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*:** DDT, DDE, DDD, and their isomers
CAS Numbers: 50-29-3, 72-55-9, 72-54-8
Date: April 2022
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: No acute-duration inhalation studies were identified.

Agency Contacts (Chemical Manager): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** DDT, DDE, DDD, and their isomers
CAS Numbers: 50-29-3, 72-55-9, 72-54-8
Date: April 2022
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL.

Rationale for Not Deriving an MRL: No intermediate-duration inhalation studies were identified.

Agency Contacts (Chemical Manager): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** DDT, DDE, DDD, and their isomers
CAS Numbers: 50-29-3, 72-55-9, 72-54-8
Date: April 2022
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies were identified.

Agency Contacts (Chemical Manager): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	DDT, DDE, DDD, and their isomers
CAS Numbers:	50-29-3, 72-55-9, 72-54-8
Date:	April 2022
Profile Status:	Final
Route:	Oral
Duration:	Acute
MRL:	0.0005 mg/kg/day (0.5 µg/kg/day)
Critical Effect:	Developmental neurobehavioral and neurological effects
Reference:	Johansson et al. 1995, 1996; Eriksson and Nordberg 1986; Eriksson et al. 1990a, 1990b, 1992, 1993
Point of Departure:	LOAEL of 0.5 mg/kg
Uncertainty Factor:	1,000
LSE Graph Keys:	59, 60, 61, 62, 63, 66, 67
Species:	Mouse

MRL Summary: An acute-duration oral MRL of 0.0005 mg/kg/day (0.5 µg/kg/day) was derived for DDT, DDE, and DDD based on increased spontaneous motor activity, delayed habituation, and decreased density of muscarinic receptors in the cerebral cortex of NMRI mice at various timepoints after a single exposure to technical DDT on PND 10. The MRL is based on a LOAEL of 0.5 mg/kg on PND 10 and 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: At least 30 animal studies have evaluated the acute-duration oral toxicity of DDT, DDE, or DDD and their related isomers in a variety of animal models including monkeys, rats, mice, dogs, and rabbits. These studies examined a wide range of potentially sensitive targets: developmental, neurodevelopmental, endocrine, hepatic, neurological, reproductive, and diabetes-related effects. The LOAELs for these outcomes range from 0.5 to 500 mg/kg/day. The lowest LOAELs for these effects (and associated NOAELs) are summarized in Table A-1; given the number of studies, data in the table are limited to studies that identified LOAELs ≤50 mg/kg/day.

A comparison of the LOAELs suggest that the neurodevelopmental outcomes are the most sensitive effect following acute-duration oral exposure, followed by other developmental, diabetes-related, liver, reproductive, neurological, and endocrine outcomes. The lowest reliable LOAEL was 0.5 mg technical DDT/kg for neurodevelopmental effects in mice identified in a group of seven related studies. Following a single exposure on PND 10, mice exhibited delays in habituation behaviors, increased motor activities, and reductions in muscarinic receptor densities in the cerebral cortex (Eriksson and Nordberg 1986; Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996). Other developmental effects including decreases in fetal weight (Fabro et al. 1984; Hart et al. 1972), retained thoracic nipples (You et al. 1998), delayed vaginal opening (Gellert and Heinrichs 1975), and increases in body weight of adult offspring (Gellert and Heinrichs 1975) were observed at doses ≥1.0 mg/kg/day. At 1 mg DDT(NS)/kg/day, a 33% decrease in fetal weight was observed in rabbits (Fabro et al. 1984); it is noted that changes in offspring weight status was a common effect following *in utero* exposure; however, the direction of change was not consistent across studies. At 2 mg *p,p'*-DDE/kg/day, increases in fasting blood glucose levels were observed in mice (Howell et al. 2014); no increases in glucose tolerance or alterations in indicators of insulin-induced glucose disposal were observed. Increased relative and/or absolute liver weights were commonly observed in rats acutely exposed to *p,p'*-DDT, *p,p'*-DDE, or technical DDT at doses ≥5 mg/kg/day (Kang et al. 2004; Kostka et al. 2000; Leavens et al. 2002; Nims et al. 1998; Tomiyama et al. 2004). Kostka et al. (2000) was the only study reporting histological alterations; necrotic liver changes were observed in rats exposed to 12 mg *p,p'*-DDT/kg/day for 14 days.

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Acute Oral Exposure to DDT, DDE, and DDD Isomers

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference/compound
Liver effects					
F344 rat	2 weeks	ND	5	Increased relative liver weight	Tomiyama et al. 2004 *p,p'*-DDT
Wistar rat	2 weeks	ND	12	Increased relative liver weight; necrotic changes	Kostka et al. 2000 Technical DDT
F344 rat	2 weeks	7.6	23	Increased relative liver weight	Nims et al. 1998 *p,p'*-DDE
F344 rat	2 weeks	8.5	25	Increased relative liver weight	Nims et al. 1998 *p,p'*-DDT
Long-Evans rat	4 days	12.5	25	Increased relative liver weight	Leavens et al. 2002 *p,p'*-DDE
Sprague-Dawley rat	10 days	ND	25	Increased absolute liver weight (42%)	Kang et al. 2004 *p,p'*-DDE
Wistar rat	5 or 12 days	ND	40	Increased in relative liver weight	dtze Waziers and Azais 1987 DDT(NS)
Neurodevelopmental effects					
NMRI mouse	Once PND 10	ND	0.5	Decreased muscarinic receptors in cerebral cortex; increased spontaneous activity at 5 months	Johansson et al. 1995 Technical DDT
NMRI mouse	Once PND 10	ND	0.5	Decreased muscarinic receptors in cerebral cortex; increased spontaneous activity at 5 and 7 months	Johansson et al. 1996 Technical DDT
NMRI mouse	Once at PND 3, 10, or 19	ND	0.5	Decrease in cerebral cortex muscarinic acetylcholine receptor binding; delayed habituation in males at 4 months of age and dosed on PND 10; no change in proportion of HA and LA binding sites or affinity constants; no changes in mice dosed on PND 3 or 19	Eriksson et al. 1992 Technical DDT

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Acute Oral Exposure to DDT, DDE, and DDD Isomers

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference/compound
NMRI mouse	Once, PND 10	ND	0.5	Increased motor activity (delayed habituation) at 4 months, increased potassium evoked acetylcholine release, reduced density of muscarinic receptors in cerebral cortex at 3 months; no change in choline acetyltransferase activity	Eriksson et al. 1990b Technical DDT
NMRI mouse	Once, PND 10	ND	0.5	Delayed habituation observed as increased motor activity at 4 months	Eriksson et al. 1990a DDT(NS)
NMRI mouse	Once, PND 10	ND	0.5	At 5 months of age: delayed habituation (increased motor activity), decrease in cortical muscarinic acetylcholine receptors, no change in high affinity or low affinity muscarinic binding sites	Eriksson et al. 1993 DDT(NS)
NMRI mouse	Once, PND 10	ND	0.5	At 7 days after exposure: increased muscarinic receptor binding, decreased high affinity and increased low affinity muscarinic binding; no effect on sodium-dependent choline uptake; no changes 24 hours after exposure	Eriksson and Nordberg 1986 DDT(NS)
Other developmental effects					
New Zealand rabbit	GDs 4–7	ND	1.0	On GD 28, 33% decreased fetal weight; decreased fetal brain and kidney weights	Fabro et al. 1984 DDT(NS)
New Zealand rabbit	GDs 7–9	ND	10	11% decreased fetal weight on day 28	Hart et al. 1972 *p,p'*-DDT
Sprague-Dawley rat	GDs 14–18	ND	10	PND 13 males retained thoracic nipples; no effect on postnatal body weights, AGD, age of preputial separation; no effect on reproductive organ weights or serum testosterone	You et al. 1998 *p,p;*-DDE
Sprague-Dawley rat	GDs 15–19	ND	28	Delayed vaginal opening (2 days)	Gellert and Heinrichs 1975 *o,p'*-DDD
Sprague-Dawley rat	GDs 15–19	ND	28	Adult offspring: 11.9% increase in body weight; No effects on estrous cycle, vaginal opening, or ovary, adrenal or anterior pituitary weights	Gellert and Heinrichs 1975 *o,p'*-DDE

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Acute Oral Exposure to DDT, DDE, and DDD Isomers

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference/compound
Sprague-Dawley rat	GDs 15–19	ND	28	Offspring: 13% increase in body weight; no effects on estrous cycle, vaginal opening, or ovary, adrenal or anterior pituitary weights	Gellert and Heinrichs 1975 *o,p'*-DDT
Sprague-Dawley rat	GDs 15–19	ND	28	In offspring: 26% decrease in ovary weight; 9% increase body weight; no effects on estrous cycle or vaginal opening	Gellert and Heinrichs 1975 *p,p'*-DDT
Neurological effects (adults)					
F344 rat	Once	25	50	Hyperirritability and tremors; more severe at 100 mg/kg/day	Tilson et al. 1987 *p,p'*-DDT
F344 rat	Once	25	50	Tremors, more severe at 75 and 100 mg/kg/day; increased brain 5-HIAA, aspartate, and glutamate	Hong et al. 1986; Hudson et al. 1985 *p,p'*-DDT
Endocrine effects					
Sprague-Dawley rat	Once	25	50	Reduced capacity to concentrate iodine in thyroid	Goldman 1981 Technical DDT
Dog	14 days	ND	50	Decreased plasma glucocorticoids	Cueto 1970 *o,p'*-DDD
Reproductive effects					
New Zealand rabbit	GDs 7–9 or 21–23	ND	10	Increased resorptions and prematurity	Hart et al. 1972 *p,p'*-DDT
New Zealand rabbit	GDs 7–9	ND	50	Increased resorptions	Hart et al. 1971 *p,p'*-DDT

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Acute Oral Exposure to DDT, DDE, and DDD Isomers

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference/compound
Diabetes-related effects					
Sprague-Dawley rat	14 days	ND	2	Altered glucose homeostasis (increased fasting glucose and insulin, insulin resistance, impaired glucose tolerance)	Liang et al. 2020 *p,p'*-DDE
C57BL/6H mouse	5 days	0.4	2	Hyperglycemia	Howell et al. 2014 *p,p'*-DDE

5-HIAA = 5-hydroxyindoleacetic acid; AGD = anogenital distance; DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; ND = not determined; PND = postnatal day

Increases in resorptions were observed in rabbits exposed to 10 mg/kg/day on GDs 7–9 (Hart et al. 1972). Neurological and endocrine effects have been observed at higher doses (≥50 mg/kg/day). The effects included tremors in adult rats after single exposures to *p,p'*-DDT (Hong et al. 1986; Hudson et al. 1985; Hwang and Van Woert 1978; Tilson et al. 1986, 1987) and decreased plasma glucocorticoids and reduced capacity to concentrate iodine in the thyroid were observed in dogs exposed to *o,p'*-DDD for 14 days (Cueto 1970) and in rats receiving a single dose to technical DDT (Goldman 1981), respectively. Neurodevelopmental effects were selected as the critical effect for derivation of the acute-duration oral MRL since it occurred at the lowest LOAEL of 0.5 mg/kg.

Selection of the Principal Studies: A group of seven related neurodevelopmental studies by the same investigators have consistently demonstrated an increase in spontaneous behaviors resulting in delayed habituation in 3–7-month-old mice (Eriksson and Nordberg 1986; Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996). Additionally, five of these studies consistently reported a decrease in the density of muscarinic cholinergic receptors in the cerebral cortex at various time points following exposure. The seven studies were selected as co-principal studies.

Summary of the Principal Studies:

Eriksson P, Nordberg A. 1986. The effects of DDT, DDOH-palmitic acid, and chlorinated paraffin on muscarinic receptors and the sodium-dependent choline uptake in the central nervous system of immature mice. Toxicol Appl Pharmacol 85:121-127.

Eriksson P, Archer T, Fredriksson A. 1990a. Altered behaviour in adult mice exposed to a single low dose of DDT and its fatty acid conjugate as neonates. Brain Res 514:141-142.

Eriksson P, Nilsson-Hakansson L, Nordberg A, et al. 1990b. Neonatal exposure to DDT and its fatty acid conjugate: Effects on cholinergic and behavioural variables in the adult mouse. Neurotoxicology 11:345-354.

Eriksson P, Ahlbom J, Fredriksson A. 1992. Exposure to DDT during a defined period in neonatal life induces permanent changes in brain muscarinic receptors and behaviour in adult mice. Brain Res 582:277-281.

Eriksson P, Johansson U, Ahlbom J, et al. 1993. Neonatal exposure to DDT induces increased susceptibility to pyrethroid (bioallethrin) exposure at adult age - changes in cholinergic muscarinic receptor and behavioural variables. Toxicology 77:21-30

Johansson U, Fredriksson A, Eriksson P. 1995. Bioallethrin causes permanent changes in behavioural and muscarinic acetylcholine receptor variables in adult mice exposed neonatally to DDT. Eur J Pharmacol 293:159-166.

Johansson U, Fredriksson A, Eriksson P. 1996. Low-dose effects of paraoxon in adult mice exposed neonatally to DDT: Changes in behavioural and cholinergic receptor variables. Environ Toxicol Pharmacol 2:307-314.

In each study, groups of 10-day-old male NMRI mice were treated by gavage with a single dose of 0 (vehicle control) or 0.5 mg DDT (technical or NS)/kg in a 20% fat emulsion vehicle. Spontaneous behavior tests evaluating locomotion, rearing, and total activity were performed at either 4 (Eriksson et al. 1990a, 1990b, 1992), 5 (Eriksson et al. 1993; Johansson et al. 1996), or 7 months of age (Johansson et al. 1995, 1996). To determine the importance of exposure time during development, Eriksson et al. (1992) also dosed groups of mice on PND 3 or 19. To evaluate densities of muscarinic receptors, mice were

sacrificed 24 hours, 7 days (Eriksson and Nordberg 1986), or 4, 5, or 7 months following exposure (Eriksson et al. 1990b, 1992; Johansson et al. 1995, 1996). Behavioral tests of spontaneous activity were conducted on 9–12 mice/group for 1 hour, and scores were summed for three 20-minute periods. During the last 40 minutes of testing, mice treated on PND 10 consistently showed significantly more activity than untreated controls (see Table A-2). This was interpreted as disruption of a simple, non-associative learning process (i.e., habituation) or a retardation in adjustment to a new environment. Mice dosed on PND 3 or 19 responded similarly to vehicle controls indicating that the developmental processes occurring on or immediately after PND 10 is particularly sensitive to exposure to technical DDT (Eriksson et al. 1992). To try to relate behavioral effects to specific neurological changes in the brain, several of the studies evaluated whether technical DDT affected the density of muscarinic acetylcholine (MACh) receptors in the brain, which are known to modulate neuronal excitability. Mice were sacrificed at various time points and crude synaptosomal P2 fractions were prepared from the cerebral cortex for measurement of MACh receptor densities. Details of sample preparation are less well described across studies; Eriksson and Nordberg (1986) reported pooling fractions from two to three animals, thereby generating a single biological replicate that was assayed in duplicate. More animals were used in other studies, but whether these samples were also pooled is unclear.

A summary of the results of these studies is found in Table A-2. Increases in motor activity were observed in mice exposed at PND 10 and tested at ≥4 months of age. Exposure at PND 10 also alters the density of MACh receptors, showing a significant ~10% increase when evaluated in the neonatal brain at 7 days post-exposure (Eriksson and Nordberg 1986), with a significant 3–30% increase when evaluated in the adult mouse brain at 3–7 months of age (Eriksson et al. 1990b, 1992, 1993; Johansson et al. 1995, 1996). The authors suggested that the changes in MACh density and behavior might be the consequence of early interference with muscarinic cholinergic transmission specifically around the age of 10 days (Eriksson et al. 1992). The differential findings at 7 days post-exposure, compared to 3–7 months post-exposure, are likely due to initial upregulation of MACh receptors followed-by downregulation, potentially due to DDT and/or metabolite levels that peak 1–7 days post-exposure (Eriksson et al. 1990b). Eriksson et al. (1990b) also measured MACh densities from P2 fractions prepared from the hippocampus and striatum, but only MACh densities within the cerebral cortex were reduced. A few studies also measured proportions of muscarinic high- and low-affinity binding sites. In 7-day-old mice, there was a significant increase in the percentage of low-affinity binding sites and a significant decrease in high-affinity binding sites (Eriksson and Nordberg 1986). According to the authors, these low-affinity binding sites correspond to the M_1 receptor in the cerebral cortex, which is thought to be associated with neuronal excitation. At later time points, no differences in high- or low-affinity proportions were observed. Other neurological tests described in these studies that yielded no significant effects include: measurements of sodium dependent choline uptake in the cerebral cortex (Eriksson and Nordberg 1986); choline acetyltransferase (ChAT) activity and potassium evoked release of ACh from the cerebral cortex (Eriksson et al. 1990b); acetylcholinesterase activity; proportions of nicotinic high- and low-affinity binding sites; and swim maze tests (Johansson et al. 1995, 1996).

