyl S-[2-(ethylsulfanyl)ethyl] phosphorodithioate" "O,O-Diethyl S-[2-(ethylthio)ethyl] dithiophosphate" "O,O-Diethyl S-[2-(ethylthio)ethyl] phosphorodithioate" "O,O-Diethyl-S-ethylmercapto-ethyl dithiophosphate" "S-2-(Ethylthio)ethyl O,O-diethyl ester of phosphorodithioic acid" "Solvigran" "Solvirex" "Thiodemeton" "Demeton" "Di Syston" "Disyston" "Disystox" "Ethylthiodemeton" "O,O-DIETHYL S-(2-(ETHYLTHIO)ETHYL)) DITHIOPHOSPHATE" "O,O-Diethyl S-2-ethylthioethyl phosphorodithioate" "O,O-diethyl-S-ethylmercapto-ethyl dithiophosphate" "O,O-ETHYL S-2(ETHYLTHIO)ETHYL PHOSPHORODITHIOATE" "O,O-DIETHYL S-(2-ETHTHIOETHYL) THIOTHIONOPHOSPHATE" "Phosphorodithioic acid O,O-diethyl S-[2-(ethylthio)ethyl] ester" "PHOSPHORODITHIONIC ACID, S2-(ETHYLTHIO)ETHYL-O,O-DIETHYL ESTER"
Regulations.gov	
11/2021	298-04-4 "Di-syston" "Disulfoton" "Dithiodemeton" "Dithiosystox" "Dution" "Ethyl thiometon" "Ethylthiometon B" "O,O-Diethyl 2-ethylthioethyl phosphorodithioate" "O,O-Diethyl S-(2-(ethylthio)ethyl) dithiophosphate" "O,O-Diethyl S-(2-(ethylthio)ethyl)phosphorodithioate"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"O,O-Diethyl S-(2-eththioethyl) phosphorodithioate" "O,O-Diethyl S-(2-eththioethyl) thiothionophosphate" "O,O-Diethyl S-(2-ethylmercaptoethyl) dithiophosphate" "O,O-Diethyl S-2-(ethylthio)ethyl phosphorodithioate" "O,O-Diethyl S-[2-(ethylsulfanyl)ethyl] phosphorodithioate" "O,O-Diethyl S-[2-(ethylthio)ethyl] dithiophosphate" "O,O-Diethyl S-[2-(ethylthio)ethyl] phosphorodithioate" "O,O-Diethyl-S-ethylmercapto-ethyl dithiophosphate" "S-2-(Ethylthio)ethyl O,O-diethyl ester of phosphorodithioic acid" "Solvigran" "Solvirex" "Thiodemeton" "Demeton" "Di Syston" "Disyston" "Disystox" "Ethylthiodemeton" "O,O-DIETHYL S-(2-(ETHYLTHIO)ETHYL)) DITHIOPHOSPHATE" "O,O-Diethyl S-2-ethylthioethyl phosphorodithioate" "O,O-diethyl-S-ethylmercapto-ethyl dithiophosphate" "O,O-ETHYL S-2(ETHYLTHIO)ETHYL PHOSPHORODITHIOATE" "O,O-DIETHYL S-(2-ETHTHIOETHYL) THIOTHIONOPHOSPHATE" "Phosphorodithioic acid O,O-diethyl S-[2-(ethylthio)ethyl] ester" "PHOSPHORODITHIONIC ACID, S2-(ETHYLTHIO)ETHYL-O,O-DIETHYL ESTER"
NIH RePORTER	
12/2021	Search Criteria Fiscal Year: Active ProjectsText Search: "BAY 19639" OR "Bayer 19639" OR "Di-syston" OR "Disulfoton" OR "Dithiodemeton" OR "Dithiosystox" OR "Dution" OR "Ekatin TD" OR "Ekatine" OR "Ethyl thiometon" OR "Ethylthiometon B" OR "Frumin" OR "Glebofos" OR "Insyst-D" OR "O,O-Diethyl 2-ethylthioethyl phosphorodithioate" OR "O,O-Diethyl S-(2-(ethylthio)ethyl) dithiophosphate" OR "O,O-Diethyl S-(2-(ethylthio)ethyl)phosphorodithioate" OR "O,O-Diethyl S-(2-eththioethyl) phosphorodithioate" OR "O,O-Diethyl S-(2-eththioethyl) thiothionophosphate" OR "O,O-Diethyl S-(2-ethylmercaptoethyl) dithiophosphate" OR "O,O-Diethyl S-2-(ethylthio)ethyl phosphorodithioate" OR "O,O-Diethyl S-[2-(ethylsulfanyl)ethyl] phosphorodithioate" OR "O,O-Diethyl S-[2-(ethylthio)ethyl] dithiophosphate" OR "O,O-Diethyl S-[2-(ethylthio)ethyl] phosphorodithioate" OR "O,O-Diethyl-S-ethylmercapto-ethyl dithiophosphate" OR "Phosphorodithioic acid, O,O-diethyl S-(2-(ethylthio)ethyl) ester" OR "Phosphorodithioic acid, O,O-diethyl S-[2-(ethylthio)ethyl] ester" OR "Phosphorodithioic acid, O,O-diethylS-[2-(ethylthio)ethyl] ester" OR "S 276" OR "S-2-(Ethylthio)ethyl O,O-diethyl ester of phosphorodithioic acid" OR "Solvigran" OR "Solvirex" OR "Thiodemeton" OR "Vuagt 1-4" OR "Vuagt 1964" OR "Demeton" OR "Di Syston" OR "Dimaz" OR "Disulfaton" OR "Disyston" OR "Disystox" OR "Ethylthiodemeton" OR "O,O-DIETHYL S-(2-(ETHYLTHIO)ETHYL)) DITHIOPHOSPHATE" OR "O,O-Diethyl S-2-ethylthioethyl phosphorodithioate" OR "O,O-diethyl-S-ethylmercapto-ethyl dithiophosphate" OR "O,O-ETHYL S-2(ETHYLTHIO)ETHYL PHOSPHORODITHIOATE" OR "O,O-DIETHYL S-(2-ETHTHIOETHYL) THIOTHIONOPHOSPHATE" OR "Phosphorodithioic acid O,O-diethyl S-[2-(ethylthio)ethyl] ester" OR "PHOSPHORODITHIONIC ACID, S2-(ETHYLTHIO)ETHYL-O,O-DIETHYL ESTER" (advanced)Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2021 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 76
- Number of records identified from other strategies: 22
- Total number of records to undergo literature screening: 98

