CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Dichlorodiphenyltrichloroethane (DDT) is an organochlorine insecticide that had a broad range of agricultural and nonagricultural applications in the United States and worldwide beginning in 1939. In 1972, DDT use was banned in the United States and in many parts of the world. Since the adoption of the Stockholm Convention in 2004, uses have continued to decline. Under the Stockholm Convention, use of DDT is primarily restricted to controlling vector-borne diseases, such as malaria and leishmaniasis; a small number of countries continue to use DDT for these purposes. In 2006, the World Health Organization (WHO) approved the use of indoor residual spraying as a measure to control disease in areas where malaria and other vector-borne pathogens remain a major health problem. Dichlorodiphenyl-dichloroethane (DDD) and dichlorodiphenyldichloroethylene (DDE) are both degradation products and metabolites of DDT. DDD was also manufactured and used as an insecticide, but to a much lesser extent than DDT. DDE is not manufactured commercially, but can be produced by the dehydrochlorination of DDT in alkaline solution and is commonly detected at concentrations in the environment that often exceed those measured for DDT. Different forms of DDT, DDE, and DDD called isomers can be found in the environment. Many of these isomers are described in human and animal studies; the six most common isomers that are detected or used in studies that might be seen throughout this profile include commercial or technical DDT, *p,p'*-DDT, *o,p'*-DDT, *p,p'*-DDE, *o,p'*-DDE, technical DDD, and *o,p'*-DDD.

Upon introduction into the environment, DDT will enter soil, water, or air. The long-range transport of DDT has resulted in the wide dispersion of DDT and its metabolites throughout the world, even into remote areas, such as the Arctic or Antarctic regions. The biodegradation of DDT and its metabolites is slow, and these compounds can bioaccumulate (increasing concentration of a chemical in an organism that exceeds that in its environment) in fatty tissues. The ban on DDT use in the early 1970s in the United States and most of the world has contributed to a decrease in the levels of these compounds in the environment over the past 40 years. Except for areas where production and use are still active, exposure of the general public to DDT, DDE, DDD, and their isomers has also been declining since the ban on the use of DDT.

The predominant route of exposure to DDT and its metabolites is through the consumption of foods either obtained from areas of the world where DDT is still used or that have the potential to contain bioaccumulated residues of DDT and its metabolites (e.g., meat, fish, poultry, dairy products). Although

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DDT and its metabolites are ubiquitous in the atmosphere, they have not been shown to significantly contribute to body burden; however, this has not been well studied. Exposure to DDT in drinking water is considered negligible because of the extremely low water solubility of DDT and the efficiency of standard drinking water processing methods. With the ban on the use of DDT, occupational exposures that result from formulation, packaging, and application activities should be negligible, except in areas where DDT use remains. Activities that result in the mobilization of DDT (e.g., site remediation) may increase exposure of workers to DDT and its metabolites.

Since the ban on DDT was instituted in the United States and most of the world in 1972 and the adoption of the Stockholm Convention, the environmental concentrations of DDT and its metabolites have been decreasing. Average adult intakes of DDT were estimated to be 62 μg/person/day in 1965 and 240 μg/person/day in 1970, before the DDT ban was instituted (Coulston 1985). The U.S. Food and Drug Administration (FDA) Total Diet Studies showed that the daily intakes of total DDT have fallen since the ban, with daily intakes (for a 16-year-old, 70-kg male) averaging 6.51, 2.38, 1.49, and 0.97 μg/person/day for 1978–1979, 1979–1980, 1984–1986, and 1986–1991, respectively (Gunderson 1995a, 1995b). As would be expected from the decline in the concentrations of DDT in the environment, the levels of DDT, DDE, and DDD measured in foodstuffs have also fallen over the last 45 years. Yet, there are still measurable quantities of DDT, DDE, and DDD in some commodities. *p,p'*-DDE was the most frequently detected isomer in studies of U.S. food samples (FDA 2006; USDA 2016). Some of the foods with detectable levels of DDT and metabolites include American cheese, butter, catfish, carrots, summer squash, celery, and salmon (FDA 2006; Huang et al. 2006; USDA 2016).

Exposures of the general public to DDT and its metabolites result in the accumulation of these compounds in adipose tissue and breast milk. Due to the persistence of DDT and its metabolites in the environment and their slow elimination from the body, the concentrations of these compounds in adipose tissue and breast milk are determined by both past and current exposures. Body burdens of DDT and its metabolites are decreasing, due to declining environmental levels. The average levels of DDT in human breast milk fat were about 2,000–5,000 ppb in the United States in the early 1970s, but have steadily declined at a rate of 11–21% per year since 1975. For example, Norén (1988) reported concentrations of *p,p'*-DDT in breast milk fat of 710, 360, 180, and 61 ppb for the years 1972, 1976, 1980, and 1984–1985, respectively. These investigators also reported concentrations of *p,p'*-DDE of 2,420, 1,530, 999, and 500 ppb for these same years, respectively. More recently, ΣDDT concentrations in pooled U.S. human breast milk samples collected in 2000–2003 were approximately 110 ppb on a lipid basis. Serum levels of *p,p'*-DDE, the main metabolite of *p,p'*-DDT, also have dropped appreciably in the last several decades,

showing a 5-fold decrease in concentration in U.S. National Health and Nutrition Examination Survey (NHANES) samples collected between 1976 and 2004 (Wattigney et al. 2015).