Table A-2. Spontaneous Activity Test Results After a Single Oral Exposure of NMRI Mice to 0.5 mg/kg Technical DDT on PND 10

Reference	Treatment (PND)	Evaluation age (months)[a]	Locomotion[b]	Rearing[b]	Total activity[b]	Muscarinic receptor density
Eriksson and Nordberg 1986	10	24 hours after dose	NT	NT	NT	-
Eriksson and Nordberg 1986	10	7 days after dose	NT	NT	NT	↑
Eriksson et al. 1990a	10	4	- ↑ ↑	↑ ↑ ↑	- ↑ ↑	NT
Eriksson et al. 1990b	10	4	- ↑ ↑	↑ ↑ ↑	- ↑ ↑	↓
Eriksson et al. 1992	10	4	- ↑ ↑	↑ ↑ ↑	- ↑ ↑	↓
Eriksson et al. 1992	3	4	- - -	- - -	- - -	-
Eriksson et al. 1992	19	4	- - -	- - -	- - -	-
Eriksson et al. 1993	10	5	- ↑ ↑	↑ ↑ ↑	- ↑ ↑	↓
Johansson et al. 1995	10	7	- ↑ ↑	↑ ↑ ↑	- ↑ ↑	↓
Johansson et al. 1996	10	5	- ↑ ↑	↑↑ ↑	- ↑ ↑	NT
Johansson et al. 1996	10	7	- ↑ ↑	↑ ↑ ↑	- ↑ ↑	↓

[a]Age at evaluation expressed in months unless indicated otherwise.
[b]Results reported (from left to right) for the 0–20-, 20–40-, and 40–60-minute measurement periods, respectively.

- (dashes) = no significant difference from vehicle controls; ↑ = increased at a particular time point, as compared with controls; ↓ = decreased, as compared with controls; DDT = dichlorodiphenyltrichloroethane; NT = not tested; PND = postnatal day

Within the group of studies, other tests were performed in attempts to further identify other exposure-related neurological effects in the cerebral cortex. Conclusions drawn from these results include: (1) DDT did not significantly alter acetylcholinesterase activity; (2) none of the treatments altered the density of nicotinic cholinergic receptors in the cortex; (3) none of the treatments altered performance in the swim maze test; (4) DDT exposure did not alter K^+-stimulated acetylcholine release; and (5) DDT did not significantly alter sodium-dependent choline uptake in the cerebral cortex.

Selection of the Point of Departure for the MRL: The data were not amenable to benchmark dose (BMD) modeling because only a single dose was evaluated. The LOAEL of 0.5 mg/kg/day was therefore chosen as the POD.

Uncertainty Factor: The LOAEL of 0.5 mg/kg was divided by a total uncertainty factor of 1,000:

- 10 for use of a LOAEL
- 10 for animal to human extrapolation
- 10 for human variability

MRL = LOAEL ÷ UFs
MRL = 0.5 mg/kg/day ÷ (10 × 10 × 10) = 0.0005 mg/kg/day (0.5 µg/kg/day)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Three additional studies by a different group of investigators evaluated neurobehavioral effects in mouse offspring after exposure *in utero* to doses ranging from 0.018 to 100 mg *o,p'*-DDT/kg/day during GDs 11–17 (Palanza et al. 1999, 2001; vom Saal et al. 1995). Palanza et al. (2001) reported no effects of *o,p'*-DDT exposure up to a high dose of 100 mg/kg/day on cliff avoidance or righting reflexes in postnatal pups. Palanza et al. (1999) administered doses of 0.018 and 0.18 *o,p'*-DDT/kg/day to pregnant dams and evaluated male offspring territorial aggression at 3 months of age. Compared to controls, treated males showed no statistically significant changes in the percent of attacking males per group or in other marks of aggression (latency to attack, number of bites, total attack time, tail rattling, or defensive behaviors). When only the attacking males from the control or the exposed groups were compared, the authors reported a reduction in aggressive behaviors in exposed males. Males exposed to 0.018 mg *o,p'*-DDT/kg/day showed a significant decrease in bite frequency and total attack time, and those exposed to 0.18 *o,p'*-DDT/kg/day also showed less tail rattling (Palanza et al. 1999). This is in contrast with a previous study reporting an increase in urine marking behavior, which is often considered a territorial behavior linked to displays of dominance and aggression (vom Saal et al. 1995). Palanza et al. (1999) also reported a small (~<12%), but significant, reduction in paired testes weight in males exposed to 0.018 mg *o,p'*-DDT/kg/day, but not 0.18 mg *o,p'*-DDT/kg/day. These studies were not considered suitable for MRL derivation due to a variety of issues, including poor reporting (e.g., no description or inclusion of statistical analysis; vom Saal et al. 1995) and inconsistencies in results across doses (Palanza et al. 1999, 2001). Since the decreased aggressive behavior effects described by Palanza et al. (1999) were observed only when select subsets of individuals were included in the analysis and vom Saal et al. (1995) reported an apparent increased aggressive behavior (e.g., increased urine marking), the collective interpretation of these results is unclear.

Agency Contacts (Chemical Managers): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** DDT, DDE, DDD, and their isomers
CAS Numbers: 50-29-3, 72-55-9, 72-54-8
Date: April 2022
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.0005 mg/kg/day (0.5 µg/kg/day)
Critical Effect: Hepatocyte hypertrophy
Reference: Harada et al. 2003, 2006
Point of Departure: $BMDL_{10}$ of 0.05 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 155
Species: Rat

MRL Summary: The chronic-duration oral MRL of 0.0005 mg/kg/day (0.5 µg/kg/day) was adopted as the intermediate-duration oral MRL for DDT, DDE, and DDD based on an increased incidence of hepatocyte hypertrophy in male rats administered *p,p'*-DDT in their diets for 78 weeks (Harada et al. 2003, 2006). The MRL is based on a BMDL of 0.05 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Numerous animal studies have evaluated the oral toxicity of DDT, DDE, or DDD and their related isomers following intermediate-duration exposure. These studies examined a wide range of potentially sensitive targets. The LOAELs for these effects range from 0.25 to 200 mg/kg/day. The most sensitive outcomes were hepatic, reproductive, developmental, immunological, and neurological effects. A summary of lowest LOAELs (and associated NOAELs) for relevant endpoints is presented in Table A-3; given the number of studies evaluating these endpoints, only LOAELs ≤20 mg/kg/day are included in the table.

As shown in Table A-3, several effects associated with intermediate-duration exposure have been observed at levels ≤0.17 mg/kg/day. These include: (1) liver effects such as hepatic hypertrophy (Harada et al. 2003, 2006; Laug et al. 1950) and hepatocyte cytoplasmic vacuolation, mitochondrial changes, and lipid droplets (Liu et al. 2017a, 2017b); (2) developmental effects including cardiac hypertension and hypertrophy (La Merrill et al. 2016) and metabolic effects consisting of impaired glucose tolerance, hyperinsulinemia, dyslipidemia, and impaired cold tolerance (La Merrill et al. 2014a, 2014b); (3) reproductive effects including decreased corpora lutea and number of implants (Lundberg 1974); and (4) metabolic syndrome (Liang et al. 2020). The lowest LOAELs for immunological effects, including decreased immunoglobulins or antibody titers in response to antigens (Banerjee 1987a, 1987b; Banerjee et al. 1997a; Banerjee et al. 1995, 1996, 1997a, 1997b; Koner et al. 1998) and for neurological effects including decreased brain lipids (Sanyal et al. 1986) were observed at higher doses.

The liver is considered a primary target for DDT, DDE, DDD, and their related isomers, and hepatic toxicity (hepatocellular hypertrophy) was chosen as the critical effect for intermediate-duration exposures. Sixteen intermediate-duration studies evaluated liver toxicity, including two recent multi-dose studies that provide incidence data for non-neoplastic lesions in the liver (Harada et al. 2003, 2006; Hojo et al. 2006). Observed effects include hepatocellular hypertrophy in rats at 0.17 mg/kg/day (Harada et al. 2003, 2006), increases in liver weight in mice exposed to 5 mg *p,p'*-DDT/kg/day (Tomiyama et al. 2004), fatty changes in hepatocytes in male rats exposed to 3.44 *p,p'*-DDT/kg/day (Hojo et al. 2006), and focal necrosis in rats at 6.6 mg DDT(NS)/kg/day (Jonsson et al. 1981). Although several other effects also identified low LOAEL values, there is more supporting and consistent evidence that the liver is the critical target.

Table A-3. Summary of Relevant LOAEL and NOAEL Values Following Intermediate Oral Exposure to DDT, DDE, or DDD Isomers

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference/compound
Liver effects					
Osborne-Mendel rat	15–27 weeks	0.05	0.25	Cellular hypertrophy and cytoplasmic eosinophilia; only qualitative data reported; effects described appear to have been minimal	Laug et al. 1950 Technical DDT
C57BL/6N mouse	8 weeks	ND	1.0	Cytoplasmic vacuolation in hepatocytes, mitochondrial changes and lipid droplets (qualitative data only); no change in AST, ALT, ALP	Liu et al. 2017a, 2017b *p,p'*-DDE
F344/DuCrj rat	26 weeks	0.21 F	0.17 M 2.2 F	Increased incidence of hepatocellular hypertrophy (6/6 exposed versus 0/6 controls) in both males and females at 1.7 and 2.2 mg/kg/day, respectively; 2/6 males at 0.17 mg/kg/day	Harada et al. 2003, 2006 *p,p'*-DDT
Sherman rat	2–6 months	0.5 M 5 F	1.7 M 20 F	Mild hypertrophy, presence of lipospheres and cell margination; effects were dose-related and more pronounced at 5 mg/kg/day; qualitative data only	Ortega 1956 Technical DDT
Sprague-Dawley rat	2 generations, 10 weeks before mating, then through mating, gestation, and lactation	0.343 M 0.73 F	3.44 M 3.75 F	P and F1 males: centrilobular hypertrophy, fatty change of hepatocytes (males only); increased relative liver weights	Hojo et al. 2006 *p,p'*-DDT
F344 rat	28 days	ND	5	Increased absolute and relative liver weight, no liver histology done	Tomiyama et al. 2004 *p,p'*-DDT
NMRI mouse	28 days	ND	6.25	increased absolute and relative liver weight	Orberg and Lundberg 1974 *p,p'*-DDT
Sprague-Dawley rat	36 weeks	ND	6.6	Hepatic focal necrosis/regeneration	Jonsson et al. 1981 DDT (NS)
Hissar albino mouse	3–12 weeks	4.0	10	Increased relative liver weight (14.7%); no liver histology done	Banerjee et al. 1986 *p,p'*-DDT

Table A-3. Summary of Relevant LOAEL and NOAEL Values Following Intermediate Oral Exposure to DDT, DDE, or DDD Isomers

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference/compound
Wistar rat	3 weeks	ND	15	Significant increase in liver weight; no liver histology done	Gupta et al. 1989 *p,p'*-DDT
Wistar rat	6 weeks	ND	20.2	Increased relative liver weight (14.7%); no liver histology done	Banerjee et al. 1996 *p,p'*-DDT
Wistar rat	6 weeks	ND	20.2	Increased relative liver weight (17.1% increase); no liver histology done	Banerjee et al. 1996 *p,p'*-DDE
Neurological effects					
Rhesus monkey	100 days	ND	10	15–20% decrease in brain lipids, central nervous system phospholipids, and cholesterol	Sanyal et al. 1986 Technical DDT
Developmental effects					
C57BL/6J mouse	GD 12–PND 5	ND	1.7	Cardiac hypertension: increased systolic and diastolic blood pressure in male offspring at 5 months; increase systolic in males and females at 7 months; cardiac hypertrophy (increased left ventricular wall thickness) in females, but not males	La Merrill et al. 2016 Prepared mixture of *p,p'*-DDT (77.2%) and *o,p'*-DDT (22.8%)
C57BL/6J mouse	GD 12–PND 5	ND	1.7	In females on high-fat diets for 12 weeks: metabolic syndrome (impaired glucose tolerance, hyperinsulinemia, dyslipidemia, impaired cold tolerance, altered bile acid metabolism); no effect on timing of puberty	La Merrill et al. 2016 Prepared mixture of *p,p'*-DDT (77.2%) and *o,p'*-DDT (22.8%)
Sprague-Dawley rat	GD 6–PND 20	5	15	Increased relative liver weight (10.1%)	Yamasaki et al. 2009 *p,p'-DDE*
Wistar rat	GDs 1–21 and LDs 1–21	1.7	16.8	Decreased body weights and growth of nursing pups	Clement and Okey 1974 *o,p'-DDT*

Table A-3. Summary of Relevant LOAEL and NOAEL Values Following Intermediate Oral Exposure to DDT, DDE, or DDD Isomers

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference/compound
Immunological effects					
Albino rat	31 days	ND	1.9	Decreased mast cells	Gabliks et al. 1975 DDT (NS)
Albino rat	8–22 weeks	2.2	5.5	Decreased relative spleen weight (17% decrease), increased serum albumin/globulin ratio and reduced IgG titers after tetanus toxoid stimulation; no effect on IgM titers, relative thymus weight, or body weight	Banerjee 1987b *p,p'*-DDT
Wistar rat	4 weeks	2.3	5.7	Decreased IgG and IgM; increased albumin/globulin ratio	Banerjee et al. 1995 *p,p'*-DDT
Hissar mouse	3–12 weeks	4.2	10.5	Decreased splenic plaque-forming cell response to T-antigen independent lipopolysaccharide at weeks 6–12; decreased IgM antibody titer at 21 mg/kg/day	Banerjee 1987a *p,p'*-DDT
Rockfeller mouse	24 weeks	4.3	10.7	Increased growth of *Mycobacterium leprae* in footpad	Banerjee et al. 1997a *p,p'*-DDT
Wistar rat	6 weeks	ND	20.2	After ovalbumin immunization: decreased serum IgG and IgM, and ovalbumin antibody titre; increased percent migration of leukocytes and macrophages; decreased footpad thickness; decreased relative spleen weight; no effect on thymus weight	Banerjee et al. 1996 *p,p'*-DDT
Reproductive effects					
NMRI mouse	28 days	ND	1.67	Prolonged length of estrus cycle; decreased number of implants (223 versus 250 in controls)	Lundberg 1973 *p,p'*-DDT
NMRI Mouse	72–74 days	ND	2.0	Decreased corpora lutea (17.2%) and small decrease in implants (125 versus 128)	Lundberg 1974 *p,p'*-DDT
New Zealand rabbit	12 weeks (3 times/week)	ND	3.0	Decreased ovulation rate and slight decrease in circulating progesterone post-insemination	Lindenau et al. 1994 Technical DDT

Table A-3. Summary of Relevant LOAEL and NOAEL Values Following Intermediate Oral Exposure to DDT, DDE, or DDD Isomers

