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.

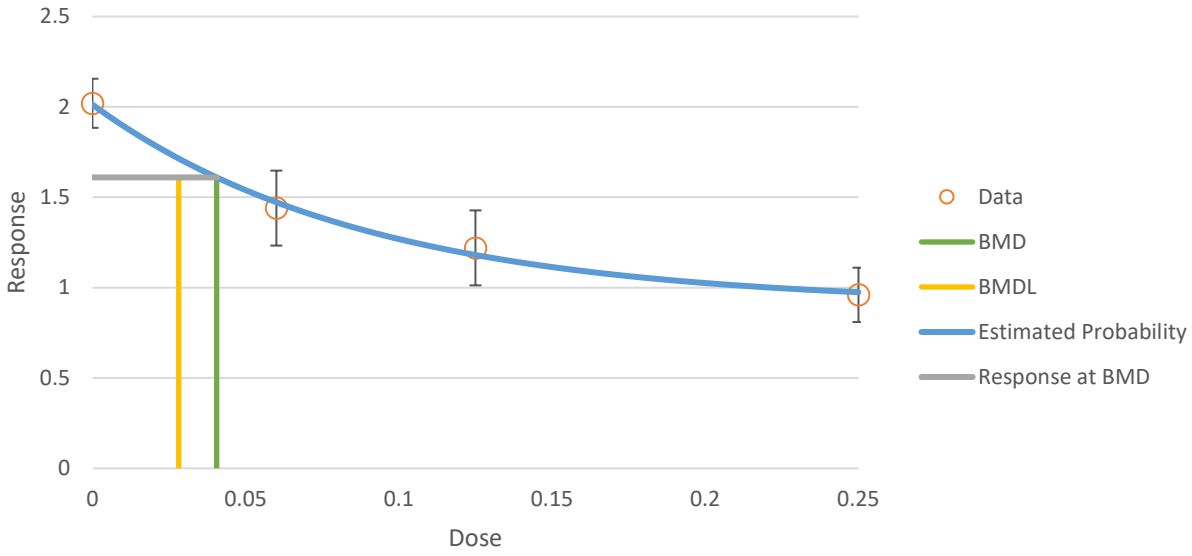
Table A-6. Results from BMD Analysis of Red Blood Cell AChE Activity in Female Wistar Rat Pups Administered Daily via Gavage for 11 Consecutive Days to Disulfoton

					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.

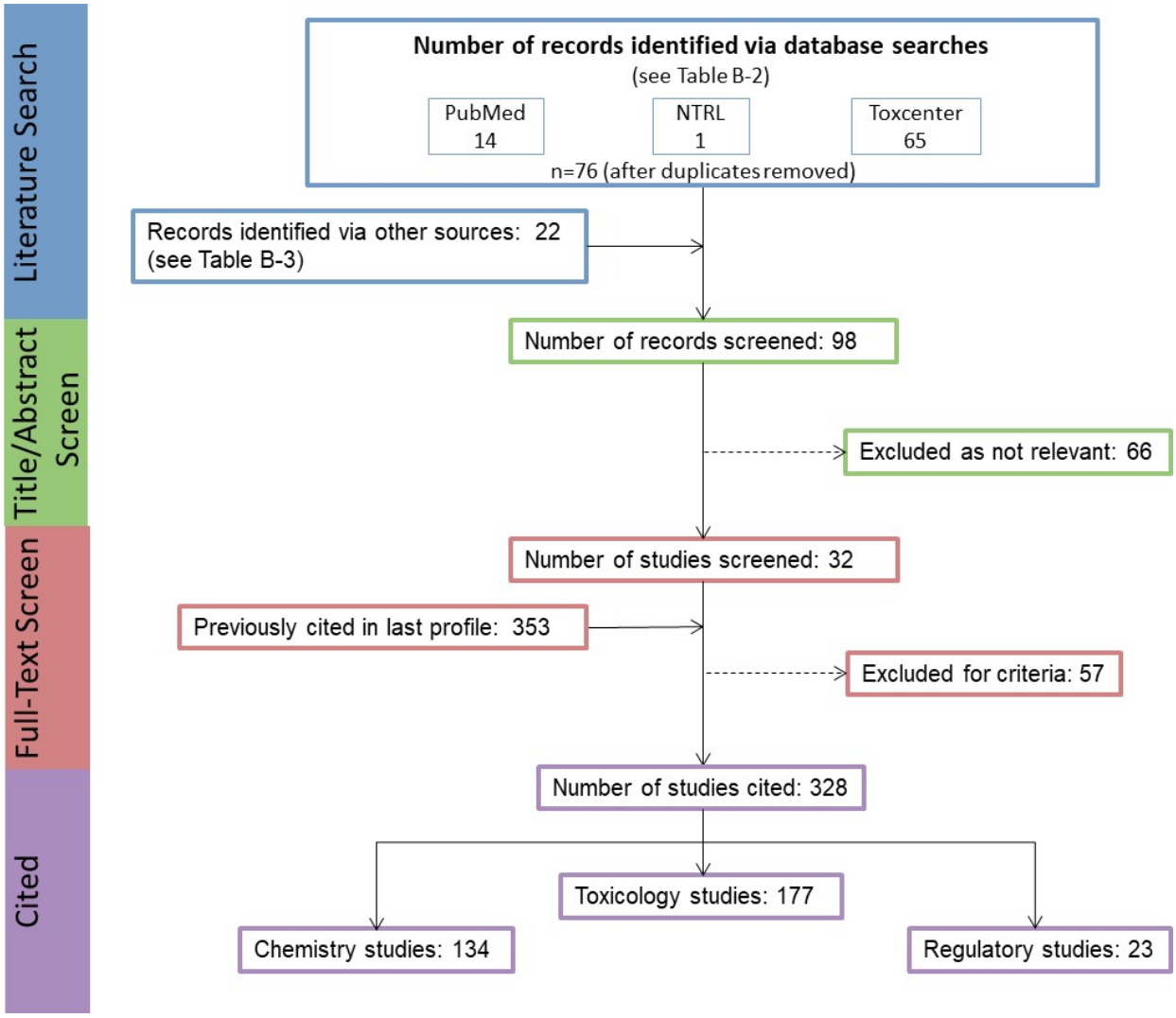
- Number of titles and abstracts screened: 98
- Number of studies considered relevant and moved to the next step: 32