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on disulfoton:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

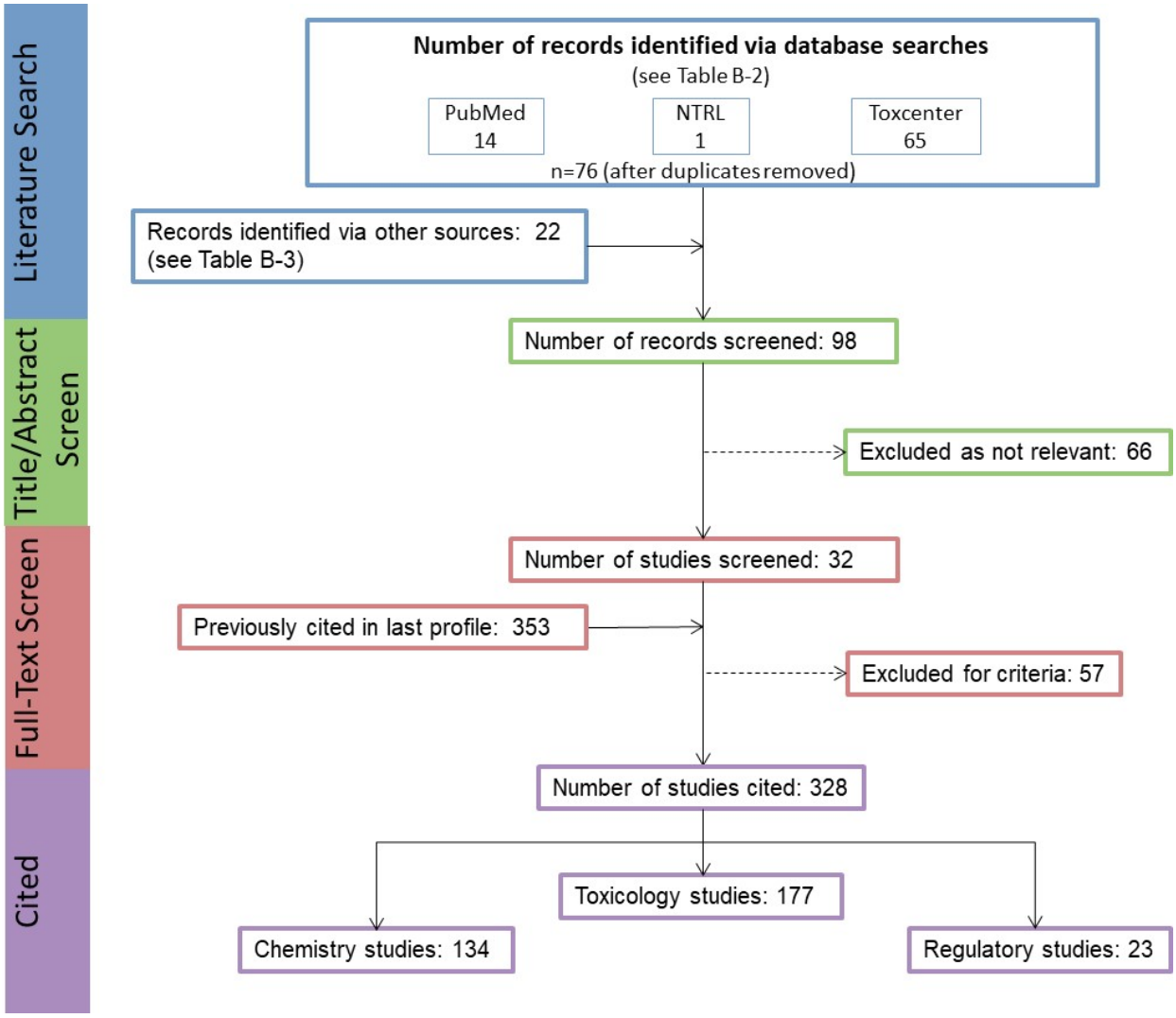
- Number of titles and abstracts screened: 98
- Number of studies considered relevant and moved to the next step: 32

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 32
- Number of studies cited in the pre-public draft of the toxicological profile: 353
- Total number of studies cited in the profile: 328

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. November 2021 Literature Search Results and Screen for Disulfoton



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR DISULFOTON

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to disulfoton, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to disulfoton:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to disulfoton. The inclusion criteria used to identify relevant studies examining the health effects of disulfoton are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of disulfoton. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the draft toxicological profile for disulfoton released for public comment in 2021. See Appendix B for the databases searched and the search strategy.

A total of 98 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of disulfoton.

Title and Abstract Screen. In the Title and Abstract Screen step, 98 records were reviewed; 1 document was considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those documents, 112 studies were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for disulfoton and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels of Significant Exposures tables in Section 2.1 of the profile (Tables 2-1, 2-2, and 2-3, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for disulfoton identified in human and animal studies are presented in Tables C-3 and C-4, respectively.