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference/compound
Sprague-Dawley rat	2-generations, 10 weeks before mating, then through mating, gestation, and lactation	0.73	3.75	F0 females: decreased estradiol levels; increased progesterone at 27.7 mg/kg/day, but no effects on F0 or F1 indices of mating and fertility, or viability of F1 and F2 offspring in any exposure group	Hojo et al. 2006 *p,p'*-DDT
B6C3F1 mouse	86–130 days	3.4	5.1	Decreased number of pups/litter at birth or PND 1; decreased fertility	Ledoux et al. 1977 Technical DDT
NMRI mouse	28 days	ND	6.25	Reduced seminal vesicles weight (28% reduced) in castrated males only; no effect on seminal vesicles or testes weight in intact animals	Orberg and Lundberg 1974 *p,p'-DDT*
Sprague-Dawley rat	104 days; 14 days *in utero*, 20 lactational days, 70 days directly	ND	35	Increased serum testosterone, increased testicular mass and relative testes weight, and decreased seminiferous tubule diameter, seminiferous epithelium thickness, and lumen diameter	Patrick et al. 2016 DDE (NS)
Sprague-Dawley rat	GD 6–PND 20	15	50	Significantly reduced weaning index and number of pups live on PND 21; no significant effects on number of litters, gestation index, gestational length, number of pups born, delivery index, birth index, or viability on PND 4	Yamasaki et al. 2009 *p,p'*-DDE
Metabolic effects					
Sprague-Dawley rat	21 days	ND	2	Metabolic syndrome (increased fat pad weight and percent body fat, altered plasma lipid profile)	Liang et al. 2020 *p,p'*-DDE

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DDD = dichlorodiphenyldichloroethane; DDE = dichloro-diphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; F = female(s); GD = gestation day; LOAEL = lowest observed adverse effect level; M = male(s); ND = not detected; NOAEL = no observed-adverse-effect level; NS = not specified; P gen = parental generation; PND = postnatal day; LD = lactation day

Selection of the Principal Study: Harada et al. (2003, 2006) reported increases in the incidence of hepatocellular hypertrophy in males exposed to ≥0.17 mg/kg/day *p,p'*-DDT. Although the incidence (2/6) was not statistically different from controls (0/6), ATSDR considered this dose associated with a 33% increased incidence to be a LOAEL. At the next highest dose (1.7 mg/kg/day), hypertrophy was observed in 6/6 males and 6/6 females. This LOAEL is supported by the Laug et al. (1950) and Liu et al. (2017a, 2017b) studies. Other liver effects included microsomal enzyme activity, proliferation, inhibition of cell communication, and oxidative stress, in both males and females made at several timepoints between 4 and 52 weeks. Laug et al. (1950) reported hepatocellular hypertrophy in rats exposed to 0.25 mg technical DDT/kg/day for 15–27 weeks. However, Laug et al. (1950) provided no incidence data or statistical analysis, and only noted that at 0.25 mg/kg/day, "some of the rats were unaffected," and the liver effects "were truly minimal." Similarly, the Liu et al. (2017a, 2017b) studies only provided qualitative evidence of hepatocellular cytoplasmic vacuolation, mitochondrial changes, and lipid droplets in mice exposed to 1.0 mg *p,p'*-DDE/kg/day for 8 weeks. Hojo et al. (2006), reported quantitative hepatocyte hypertrophy incidence results that were consistent with the findings in Harada et al. (2003, 2006) and identified a LOAEL of 3.44 mg *p,p'*-DDT/kg/day and a NOAEL of 0.343 mg/kg/day. Because the Harada et al. (2003, 2006) study provides a better description of the dose-response relationship for liver lesions, it was selected as the basis of the MRL.

Summary of the Principal Study:

Harada T, Yamaguchi S, Ohtsuka R, et al. 2003. Mechanisms of promotion and progression of preneoplastic lesions in hepatocarcinogenesis by DDT in F344 rats. Toxicol Pathol 31(1):87-98.

Harada T, Ohtsuka R, Takeda M, et al. 2006. Hepatocarcinogenesis by DDT in rats. J Toxicol Pathol 19:155-167.

Groups of 20 male and 20 female Fisher (F344/DuCrj) rats, 5 weeks of age, were administered 0, 5, 50, or 500 ppm *p,p'*-DDT in feed for 26 weeks (Harada et al. 2003, 2006). The study report provided intakes of 0, 0.17, 1.7, or 19.1 mg *p,p'*-DDT/kg/day (males) and 0, 0.21, 2.2, or 25.2 mg/kg/day (females), based on average feed consumption and body weight throughout a 2-year feeding study. These were adopted as the exposure doses for the 26-week collection point and are considered accurate for the following reasons: (1) the reported average food consumptions at all doses were comparable between the 2-year study and a pilot 4-week study; and (2) mean body weights of rats exposed to at least the two lowest doses were comparable to controls. Animals were sacrificed and livers were examined for: (1) cell proliferation (percent proliferating cell nuclear antigen [PCNA] labeling index), (2) GJIC (number of GJIC protein Cx32 spots), (3) microsomal enzyme induction (e.g., PROD activity and P450 isozyme contents, (4) oxidative stress (LPO and 8-OHdG), and (5) histopathology.

No clinical signs, mortalities, or body weight changes compared with controls were noted during the first year of this 2-year study. At 26 weeks, the liver lesions included: (1) hepatocellular hypertrophy at 26 weeks in 100% (6/6) of male and female rats treated with doses of ≥1.7 and 2.2 mg/kg/day, respectively. In low-dose males (0.17 mg/kg/day), 2/6 rats had hypertrophy (0/6 in controls), but the incidence was not statistically significantly elevated compared with controls and (2) large eosinophilic altered hepatocellular foci (AHF) were observed in high-dose males (19.1 mg/kg/day), but not females. In addition to these lesions, the following effects were noted in the livers: (1) significantly decreased hepatic levels of GJIC protein Cx32 spots were observed in males starting at 1.7 mg/kg/day and in females at 25.2 mg/kg/day, (2) statistically significantly increased hepatic levels of CYP1A2 and CYP3A2 protein were observed starting at 0.17 mg/kg/day and increased PROD activity and CYP2B1 and CYP4A1 levels starting at 1.7 mg/kg/day in males. In females, PROD activity, and CYP2B1 and CYP3A2 levels increased starting at 2.2 mg/kg/day, and (3) signs of oxidative stress were only observed at higher doses. Hepatic LPO contents significantly increased starting at 1.7 or 2.2 mg/kg/day in males

and females, respectively, and 8-OHdG levels increased in males only at 19.2 mg/kg/day. No significant changes in cell proliferation were noted in the livers of exposed animals compared with controls.

Selection of the Point of Departure for the MRL: Male rat incidence data for 26 weeks of exposure (Table A-4) were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS; version 3.2) using a benchmark response (BMR) of 10% extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (chi-square p-value >0.1), visual inspection of the dose-response curve, BMDL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest $BMDL_{10}$ values were selected as potential PODs when the difference between the $BMDL_{10}$ estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen.

Table A-4. Incidences for Hepatic Hypertrophy in Male F344/DuCrj Rats After a 26-Week Exposure to *p,p'*-DDT in the Diet

Dose (mg/kg/day)	Incidence at 26 weeks/number
0	0/6
0.17	2/6
1.7	6/6
19.1	6/6

DDT = dichlorodiphenyltrichloroethane; N = total number of animals examined

Source: Harada et al. 2003, 2006

Only the Logistic and Probit models provided an adequate fit to the data. BMDLs were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Logistic). The frequentist, restricted Logistic model estimated a BMD_{10} and $BMDL_{10}$ of 0.14 and 0.064 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-5 and the model fit for the selected model is shown in Figure A-1.

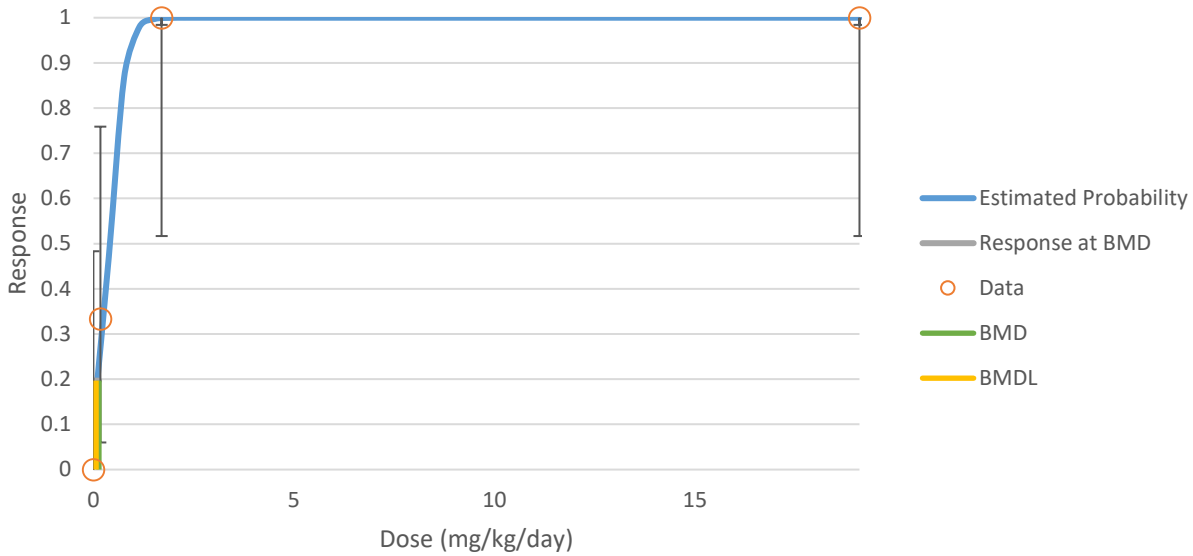
Table A-5. Model Predictions for Hepatocyte Hypertrophy in Male F344/DuCrj Rats Administered *p,p'*-DDT in Their Diet For 26 Weeks (Harada et al. 2003, 2006)

Model	BMC_{10}[a]	$BMCL_{10}$[a]	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Dichotomous Hill			1.00	11.64	-0.0003	-0.0006
Gamma[d]			1.00	9.65	-0.0003	-0.005
Log-Logistic[e]			1.00	11.64	-0.002	-0.0007
Multistage Degree 3[f]			1.00	13.64	-0.0003	3.45×10^{-8}
Multistage Degree 2[f]			1.00	11.64	-0.0003	-1.38×10^{-7}
Multistage Degree 1[f]			0.95	11.79	-0.0003	-0.19
Weibull[d]			0.99	11.67	-0.0003	-0.03
Logistic[g]	**0.14**	**0.064**	**0.77**	**11.37**	**-0.85**	**0.62**
Log-Probit			1.00	11.64	-0.0003	1.12×10^{-9}
Probit	0.24	0.15	0.35	15.44	0.24	1.18

[a]BMCLs <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.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. BMCLs for models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC was selected (Logistic).

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); BMD = benchmark dose; DDT = dichlorodiphenyltrichloroethane

Figure A-1. Fit of Logistic Model to Data for Hepatocyte Hypertrophy in Rats Administered *p,p'*-DDT in Their Diet for 26 Weeks (Harada et al. 2003, 2006)



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

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

MRL = BMDL ÷ UFs
MRL = 0.064 mg/kg/day ÷ (10 x 10) = 0.0006 mg/kg/day

Since the MRL based on hepatocellular hypertrophy at 26 weeks is slightly higher than the acute-oral MRL of 0.0005 mg/kg/day, the intermediate-duration oral database was not considered adequate for derivation of an MRL. ATSDR opted to adopt the chronic-duration oral MRL of 0.0005 mg/kg/day based on hepatocellular hypertrophy at 78 weeks (see chronic oral MRL worksheet) as the intermediate-duration oral MRL.

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The identification of the liver as the most sensitive target of toxicity is supported by a number of laboratory animal species reporting liver effects following intermediate-duration oral exposure to several DDT, DDE, and DDD isomers (Banerjee et al. 1986, 1996; Gupta et al. 1989; Harada et al. 2003, 2006; Hojo et al. 2006; Jonsson et al. 1981; Laug et al. 1950; Liu et al. 2017a, 2017b; Orberg and Lundberg 1974; Ortega 1956; Yamasaki et al. 2009). Four epidemiology studies have evaluated the possible associations between serum or cord blood DDT or DDE levels and serum or urinary biomarkers of liver damage or dysfunction (Freire et al. 2015a, 2015b; Morgan and Lin 1978; Serdar et al. 2014; Sunyer et al. 2008). The results of these studies do not provide consistent evidence for associations between levels of DDT/DDE/DDD biomarkers and alterations in serum levels of alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, lactate dehydrogenase, or bilirubin (Freire et al. 2015a, 2015b; Morgan and Lin 1978; Serdar et al. 2014). One study did find an association between cord blood DDE or DDT levels and urinary porphyrin levels (Sunyer et al. 2008).

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** DDT, DDE, DDD, and their isomers
CAS Numbers: 50-29-3, 72-55-9, 72-54-8
Date: April 2022
Profile Status: Final
Route: Oral
Duration: Chronic
MRL: 0.0005 mg/kg/day (0.5 µg/kg/day)
Critical Effect: Hepatocellular hypertrophy
Reference: Harada et al. 2003, 2006
Point of Departure: $BMDL_{10}$ of 0.05 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 155
Species: Rat

MRL Summary: A chronic-duration oral MRL of 0.0005 mg/kg/day (0.5 µg/kg/day) was derived for DDT, DDE, and DDD based on an increased incidence of hepatocyte hypertrophy in rats administered *p,p'*-DDT in their diets for 78 weeks (Harada et al. 2003, 2006). The MRL is based on a $BMDL_{10}$ of 0.05 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: At least 35 animal studies have evaluated the chronic oral toxicity of DDT, DDE, or DDD and their related isomers. These studies examined a wide range of potentially sensitive targets; the most sensitive effects appear to be hepatic, body weight, developmental, hematological, and neurological outcomes. A summary of the lowest reliable LOAELs (and associated NOAELs) for these sensitive endpoints is presented in Table A-6; the table is limited to LOAELs of ≤27 mg/kg/day, because of the large number of chronic-duration studies.

A comparison of the lowest LOAELs identified in animal studies suggests that the liver may be the most sensitive target, followed by body weight, developmental, neurological, and hematological alterations. Sixteen studies examined the liver in rats, mice, monkeys, hamsters, and dogs chronically exposed to DDT, DDE, or DDD (Cabral et al. 1982a; Deichmann et al. 1967; Del Pup et al. 1978; Durham et al. 1963; Fitzhugh and Nelson 1947; Graillot et al. 1975; Harada et al. 2003, 2006; Lehman 1965; NCI 1978 [six studies]; Rossi et al. 1983; Takayama et al. 1999). Additionally, a human study examined potential liver effects following 12–18-month dietary exposure to 0.5 mg/kg/day but did not find alterations in parameters of liver function (Hayes et al. 1956). In laboratory animals, fatty metamorphosis, hepatocellular hypertrophy, necrosis, altered hepatocellular foci, or amyloidosis have been observed at LOAELs of 0.17–49 mg/kg for technical DDT, *p,p'*-DDT, or *p,p'*-DDE. In contrast to these findings, NCI (1978) reported NOAELs of 231 and 142 mg/kg/day in rats and mice, respectively, exposed to technical DDD for 78 weeks, suggesting that the rodent liver may be less sensitive from chronic exposure to DDD, compared with DDT or DDE. At 0.4 mg/kg/day, increases in body weight gain were observed in the P0 and F1 (categorized as a developmental effect) rats exposed to *p,p'*-DDT in a 2-generation study involving lifetime exposure (Tomatis et al. 1972). The lowest LOAEL for both neurological and hematological effects is 19.1 mg *p,p'*-DDT/kg/day (Harada et al. 2003, 2006; Tomita et al. 2013); effects observed at this dose level included tremors, reductions in hemoglobin levels, and increased hematopoiesis in the bone marrow. Liver effects were selected as the critical effect because the lowest LOAEL was for liver effects, and there are extensive data supporting it as a critical effect.