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of DDT, DDE, DDD, and their isomers comes from numerous epidemiology studies examining possible associations between levels of DDT, DDE, or DDD in human tissues or fluids and occurrence of various noncancer and cancer health outcomes, as well as from over 150 oral toxicity studies in laboratory animals. A few early controlled-exposure studies of human subjects are available, and very few inhalation or dermal studies, in either humans or animals, were identified.

Inconsistent evidence (some studies reported associations, others did not) has been provided by the epidemiological studies of most of the noncancer and cancer outcomes, with the exception of studies providing consistent evidence for:

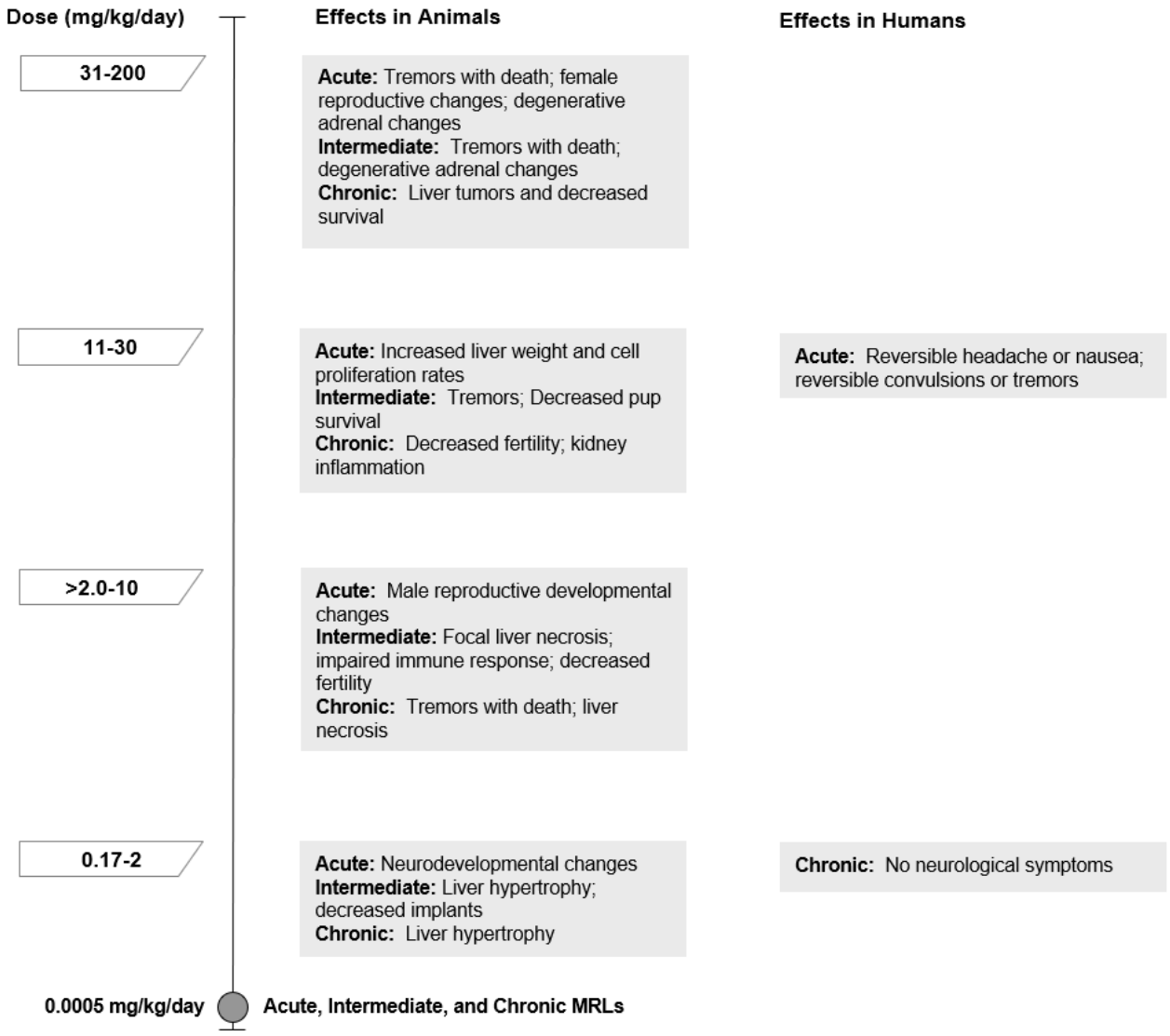
- associations between maternal exposure and prevalence for wheeze in infants or children;
- no associations with male reproductive system birth defects;
- associations with prevalence of Type 2 diabetes mellitus (DMT2);
- associations with liver cancer; and
- no associations with breast cancer in women, pancreatic cancer, or endometrial cancer.