Human studies evaluating noncancerous effects are primarily case reports of accidental or intentional exposure, and few epidemiological studies on occupational exposure that have examined a limited number of health endpoints. However, these studies substantially indicate that the neurological system is most susceptible to disulfoton toxicity. Animal studies have examined a wide range of potential endpoints following oral exposure, while inhalation studies were limited to intermediate studies of neurotoxicity and a broad range of systemic effects. Dermal studies were limited to examining acute

lethality, neurological outcomes, and varying systemic effects. Neurological effects, including developmental neurotoxicity, is considered the most sensitive outcome, as the effects seen at low inhalation concentrations and oral doses were used in deriving inhalation and oral MRLs. Studies examining the neurological endpoints were carried through Steps 4–8 of the systematic review. There were 112 studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review.

Table C-3. Overview of the Health Outcomes for Disulfoton Evaluated in Human Studies

	Body Weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation Studies																	
Cohort	0	2	0	1	0	0	0	0	1	0	0	0	2	0	0	0	2
	0	1	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case series	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Oral Studies																	
Cohort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Population	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Case series	0	1	1	0	0	0	0	1	0	0	0	0	3	0	0	0	0
	0	1	1	0	0	0	0	1	0	0	0	0	3	0	0	0	0
Dermal Studies																	
Cohort	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case series	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

Table C-4. Overview of the Health Outcomes for Disulfoton Evaluated in Experimental Animal Studies

	Body Weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation Studies																	
Acute-duration	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0
Intermediate-duration	3	2	2	2	2	1	2	2	1	2	2	2	3	2	0	0	1
	1	2	0	1	1	0	0	0	0	0	1	1	2	0	0	0	0
Chronic-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Oral Studies																	
Acute-duration	10	1	0	1	0	0	3	0	0	1	4	1	21	3	4	0	0
	9	1	0	1	0	0	3	0	0	0	4	1	21	2	4	0	0
Intermediate-duration	9	3	3	2	2	4	2	4	1	4	2	2	14	4	3	0	0
	8	0	0	0	0	0	1	1	0	0	0	0	14	1	3	0	0
Chronic-duration	3	2	3	4	5	6	4	4	3	7	4	4	7	4	0	0	4
	1	1	0	1	0	1	1	2	1	4	2	1	7	1	0	0	0
Dermal Studies																	
Acute-duration	1	1	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0
	0	1	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0
Intermediate-duration	2	2	1	2	2	0	1	1	2	0	1	1	2	1	0	0	0
	1	2	0	2	0	0	1	1	0	0	0	1	2	1	0	0	0
Chronic-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10	

*Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational epidemiological studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational epidemiological studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of disulfoton health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-8 and C-9, respectively.

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Table C-8. Summary of Risk of Bias Assessment for Disulfoton––Observational Epidemiology Studies

	Risk of bias criteria and ratings						
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
Reference	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Outcome: Neurological effects							
Cohort studies							
Brokopp et al. 1981	+	–	+	++	+	++	First
Gómez-Arroyo et al. 2000	+	+	+	+	+	++	First
Wolfe et al. 1978	–	–	–	+	+	+	Third
Case studies							
Futagami et al. 1995	NA	+	NA	–	++	++	Second
Hattori et al. 1982	NA	+	NA	++	++	++	First
Savage et al. 1971	NA	+	NA	+	+	+	First
Yashiki et al. 1990	NA	+	NA	++	++	++	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

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Table C-9. Risk of Bias Assessment for Select Endpoints for Disulfoton–Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Outcome: Developmental effects									
Oral acute exposure									
Lamb and Hixson 1983 (rats)	++	+	+	+	+	+	+	++	First
Tesh et al. 1982 (rabbits)	+	+	+	+	–	+	+	+	First
Oral intermediate exposure									
Hixson and Hathaway 1986 (rats)	++	+	++	+	++	+	+	++	First
Klaus 2006c (rats)	+	+	+	+	++	+	+	++	First
Ryan et al. 1970 (rats)	–	+	–	+	–	–	–	+	Third
Sheets 2005 (rats)	++	++	+	+	+	+	++	++	First
Taylor 1965a (rats)	–	–	+	+	+	+	+	–	Second
Outcome: Neurological effects									
Inhalation acute exposure									
Doull 1957 (mice)	+	+	+	–	–	+	+	++	First
Doull 1957 (rats)	+	+	+	–	–	+	+	++	First
DuBois and Kinoshita 1971 (rats)	–	+	+	–	+	+	+	++	First

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Table C-9. Risk of Bias Assessment for Select Endpoints for Disulfoton–Experimental Animal Studies

	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Thyssen 1978 (rats)	+	–	+	–	+	+	++	++	First
Inhalation intermediate exposure									
Shiotsuka 1988 (rats)	++	+	++	+	+	+	+	++	First
Shiotsuka 1989 (rats)	++	+	++	–	+	+	+	++	First
Thyssen 1980 (rats)	++	+	+	–	+	+	+	++	First
Thyssen 1980 (rats)	+	+	+	–	+	+	+	++	First
Oral acute exposure									
Costa and Murphy 1983a (rats)	–	+	+	+	–	+	+	+	First
Costa et al. 1984 (rats)	–	+	+	+	–	+	+	++	First
Costa et al. 1986 (rats)	–	+	+	+	–	+	+	+	First
Costa et al. 1986(rats)	–	+	+	+	–	+	+	+	First
Crawford and Anderson 1974 (rats)	–	–	–	+	+	–	+	+	Third
Fitzgerald and Costa 1992 (rats)	+	–	+	+	+	+	+	++	First
Fitzgerald and Costa 1993 (rats)	++	+	+	+	+	+	+	++	First
Klaus 2006a (rats)	++	+	+	+	++	+	+	++	First