Table A-6. Summary of Relevant LOAEL and NOAEL Values Following Chronic Oral Exposure to DDT, DDE, and DDD Isomers

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference/compound
Hepatic effects					
F344/DuCrj rat	2 years	ND	0.17 M 2.2 F	Increased incidence of hepatocellular hypertrophy	Harada et al. 2003, 2006 *p,p'*-DDT
B6C3F1 mouse	78 weeks	ND	3.7 M	Amyloidosis (males only)	NCI 1978 Technical DDT
Cynomolgus monkey	130 months	ND	6.4 F	Fatty changes	Takayama et al. 1999 *p,p'*-DDT
Osborne-Mendel rat	2 years	ND	7	Focal hepatocellular necrosis	Fitzhugh and Nelson 1947 Technical DDT
Osborne-Mendel rat	27 months	ND	20	Focal hepatocellular necrosis	Deichmann et al. 1967 DDT (NS)
Syrian hamster	Lifetime	10 M	20 M	Focal necrosis, hepatocyte hypertrophy, no increase in tumors	Cabral et al. 1982a Technical DDT
Osborne-Mendel rat	78 weeks	ND	23 M	Fatty metamorphosis	NCI 1978 Technical DDT
Neurological effects					
F344/DuCrj rat	2 years	1.7 M 2.2 F	19.1 M 25.2 F	Whole body tremors weeks 70–104	Harada et al. 2003, 2006 *p,p'*-DDT
Developmental effects					
CF1 mouse	2-generation study involving lifetime exposure		0.4	Increased offspring body weight: >50% increase at some time-points (particularly in males) between 5 and 18 months; no dose-dependent pattern	Tomatis et al. 1972 *p,p'*-DDT
Sprague-Dawley rat	2-generation	1.9	18.6	Tail abnormalities (constriction rings in 13.2–25.5% incidence); no effect on birth weights or body weights at weaning	Ottoboni 1969 Technical DDT

Table A-6. Summary of Relevant LOAEL and NOAEL Values Following Chronic Oral Exposure to DDT, DDE, and DDD Isomers

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference/compound
Hematological effects					
F344 rat	Up to 104 weeks	0.17	1.7	Reduced hemoglobin and mean corpuscular volume at week 78, but not at 104 weeks; increased hematopoiesis in bone marrow	Tomita et al. 2013 *p,p'*-DDT
Osborne-Mendel rat	27 months		20	Hemolysis in spleen	Deichmann et al. 1967 DDT (NS)
Body weight effects					
CF1 mouse	2-generation study involving lifetime exposure		0.4	Significant increase in body weights in P0 females (up to 60% increase) compared with controls between 3 and 18 months; largest increases at lowest dose	Tomatis et al. 1972 *p,p'*-DDT
F344/DuCrj rat	2 years	1.7	19.1	12% decreased mean body weight	Harada et al. 2003, 2006 *p,p'*-DDT

DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; F = female(s); LOAEL = lowest observed adverse effect level; M = male(s); NOAEL = no observed-adverse-effect level; NS = not specified

Selection of the Principal Study: The Harada et al. (2003, 2006) study was selected as the basis of the chronic-duration oral MRL because it identified the lowest LOAEL for liver effects and provides adequate data to describe the dose-response relationship at low-dose levels.

Summary of the Principal Study:

Harada T, Yamaguchi S, Ohtsuka R, et al. 2003. Mechanisms of promotion and progression of preneoplastic lesions in hepatocarcinogenesis by DDT in F344 rats. Toxicol Pathol 31(1):87-98.

Harada T, Ohtsuka R, Takeda M, et al. 2006. Hepatocarcinogenesis by DDT in rats. J Toxicol Pathol 19:155-167.

Starting at 5 weeks of age, groups of 40 male and 40 female Fisher (F344/DuCrj) rats and a satellite group of 20 males and 20 females were fed *p,p'*-DDT in their diets at dietary concentrations of 0, 5, 50, or 500 ppm (Harada et al. 2003, 2006). The study report provided intakes of 0, 0.17, 1.7, or 19.1 mg *p,p'*-DDT/kg/day (males) and 0, 0.21, 2.2, or 25.2 mg/kg/day (females), based on average feed consumption and body weight throughout the 2-year feeding study. Six males and six females from each dose group were sacrificed after 26, 52, and 78 weeks of treatment and the following endpoints in the liver were monitored: (1) cell proliferation activity in the liver (immunohistochemistry staining for PCNA); (2) GJIC (immunohistochemistry analysis for hepatic gap junction protein connexin 32 [Cx32]); (3a) hepatic microsomal enzyme activity (PROD activity) and (3b) cytochrome P450 isozyme contents; hepatic levels of oxidative stress markers: (4a) LPO and (4b) 8-OHdG; (5) absolute and relative liver weights; and (6) histopathological examination of livers with morphometry.

Male and female rats in the high-dose group (19.1 and 25.2 mg/kg/day) had whole body tremors in weeks 70–104; females appeared more sensitive to tremors. There was no treatment-related mortality during the study. Mean body weight decreases of 12 and 25% were observed in males at 19.1 mg/kg/day and females at 25.2 mg/kg/day, respectively, but it is unclear when this was determined during the study. Body weights of rats at lower doses were not significantly different from controls. There was a tendency for increased food intake in males at 19.1 mg/kg/day, though not statistically different from controls. Non-neoplastic and neoplastic lesions were observed in the liver. Absolute and relative liver weight data were provided for the treated groups but not for the control group, so the magnitude of the changes (increases) compared with controls cannot be determined. Centrilobular hepatocellular hypertrophy was reported in males at all doses and in females at 2.2 and 25.2 mg/kg/day; incidence and severity showed a dose-related response and were related to elevated microsomal activity. Increased incidences of eosinophilic altered hepatocellular foci (AHF) were observed in males dosed with ≥1.7 mg/kg/day and females dosed with ≥2.2 mg/kg/day. The number and size of AHF increased with treatment time and dose and appeared earlier in males; AHFs were often located close to, or within, hypertrophic regions. Males in the 1.7 and 19.1 mg/kg/day groups had a significantly increased incidence of hepatocellular adenomas first seen on week 104. Females in the 25.2 mg/kg/day group also showed a significantly increased incidence of hepatocellular adenomas on week 104. Total incidences in the 0, 0.17, 1.7, and 19.1 mg/kg/day males were 0/40, 0/40, 5/40, and 22/40, respectively; corresponding incidences in females at 0, 0.21, 2.2, and 25.2 mg/kg/day were 0/40, 0/40, 0/40, and 16/40. Significantly increased incidence of hepatocellular carcinomas occurred only in males at 19.1 mg/kg/day (14/40 versus 0/40 in all other groups).

There was no cell proliferation in the liver (as measured by the percent PCNA LI in the liver) at any dose for either sex. Significant decreases in liver GJIC (as measured by number of GJIC protein Cx32) occurred at the mid- and high-dose throughout the duration of the study. A significant decrease in GJIC protein Cx32 was found in males in the low-dose group at 78 weeks, but not at any other time point. There were significant changes in hepatic microsomal enzyme activity and P450 isozyme contents.

Significantly increased PROD activity (males: ≥0.17 mg/kg/day; females: ≥2.2 mg/kg/day) occurred throughout the study; except for males at the highest dose where the increase was not significant after 52 weeks of exposure. Rats of both sexes in the mid- and high-dose groups showed dose-dependent significant increases of CYP2B1 and CYP3A2 enzymes. There were no dose-dependent, treatment-related changes in CYP1A2 or CYP4A1 enzymes in either sex. Oxidative stress was evident in increased hepatic lipid peroxide in males at 50 and 500 ppm; females showed inconsistent increases with significant differences occurring at 26 and 104 weeks at the mid dose, and only at 26 weeks at the high dose. Increased 8-OHdG levels were significant at the highest dose in both males and females.

Selection of the Point of Departure for the MRL: The Harada et al. (2003, 2006) study identified a LOAEL of 0.17 mg/kg/day for hepatocellular hypertrophy in male rats exposed to *p,p'*-DDT for 78 or 104 weeks. The lowest LOAEL in female rats was 2.2 mg/kg/day also for hepatocellular hypertrophy. BMD modeling was conducted to identify a POD using incidence data for hepatocellular hypertrophy in males because consistent evidence across multiple studies suggest males are more sensitive to liver toxicity due to exposure to DDT isomers than females.

Male rat incidence data for 78 and 104 weeks of exposure (Table A-7) were fit to all available dichotomous models in EPA's BMDS (version 3.2) using a BMR of 10% extra risk. Adequate model fit and model selection were done as described in the intermediate-duration oral MRL section.

No dichotomous models provided adequate fit to the increased incidence of hepatocyte hypertrophy in male rats at 104 weeks using the full dataset or with the highest dose dropped. For the 78-week data, only the Logistic and Probit models provided an adequate fit to the data. BMDLs were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Logistic). The frequentist, restricted Logistic model estimated a BMD_{10} and a $BMDL_{10}$ of 0.10 and 0.055 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-8 and the model fit for the selected model is shown in Figure A-2.

Table A-7. Incidences for Hepatic Hypertrophy in Male F344/DuCrj Rats after 78- and 104-Week Exposure to *p,p'*-DDT in the Diet

Dose (mg/kg/day)	Incidence at 78 weeks/N	Incidence at 104 weeks/N
0	0/8	0/35
0.17	4/8	15/30
1.7	8/8	33/36
19.1	7/7	31/33

N = total number of animals examined; DDT = dichlorodiphenyltrichloroethane

Source: Harada et al. 2003, 2006

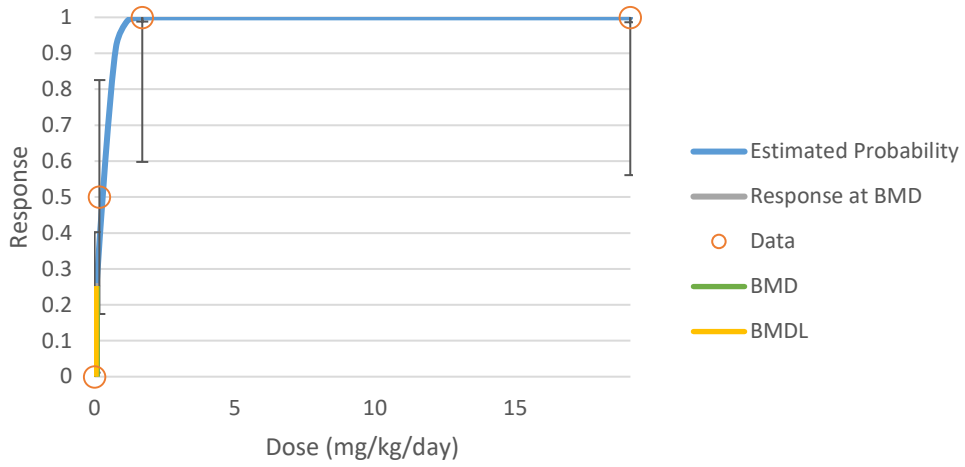
Table A-8. Model Predictions for Hepatocyte Hypertrophy in Male F344/DuCrj Rats Administered *p,p'*-DDT in Their Diet For 78 Weeks (Harada et al. 2003, 2006)

Model	BMC_{10}[a]	$BMCL_{10}$[a]	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Dichotomous Hill			0.97	17.09	-0.0003	-0.0004
Gamma[d]			1.00	13.09	-0.0003	-0.002
Log-Logistic[e]			1.00	15.09	-0.0005	-0.0004
Multistage Degree 3[f]			1.00	17.09	-0.0003	7.34×10^{-9}
Multistage Degree 2[f]			1.00	15.09	-0.0003	-1.26×10^{-7}
Multistage Degree 1[f]			1.00	15.11	-0.0004	-0.03
Weibull[d]			1.00	13.10	-0.0003	-0.006
Logistic[g]	**0.10**	**0.055**	**0.45**	**17.03**	**-1.28**	**1.01**
Log-Probit			1.00	17.09	-0.0004	-6.07×10^{-6}
Probit	0.21	0.14	0.14	21.90	0.85	1.15

[a]BMCLs <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.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. BMCLs for models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC was selected (Logistic).

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); BMD = benchmark dose; DDT = dichlorodiphenyltrichloroethane

Figure A-2. Fit of Logistic Model to Data for Hepatocyte Hypertrophy in Rats Administered *p,p'*-DDT in Their Diet for 78 Weeks (Harada et al. 2003, 2006)



Uncertainty Factor: The $BMDL_{10}$ is divided by a total uncertainty factor of 100:

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

$MRL = BMDL_{10} \div UFs$
$MRL = 0.055 \text{ mg/kg/day} \div (10 \times 10) = 0.0005 \text{ mg/kg/day}$ (0.5 µg/kg/day)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The identification of the liver as the most sensitive target of toxicity is supported by studies in several laboratory animal species reporting liver effects following chronic-duration oral exposure to DDT, DDE, and DDD isomers (Cabral et al. 1982a; Deichmann et al. 1967; Del Pup et al. 1978; Durham et al. 1963; Fitzhugh and Nelson 1947; Graillot et al. 1975; Harada et al. 2003, 2006; Lehman 1965; NCI 1978; Rossi et al. 1983; Takayama et al. 1999). The observed effects included fatty metamorphosis, hepatocellular hypertrophy, necrosis, altered hepatocellular foci, and amyloidosis. No liver effects (as assessed via serum liver enzyme levels) were observed in an experimental human study involving exposure to 0.5 mg technical DDT/kg/day (Hayes et al. 1956). Similarly, environmental exposure studies did not find alterations in serum clinical markers of liver damage or dysfunction associated with serum blood DDT or DDE levels (Freire et al. 2015a, 2015b; Morgan and Lin 1978; Serdar et al. 2014). Sunyer et al. (2008) did find an association between cord blood DDE or DDT levels and urinary porphyrin levels (Sunyer et al. 2008).

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APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR DDT, DDE, and DDD

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 DDT, DDE, and DDD.

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 DDT, DDE, and DDD. 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 DDT, DDE, and DDD 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 DDT, DDE, and DDD 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

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

Developmental effects
Other noncancer effects
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 DDT, DDE, and DDD released for public comment in 2019; thus, the literature search was restricted to studies published between November 2015 and April 2020. The following main databases were searched in April 2020:

- 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 DDT, DDE, and DDD. 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 DDT, DDE, and DDD 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	
04/2020	((((("DDT/toxicity"[mh] OR "DDT/adverse effects"[mh] OR "DDT/poisoning"[mh] OR "DDT/pharmacokinetics"[mh]) OR ("DDT"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("DDT"[mh] AND toxicokinetics[mh:noexp]) OR ("DDT/blood"[mh] OR "DDT/cerebrospinal fluid"[mh] OR "DDT/urine"[mh]) OR ("DDT"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("DDT"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("DDT/antagonists and inhibitors"[mh]) OR ("DDT/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("DDT"[mh] AND cancer[sb]) OR ("DDT/pharmacology"[majr] AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh]))) OR (("dichlorodiphenyl dichloroethylene/toxicity"[mh] OR "dichlorodiphenyl dichloroethylene/adverse effects"[mh] OR "dichlorodiphenyl dichloroethylene/poisoning"[mh] OR "dichlorodiphenyl dichloroethylene/pharmacokinetics"[mh]) OR ("dichlorodiphenyl dichloroethylene"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("dichlorodiphenyl dichloroethylene"[mh] AND toxicokinetics[mh:noexp]) OR ("dichlorodiphenyl dichloroethylene/blood"[mh] OR "dichlorodiphenyl dichloroethylene/cerebrospinal fluid"[mh] OR "dichlorodiphenyl dichloroethylene/urine"[mh]) OR ("dichlorodiphenyl dichloroethylene"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("dichlorodiphenyl dichloroethylene"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional

Table B-2. Database Query Strings

Database search date	Query string
	activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (rna[mh] OR dna[mh])) OR "rna, messenger"[mh] OR "rna, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("dichlorodiphenyl dichloroethylene/antagonists and inhibitors"[mh]) OR ("dichlorodiphenyl dichloroethylene/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("dichlorodiphenyl dichloroethylene"[mh] AND cancer[sb]) OR ("dichlorodiphenyl dichloroethylene/pharmacology"[majr] AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh])) OR ("Dichlorodiphenyldichloroethane/toxicity"[mh] OR "Dichlorodiphenyldichloroethane/adverse effects"[mh] OR "Dichlorodiphenyldichloroethane/poisoning"[mh] OR "Dichlorodiphenyldichloroethane/pharmacokinetics"[mh]) OR ("Dichlorodiphenyldichloroethane"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Dichlorodiphenyldichloroethane"[mh] AND toxicokinetics[mh:noexp]) OR ("Dichlorodiphenyldichloroethane/blood"[mh] OR "Dichlorodiphenyldichloroethane/cerebrospinal fluid"[mh] OR "Dichlorodiphenyldichloroethane/urine"[mh]) OR ("Dichlorodiphenyldichloroethane"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Dichlorodiphenyldichloroethane"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (rna[mh] OR dna[mh])) OR "rna, messenger"[mh] OR "rna, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Dichlorodiphenyldichloroethane/antagonists and inhibitors"[mh]) OR ("Dichlorodiphenyldichloroethane/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Dichlorodiphenyldichloroethane"[mh] AND cancer[sb]) OR ("Dichlorodiphenyldichloroethane/pharmacology"[majr] AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh])) OR ("Mitotane/toxicity"[mh] OR "Mitotane/adverse effects"[mh] OR "Mitotane/poisoning"[mh] OR "Mitotane/pharmacokinetics"[mh]) OR ("Mitotane"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Mitotane"[mh] AND toxicokinetics[mh:noexp]) OR ("Mitotane/blood"[mh] OR "Mitotane/cerebrospinal fluid"[mh] OR "Mitotane/urine"[mh]) OR ("Mitotane"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Mitotane"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (rna[mh] OR dna[mh])) OR "rna, messenger"[mh] OR "rna, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene

Table B-2. Database Query Strings

Database search date	Query string
	expression profiling"[mh])) OR ("Mitotane/antagonists and inhibitors"[mh]) OR ("Mitotane/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Mitotane"[mh] AND cancer[sb]) OR ("Mitotane/pharmacology"[majr] AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh])) OR ("2,2-(2-chlorophenyl-4'-chlorophenyl)-1,1-dichloroethene"[nm]))))) AND (2016/11/01:3000[mhda] OR 2016/11/01:3000[crdt] OR 2016/11/01:3000[edat] OR 2015/11/01:3000[dp])
	(("(o-Chlorophenyl)-1-(p-chlorophenyl)-2,2,2-trichloroethane"[tw] OR "1-(2-Chlorophenyl)-1-(4-chlorophenyl)-2,2,2-trichloroethane"[tw] OR "1-(2'-Chlorophenyl)-1-(4'-chlorophenyl)-2,2-dichloroethane"[tw] OR "1-(2-Chlorophenyl)-1-(4-chlorophenyl)-2,2-dichloroethane"[tw] OR "1-(2-Chlorophenyl)-1-(4-chlorophenyl)-2,2-dichloroethylene"[tw] OR "1-(o-Chlorophenyl)-1-(p-chlorophenyl)-2,2-dichloroethane"[tw] OR "1,1'-(2,2,2-Trichloroethylidene)bis(4-chlorobenzene)"[tw] OR "1,1'-(2,2-Dichloroethylidene)bis(4-chlorobenzene)"[tw] OR "1,1'-(Dichloroethenylidene)bis(4-chlorobenzene)"[tw] OR "1,1,1-Trichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane"[tw] OR "1,1,1-Trichloro-2-(p-chlorophenyl)-2-(o-chlorophenyl)ethane"[tw] OR "1,1,1-Trichloro-2,2-bis (p-chlorophenyl)ethane"[tw] OR "1,1,1-Trichloro-2,2-bis(4,4'-dichlorodiphenyl)ethane"[tw] OR "1,1,1-Trichloro-2,2-bis(4-chlorophenyl) ethane"[tw] OR "1,1,1-Trichloro-2,2-bis(4-chlorophenyl)ethane"[tw] OR "1,1,1-Trichloro-2,2-bis(p-chlorophenyl)ethane"[tw] OR "1,1,1-Trichloro-2,2-di(4-chlorophenyl)-ethane"[tw] OR "1,1,1-Trichloro-2,2-di(p-chlorophenyl)ethane"[tw] OR "1,1,1-Trichloro-2-2,2-bis(p-chlorophenyl)ethane"[tw] OR "1,1-Bis(4-chlorophenyl)-2,2,2-trichloroethane"[tw] OR "1,1-Bis(4-chlorophenyl)-2,2-dichloroethane"[tw] OR "1,1-Bis(4-chlorophenyl)-2,2-dichloroethene"[tw] OR "1,1-Bis(p-chlorophenyl)-2,2,2-trichloroethane"[tw] OR "1,1-Bis-(p-chlorophenyl)-2,2,2-trichloroethane"[tw] OR "1,1-Bis(p-chlorophenyl)-2,2-dichloroethane"[tw] OR "1,1-Bis(p-chlorophenyl)-2,2-dichloroethylene"[tw] OR "1,1-Dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane"[tw] OR "1,1-Dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethene"[tw] OR "1,1-Dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethylene"[tw] OR "1,1-Dichloro-2-(p-chlorophenyl)-2-(o-chlorophenyl)ethane"[tw] OR "1,1-Dichloro-2,2-bis(2,4'-dichlorophenyl)ethane"[tw] OR "1,1'-Dichloro-2,2-bis(4-chlorophenyl)ethane"[tw] OR "1,1-Dichloro-2,2-bis(4-chlorophenyl)ethane"[tw] OR "1,1-Dichloro-2,2-bis(para-chlorophenyl) ethylene"[tw] OR "1,1-Dichloro-2,2-bis(parachlorophenyl)ethane"[tw] OR "1,1-Dichloro-2,2-bis(p-chlorophenyl)ethane"[tw] OR "1,1-Dichloro-2,2-bis(p-chlorophenyl)ethene"[tw] OR "1,1-Dichloro-2,2-bis(p-chlorophenyl)ethylene"[tw] OR "1,1-Dichloro-2,2-di(4-chlorophenyl)ethane"[tw] OR "1,1-Dichloro-2,2-di(p-chlorophenyl)ethylene"[tw] OR "1,1-Dichloroethylididenebis(4-chlorobenzene)"[tw] OR "1-Chloro-2-(2,2,2-trichloro-1-(4-chlorophenyl)ethyl)benzene"[tw] OR "1-Chloro-2-(2,2-dichloro-1-(4-chlorophenyl)ethyl)benzene"[tw] OR "2-(2-Chlorophenyl)-2-(4-chlorophenyl)-1,1,1-trichloroethane"[tw] OR "2-(2-Chlorophenyl)-2-(4-chlorophenyl)-1,1-dichloroethane"[tw] OR "2-(2-Chlorophenyl)-2-(4-chlorophenyl)-1,1-dichloroethylene"[tw] OR "2-(o-Chlorophenyl)-2-(p-chlorophenyl)-1,1-dichloroethane"[tw] OR "2-(p-Chlorophenyl)-2-(o-chlorophenyl)-1,1-dichloroethane"[tw] OR "2,2-(2-Chlorophenyl-4'-chlorophenyl)-1,1-dichloroethene"[tw] OR "2,2,2,o,p'-Pentachlorethylidenbisbenzol"[tw] OR "2,2,2,o,p'-pentachloroethylidenebisbenzene"[tw] OR "2,2,2-Trichloro-1,1-bis(4-chlorophenyl)ethane"[tw] OR "2,2,o,p'-tetrachlorovinylidenebisbenzene"[tw] OR "2,2,o,p'-Tetrachlorvinylidenbisbenzol"[tw] OR "2,2-Bis(2-chlorophenyl-4-chlorophenyl)-1,1-dichloroethane"[tw] OR "2,2-Bis(4-chlorophenyl)-1,1-dichloroethane"[tw] OR "2,2-Bis(4-chlorophenyl)-1,1-dichloroethene"[tw] OR "2,2-Bis(4-chlorophenyl)-1,1-dichloroethylene"[tw] OR "2,2-Bis(o,p-chlorophenyl)-1,1,1-trichloroethane"[tw] OR "2,2-

Table B-2. Database Query Strings

Database search date	Query string
	bis(para-Chlorophenyl)-1,1-dichloroethane"[tw] OR "2,2-bis(p-Chlorophenyl)-1,1,1-trichloroethane"[tw] OR "2,2-Bis(p-chlorophenyl)-1,1-dichloroethane"[tw] OR "2,2-Bis(p-chlorophenyl)-1,1-dichloroethylene"[tw] OR "2,2-Bis(p-chlorphenyl)-1,1-dichlorethylen"[tw] OR "2,2-Di(p-chlorophenyl)-1,1-dichloroethane"[tw] OR "2,2-Di(p-chlorophenyl)-1,1-dichloroethylene"[tw] OR "2,2-Dichloro-1,1-bis(4-chlorophenyl)ethylene"[tw] OR "2,4'-Dichlorodiphenyldichloroethane"[tw] OR "2,4'-Dichlorodiphenyldichloroethylene"[tw] OR "2,4'-Dichlorodiphenyltrichloroethane"[tw] OR "2,4'-Dichlorophenyldichlorethane"[tw] OR "2-o-Chlorophenyl-2-p-chlorophenyl-1,1,1-trichloroethane"[tw] OR "4,4'-1,1-Dichloro-2,2-bis(p-chlorophenyl)ethane"[tw] OR "4,4'-Dichlorodiphenyldichloroethane"[tw] OR "4,4'-Dichlorodiphenyldichloroethene"[tw] OR "4,4'-Dichlorodiphenyldichloroethylene"[tw] OR "4,4'-Dichlorodiphenyltrichloroethane"[tw] OR "4,4-Dichlorodiphenyl-trichloroethane"[tw] OR "alpha,alpha-Bis(p-chlorophenyl)- beta,beta,beta-trichlorethane"[tw] OR "alpha,alpha-Bis(p-chlorophenyl)-beta,beta,beta-trichloroethane"[tw] OR "D.D.T."[tw] OR "DDE"[tw] OR "DDT"[tw] OR "DDT3"[tw] OR "DDTs"[tw] OR "Dichloro dichlorophenyl ethylene"[tw] OR "Dichloro diphenyl dichlorethane"[tw] OR "Dichloro diphenyl dichloroethane"[tw] OR "Dichloro diphenyl trichloroethane"[tw] OR "Dichlorodifeniltrichlorethane"[tw] OR "Dichlorodiphenydichloroethane"[tw] OR "Dichlorodiphenyl dichloroethane"[tw] OR "Dichlorodiphenyl dichloroethene"[tw] OR "Dichlorodiphenyl dichloroethylene"[tw] OR "Dichlorodiphenyldichloroethane"[tw] OR "Dichlorodiphenyldichloroethene"[tw] OR "Dichlorodiphenyldichloroethylene"[tw] OR "Dichlorodiphenyltrichloroethane"[tw] OR "MITOTANE"[tw] OR "o,p'-1,1,1-Trichloro-2-2,2-bis(p-chlorophenyl)ethane"[tw] OR "o,p'-Chlorophenothane"[tw] OR "o,p'-Dichlorodiphenyldichloroethane"[tw] OR "O,P'-DICHLORODIPHENYLDICHLOROETHYLENE"[tw] OR "o,p'-Dichlorodiphenyltrichloroethane"[tw] OR "p,p'-(Dichlorodiphenyl)-2,2-dichloroethylene"[tw] OR "p,p-DDX"[tw] OR "p,p'-Dichlorodiphenoldichloroethylene"[tw] OR "p,p'-Dichlorodiphenyl dichloroethylene"[tw] OR "p,p'-Dichlorodiphenyl-2,2-dichloroethylene"[tw] OR "p,p'-Dichlorodiphenyldichloroethane"[tw] OR "p,p'-Dichlorodiphenyldichloroethene"[tw] OR "p,p'-Dichlorodiphenyldichloroethylene"[tw] OR "p,p'-Dichlorodiphenylethylene dichloride"[tw] OR "p,p'-Dichlorodiphenyltrichloroethane"[tw] OR "p,p'-Dichlorodiphenyltrichloromethylmethane"[tw] OR "para,para'-Dichlorodiphenyldichloroethane"[tw] OR "para,para'-Dichlorodiphenyldichloroethene"[tw] OR "para,para'-Dichlorodiphenyldichloroethylene"[tw] OR "para,para'-Dichlorodiphenyltrichloroethane"[tw] OR "Tetrachlorodiphenylethane"[tw] OR "Trichlorobis(4'-chlorophenyl)ethane"[tw] OR "Trichlorobis(4-chlorophenyl)ethane"[tw] OR "2,4'-DDD"[tw] OR "2,4-DDD"[tw] OR "4,4' DDD"[tw] OR "4,4'-DDD"[tw] OR "4,4-DDD"[tw] OR "DDD o p"[tw] OR "DDD, 2,4'-"[tw] OR "DDD, o,p'-"[tw] OR "DDD, p,p'-"[tw] OR "o,p'-DDD"[tw] OR "p,p'-DDD"[tw] OR "para,para'-DDD"[tw] OR "para-para DDD"[tw] OR "pp-DDD total"[tw] OR "4,4'-TDE"[tw] OR "o,p'-TDE"[tw] OR "o,p-TDE"[tw] OR "p,p'-TDE"[tw] OR "p,p-TDE"[tw] OR "TDE (ISO)"[tw] OR "CB 313"[tw] OR "CB313"[tw] OR "ME 1700"[tw] OR "Me-700"[tw] OR "PEB1"[tw] OR "Aavero-extra"[tw] OR "Agritan"[tw] OR "Anofex"[tw] OR "Arkotine"[tw] OR "Azotox M 33"[tw] OR "Benzochloryl"[tw] OR "Bosan Supra"[tw] OR "Bovidermol"[tw] OR "Chloditan"[tw] OR "Chlodithan"[tw] OR "Chlodithane"[tw] OR "Chlofenotan"[tw] OR "Chlorophenothan"[tw] OR "Chlorophenothane"[tw] OR "Chlorophenothanum"[tw] OR "Chlorophenotoxum"[tw] OR "Chlorphenothan"[tw] OR "Chlorphenotoxum"[tw] OR "Citox"[tw] OR "Clofenotan"[tw] OR "Clofenotane"[tw] OR "Clofenotanum"[tw] OR "De De tane"[tw] OR "Deoval"[tw] OR "Detoxan"[tw] OR "Dibovin"[tw] OR "Dicophane"[tw] OR "Dicophaner"[tw] OR "Didigam"[tw] OR "Didimac"[tw] OR "Dilene"[tw] OR "Dodat"[tw] OR "Dykol"[tw] OR "Estonate"[tw] OR "Genitox"[tw] OR "Gesafid"[tw] OR "Gesapon"[tw] OR "Gesarex"[tw] OR "Gesarol"[tw] OR "Guesapon"[tw] OR "Guesarol"[tw] OR "Gyron"[tw] OR "HEPT"[tw] OR "Hildit"[tw] OR "Ivoran"[tw] OR "Ixodex"[tw] OR "Khlodithan"[tw] OR "Klorfenoton"[tw] OR "Kopsol"[tw] OR "Lysodren"[tw]

