

## 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.

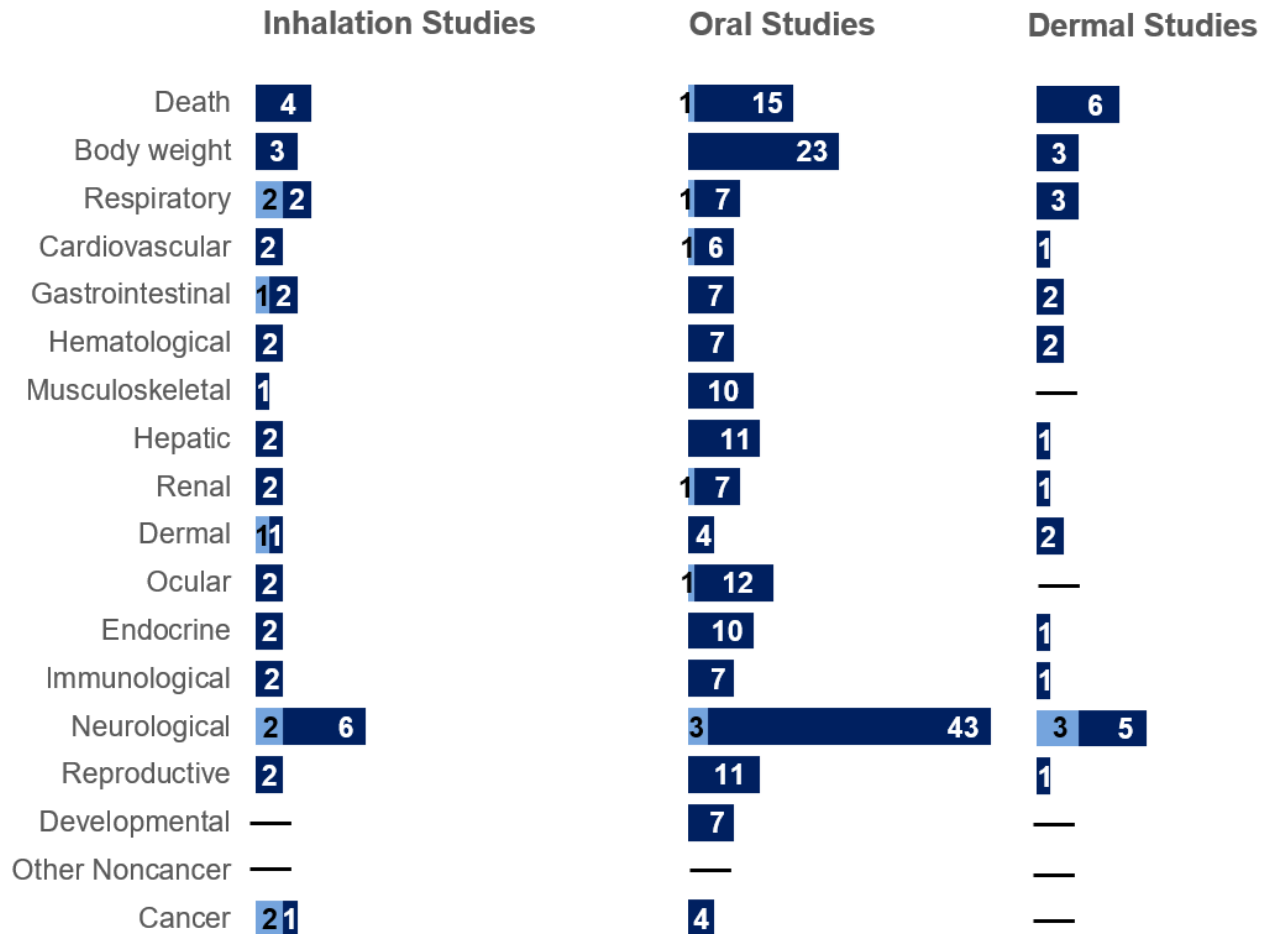
As Figure 6-1 shows, information on the health effects in humans exposed to disulfoton is limited and is primarily based on oral ingestion. In these studies, pesticide containing disulfoton was accidentally or purposefully ingested by an individual and primarily the neurological system was affected. 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.

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**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.

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**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,

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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.

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**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).

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**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 sternbrae 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;

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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-Paruszevska 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  $\beta$ -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.

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**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



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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.

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**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.

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**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.