Although the epidemiological studies provided consistent evidence of associations for some health effects, these studies are observational and do not establish causality; the observed statistical association may be due to effects of other factors, such as exposure to other pollutants. Likewise, the absence of an association does not necessarily imply the absence of a causal relationship. The available epidemiological studies do not provide sufficient data to describe exposure-response relationships for potential health outcomes associated with exposure to DDT, DDD, or DDE. Another limitation of the epidemiological database is that most studies lacked statistical control for exposure to other compounds, particularly highly lipophilic compounds such as polychlorinated biphenyls (PCBs), chlorodibenzo-*p*-dioxins (CDDs), and chlorodibenzofurans (CDFs), which may co-migrate with DDT and could be the causative agent.

As illustrated in Figure 1-1, toxicity studies of laboratory animals provide sufficient evidence to identify neurological effects including neurodevelopmental effects, liver effects, reproductive and developmental reproductive effects, and immunological effects as sensitive toxicity targets of acute-, intermediate-, and

chronic-duration oral exposure to isomers of DDT, DDE, or DDD. Figure 1-1 also illustrates the chronic-duration oral exposure levels associated with liver tumors in laboratory animals. In most cases, the doses associated with adverse effects in laboratory animals are higher than could be reasonably anticipated from background exposures in the United States (see Section 1.1).

Figure 1-1. Health Effects Following Oral Exposure to DDT, DDE, and DDD



Hepatic Effects. Inconsistent evidence for liver effects has been provided by epidemiological studies examining possible associations between levels of DDT or DDE in blood and serum or urinary markers of liver damage or dysfunction (i.e., some studies reported associations and others reported no associations). Two studies found no significant associations with indicators of liver damage (e.g., increased aspartate aminotransferase [AST], alanine aminotransferase [ALT], or bilirubin) in subjects from a heavily contaminated region and a group of U.S. agricultural workers (Freire et al. 2015a, 2015b; Morgan and Lin 1978). However, significant associations with indicators of liver damage were found in analyses for serum indicators from the U.S. general population (Serdar et al. 2014) and of urinary porphyrin levels in a group of children from a contaminated region (Sunyer et al. 2008).

In contrast, results from numerous studies of orally-exposed laboratory animals indicate that the liver is a sensitive toxicity target of DDT, DDE, and DDD isomers. Acute-, intermediate-, and chronic-duration oral exposures have been shown to cause dose-related, mild-to-severe hepatic effects in numerous animal studies.

After acute oral exposure to technical DDT or unspecified DDT, *p,p'*-DDT, *p,p'*-DDE, unspecified DDE, or unspecified DDD, a number of hepatic effects have been observed including induction of liver microsomal xenobiotic metabolizing enzymes often associated with increased liver weight, increased serum levels of liver enzymes (suggestive of liver injury), and histological changes in the liver including cellular hypertrophy and necrosis (Agarwal et al. 1978; de Waziers and Azais 1987; Garcia and Mourelle 1984; Kang et al. 2004; Kostka et al. 2000; Leavens et al. 2002; Nims et al. 1998; Pasha 1981; Tomiyama et al. 2003, 2004). After intermediate-duration exposure to technical DDT, *p,p'*-DDT, or *p,p'*-DDE, an array of hepatic effects, similar to those observed after acute exposure, have been observed in rats and mice (Gupta et al. 1989; Harada et al. 2003, 2006; Hojo et al. 2006; Jonsson et al. 1981; Laug et al. 1950; Orberg and Lundberg 1974; Ortega 1956; Yamasaki et al. 2009; Tomiyama et al. 2004). The lowest reliable intermediate-duration animal lowest-observed-adverse effect level (LOAEL) for liver effects is 0.17 mg *p,p'*-DDT/kg/day in the diet reported for cellular hypertrophy in rats exposed for 26 weeks; the no-observed-adverse-effect level (NOAEL) from this study was 0.17 mg/kg/day (Harada et al. 2003, 2006). Nonneoplastic liver lesions have been observed in rats, mice, hamsters, monkeys, and dogs after chronic oral exposure to DDT and related compounds (Cabral et al. 1982a; Deichmann et al. 1967; Durham et al. 1963; Fitzhugh and Nelson 1947; Graillot et al. 1975; Harada et al. 2003, 2006; Hojo et al. 2006; Laug et al. 1950; Lehman 1965; NCI 1978; Rossi et al. 1983; Takayama et al. 1999). The lowest reliable chronic-duration animal LOAEL for nonneoplastic histological changes in the liver is 0.17 mg

p,p'-DDT/kg/day for hepatocellular hypertrophy in male rats exposed in the diet for 2 years (Harada et al. 2003, 2006).