Table B-2. Database Query Strings

Database search date	Query string
	OR "Mitotan"[tw] OR "Mitotanum"[tw] OR "Mutoxan"[tw] OR "Neocid"[tw] OR "Neocidol"[tw] OR "Opeprim"[tw] OR "Parachlorocidum"[tw] OR "Pentachlorin"[tw] OR "Pentech"[tw] OR "Penticidum"[tw] OR "p'-Zeidane"[tw] OR "Rhothane"[tw] OR "Rhothane D-3"[tw] OR "Rodentrak"[tw] OR "Rothane"[tw] OR "Rukseam"[tw] OR "Santobane"[tw] OR "Tafidex"[tw] OR "Zerdane"[tw] OR ("DDD"[tw] NOT ("ATC-DDD"[tw] OR "daily defined dose"[tw] OR "daily defined doses"[tw] OR "data-driven detection"[tw] OR "ddd pacemaker"[tw] OR "DDD-028"[tw] OR "ddd/100"[tw] OR "ddd/1000"[tw] OR "ddd/sgn"[tw] OR "defined daily dose"[tw] OR "defined daily doses"[tw] OR "degenerative disc disease"[tw] OR "degenerative disk disease"[tw] OR "dense deposit disease"[tw] OR "depersonalization/derealization disorder"[tw] OR "Depression due to Dementia"[tw] OR "digital differential display"[tw] OR "direct disk diffusion"[tw] OR "disc degenerative disease"[tw] OR "disk degenerative disease"[tw] OR "difference-in-difference-in-differences"[tw] OR "direct detection device" OR "direct detector device"[tw] OR "Direct electron detectors"[tw] OR "distal-dorsal difference"[tw] OR "Dowling-Degos disease"[tw] OR "Drew-Dickerson dodecamer"[tw] OR "drinking day"[tw] OR "Drug Discovery and Development"[tw] OR "drunk driving detection"[tw] OR "lumbar disc disease"[tw] OR "lumbar disk disease"[tw] OR "pacing"[tw] OR ("dual chamber"[tw] AND "pacemaker"[tw]) OR "DDD Study"[Corporate Author]))) NOT medline[sb]) AND (2016/11/01:3000[mhda] OR 2016/11/01:3000[crdt] OR 2016/11/01:3000[edat] OR 2015/11/01:3000[dp])
	("(o-Chlorophenyl)-1-(p-chlorophenyl)-2,2,2-trichloroethane"[tw] OR "1-(2-Chlorophenyl)-1-(4-chlorophenyl)-2,2,2-trichloroethane"[tw] OR "1-(2'-Chlorophenyl)-1-(4'-chlorophenyl)-2,2-dichloroethane"[tw] OR "1-(2-Chlorophenyl)-1-(4-chlorophenyl)-2,2-dichloroethane"[tw] OR "1-(2-Chlorophenyl)-1-(4-chlorophenyl)-2,2-dichloroethylene"[tw] OR "1-(o-Chlorophenyl)-1-(p-chlorophenyl)-2,2-dichloroethane"[tw] OR "1,1'-(2,2,2-Trichloroethylidene)bis(4-chlorobenzene)"[tw] OR "1,1'-(2,2-Dichloroethylidene)bis(4-chlorobenzene)"[tw] OR "1,1'-(Dichloroethenylidene)bis(4-chlorobenzene)"[tw] OR "1,1,1-Trichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane"[tw] OR "1,1,1-Trichloro-2-(p-chlorophenyl)-2-(o-chlorophenyl)ethane"[tw] OR "1,1,1-Trichloro-2,2-bis (p-chlorophenyl)ethane"[tw] OR "1,1,1-Trichloro-2,2-bis(4,4'-dichlorodiphenyl)ethane"[tw] OR "1,1,1-Trichloro-2,2-bis(4-chlorophenyl) ethane"[tw] OR "1,1,1-Trichloro-2,2-bis(4-chlorophenyl)ethane"[tw] OR "1,1,1-Trichloro-2,2-bis(p-chlorophenyl)ethane"[tw] OR "1,1,1-Trichloro-2,2-di(4-chlorophenyl)-ethane"[tw] OR "1,1,1-Trichloro-2,2-di(p-chlorophenyl)ethane"[tw] OR "1,1,1-Trichloro-2-2,2-bis(p-chlorophenyl)ethane"[tw] OR "1,1-Bis(4-chlorophenyl)-2,2,2-trichloroethane"[tw] OR "1,1-Bis(4-chlorophenyl)-2,2-dichloroethane"[tw] OR "1,1-Bis(4-chlorophenyl)-2,2-dichloroethene"[tw] OR "1,1-Bis(p-chlorophenyl)-2,2,2-trichloroethane"[tw] OR "1,1-Bis-(p-chlorophenyl)-2,2,2-trichloroethane"[tw] OR "1,1-Bis(p-chlorophenyl)-2,2-dichloroethane"[tw] OR "1,1-Bis(p-chlorophenyl)-2,2-dichloroethylene"[tw] OR "1,1-Dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane"[tw] OR "1,1-Dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethene"[tw] OR "1,1-Dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethylene"[tw] OR "1,1-Dichloro-2-(p-chlorophenyl)-2-(o-chlorophenyl)ethane"[tw] OR "1,1-Dichloro-2,2-bis(2,4'-dichlorophenyl)ethane"[tw] OR "1,1'-Dichloro-2,2-bis(4-chlorophenyl)ethane"[tw] OR "1,1-Dichloro-2,2-bis(4-chlorophenyl)ethane"[tw] OR "1,1-Dichloro-2,2-bis(para-chlorophenyl) ethylene"[tw] OR "1,1-Dichloro-2,2-bis(parachlorophenyl)ethane"[tw] OR "1,1-Dichloro-2,2-bis(p-chlorophenyl)ethane"[tw] OR "1,1-Dichloro-2,2-bis(p-chlorophenyl)ethene"[tw] OR "1,1-Dichloro-2,2-bis(p-chlorophenyl)ethylene"[tw] OR "1,1-Dichloro-2,2-di(4-chlorophenyl)ethane"[tw] OR "1,1-Dichloro-2,2-di(p-chlorophenyl)ethylene"[tw] OR "1,1-Dichloroethylididenebis(4-chlorobenzene)"[tw] OR "1-Chloro-2-(2,2,2-trichloro-1-(4-chlorophenyl)ethyl)benzene"[tw] OR "1-Chloro-2-(2,2-dichloro-1-(4-

Table B-2. Database Query Strings

Database search date	Query string
	chlorophenyl)ethyl)benzene"[tw] OR "2-(2-Chlorophenyl)-2-(4-chlorophenyl)-1,1,1-trichloroethane"[tw] OR "2-(2-Chlorophenyl)-2-(4-chlorophenyl)-1,1-dichloroethane"[tw] OR "2-(2-Chlorophenyl)-2-(4-chlorophenyl)-1,1-dichloroethylene"[tw] OR "2-(o-Chlorophenyl)-2-(p-chlorophenyl)-1,1-dichloroethane"[tw] OR "2-(p-Chlorophenyl)-2-(o-chlorophenyl)-1,1-dichloroethane"[tw] OR "2,2-(2-Chlorophenyl-4'-chlorophenyl)-1,1-dichloroethene"[tw] OR "2,2,2,o,p'-Pentachlorethylidenbisbenzol"[tw] OR "2,2,2,o,p'-pentachloroethylidenebisbenzene"[tw] OR "2,2,2-Trichloro-1,1-bis(4-chlorophenyl)ethane"[tw] OR "2,2,o,p'-tetrachlorovinylidenebisbenzene"[tw] OR "2,2,o,p'-Tetrachlorvinylidenbisbenzol"[tw] OR "2,2-Bis(2-chlorophenyl-4-chlorophenyl)-1,1-dichloroethane"[tw] OR "2,2-Bis(4-chlorophenyl)-1,1-dichloroethane"[tw] OR "2,2-Bis(4-chlorophenyl)-1,1-dichloroethene"[tw] OR "2,2-Bis(4-chlorophenyl)-1,1-dichloroethylene"[tw] OR "2,2-Bis(o,p-chlorophenyl)-1,1,1-trichloroethane"[tw] OR "2,2-bis(para-Chlorophenyl)-1,1-dichloroethane"[tw] OR "2,2-bis(p-Chlorophenyl)-1,1,1-trichloroethane"[tw] OR "2,2-Bis(p-chlorophenyl)-1,1-dichloroethane"[tw] OR "2,2-Bis(p-chlorophenyl)-1,1-dichloroethylene"[tw] OR "2,2-Bis(p-chlorphenyl)-1,1-dichlorethylen"[tw] OR "2,2-Di(p-chlorophenyl)-1,1-dichloroethane"[tw] OR "2,2-Di(p-chlorophenyl)-1,1-dichloroethylene"[tw] OR "2,2-Dichloro-1,1-bis(4-chlorophenyl)ethylene"[tw] OR "2,4'-Dichlorodiphenyldichloroethane"[tw] OR "2,4'-Dichlorodiphenyldichloroethylene"[tw] OR "2,4'-Dichlorodiphenyltrichloroethane"[tw] OR "2,4'-Dichlorophenyldichlorethane"[tw] OR "2-o-Chlorophenyl-2-p-chlorophenyl-1,1,1-trichloroethane"[tw] OR "4,4'-1,1-Dichloro-2,2-bis(p-chlorophenyl)ethane"[tw] OR "4,4'-Dichlorodiphenyldichloroethane"[tw] OR "4,4'-Dichlorodiphenyldichloroethene"[tw] OR "4,4'-Dichlorodiphenyldichloroethylene"[tw] OR "4,4'-Dichlorodiphenyltrichloroethane"[tw] OR "4,4-Dichlorodiphenyl-trichloroethane"[tw] OR "alpha,alpha-Bis(p-chlorophenyl)- beta,beta,beta-trichlorethane"[tw] OR "alpha,alpha-Bis(p-chlorophenyl)-beta,beta,beta-trichloroethane"[tw] OR "D.D.T."[tw] OR "DDE"[tw] OR "DDT"[tw] OR "DDT3"[tw] OR "DDTs"[tw] OR "Dichloro dichlorophenyl ethylene"[tw] OR "Dichloro diphenyl dichlorethane"[tw] OR "Dichloro diphenyl dichloroethane"[tw] OR "Dichloro diphenyl trichloroethane"[tw] OR "Dichlorodifeniltrichlorethane"[tw] OR "Dichlorodiphenydichloroethane"[tw] OR "Dichlorodiphenyl dichloroethane"[tw] OR "Dichlorodiphenyl dichloroethene"[tw] OR "Dichlorodiphenyl dichloroethylene"[tw] OR "Dichlorodiphenyldichloroethane"[tw] OR "Dichlorodiphenyldichloroethene"[tw] OR "Dichlorodiphenyldichloroethylene"[tw] OR "Dichlorodiphenyltrichloroethane"[tw] OR "MITOTANE"[tw] OR "o,p'-1,1,1-Trichloro-2-2,2-bis(p-chlorophenyl)ethane"[tw] OR "o,p'-Chlorophenothane"[tw] OR "o,p'-Dichlorodiphenyldichloroethane"[tw] OR "O,P'-DICHLORODIPHENYLDICHLOROETHYLENE"[tw] OR "o,p'-Dichlorodiphenyltrichloroethane"[tw] OR "p,p'-(Dichlorodiphenyl)-2,2-dichloroethylene"[tw] OR "p,p-DDX"[tw] OR "p,p'-Dichlorodiphenoldichloroethylene"[tw] OR "p,p'-Dichlorodiphenyl dichloroethylene"[tw] OR "p,p'-Dichlorodiphenyl-2,2-dichloroethylene"[tw] OR "p,p'-Dichlorodiphenyldichloroethane"[tw] OR "p,p'-Dichlorodiphenyldichloroethene"[tw] OR "p,p'-Dichlorodiphenyldichloroethylene"[tw] OR "p,p'-Dichlorodiphenylethylene dichloride"[tw] OR "p,p'-Dichlorodiphenyltrichloroethane"[tw] OR "p,p'-Dichlorodiphenyltrichloromethylmethane"[tw] OR "para,para'-Dichlorodiphenyldichloroethane"[tw] OR "para,para'-Dichlorodiphenyldichloroethene"[tw] OR "para,para'-Dichlorodiphenyldichloroethylene"[tw] OR "para,para'-Dichlorodiphenyltrichloroethane"[tw] OR "Tetrachlorodiphenylethane"[tw] OR "Trichlorobis(4'-chlorophenyl)ethane"[tw] OR "Trichlorobis(4-chlorophenyl)ethane"[tw] OR "2,4'-DDD"[tw] OR "2,4-DDD"[tw] OR "4,4' DDD"[tw] OR "4,4'-DDD"[tw] OR "4,4-DDD"[tw] OR "DDD o p"[tw] OR "DDD, 2,4'-"[tw] OR "DDD, o,p'-"[tw] OR "DDD, p,p'-"[tw] OR "o,p'-DDD"[tw] OR "p,p'-DDD"[tw] OR "para,para'-DDD"[tw] OR "para-para DDD"[tw] OR "pp-DDD total"[tw] OR "4,4'-TDE"[tw] OR "o,p'-TDE"[tw] OR "o,p-TDE"[tw] OR "p,p'-TDE"[tw] OR "p,p-TDE"[tw] OR "TDE (ISO)"[tw] OR "CB 313"[tw] OR "CB313"[tw] OR "ME 1700"[tw]

Table B-2. Database Query Strings

Database search date	Query string
	OR "Me-700"[tw] OR "PEB1"[tw] OR "Aavero-extra"[tw] OR "Agritan"[tw] OR "Anofex"[tw] OR "Arkotine"[tw] OR "Azotox M 33"[tw] OR "Benzochloryl"[tw] OR "Bosan Supra"[tw] OR "Bovidermol"[tw] OR "Chloditan"[tw] OR "Chlodithan"[tw] OR "Chlodithane"[tw] OR "Chlofenotan"[tw] OR "Chlorophenothan"[tw] OR "Chlorophenothane"[tw] OR "Chlorophenothanum"[tw] OR "Chlorophenotoxum"[tw] OR "Chlorphenothan"[tw] OR "Chlorphenotoxum"[tw] OR "Citox"[tw] OR "Clofenotan"[tw] OR "Clofenotane"[tw] OR "Clofenotanum"[tw] OR "De De tane"[tw] OR "Deoval"[tw] OR "Detoxan"[tw] OR "Dibovin"[tw] OR "Dicophane"[tw] OR "Dicophaner"[tw] OR "Didigam"[tw] OR "Didimac"[tw] OR "Dilene"[tw] OR "Dodat"[tw] OR "Dykol"[tw] OR "Estonate"[tw] OR "Genitox"[tw] OR "Gesafid"[tw] OR "Gesapon"[tw] OR "Gesarex"[tw] OR "Gesarol"[tw] OR "Guesapon"[tw] OR "Guesarol"[tw] OR "Gyron"[tw] OR "HEPT"[tw] OR "Hildit"[tw] OR "Ivoran"[tw] OR "Ixodex"[tw] OR "Khlodithan"[tw] OR "Klorfenoton"[tw] OR "Kopsol"[tw] OR "Lysodren"[tw] OR "Mitotan"[tw] OR "Mitotanum"[tw] OR "Mutoxan"[tw] OR "Neocid"[tw] OR "Neocidol"[tw] OR "Opeprim"[tw] OR "Parachlorocidum"[tw] OR "Pentachlorin"[tw] OR "Pentech"[tw] OR "Penticidum"[tw] OR "p'-Zeidane"[tw] OR "Rhothane"[tw] OR "Rhothane D-3"[tw] OR "Rodentrak"[tw] OR "Rothane"[tw] OR "Rukseam"[tw] OR "Santobane"[tw] OR "Tafidex"[tw] OR "Zerdane"[tw] OR ("DDD"[tw] NOT ("ATC-DDD"[tw] OR "daily defined dose"[tw] OR "daily defined doses"[tw] OR "data-driven detection"[tw] OR "ddd pacemaker"[tw] OR "DDD-028"[tw] OR "ddd/100"[tw] OR "ddd/1000"[tw] OR "ddd/sgn"[tw] OR "defined daily dose"[tw] OR "defined daily doses"[tw] OR "degenerative disc disease"[tw] OR "degenerative disk disease"[tw] OR "dense deposit disease"[tw] OR "depersonalization/derealization disorder"[tw] OR "Depression due to Dementia"[tw] OR "digital differential display"[tw] OR "direct disk diffusion"[tw] OR "disc degenerative disease"[tw] OR "disk degenerative disease"[tw] OR "difference-in-difference-in-differences"[tw] OR "direct detection device" OR "direct detector device"[tw] OR "Direct electron detectors"[tw] OR "distal-dorsal difference"[tw] OR "Dowling-Degos disease"[tw] OR "Drew-Dickerson dodecamer"[tw] OR "drinking day"[tw] OR "Drug Discovery and Development"[tw] OR "drunk driving detection"[tw] OR "lumbar disc disease"[tw] OR "lumbar disk disease"[tw] OR "pacing"[tw] OR ("dual chamber"[tw] AND "pacemaker"[tw]) OR "DDD Study"[Corporate Author]))) AND ((("pesticides/toxicity"[mh] OR "pesticides/adverse effects"[mh] OR "pesticides/poisoning"[mh] OR "pesticides/pharmacokinetics"[mh]) OR ("pesticides"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("pesticides"[mh] AND toxicokinetics[mh:noexp]) OR ("pesticides/blood"[mh] OR "pesticides/cerebrospinal fluid"[mh] OR "pesticides/urine"[mh]) OR ("pesticides"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("pesticides"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("pesticides/antagonists and inhibitors"[mh]) OR ("pesticides/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("pesticides"[mh] AND cancer[sb]) OR ("endocrine disruptors/toxicity"[mh] OR "endocrine disruptors/adverse effects"[mh] OR "endocrine disruptors/poisoning"[mh] OR "endocrine disruptors/pharmacokinetics"[mh]) OR ("endocrine disruptors"[mh] AND ("environmental