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Table C-9. Risk of Bias Assessment for Select Endpoints for Disulfoton–Experimental Animal Studies

	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Klaus 2006b (rats)	+	+	–	+	–	+	+	++	First
Lamb and Hixson 1983 (rats)	++	+	+	+	+	+	+	++	First
EPA 2007 (rats)	++	+	+	+	++	+	+	++	First
EPA 2007 (rats)	++	+	+	+	++	+	+	++	First
EPA 2007 (rats)	++	+	+	+	++	+	+	++	First
EPA 2007 (rats)	++	+	+	+	++	+	+	++	First
Matsuda et al. 2000 (rats)	–	+	+	+	+	+	+	++	First
Mihail 1978 (mice)	– –	+	+	+	–	+	+	+	First
Mihail 1978 (rats)	– –	+	+	+	–	+	+	++	First
Mihail 1978 (Beagle dogs)	– –	+	+	+	–	+	+	+	First
Schwab et al. 1981 (rats)	–	+	+	+	+	+	+	++	First
Schwab and Murphy 1981 (rats)	+	+	++	+	+	+	+	++	First
Schwab et al. 1983 (rats)	–	+	+	+	+	+	+	+	First
Sheets 1993a (rats)	++	++	++	+	+	+	++	++	First
Su et al. 1971 (rats)	+	+	+	+	–	+	+	+	First
Yagle and Costa 1996 (rats)	–	+	+	–	+	+	+	++	First

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Table C-9. Risk of Bias Assessment for Select Endpoints for Disulfoton–Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Oral intermediate exposure									
Christenson and Wahle 1993 (rat)	++	+	++	–	+	++	+	++	First
Clark and Pearson 1973 (rats)	+	+	+	+	+	+	+	+	First
Clark and Stavinoha 1971 (mice)	–	–	–	–	–	+	–	+	Third
Clark and Stavinoha 1971 (rats)	–	–	–	–	–	+	–	+	Third
Clark et al. 1971 (mice)	+	+	+	+	+	+	+	++	First
Hayes 1985 (rats)	+	++	++	+	++	+	+	++	First
Hikita et al. 1973 (Beagle dogs)	–	–	+	+	+	+	+	++	First
Hixson and Hathaway 1986 (rats)	++	+	++	+	++	+	+	++	First
Hoffman and Welscher 1975 (Beagle dogs)	++	+	++	+	+	++	++	++	First
Klaus 2006c (rats)	+	+	+	+	++	+	+	++	First
Klotzsche 1972 (rats)	–	–	+	+	+	+	+	++	First
Rivett et al. 1972 (rats)	++	+	++	+	+	+	+	++	First

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Table C-9. Risk of Bias Assessment for Select Endpoints for Disulfoton–Experimental Animal Studies

	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Robinson et al. 1978 (rats)	+	+	+	+	+	–	+	++	First
Ryan et al. 1970 (rats)	–	+	–	+	–	–	–	+	Third
Schwab and Murphy 1981 (rats)	+	+	+	+	+	+	+	++	First
Sheets 1993b (rats)	++	++	+	++	++	++	++	++	First
Sheets 2005 (rats)	+	+	+	+	++	++	+	++	First
Stavinoha et al. 1969 (rats)	–	+	–	–	+	+	+	++	Second
Oral chronic exposure									
Carpy et al. 1975 (rats)	+	+	+	+	+	+	+	++	First
Hayes 1983 (mice)	++	++	++	+	+	++	+	++	First
Hayes 1985 (rats)	+	++	++	+	++	+	+	++	First
Hoffman and Welscher 1975 (Beagle dogs)	++	+	++	+	+	++	++	++	First
Jones et al. 1999 (Beagle dogs)	++	+	+	–	+	+	+	++	First
Uga et al. 1977 (Beagle dogs)	–	–	+	–	+	+	+	++	First
Dermal acute exposure									
Croutch and Sheets 2000 (rats)	++	+	+	+	+	+	+	++	First

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Table C-9. Risk of Bias Assessment for Select Endpoints for Disulfoton–Experimental Animal Studies

	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Flucke 1986 (rabbits)	++	+	+	+	+	+	+	++	First
Dermal intermediate exposure									
Flucke 1986 (rabbits)	++	+	+	+	+	+	+	++	First
Flucke 1988 (rabbits)	++	+	+	+	+	+	++	++	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to disulfoton and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence**: the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence**: the true effect may be reflected in the apparent relationship
- **Low confidence**: the true effect may be different from the apparent relationship
- **Very low confidence**: the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study, observation epidemiology, human-controlled exposures and experimental animals. Unless there was a clear need for delineation in the confidence for a particular outcome, confidence assessments were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to disulfoton and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key study design features was determined for individual studies using four "yes or no" questions which were customized for observational epidemiology, human-controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human-controlled exposure studies, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence**: Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence**: Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence**: Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence**: Studies in which the response to one or none of the questions was "yes".

Table C-10. Key Features of Study Design for Human-Controlled Exposure Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-11. Key Features of Study Design for Observational Epidemiology Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-12. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining neurologic effects observed in observational epidemiology and animal experimental studies are presented in Tables Table **C-13** and Table **C-14**, respectively.

A summary of the initial confidence ratings for each outcome is presented in Table C-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-16.