Neurological and Neurodevelopmental Effects. In controlled-exposure studies of adult volunteers and reports of accidental or intentional ingestion, the nervous system appears to be one of the primary target systems for acute high-dose DDT toxicity, producing reversible perspiration, headache, and nausea at doses ≥16 mg DDT/kg, progressing to reversible convulsions or tremors at dose levels of about 22 mg DDT/kg and higher (Francone et al. 1952; Garrett 1947; Hayes 1982; Hsieh 1954; Mulhens 1946; Velbinger 1947a, 1947b). However, these types of neurological symptoms were not reported in adult volunteers who ingested low dose levels of about 0.05 or 0.5 mg DDT/kg/day for 12–18 months (Hayes et al. 1956).

Inconsistent evidence has been provided by epidemiological studies examining possible associations between serum levels of DDT, DDE, or DDD in adults or adolescents and deficits in cognitive or mental status tests or risks for neurological conditions, such as Alzheimer's disease, Parkinson's disease, or attention deficient disorder (Kim et al. 2015a, 2015b, 2015c; Lee et al. 2007a, 2016a, 2016b; Medehouenou et al. 2014; Richardson et al. 2014; Rocha-Amador et al. 2009; Steenland et al. 2014; Weisskopf et al. 2010). Inconsistent evidence also has been provided by epidemiological studies that evaluated possible associations between DDT, DDE, or DDD levels in maternal serum, milk, or cord blood and various neurodevelopmental endpoints, including:

- neurobehavioral endpoints in infants ≤2 years of age (Engel et al. 2007; Eskenazi et al. 2006; Fenster et al. 2007; Forns et al. 2012b; Gascon et al. 2013; Gladen and Rogan 1991; Gladen et al. 1988; Hoyer et al. 2015; Jusko et al. 2012; Pan et al. 2009; Ribas-Fito et al. 2003a; Bahena-Medina et al. 2011; Sagiv et al. 2008; Stewart et al. 2000; Torres-Sanchez et al. 2007, 2013);
- behavioral problems, attention and ADHD in offspring (Forns et al. 2012a, 2016; Kyriklaki et al. 2016; Sagiv et al. 2010; Sioen et al. 2013; Strom et al. 2014);
- neurobehavioral endpoints (including IQ) in older children (Gaspar et al. 2015a, 2015b; Gladen and Rogan 1991; Jusko et al. 2012; Kyriklaki et al. 2016; Lyall et al. 2016; Orenstein et al. 2014; Osorio-Valencia et al. 2015; Ribas-Fito et al. 2006, 2007; Sagiv et al. 2012; Torres-Sanchez et al. 2013); and
- other neurological endpoints in children, such as visual evoked potential deficits (Ren et al. 2011; Riva et al. 2004) and neural tube defects (Cartier et al. 2014).

Tremors, hyperirritability, convulsions, and intermittent myoclonic movements have been described in mature laboratory animals following oral exposure to technical DDT, *p,p'*-DDT, or *p,p'*-DDE at acute-duration doses ≥50 mg/kg/day (Herr and Tilson 1987; Herr et al. 1985; Hietanen and Vainio 1976; Hong et al. 1986; Hudson et al. 1985; Hwang and Van Woert 1978; Pranzatelli and Tkach 1992; Pratt et al. 1986; Tilson et al. 1987; Tomiyama et al. 2003), intermediate-duration doses ≥28 mg/kg/day (Cranmer et al. 1972; Hojo et al. 2006; NCI 1978; Rossi et al. 1977), or chronic-duration doses ≥7 mg/kg/day (Harada et al. 2003, 2006; NCI 1978; Rossi et al. 1983; Takayama et al. 1999), but no tremors were observed in acute- or chronic-duration studies of laboratory animals orally exposed to technical DDD at doses as high as 231 mg/kg/day (NCI 1978).

Acute-duration oral exposure of adult laboratory animals to DDT also has been associated with increases in brain biogenic amine and neurotransmitter levels at doses ≥50 mg *p,p'*-DDT/kg (Hong et al. 1986; Hrdina et al. 1973; Hudson et al. 1985; Hwang and Van Woert 1978; Tilson et al. 1986). Young laboratory mice appear to be particularly sensitive to brain neurochemical changes and associated behavioral changes from exposure to low doses of technical DDT during critical windows of neurodevelopment. Increased spontaneous motor activity (reduced habituation) and decreased cerebral cortex muscarinic receptors were observed in 4–7-month-old mice exposed to 0.5 mg/kg/day technical DDT on postnatal day (PND) 10, but not on PND 3 or 18 (Eriksson and Nordberg 1986; Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996, supported by Talts et al. 1998).

Reproductive and Developmental Reproductive Effects. Possible associations between exposure to DDT (isomers and metabolites), as assessed by levels in biological media (mostly serum), and human reproductive outcomes have been examined in numerous epidemiological studies.