Table B-2. Database Query Strings

Database search date	Query string
	exposure"[mh] OR ci[sh])) OR ("endocrine disruptors"[mh] AND toxicokinetics[mh:noexp]) OR ("endocrine disruptors/blood"[mh] OR "endocrine disruptors/cerebrospinal fluid"[mh] OR "endocrine disruptors/urine"[mh]) OR ("endocrine disruptors"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("endocrine disruptors"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("endocrine disruptors/antagonists and inhibitors"[mh]) OR ("endocrine disruptors/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("endocrine disruptors"[mh] AND cancer[sb]) OR ("environmental pollutants/toxicity"[mh] OR "environmental pollutants/adverse effects"[mh] OR "environmental pollutants/poisoning"[mh] OR "environmental pollutants/pharmacokinetics"[mh]) OR ("environmental pollutants"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("environmental pollutants"[mh] AND toxicokinetics[mh:noexp]) OR ("environmental pollutants/blood"[mh] OR "environmental pollutants/cerebrospinal fluid"[mh] OR "environmental pollutants/urine"[mh]) OR ("environmental pollutants"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "environmental pollutants"[mh])) OR ("environmental pollutants"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("environmental pollutants/antagonists and inhibitors"[mh]) OR ("environmental pollutants/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("environmental pollutants"[mh] AND cancer[sb])) OR ("Hydrocarbons, Chlorinated/toxicity"[mh] OR "Hydrocarbons, Chlorinated/adverse effects"[mh] OR "Hydrocarbons, Chlorinated/poisoning"[mh] OR "Hydrocarbons, Chlorinated/pharmacokinetics"[mh]) OR ("Hydrocarbons, Chlorinated"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR (("Hydrocarbons, Chlorinated"[mh] AND toxicokinetics[mh:noexp]) OR ("Hydrocarbons, Chlorinated/blood"[mh] OR "Hydrocarbons, Chlorinated/cerebrospinal fluid"[mh] OR "Hydrocarbons, Chlorinated/urine"[mh]) OR ("Hydrocarbons, Chlorinated"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Hydrocarbons, Chlorinated"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND

Table B-2. Database Query Strings

Database search date	Query string
	("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Hydrocarbons, Chlorinated/antagonists and inhibitors"[mh]) OR ("Hydrocarbons, Chlorinated/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Hydrocarbons, Chlorinated"[mh] AND cancer[sb]))) AND (2016/11/01:3000[mhda] OR 2016/11/01:3000[crdt] OR 2016/11/01:3000[edat] OR 2015/11/01:3000[dp])
	(DDT OR DDE) AND ("environmental pollutants"[mh] OR "environmental pollution"[mh] OR "animals, wild"[mh] OR "ecotoxicology"[mh] OR "fishes"[mh] OR "birds"[mh] OR "amphibians"[mh] OR "reptiles"[mh] OR "Mammals"[Mesh:noexp] OR "Artiodactyla"[mh] OR "Carnivora"[mh] OR "Cetacea"[mh] OR "Chiroptera"[mh] OR "Hyraxes"[mh] OR "Lagomorpha"[mh] OR "Marsupialia"[mh] OR "Monotremata"[mh] OR "Perissodactyla"[mh] OR "Proboscidea Mammal"[mh] OR "Rodentia "[mh] OR "Scandentia"[mh] OR "Sirenia "[mh] OR "Xenarthra"[mh] OR "Gorilla"[mh] OR "Pan paniscus"[mh] OR "Pan troglodytes"[mh] OR "Pongo"[mh] OR "hominidae"[Mesh:noexp] OR "Cercopithecidae"[mh] OR "Hylobatidae"[mh] OR "catarrhini" OR "Platyrrhini"[mh] OR "Tarsii"[mh] OR "haplorhini"[mh:noexp] OR "Strepsirhini"[mh] OR "primates"[mh:noexp] OR "Oligochaeta"[mh] OR "Bees"[mh] OR ecotox* OR phytotox* OR ec50* OR lc50* OR "lethal concentration"[tw] OR aquatic OR wildlife OR Alga OR Algae OR Amphibian* OR Avian OR bird OR birds OR Chironomid* OR Chironomus OR Collembolan OR Daphnia OR Daphnid* OR Earthworm* OR Fish OR Medaka OR Minnow OR plant OR Mollusc* OR bioaccumulat* OR biomagnifica* OR biomonitor* OR biotransform* OR bioconcentrat*) AND 2015 : 3000[dp] Filter: Reviews
NTRL	
04/2020	searched in fulltext or in title/keyword (names found in Pubmed): "50-29-3" OR "72-55-9" OR "72-54-8" OR "789-02-6" OR "3424-82-6" OR "53-19-0" " o-Chlorophenyl -1- p-chlorophenyl -2,2,2-trichloroethane" OR "1- 2-Chlorophenyl -1- 4-chlorophenyl -2,2,2-trichloroethane" OR "1- 2-Chlorophenyl -1- 4-chlorophenyl -2,2-dichloroethane" OR "1- 2-Chlorophenyl -1- 4-chlorophenyl -2,2-dichloroethylene" OR "1- o-Chlorophenyl -1- p-chlorophenyl -2,2-dichloroethane" OR "1,1 - 2,2,2-Trichloroethylidene bis 4-chlorobenzene " OR "1,1 - 2,2-Dichloroethylidene bis 4-chlorobenzene " OR "1,1,1-Trichloro-2- o-chlorophenyl -2- p-chlorophenyl ethane" OR "1,1,1-Trichloro-2- p-chlorophenyl -2- o-chlorophenyl ethane" OR "1,1,1-Trichloro-2,2-bis p-chlorophenyl ethane" OR "1,1,1-Trichloro-2,2-bis 4-chlorophenyl ethane" OR "1,1,1-Trichloro-2,2-bis 4-chlorophenyl ethane" OR "1,1,1-Trichloro-2,2-bis p-chlorophenyl ethane" OR "1,1,1-Trichloro-2,2-di 4-chlorophenyl -ethane" OR "1,1,1-Trichloro-2,2-di p-chlorophenyl ethane" OR "1,1-Bis 4-chlorophenyl -2,2,2-trichloroethane" OR "1,1-Bis 4-chlorophenyl -2,2-dichloroethane" OR "1,1-Bis 4-chlorophenyl -2,2-dichloroethene" OR "1,1-Bis p-chlorophenyl -2,2,2-trichloroethane" OR "1,1-Bis- p-chlorophenyl -2,2,2-trichloroethane" OR "1,1-Bis p-chlorophenyl -2,2-dichloroethane" OR "1,1-Bis p-chlorophenyl -2,2-dichloroethylene" OR "1,1-Dichloro-2- o-chlorophenyl -2- p-chlorophenyl ethane" OR "1,1-Dichloro-2- o-chlorophenyl -2- p-chlorophenyl ethylene" OR "1,1-Dichloro-2- p-chlorophenyl -2- o-chlorophenyl ethane" OR "1,1 -Dichloro-2,2-bis 4-chlorophenyl ethane" OR "1,1-Dichloro-2,2-bis 4-chlorophenyl ethane" OR "1,1-Dichloro-2,2-bis p-chlorophenyl ethane" OR "1,1-

Table B-2. Database Query Strings

Database search date	Query string
	Dichloro-2,2-bis p-chlorophenyl ethene" OR "1,1-Dichloro-2,2-bis p-chlorophenyl ethylene" OR "1,1-Dichloro-2,2-di 4-chlorophenyl ethane" OR "1-Chloro-2- 2,2,2-trichloro-1- 4-chlorophenyl ethyl benzene" OR "2- 2-Chlorophenyl -2- 4-chlorophenyl -1,1,1-trichloroethane" OR "2- 2-Chlorophenyl -2- 4-chlorophenyl -1,1-dichloroethane" OR "2- o-Chlorophenyl -2- p-chlorophenyl -1,1-dichloroethane" OR "2,2- 2-Chlorophenyl-4 -chlorophenyl -1,1-dichloroethene" OR "2,2-Bis 2-chlorophenyl-4-chlorophenyl -1,1-dichloroethane" OR "2,2-Bis 4-chlorophenyl -1,1-dichloroethane" OR "2,2-Bis 4-chlorophenyl -1,1-dichloroethene" OR "2,2-Bis 4-chlorophenyl -1,1-dichloroethylene" OR "2,2-Bis o, p-chlorophenyl -1,1,1-trichloroethane" OR "2,2-bis p-Chlorophenyl -1,1,1-trichloroethane" OR "2,2-Bis p-chlorophenyl -1,1-dichloroethane" OR "2,2-Bis p-chlorophenyl -1,1-dichloroethylene" OR "2,4 -Dichlorodiphenyldichloroethane" OR "2,4 -Dichlorodiphenyldichloroethylene" OR "2,4 -Dichlorodiphenyltrichloroethane" OR "2-o-Chlorophenyl-2-p-chlorophenyl-1,1,1-trichloroethane" OR "4,4 -Dichlorodiphenyldichloroethane" OR "4,4 -Dichlorodiphenyldichloroethene" OR "4,4 -Dichlorodiphenyldichloroethylene" OR "4,4 -Dichlorodiphenyltrichloroethane" OR "4,4-Dichlorodiphenyl-trichloroethane" OR "Dichloro dichlorophenyl ethylene" OR "Dichloro diphenyl dichloroethane" OR "Dichloro diphenyl trichloroethane" OR "Dichlorodiphenyl dichloroethane" OR "Dichlorodiphenyl dichloroethene" OR "Dichlorodiphenyl dichloroethylene" OR "Dichlorodiphenyldichloroethane" OR "Dichlorodiphenyldichloroethene" OR "Dichlorodiphenyldichloroethylene" OR "Dichlorodiphenyltrichloroethane" OR "MITOTANE" OR "o, p -Dichlorodiphenyldichloroethane" OR "O, P -DICHLORODIPHENYLDICHLOROETHYLENE" OR "o, p -Dichlorodiphenyltrichloroethane" OR "p, p - Dichlorodiphenyl -2,2-dichloroethylene" OR "p, p-DDX" OR "p, p -Dichlorodiphenyl dichloroethylene" OR "p, p -Dichlorodiphenyl-2,2-dichloroethylene" OR "p, p -Dichlorodiphenyldichloroethane" OR "p, p -Dichlorodiphenyldichloroethene" OR "p, p -Dichlorodiphenyldichloroethylene" OR "p, p -Dichlorodiphenyltrichloroethane" OR "para, para -Dichlorodiphenyldichloroethylene" OR "Tetrachlorodiphenylethane" OR "2,4 -DDD" OR "2,4-DDD" OR "4,4 DDD" OR "4,4 -DDD" OR "4,4-DDD" OR "o, p -DDD" OR "p, p -DDD" OR "4,4 -TDE" OR "o, p -TDE" OR "o, p-TDE" OR "p, p -TDE" OR "p, p-TDE" OR "PEB1" OR "Chloditan" OR "Chlodithan" OR "Chlodithane" OR "Chlorophenothane" OR "Dicophane" OR "Dilene" OR "Dodat" OR "Gyron" OR "HEPT" OR "Ixodex" OR "Lysodren" OR "Mitotan" OR "Neocid" OR "Neocidol" OR "Opeprim" OR "Rhothane" OR "Rothane" "2,4 -DDE" OR "2,4-DDE" OR "4,4 -DDE" OR "4,4-DDE" OR "DDE o p" OR "DDE, 2,4 -" OR "DDE, o,p -" OR "DDE, p,p -" OR "o,p -DDE" OR "ortho-para DDE" OR "p,p - DDE" OR "p,p -DDE" OR "para,para -DDE" OR "para-para DDE" OR "pp-DDE total"
Toxcenter	
04/2020	(FILE 'HOME' ENTERED AT 13:07:33 ON 01 APR 2020) FILE 'TOXCENTER' ENTERED AT 13:07:58 ON 01 APR 2020 CHARGED TO COST=EH038.06.01.LB.02 L1 50073 SEA FILE=TOXCENTER 50-29-3 OR 72-55-9 OR 72-54-8 OR 789-02-6 OR 3424-82-6 OR 53-19-0 L2 0 SEA FILE=TOXCENTER 8017-34-3 L3 48315 SEA FILE=TOXCENTER L1 NOT PATENT/DT L4 1894 SEA FILE=TOXCENTER L3 AND ED>=20161101 L5 2407 SEA FILE=TOXCENTER L3 AND PY>2015 ACT TOXQUERY/Q ---------

Table B-2. Database Query Strings

Database search date	Query string
	L6 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L7 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L8 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L9 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L10 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L18 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L19 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L20 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L21 QUE (ENDOCRIN? AND DISRUPT?)
	L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L28 QUE (NEPHROTOX? OR HEPATOTOX?)
	L29 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L30 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L31 QUE 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 OR L30
	L32 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE

Table B-2. Database Query Strings

Database search date	Query string
	OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE
	OR PORCINE OR MONKEY? OR MACAQUE?)
	L33 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L34 QUE L31 OR L32 OR L33
	L35 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L36 QUE L34 OR L35

	L37 2489 SEA FILE=TOXCENTER L4 OR L5
	L38 1588 SEA FILE=TOXCENTER L37 AND L36
	L39 1355 SEA FILE=TOXCENTER L37 AND L31
	L40 1045 SEA FILE=TOXCENTER L39 AND L4
	L41 358 SEA FILE=TOXCENTER L39 AND MEDLINE/FS
	L42 997 SEA FILE=TOXCENTER L39 NOT MEDLINE/FS
	L43 1138 DUP REM L41 L42 (217 DUPLICATES REMOVED)
	ANSWERS '1-1138' FROM FILE TOXCENTER
	L*** DEL 358 S L39 AND MEDLINE/FS
	L*** DEL 358 S L39 AND MEDLINE/FS
	L44 358 SEA FILE=TOXCENTER L43
	L*** DEL 997 S L39 NOT MEDLINE/FS
	L*** DEL 997 S L39 NOT MEDLINE/FS
	L45 780 SEA FILE=TOXCENTER L43
	L46 780 SEA FILE=TOXCENTER (L44 OR L45) NOT MEDLINE/FS
	L47 51562 SEA FILE=TOXCENTER L1 OR DDT/TI OR DDE/TI
	L48 49787 SEA FILE=TOXCENTER L47 NOT PATENT/DT
	L49 2118 SEA FILE=TOXCENTER L48 AND ED>20161101
	L50 1140 SEA FILE=TOXCENTER L49 AND (ENVIRONMENT? OR ECOTOX? OR ECOLOG?
	OR PHYTOTOX? OR EC50? OR LC50? OR "LETHAL CONCENTRATION" OR
	AQUATIC OR WILDLIFE OR ALGA OR ALGAE OR AMPHIBIAN? OR AVIAN OR
	BIRD OR BIRDS OR CHIRONOMID? OR CHIRONOMUS OR COLLEMBOLAN)
	L51 513 SEA FILE=TOXCENTER L49 AND (DAPHNIA OR DAPHNID? OR EARTHWORM?
	OR FISH OR FISHES OR MEDAKA OR MINNOW OR PLANT OR MOLLUSC? OR
	BIOACCUMULAT? OR BIOMAGNIFICA? OR BIOMONITOR? OR BIOTRANSFORM?
	OR BIOCONCENTRAT?)
	L52 1318 SEA FILE=TOXCENTER L50 OR L51
	L53 191 SEA FILE=TOXCENTER L52 AND BIOSIS/FS
	L54 14 SEA FILE=TOXCENTER L53 AND (REVIEW? OR SYNTHESIS OR METASYNTHES
	IS OR SEARCH? OR SYSTEMATIC?)
	L55 14 DUP REM L54 (0 DUPLICATES REMOVED)
	ANSWERS '1-14' FROM FILE TOXCENTER
	L56 9 SEA FILE=TOXCENTER L54 NOT L46