Table C-13. Presence of Key Features of Study Design for Disulfoton—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled Exposure	Exposure prior to outcome	Outcome assess on individual level	Comparison group	
Outcome: Neurological effects					
Cohort studies					
Brokopp et al. 1981	Yes	No	Yes	Yes	Moderate
Gómez-Arroyo et al. 2000	Yes	Yes	Yes	Yes	High
Wolfe et al. 1978	Yes	Yes	Yes	No	Moderate
Case studies					
Futagami et al. 1995	NA	NA	Yes	Yes	Low
Hattori et al. 1982	NA	NA	Yes	Yes	Low

Table C-13. Presence of Key Features of Study Design for Disulfoton—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled Exposure	Exposure prior to outcome	Outcome assess on individual level	Comparison group	
Savage et al. 1971	NA	NA	Yes	No	Low
Yashiki et al. 1990	NA	NA	Yes	Yes	Low

NA = Not applicable

Table C-14. Presence of Key Features of Study Design for Disulfoton–Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Developmental					
Oral acute exposure					
Lamb and Hixson (rats)	Yes	Yes	Yes	Yes	High
Tesh et al. 1982 (rabbits)	No	Yes	Yes	Yes	Moderate
Oral intermediate exposure					
Hixson and Hathaway 1986 (rats)	Yes	Yes	Yes	Yes	High
Klaus 2006c (rats)	Yes	Yes	Yes	Yes	High
Ryan et al. 1970 (rats)	Yes	Yes	Yes	No	Moderate
Sheets 2005 (rats)	Yes	Yes	Yes	Yes	High
Taylor 1965a (rats)	Yes	Yes	Yes	Yes	High
Outcome: Neurologic					
Inhalation acute exposure					
Doull 1957 (mice)	No	Yes	Yes	Yes	Moderate
Doull 1957 (rats)	No	Yes	Yes	Yes	Moderate
DuBois and Kinoshita 1971 (rats)	Yes	Yes	Yes	No	Moderate
Thyssen 1978 (rats)	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for Disulfoton–Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Inhalation intermediate exposure					
Shiotsuka 1988 (rats)	Yes	Yes	Yes	Yes	High
Shiotsuka 1989 (rats)	Yes	Yes	Yes	Yes	High
Thyssen 1980 (rats)	Yes	Yes	Yes	Yes	High
Thyssen 1980 (rats)	Yes	Yes	Yes	Yes	High
Oral acute exposure					
Costa and Murphy 1983a (rats)	Yes	No	Yes	Yes	Moderate
Costa et al. 1984 (rats)	Yes	No	Yes	Yes	Moderate
Costa et al. 1986 (rats)	Yes	No	Yes	Yes	Moderate
Crawford and Anderson 1974 (rats)	No	Yes	Yes	No	Low
Fitzgerald and Costa 1992 (rats)	Yes	Yes	Yes	Yes	High
Fitzgerald and Costa 1993 (rats)	Yes	Yes	Yes	Yes	High
Klaus 2006a (rats)	Yes	Yes	Yes	Yes	High
Klaus 2006b (rats)	Yes	Yes	Yes	Yes	High
Lamb and Hixson 1983 (rats)	Yes	Yes	Yes	Yes	High
EPA 2007 (rats)	Yes	Yes	Yes	Yes	High
EPA 2007 (rats)	Yes	Yes	Yes	Yes	High
EPA 2007 (rats)	Yes	Yes	Yes	Yes	High
EPA 2007 (rats)	Yes	Yes	Yes	Yes	High
Matsuda et al. 2000 (rats)	yes	No	Yes	No	Low
Mihail 1978 (Beagle dogs)	No	No	Yes	Yes	Low
Mihail 1978 (mice)	No	No	Yes	Yes	Low
Mihail 1978 (rats)	No	No	Yes	Yes	Low
Schwab et al. 1981 (rats)	Yes	Yes	Yes	Yes	High
Schwab and Murphy 1981 (rats)	Yes	Yes	Yes	Yes	High
Schwab et al. 1983 (rats)	Yes	Yes	Yes	Yes	High
Sheets 1993a (rats)	Yes	Yes	Yes	Yes	High
Su et al. 1971 (rats)	Yes	No	Yes	No	Low
Yagle and Costa 1996 (rats)	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for Disulfoton–Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Oral intermediate exposure					
Christenson and Wahle 1993 (rat)	Yes	Yes	Yes	Yes	High
Clark and Pearson 1973	Yes	Yes	No	Yes	Moderate
Clark and Stavinoha 1971 (mice)	Yes	No	Yes	No	Low
Clark and Stavinoha 1971 (rats)	Yes	No	Yes	No	Low
Clark et al. 1971 (mice)	Yes	Yes	Yes	Yes	High
Hayes 1985 (rats)	Yes	Yes	Yes	Yes	High
Hikita et al. 1973 (dog)	Yes	No	Yes	Yes	Moderate
Hixson and Hathaway 1986 (rats)	Yes	Yes	Yes	Yes	High
Hoffman and Welscher 1975 (dogs)	Yes	No	Yes	Yes	Moderate
Klaus 2006c (rats)	Yes	Yes	Yes	Yes	High
Klotzsche 1972 (rats)	Yes	Yes	Yes	Yes	High
Rivett et al. 1972	Yes	Yes	Yes	Yes	High
Robinson et al. 1978 (rats)	Yes	Yes	Yes	Yes	High
Ryan et al. 1970 (rats)	Yes	Yes	Yes	No	Moderate
Schwab and Murphy 1981 (rats)	Yes	Yes	Yes	Yes	High
Sheets 1993b (rats)	Yes	Yes	Yes	Yes	High
Sheets 2005 (rats)	Yes	Yes	Yes	Yes	High
Stavinoha et al. 1969 (rats)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Carpy et al. 1975 (rats)	Yes	Yes	Yes	Yes	High
Hayes 1983 (mice)	Yes	Yes	Yes	Yes	High
Hayes 1985 (rats)	Yes	Yes	Yes	Yes	High
Hoffman and Welscher 1975 (beagle dogs)	Yes	No	Yes	Yes	Moderate
Jones et al. 1999 (beagle dogs)	Yes	No	Yes	Yes	Moderate
Uga et al. 1977 (beagle dogs)	Yes	No	Yes	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for Disulfoton–Experimental Animal Studies