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

	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
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:

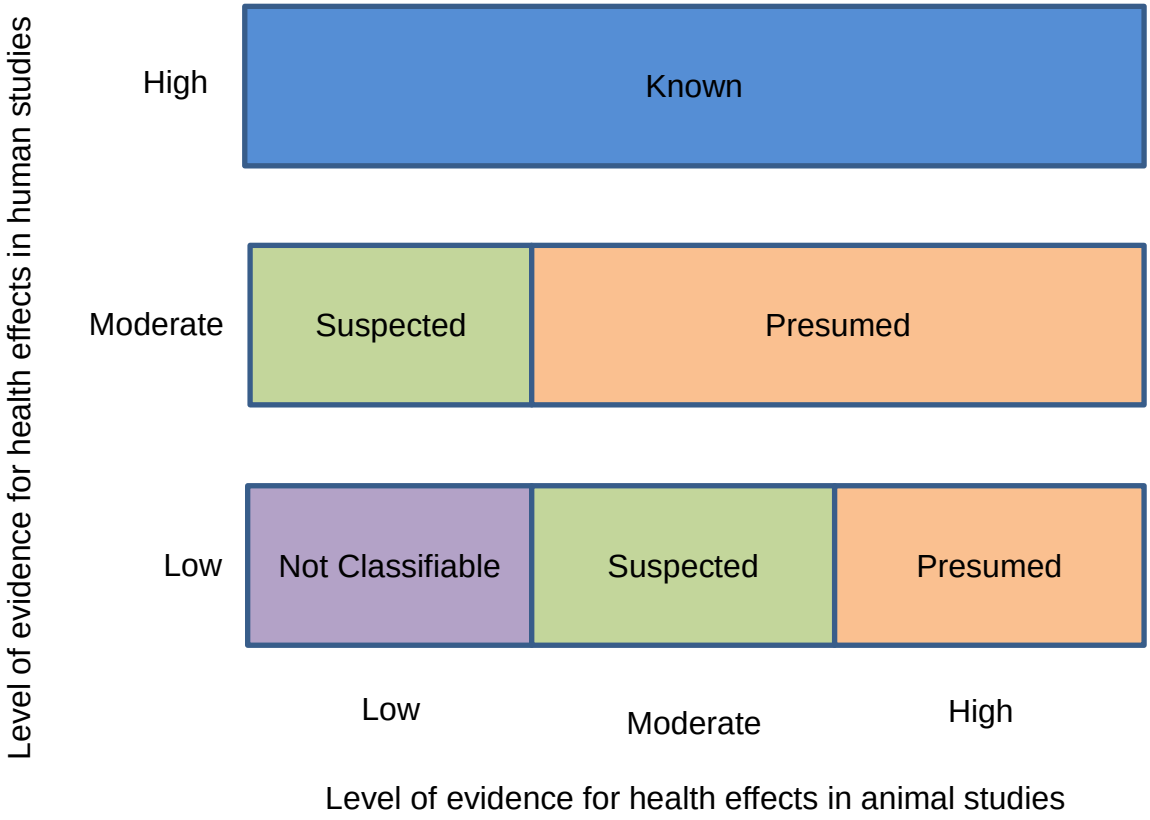
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