The available studies provide inconsistent evidence for associations with each of the reproductive effects evaluated in adults (*time to pregnancy* [Axmon et al. 2006; Buck Louis 2014; Buck Louis et al. 2013; Chevrier et al. 2013; Cohn et al. 2003; Harley et al. 2008; Law et al. 2005], *uterine alterations such as endometriosis* [Cooney et al. 2010; Porpora et al. 2009; Trabert et al. 2015; Upson et al. 2013], *menstrual cycle changes* [Cooper et al. 2005; Denham et al. 2005; Gallo et al. 2016; Ouyang et al. 2005; Toft et al. 2008; Windham et al. 2005), *early age at menopause* [Cooper et al. 2002; Grindler et al. 2015], *levels of reproductive sex hormones* [Blanco-Muñoz et al. 2012; Emeville et al. 2013; Ferguson et al. 2012; Freire et al. 2014; Giwercman et al. 2006; Goncharov et al. 2009; Hagmar et al. 2001; Haugen et al. 2011; Martin et al. 2002; Perry et al. 2006; Rignell-Hydbom et al. 2004; Rylander et al. 2006; Schell et al. 2014; Turyk et al. 2006; Windham et al. 2005], and *semen parameters* [Aneck-Hahn et al. 2007; Charlier and

Foidart 2005; Dallinga et al. 2002; Hauser et al. 2003; de Jager et al. 2006; Messaros et al. 2009; Pant et al. 2007; Rignell-Hydbom et al. 2005b; Toft et al. 2006]).

Additionally, there is inconsistent evidence for associations between DDT, DDE, or DDD dosimetrics and puberty onset outcomes in studies of preadolescents/adolescents (Croes et al. 2015; Den Hond et al. 2011; Dhooge et al. 2011; Lam et al. 2014, 2015). In contrast, there is consistent evidence from studies of adults suggesting that serum levels of DDT, DDD, or DDE currently found in the U.S. general populations may not present increased risks for abortion or premature delivery, but increased risk may exist in countries where DDT is still being used (Korrick et al. 2001; Longnecker et al. 2005; Ouyang et al. 2014; Torres-Arreola et al. 2003; Venners et al. 2005; Wood et al. 2007). In epidemiological studies of possible associations between DDT, DDE, or DDD levels in maternal serum, cord blood, breast milk, or placenta and reproductive outcomes in human offspring, no consistent evidence was found for associations for increased risk for the male birth defects, cryptorchidism or hypospadias (Bhatia et al. 2005; Brucker-Davis et al. 2008; Damgaard et al. 2006; Fernandez et al. 2007; Giordano et al. 2010; Longnecker et al. 2002) and for reproductive outcomes in adult offspring, such as sex hormone levels and menstrual cycle in adult daughters or sex hormone levels and sperm parameters in adult sons (Han et al. 2016; Kristensen et al. 2016; Vasiliu et al. 2004; Vested et al. 2014).

Reproductive effects of DDT and related compounds in mature and developing laboratory animals have been observed at relatively high dose levels (>1 mg/kg/day).

After acute-duration exposure, decreased male reproductive tissue weight was observed at doses of DDT (not specified [NS]), *p,p'*-DDT, or *p,p'*-DDE ≥50 mg/kg/day (Kang et al. 2004; Kelce et al. 1995, 1997); and increased weight of the uterus was observed in females at ≥100 mg *o,p'*-DDT/kg/day (Clement and Okey 1972; Diel et al. 2000). Decreased fertility has been observed after intermediate-duration exposure to doses of technical DDT ≥5.1 mg/kg/day (Bernard and Gaertner 1964; Jonsson et al. 1976; Ledoux et al. 1977). In chronic multi-generation-exposure-duration studies, no adverse effects on reproduction functions were observed in rats fed up to 18.6 mg technical-grade DDT/kg/day (Ottoboni 1969) and 27.7 mg *p,p'*-DDT/kg/day (Hojo et al. 2006), and dogs fed up to 10 mg technical DDT/kg/day (Ottoboni et al. 1977), but decreased fertility was reported in a 3-generation study of mice fed 20 mg technical DDT/kg/day (Keplinger et al. 1970). No treatment-related histopathological effects on the ovaries, uterus, mammary glands, or prostate were found in rats fed for 78 weeks with doses up to 45 mg technical DDT/kg/day, 59 mg *p,p'*-DDE/kg/day, or 231 mg technical DDD/kg/day, or mice fed up 30.2 mg

technical DDT/kg/day, 49 mg *p,p'*-DDE/kg/day, or 142 mg technical DDD/kg/day (NCI 1978). Reproductive function (e.g., fertility) was not evaluated in the NCI (1978) study.