Reference	Key feature: Concurrent Control Group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Dermal acute exposure					
Croutch and Sheets 2000 (rats)	Yes	Yes	Yes	Yes	High
Flucke 1986 (rabbits)	Yes	Yes	Yes	Yes	High
Dermal intermediate exposure					
Flucke 1986 (rabbits)	Yes	No	Yes	Yes	Moderate
Flucke 1988 (rabbits)	Yes	No	Yes	Yes	Moderate

Table C-15. Initial Confidence Rating for Disulfoton Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Developmental Effects		
Oral acute exposure		
Animal Studies		
Lamb and Hixson (rats)	High	High
Tesh et al. 1982 (rabbits)	Moderate	
Oral intermediate exposure		
Animal Studies		
Hixson and Hathaway 1986 (rats)	High	High
Klaus 2006c (rats)	High	
Ryan et al. 1970 (rats)	Moderate	
Sheets 2005 (rats)	High	
Taylor 1965a (rats)	High	
Outcome: Neurological Effects		
Inhalation acute exposure		
Animal Studies		
Doull 1957 (mice)	Moderate	High
Doull 1957 (rats)	Moderate	
DuBois and Kinoshita 1971 (rats)	Moderate	
Thyssen 1978 (rats)	High	

Table C-15. Initial Confidence Rating for Disulfoton Health Effects Studies

	Initial study confidence	Initial confidence rating
Inhalation intermediate exposure		
Human Studies		
Wolfe et al. 1978	Moderate	Moderate
Animal Studies		
Shiotsuka 1988 (rats)	High	High
Shiotsuka 1989 (rats)	High	
Thyssen 1980 (rats)	High	
Thyssen 1980 (rats)	High	
Inhalation chronic exposure		
Human Studies		
Gómez-Arroyo et al. 2000	High	High
Oral acute exposure		
Human Studies		
Futagami et al. 1995	Low	Low
Hattori et al. 1982	Low	
Yashiki et al. 1990	Low	
Animal studies		
Costa and Murphy 1983a (rats)	Moderate	High
Costa et al. 1984 (rats)	Low	
Costa et al. 1986 (rats)	High	
Crawford and Anderson 1974 (rats)	High	
Fitzgerald and Costa 1992 (rats)	High	
Fitzgerald and Costa 1993 (rats)	Low	
Klaus 2006a (rats)	High	
Klaus 2006b (rats)	High	
Lamb and Hixson 1983 (rats)	Low	
EPA 2007 (rats)	High	
EPA 2007 (rats)	High	
EPA 2007 (rats)	High	
EPA 2007 (rats)	High	
Matsuda et al. 2000 (rats)	Low	
Mihail 1978 (Beagle dogs)	Low	
Mihail 1978 (mice)	High	
Mihail 1978 (rats)	High	
Schwab et al. 1981 (rats)	High	
Schwab and Murphy 1981 (rats)	High	
Schwab et al. 1983 (rats)	Low	
Sheets 1993a (rats)	High	
Su et al. 1971 (rats)	Moderate	
Yagle and Costa 1996 (rats)	Moderate	

Table C-15. Initial Confidence Rating for Disulfoton Health Effects Studies

	Initial study confidence	Initial confidence rating
Oral intermediate exposure		
Animal studies		
Christenson and Wahle 1993 (rat)	High	High
Clark and Pearson 1973	Moderate	
Clark and Stavinoha 1971 (mice)	Low	
Clark and Stavinoha 1971 (rats)	Low	
Clark et al. 1971 (mice)	High	
Hayes 1985 (rats)	High	
Hikita et al. 1973 (dog)	Moderate	
Hixson and Hathaway 1986 (rats)	High	
Hoffman and Welscher 1975 (dogs)	Moderate	
Klaus 2006c (rats)	High	
Klotzsche 1972 (rats)	High	
Rivett et al. 1972	High	
Robinson et al. 1978 (rats)	High	
Ryan et al. 1970 (rats)	Moderate	
Schwab and Murphy 1981 (rats)	High	
Sheets 1993b (rats)	High	
Sheets 2005 (rats)	High	
Stavinoha et al. 1969 (rats)	High	
Oral chronic exposure		
Animal studies		
Carpy et al. 1975 (rats)	High	High
Hayes 1983 (mice)	High	
Hayes 1985 (rats)	High	
Hoffman and Welscher 1975 (beagle dogs)	Moderate	
Jones et al. 1999 (beagle dogs)	Moderate	
Uga et al. 1977 (beagle dogs)	Moderate	
Dermal acute exposure		
Human studies		
Savage et al. 1971	Low	Low
Animal studies		
Croutch and Sheets 2000 (rats)	High	High
Flucke 1986 (rabbits)	High	
Dermal intermediate exposure		
Human studies		
Wolfe et al. 1978	Moderate	Moderate
Animal studies		
Flucke 1986 (rabbits)	Moderate	Moderate
Flucke 1988 (rabbits)	Moderate	

Table C-15. Initial Confidence Rating for Disulfoton Health Effects Studies

	Initial study confidence	Initial confidence rating
Dermal chronic exposure		
Human studies		
Brokopp et al. 1981	Moderate	Moderate

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for neurological effects are presented in Table C-15. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with disulfoton exposure is presented in Table C-17.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-5, C-6, and C-7). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
  - No downgrade if most studies are in the risk of bias first tier
  - Downgrade one confidence level if most studies are in the risk of bias second tier
  - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
  - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
  - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
  - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
  - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary

- Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
- Downgrade one confidence level if one of the factors is considered indirect
- Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., “healthy worker” effect) or residual bias suggesting a spurious effect (e.g., recall bias).

Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:

- Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level if there is a high degree of consistency in the database

The results of this assessment are presented in Table C-16, and the final confidence in the body of literature for the neurological endpoint is presented in Table C-17.

Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Developmental effects			
Animal studies	High	None	High
Outcome: Neurological effects			
Human studies	High	-1 Indirectness – length of time between exposure and outcome assessment	Moderate
Animal studies	High	+1 Consistency in the body of evidence	High

Table C-17. Confidence in the Body of Evidence for Disulfoton

	Confidence in body of evidence	
Outcome	Human Studies	Animal Studies
Developmental effects	No data	High
Neurological effects	Moderate	High

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for disulfoton, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence**: High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence**: Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence**: Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome or very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for disulfoton is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for Disulfoton

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human Studies			
Developmental effects	No data		No data
Neurological effects	Moderate	Health Effect	Moderate
Animal Studies			
Developmental effects	High	Health Effect	High
Neurological effects	High	Health Effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

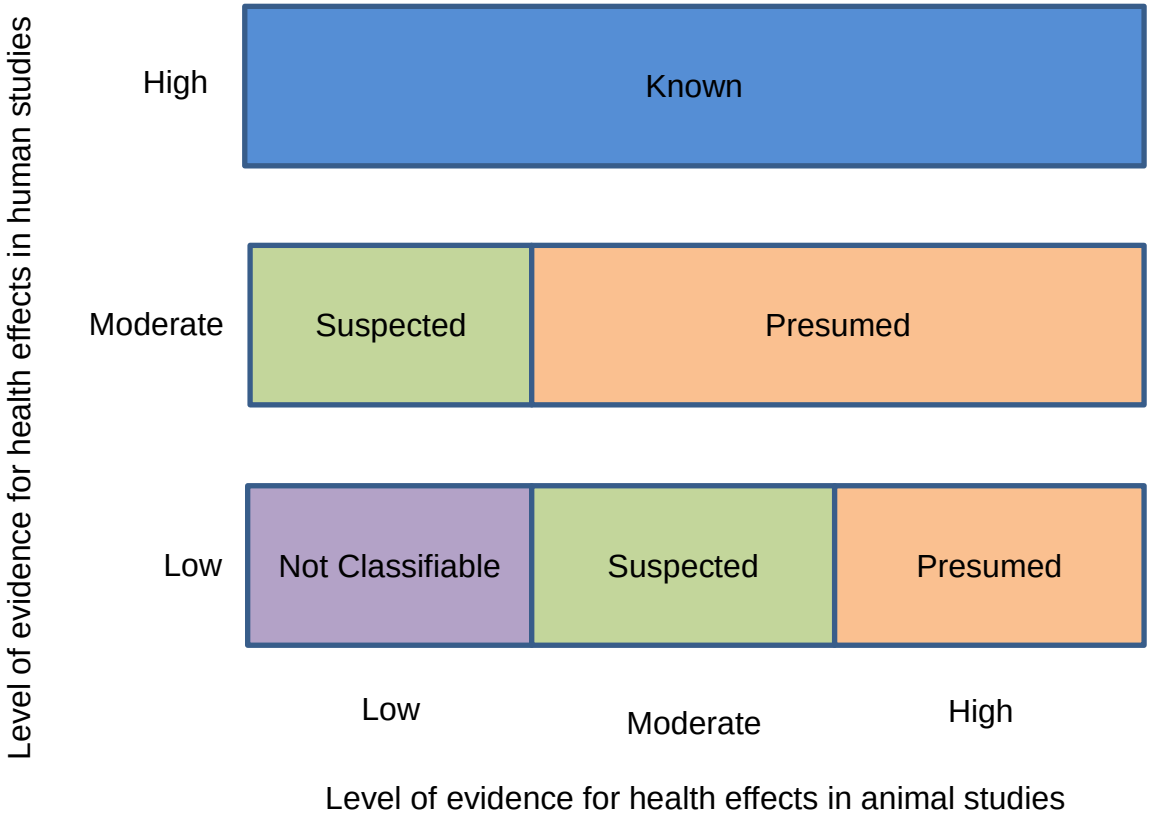
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known**: A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.

- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected**: A health effect in this category would have
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of “not identified” was used. If the

human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used.

The hazard identification conclusions for disulfoton are listed below and summarized in Table C-19.

Presumed Health Effects

- Neurological effects following oral exposure.
  - Moderate evidence from human case studies (Futagami et al. 1995; Hattori et al. 1982; Yashiki et al. 1990).
  - High level of evidence in rats and dogs from acute exposure to disulfoton (Fitzgerald and Costa 1993; Lamb and Hixson 1983; Schwab and Murphy 1981; Sheets 1993a; Yagle and Costa 1996), and intermediate exposure to disulfoton including mice (Clark et al. 1971; Hayes 1985; Hixson and Hathaway 1986; Hoffman and Welscher 1975; Sheets 1993b), and chronic exposure to disulfoton to rats, dogs, and mice (Carpy et al. 1975; Hayes 1983; Hayes 1985; Hoffman and Welscher 1975; Jones et al. 1999).
- Neurological effects following inhalation exposure.
  - Low evidence from human studies due to confounding and low number of studies (Gómez-Arroyo et al. 2000; Wolfe et al. 1978).
  - High level of evidence in rats and mice from acute exposure to disulfoton (Doull 1957; DuBois and Kinoshita 1971; Thyssen 1978), and intermediate exposure to disulfoton in rats (Shiotsuka 1988, 1989; Thyssen 1980).
- Developmental effects following oral exposure.
  - No studies in humans examined developmental effects.
  - High level of evidence in rats and rabbits from acute exposure to disulfoton (Lamb and Hixson 1983; Tesh et al. 1982), and intermediate exposure to disulfoton in rats (Hixson and Hathaway 1986; Klaus 2006c; Ryan et al. 1970; Sheets 2005; Taylor 1965a).