Table B-2. Database Query Strings

Database search date	Query string
	D SCAN L56 D SCAN L46

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
04/2020	Compounds searched: 50-29-3; 72-55-9; 72-54-8; 789-02-6; 3424-82-6; 53-19-0
NTP	
04/2020	limited 2015-present 50-29-3 72-55-9 72-54-8 789-02-6 3424-82-6 53-19-0
NIH RePORTER	
07/2021	Searched only names found in Pubmed. (advanced)Limit to: Project Title, Project Terms, Project Abstracts Fiscal Year: Active Projects Text Search: "D.D.T." OR "DDE" OR "DDT" OR "DDT3" OR "DDTs" OR "Dichloro dichlorophenyl ethylene" OR "Dichloro diphenyl dichloroethane" OR "Dichloro diphenyl trichloroethane" OR "Dichlorodiphenyl dichloroethane" OR "Dichlorodiphenyl dichloroethene" OR "Dichlorodiphenyl dichloroethylene" OR "Dichlorodiphenyldichloroethane" OR "Dichlorodiphenyldichloroethene" OR "Dichlorodiphenyldichloroethylene" OR "Dichlorodiphenyltrichloroethane" OR "MITOTANE" OR "o, p'-Dichlorodiphenyldichloroethane" OR "O, P'-DICHLORODIPHENYLDICHLOROETHYLENE" OR "o, p'-Dichlorodiphenyltrichloroethane" OR "p, p'-(Dichlorodiphenyl)-2,2-dichloroethylene" OR "p, p-DDX" OR "p, p'-Dichlorodiphenyl dichloroethylene" OR "p, p'-Dichlorodiphenyl-2,2-dichloroethylene" OR "p, p'-Dichlorodiphenyldichloroethane" OR "p, p'-Dichlorodiphenyldichloroethene" OR "p, p'-Dichlorodiphenyldichloroethylene" OR "p, p'-Dichlorodiphenyltrichloroethane" OR "para, para'-Dichlorodiphenyldichloroethylene" OR "Tetrachlorodiphenylethane" OR "2,4'-DDD" OR "2,4-DDD" OR "4,4' DDD" OR "4,4'-DDD" OR "4,4-DDD" OR "o, p'-DDD" OR "p, p'-DDD" OR "4,4'-TDE" OR "o, p'-TDE" OR "o, p-TDE" OR "p, p'-TDE" OR "p, p-TDE" OR "PEB1" OR "Chloditan" OR "Chlodithan" OR "Chlodithane" OR "Chlorophenothane" OR "Dicophane" OR "Dilene" OR "Dodat" OR "Gyron" OR "HEPT" OR "Ixodex" OR "Lysodren" OR "Mitotan" OR "Neocid" OR "Neocidol" OR "Opeprim" OR "Rhothane" OR "Rothane" OR "DDD" "(o-Chlorophenyl)-1-(p-chlorophenyl)-2,2,2-trichloroethane" OR "1-(2-Chlorophenyl)-1-(4-chlorophenyl)-2,2,2-trichloroethane" OR "1-(2-Chlorophenyl)-1-(4-chlorophenyl)-2,2-dichloroethane" OR "1-(2-Chlorophenyl)-1-(4-chlorophenyl)-2,2-dichloroethylene" OR "1-(o-Chlorophenyl)-1-(p-chlorophenyl)-2,2-dichloroethane" OR "1,1'-(2,2,2-Trichloroethylidene)bis(4-chlorobenzene)" OR "1,1'-(2,2-Dichloroethylidene)bis(4-

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	chlorobenzene)" OR "1,1,1-Trichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane" OR "1,1,1-Trichloro-2-(p-chlorophenyl)-2-(o-chlorophenyl)ethane" OR "1,1,1-Trichloro-2,2-bis (p-chlorophenyl)ethane" OR "1,1,1-Trichloro-2,2-bis(4-chlorophenyl) ethane" OR "1,1,1-Trichloro-2,2-bis(4-chlorophenyl)ethane" OR "1,1,1-Trichloro-2,2-bis(p-chlorophenyl)ethane" OR "1,1,1-Trichloro-2,2-di(4-chlorophenyl)-ethane" OR "1,1,1-Trichloro-2,2-di(p-chlorophenyl)ethane" OR "1,1-Bis(4-chlorophenyl)-2,2,2-trichloroethane" OR "1,1-Bis(4-chlorophenyl)-2,2-dichloroethane" OR "1,1-Bis(4-chlorophenyl)-2,2-dichloroethene" OR "1,1-Bis(p-chlorophenyl)-2,2,2-trichloroethane" OR "1,1-Bis-(p-chlorophenyl)-2,2,2-trichloroethane" OR "1,1-Bis(p-chlorophenyl)-2,2-dichloroethane" OR "1,1-Bis(p-chlorophenyl)-2,2-dichloroethylene" OR "1,1-Dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane" OR "1,1-Dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethylene" OR "1,1-Dichloro-2-(p-chlorophenyl)-2-(o-chlorophenyl)ethane" "1,1'-Dichloro-2,2-bis(4-chlorophenyl)ethane" OR "1,1-Dichloro-2,2-bis(4-chlorophenyl)ethane" OR "1,1-Dichloro-2,2-bis(p-chlorophenyl)ethane" OR "1,1-Dichloro-2,2-bis(p-chlorophenyl)ethene" OR "1,1-Dichloro-2,2-bis(p-chlorophenyl)ethylene" OR "1,1-Dichloro-2,2-di(4-chlorophenyl)ethane" OR "1-Chloro-2-(2,2,2-trichloro-1-(4-chlorophenyl)ethyl)benzene" OR "2-(2-Chlorophenyl)-2-(4-chlorophenyl)-1,1,1-trichloroethane" OR "2-(2-Chlorophenyl)-2-(4-chlorophenyl)-1,1-dichloroethane" OR "2-(o-Chlorophenyl)-2-(p-chlorophenyl)-1,1-dichloroethane" OR "2,2-(2-Chlorophenyl-4'-chlorophenyl)-1,1-dichloroethene" OR "2,2-Bis(2-chlorophenyl-4-chlorophenyl)-1,1-dichloroethane" OR "2,2-Bis(4-chlorophenyl)-1,1-dichloroethane" OR "2,2-Bis(4-chlorophenyl)-1,1-dichloroethene" OR "2,2-Bis(4-chlorophenyl)-1,1-dichloroethylene" OR "2,2-Bis(o, p-chlorophenyl)-1,1,1-trichloroethane" OR "2,2-bis(p-Chlorophenyl)-1,1,1-trichloroethane" OR "2,2-Bis(p-chlorophenyl)-1,1-dichloroethane" OR "2,2-Bis(p-chlorophenyl)-1,1-dichloroethylene" OR "2,4'-Dichlorodiphenyldichloroethane" OR "2,4'-Dichlorodiphenyldichloroethylene" OR "2,4'-Dichlorodiphenyltrichloroethane" OR "2-o-Chlorophenyl-2-p-chlorophenyl-1,1,1-trichloroethane" OR "4,4'-Dichlorodiphenyldichloroethane" OR "4,4'-Dichlorodiphenyldichloroethene" OR "4,4'-Dichlorodiphenyldichloroethylene" OR "4,4'-Dichlorodiphenyltrichloroethane" OR "4,4-Dichlorodiphenyl-trichloroethane"
Other	Identified throughout the assessment process

The 2020 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 2,008
- Number of records identified from other strategies: 28
- Total number of records to undergo literature screening: 2,036

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on DDT, DDE, and DDD:

- 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.

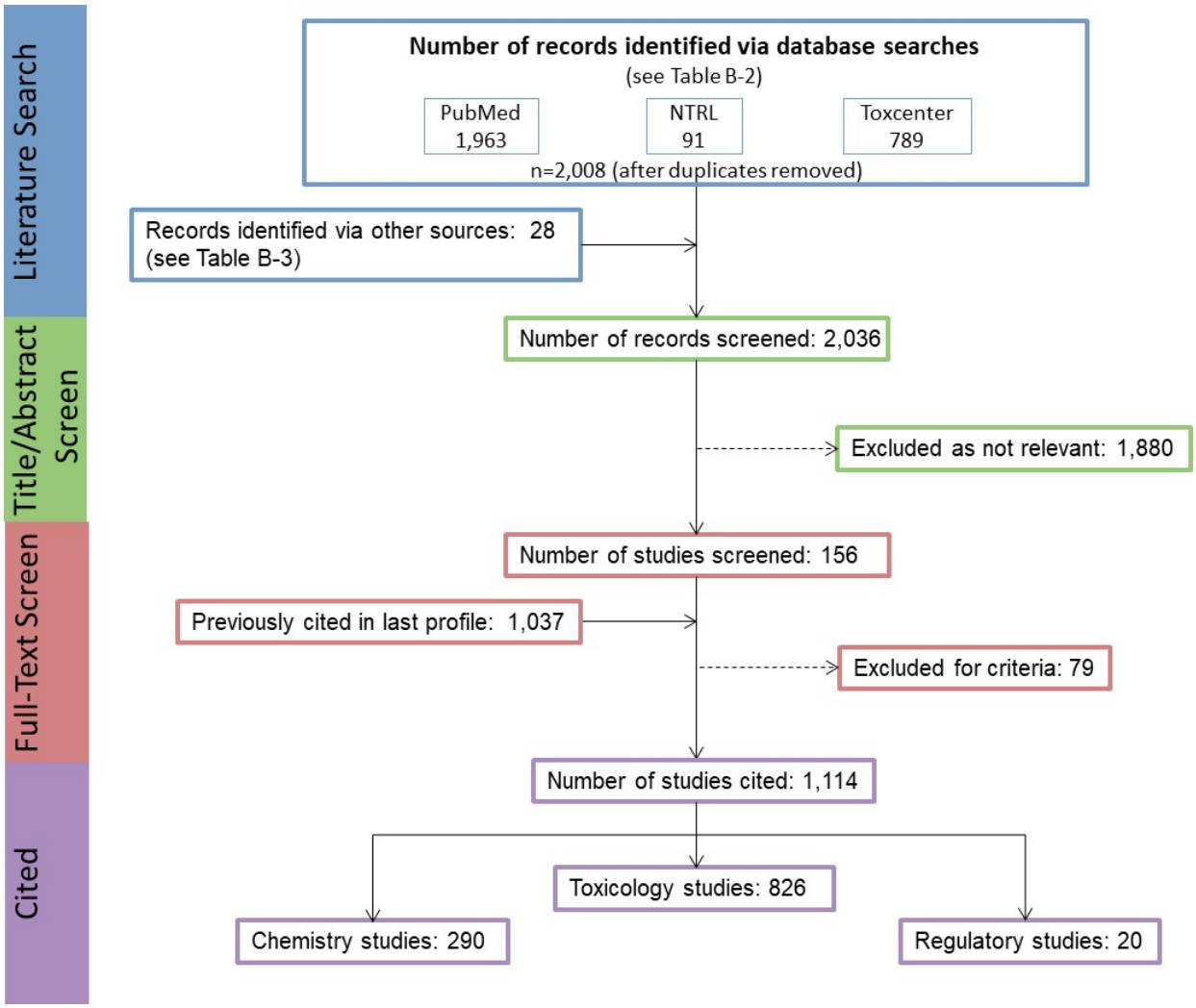
- Number of titles and abstracts screened: 2,036
- Number of studies considered relevant and moved to the next step: 156

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: 156
- Number of studies cited in the pre-public draft of the toxicological profile: 1,037
- Total number of studies cited in the profile: 1,114

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

Figure B-1. November 2016 Literature Search Results and Screen for DDT, DDE, and DDD



APPENDIX C. 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 C-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 C-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]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE (2)									
51 (3)	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									

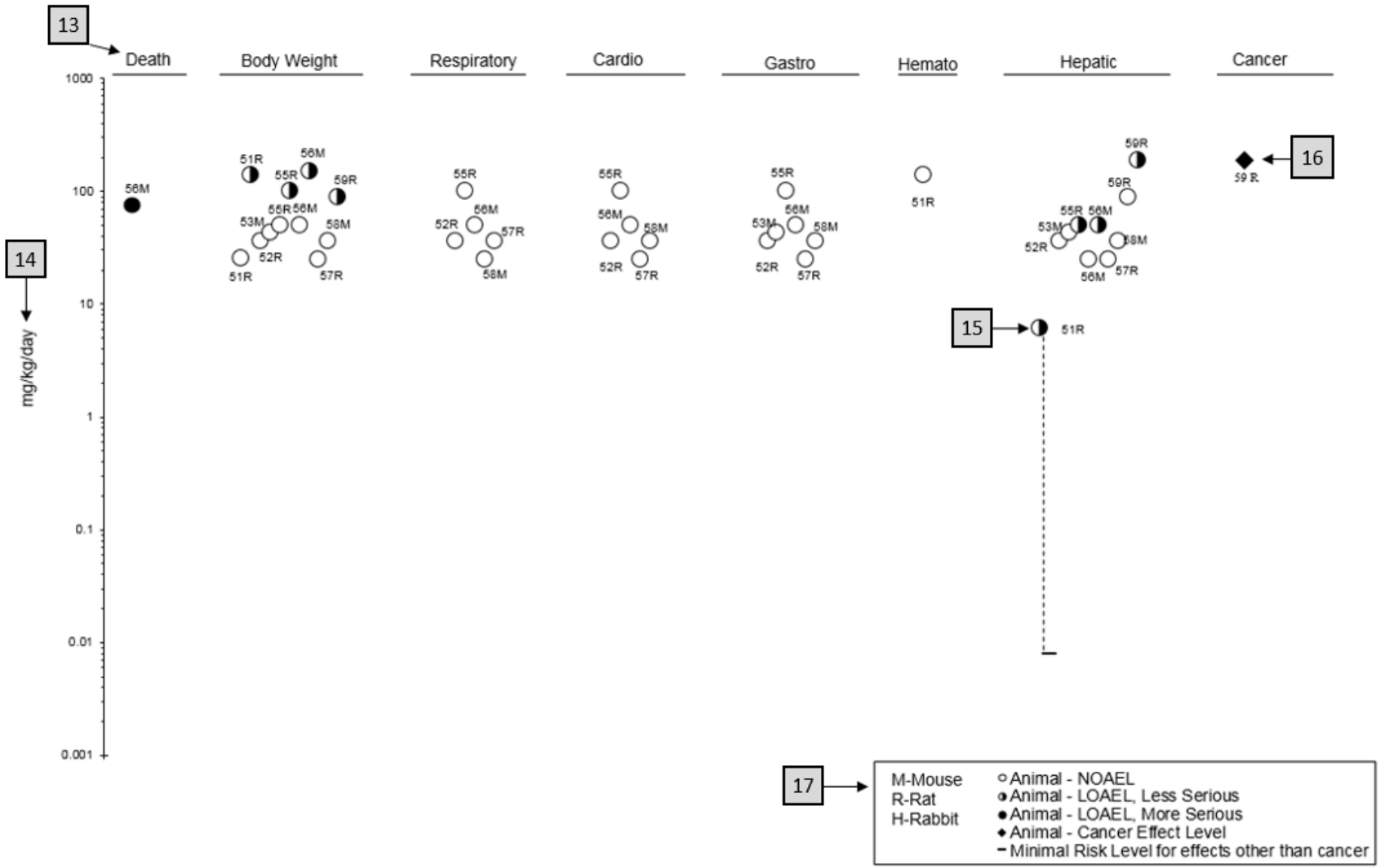
(11)

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

[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 D. 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 E. 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 F. 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
AGD	anogenital distance
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
ΣDDT	Sum of total DDT, DDD, and DDT levels
DMT2	Type 2 diabetes mellitus
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
HR	hazard ratio
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
ROS	reactive oxygen species
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

>	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
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–	negative
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