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)

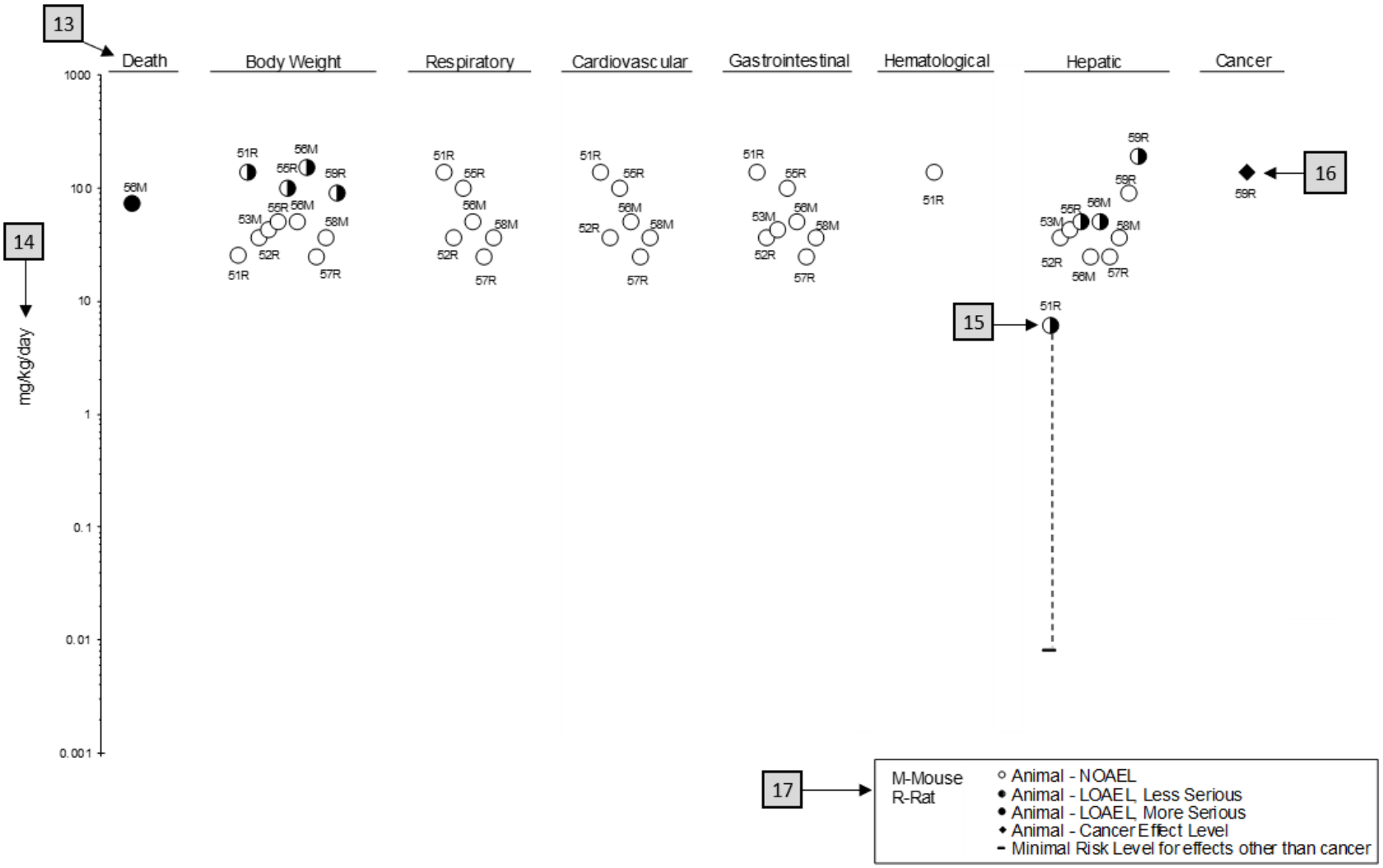
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 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