Not Classifiable Health Effects

- Neurological effects following dermal exposure.
  - Low evidence from human studies (Brokopp et al. 1981; Savage et al. 1971; Wolfe et al. 1978).
  - Low level of evidence in rabbit from acute and intermediate exposure to disulfoton (Flucke 1986).
- Developmental effects following inhalation or dermal exposure.
  - No studies in human or animals examined developmental effects following inhalation or dermal exposure to disulfoton.

Table C-19. Hazard Identification Conclusions for Disulfoton

Outcome	Hazard identification
Developmental effects	Presumed health effect following oral exposure
	Not classifiable (inhalation and dermal exposure)
Neurological effects	Presumed health effect following inhalation and oral exposure
	Not classifiable (dermal exposure)

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints 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?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance 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. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

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

To derive an MRL, ATSDR generally selects the most sensitive 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 no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are 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) Figure key. 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 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, 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.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse 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. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. 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. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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.

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

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) 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.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

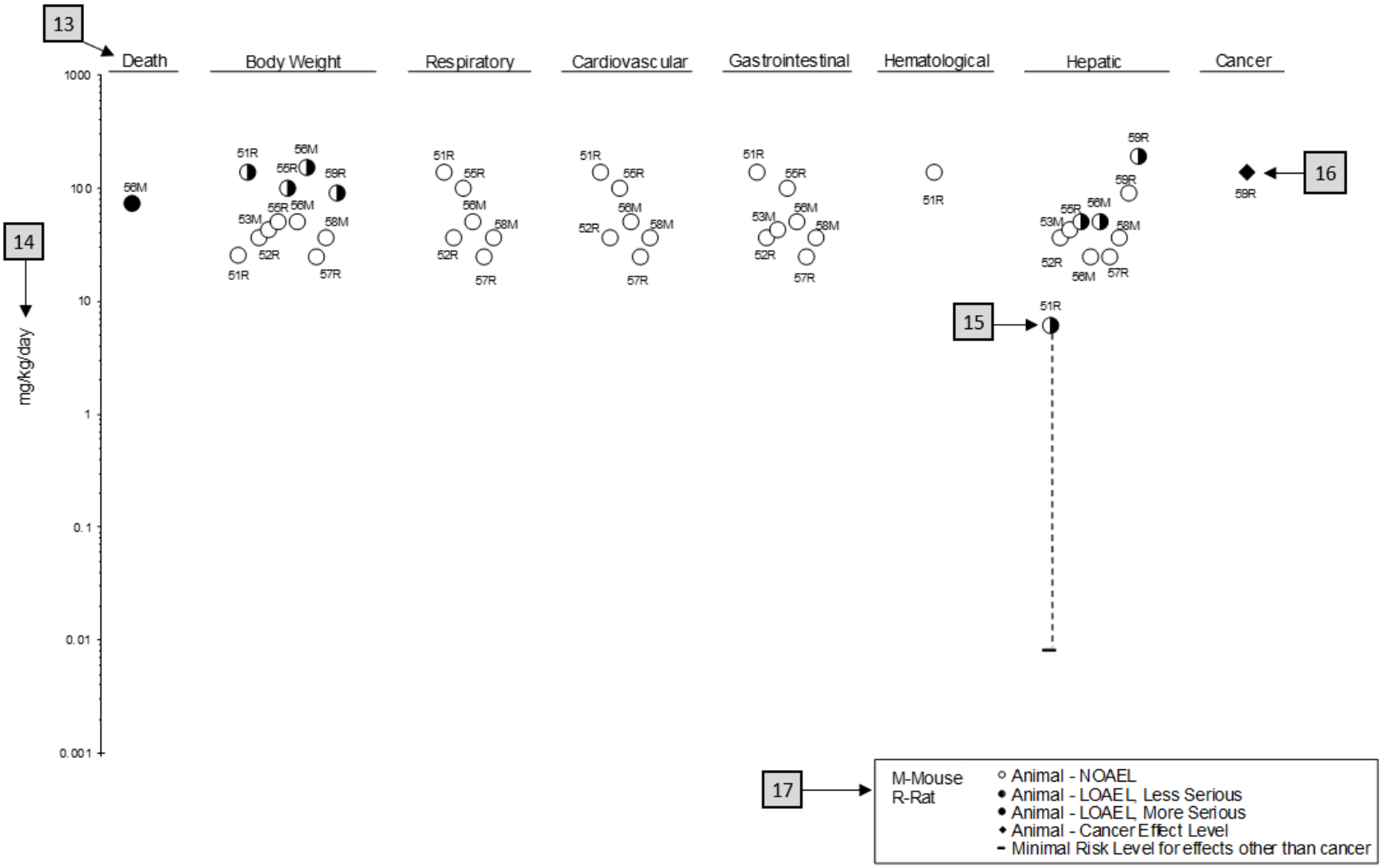
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

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

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

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

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

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

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

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

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

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

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

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

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 effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

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

Excretion—The process by which metabolic waste products are removed from the body.

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

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

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and 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)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

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

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

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

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

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

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

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

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

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

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

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

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

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

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

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

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

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

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

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

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

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

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

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

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

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

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

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

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

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

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

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

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

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

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

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

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

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

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

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

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

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

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

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

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

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result