Gestational exposure of laboratory animals to *p,p'*-DDT or *p,p'*-DDE has been associated with decreased prostate weight and decreased anogenital distance (AGD) in male offspring at doses ≥10 mg/kg/day (Gray et al. 1999; Kelce et al. 1995; Loeffler and Peterson 1999; You et al. 1998); decreased fertility in male and female offspring exposed to 50 mg/kg/day on gestation days (GDs) 6–20 (Yamasaki et al. 2009); and increased resorptions after impregnation of female offspring exposed to ≥10 mg/kg/day on GDs 7–9 (Hart et al. 1971, 1972). Gestational exposure to *o,p'*-DDD or *p,p'*-DDT also has been associated with delayed vaginal opening and increased ovary weight in female offspring exposed to 28 mg/kg/day on GDs 15–19, but not after GD 15–19 exposure to *o,p'*-DDT or *o,p'*-DDE at the same dose level (Gellert and Heinrichs 1975).

Exposure during gestation and lactation was associated with decreased fertility in female offspring at a high dose level of *o,p'*-DDT (128 mg/kg/day), but not at ~5–6-fold lower doses of *o,p'*-DDT (26 mg/kg/day) or *p,p'*-DDT (16.8 mg/kg/day) (Clement and Okey 1974).

Immunological Effects. Inconsistent evidence for associations between serum levels of *p,p'*-DDE or *p,p'*-DDT and immune function biomarkers (e.g., immunoglobulin serum levels or counts of white blood cell or lymphocyte subtypes) or immune-related conditions (e.g., asthma, bronchitis, eczema) has been provided by epidemiological studies of adults (Cooper et al. 2004; Miyake et al. 2011; Vine et al. 2001) and children (Karmaus et al. 2001, 2003, 2005a, 2005b; Meng et al. 2016; Perla et al. 2015). Consistent evidence comes from several studies of associations between levels of DDE in cord blood or maternal serum during pregnancy and prevalence of wheeze (or airway obstruction) in infant or child offspring (Gascon et al. 2012, 2014; Hansen et al. 2016; Sunyer et al. 2005, 2006). In other epidemiological studies, however, inconsistent evidence was provided for associations between maternal DDE exposure biometrics (cord blood, maternal serum, or breast milk) and prevalence of asthma, blood levels of biomarkers associated with asthma, and prevalence of infections in offspring (Cupul-Uicab et al. 2014; Dallaire et al. 2004; Dewailly et al. 2000; Gascon et al. 2012; Glynn et al. 2008; Hansen et al. 2014; Jusko et al. 2016a, 2016b; Sunyer et al. 2006, 2010).

A single acute-duration study in hamsters exposed to 4.3 mg DDT (NS)/kg/day for 10 days found no effect on antibody titers to *Salmonella typhi* (Shiplov et al. 1972). In contrast, the potential for intermediate-duration exposures to technical DDT, *p,p'*-DDT, *p,p'*-DDE, *p,p'*-DDD, or *o,p'*-DDD in the

diet to suppress or stimulate various immune responses has been examined in rats, mice, and rabbits, with doses associated with immune system perturbations, such as decreased immunoglobulin serum levels and impaired immune response after antigen challenge, ranging from about 2.3 to 20 mg/kg/day (Banerjee 1987a, 1987b; Banerjee et al. 1986, 1995, 1996, 1997a, 1997b; Gabliks et al. 1975; Hamid et al. 1974; Koner et al. 1998; Rehana and Rao 1992; Street and Sharma 1975). In these studies, *p,p'*-DDT was the most widely used test material.

Metabolic Effects/Type 2 Diabetes Mellitus (Other Noncancer Effects). Thirty-four epidemiological studies have examined possible associations between human DDT exposure biometrics (e.g., serum or adipose levels of DDT, DDE, or DDD) and prevalence of DMT2 or biomarkers indicative of DMT2 or other metabolic effects (e.g., fasting blood glucose, insulin, HbA1C, homeostatic model assessment insulin resistance, insulin resistance, leptin, or adiponectin). A clear majority of studies, including several meta-analyses, provide evidence for a positive association between DDT exposure biometrics in groups of humans and increased prevalence of DMT2 (e.g., Evangelou et al. 2016; Fakhri et al. 2017; Lee et al. 2010, 2011a; Tang et al. 2014; Taylor et al. 2013; Turyk et al. 2009; Wu et al. 2013).

No animal studies were identified that empirically examined whether isomers of DDT, DDE, or DDD are associated with DMT2; this is likely due in part to limitations in animal models for this disease. A limited number of mechanistic animal studies, however, have begun to evaluate whether these compounds have obesogenic properties by investigating the effects of exposure to DDT and related compounds on energy utilization and metabolic homeostasis. Elevated fasting blood glucose levels were observed in adult mice 3 weeks following 5-day oral exposure to 2 mg/kg/day *p,p'*-DDE, but not 0.4 mg/kg/day, but fasting blood glucose levels were not elevated after 4, 8, or 13 weeks of exposure (Howell et al. 2014, 2015). In another study, a challenge with a high-fat diet resulted in glucose intolerance, insulin resistance, mild dyslipidemia, and signs of compromised thermogenesis in adult mice exposed during gestation and early life to 1.7 mg/kg/day of a mixture of *p,p'*-DDT and *o,p'*-DDT (La Merrill et al. 2014a, 2014b).

Cancer. Numerous epidemiological studies have examined possible associations between levels of DDT, DDD, or DDE in serum or adipose tissues and risks of several types of cancer in groups of humans from many regions throughout the world, including the United States. Consistent evidence for associations between serum DDT levels and increased risk of liver cancer was provided by case-control studies of three Chinese populations and one U.S. population (Cocco et al. 2000; McGlynn et al. 2006; Persson et al. 2012; Zhao et al. 2012), whereas consistent evidence for no associations with increased risk of breast

cancer was provided by 38 studies from regions throughout the world (see meta-analyses by Ingber et al. 2013; Lopez-Cervantes et al. 2004; Park et al. 2014). Each of the meta-analyses noted that exposure metrics in most of the breast cancer case-control studies were measured in mature adult women and may not reflect exposure during early life periods when the breast may be vulnerable. Cohn (2011) postulated that the lack of an association might be due to the lack of exposure metrics during a critical early period of life. Inconsistent evidence was provided for associations from >10 case-control studies of non-Hodgkin's lymphoma (NHL) (Bertrand et al. 2010; Brauner et al. 2012; Cocco et al. 2008; De Roos et al. 2005; Engel et al. 2007; Hardell et al. 2001, 2009; Laden et al. 2010; Quintana et al. 2004; Rothman et al. 1997; Spinelli et al. 2007; Viel et al. 2011), 7 studies of prostate cancer (Aronson et al. 2010; Emeville et al. 2015; Hardell et al. 2006a; Pi et al. 2016a; Ritchie et al. 2003; Sawada et al. 2010; Xu et al. 2010), and 5 studies of testicular cancer (Biggs et al. 2008; Giannandrea et al. 2011; Hardell et al. 2006b; McGlynn et al. 2008; Purdue et al. 2009). Consistent evidence for no associations was found in three case-control studies of pancreatic cancer (Gasull et al. 2010; Hardell et al. 2007; Hoppin et al. 2000) and two case-control studies of endometrial cancer (Hardell et al. 2004; Sturgeon et al. 1998). No evidence for associations was found in single case-control studies for bladder cancer (Boada et al. 2016) and colorectal cancer (Howsam et al. 2004) and single studies of mortality rates from multiple myeloma (Cocco et al. 2000) or all cancers (Austin et al. 1989).

The liver and lung appear to the primary cancer targets for isomers of DDT, DDE, and DDD in laboratory animals orally exposed to doses that exceed anticipated human exposures. Chronic oral exposure to technical DDT or *p,p'*-DDT increased incidences of liver tumors in several strains of mice (Innes et al. 1969; Kashyap et al. 1977; Terracini et al. 1973; Thorpe and Walker 1973; Tomatis et al. 1972, 1974a; Turusov et al. 1973) and rats (Cabral et al. 1982b; Fitzhugh and Nelson 1947; Harada et al. 2003, 2006; Rossi et al. 1977), and increased incidences of pulmonary adenomas or lung tumors in mice (Kashyap et al. 1977; Shabad et al. 1973). Long-term exposures to DDT failed to induce significant increases in tumors in monkeys (Adamson and Sieber 1979, 1983; Durham et al. 1963 Takayama et al. 1999) or dogs (Lehman 1965), and evidence of DDT carcinogenicity in hamsters is equivocal (Agthe et al. 1970; Cabral et al. 1982a; Graillot et al. 1975; Rossi et al. 1983). Chronic-duration oral exposures to *p,p'*-DDE induced liver tumors in male and female mice (NCI 1978; Tomatis et al. 1974a) and in hamsters (Rossi et al. 1983), but did not induce significant increases in tumor incidence in rats (NCI 1978). Only two studies evaluated DDD; *p,p'*-DDE induced liver tumors and lung adenomas in CF-1 mice (Tomatis et al. 1974a, 1974b), but chronic-duration exposure to technical DDD did not increase incidence of tumors in either mice or rats (NCI 1978).

The U.S. Department of Health and Human Services (HHS) determined that DDT is "reasonably anticipated to be a human carcinogen," based on sufficient evidence of carcinogenicity in experimental animals (NTP 2016). The U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) last revised carcinogenicity assessments for DDT, DDD, and DDE in 1988, classifying each as a "probable human carcinogen" (Group B2), based on sufficient evidence of carcinogenicity in animals (IRIS 2002a, 2002b, 2003). The International Agency for Research on Cancer (IARC) determined that DDT is "probably carcinogenic to humans," based on limited evidence in humans and sufficient evidence in experimental animals (IARC 2017).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was not considered adequate for deriving inhalation MRLs due to the limited available inhalation data for DDT, DDE, and DDD. The oral database was considered adequate for derivation of acute-, intermediate-, and chronic-duration oral MRLs for DDT, DDE, and DDD. The liver and early neurological development are the most sensitive targets following oral exposure to DDT (metabolites and isomers). Other developmental and reproductive endpoints also have relatively low LOAEL values, as illustrated in Figure 1-2. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-2. Summary of Sensitive Targets of DDT, DDE, and DDD – Oral

Neurodevelopment and the liver are the most sensitive targets of DDT, DDE, DDD, and their related isomers

Numbers in circles are the lowest LOAELs (mg/kg/day) for all health effects in animals.

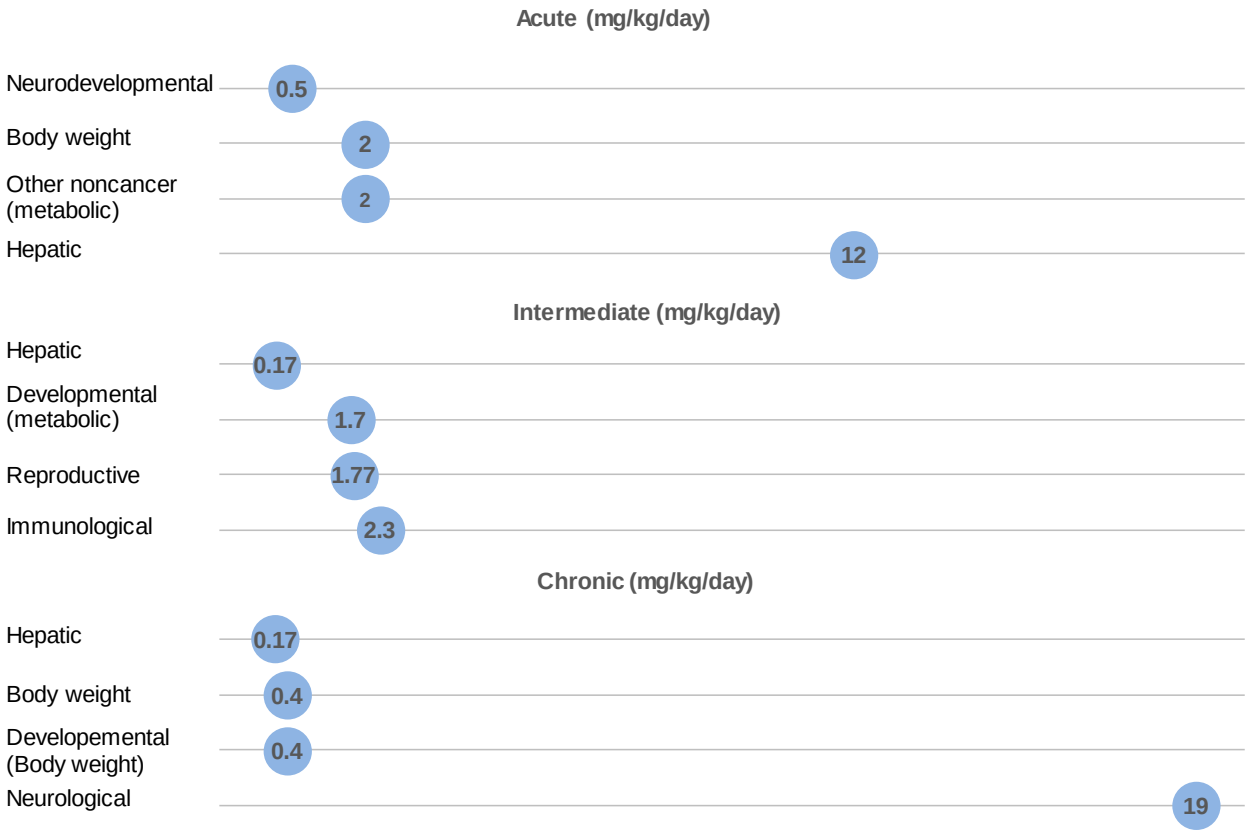


Table 1-1. Minimal Risk Levels (MRLs) for DDT, DDE, and DDD[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty and modifying factors	Reference
Inhalation exposure					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	0.0005 (0.5 µg/kg/day)	Increased motor activity (delayed habituation) after exposure on PND 10 (neurodevelopmental)	0.5 (LOAEL)	UF: 1,000	Eriksson and Nordberg 1986; Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996
Intermediate	0.0005 (0.5 µg/kg/day)	Hepatocellular hypertrophy	0.05 ($BMDL_{10}$)	UF: 100	Harada et al. 2003, 2006
Chronic	0.0005 (0.5 µg/kg/day)	Hepatocellular hypertrophy	0.05 ($BMDL_{10}$)	UF: 100	Harada et al. 2003, 2006

[a]See Appendix A for additional information on MRLs.

BMDL = 95% lower confidence limit on the BMD associated with 10% extra risk; DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; LOAEL = lowest-observed-adverse-effect level; PND = postnatal day; UF = uncertainty factor