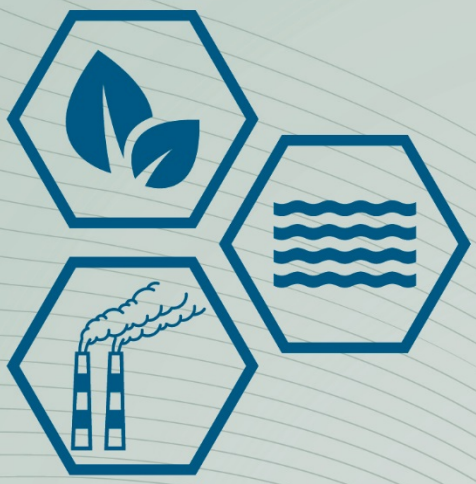

Toxicological Profile for DDT, DDE, and DDD

April 2022

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

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DISCLAIMER

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

FOREWORD

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

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

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

Each profile includes the following:

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

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and

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

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

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

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*Legislative Background

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

VERSION HISTORY

Date	Description
April 2022	Final toxicological profile released
December 2019	Draft for public comment toxicological profile released
November 2008	Addendum to the toxicological profile released
September 2002	Final toxicological profile released
May 1994	Final toxicological profile released
August 1990	Final toxicological profile released

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

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

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

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

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

1. RELEVANCE TO PUBLIC HEALTH

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:

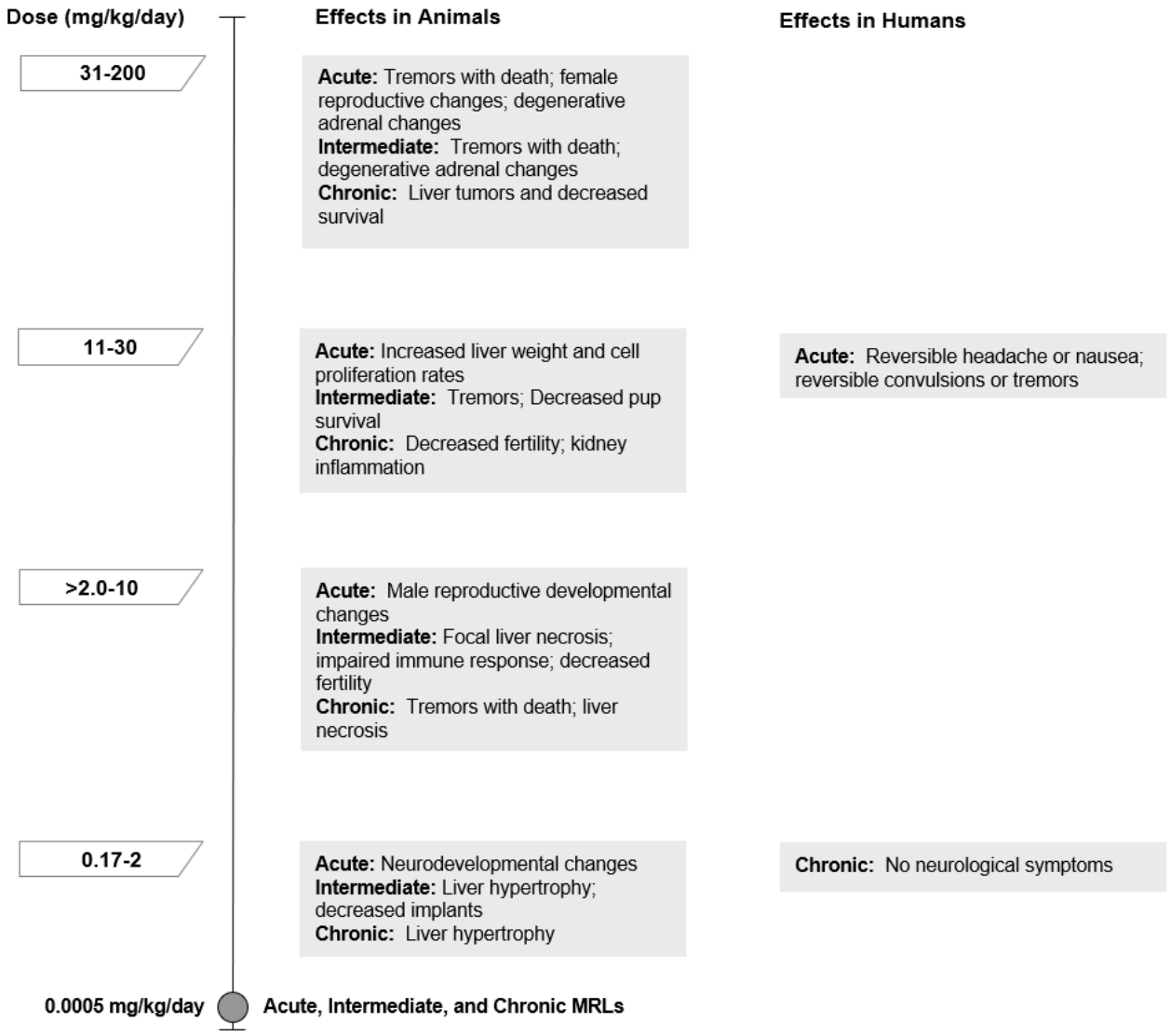
- associations between maternal exposure and prevalence for wheeze in infants or children;
- no associations with male reproductive system birth defects;
- associations with prevalence of Type 2 diabetes mellitus (DMT2);
- associations with liver cancer; and
- no associations with breast cancer in women,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

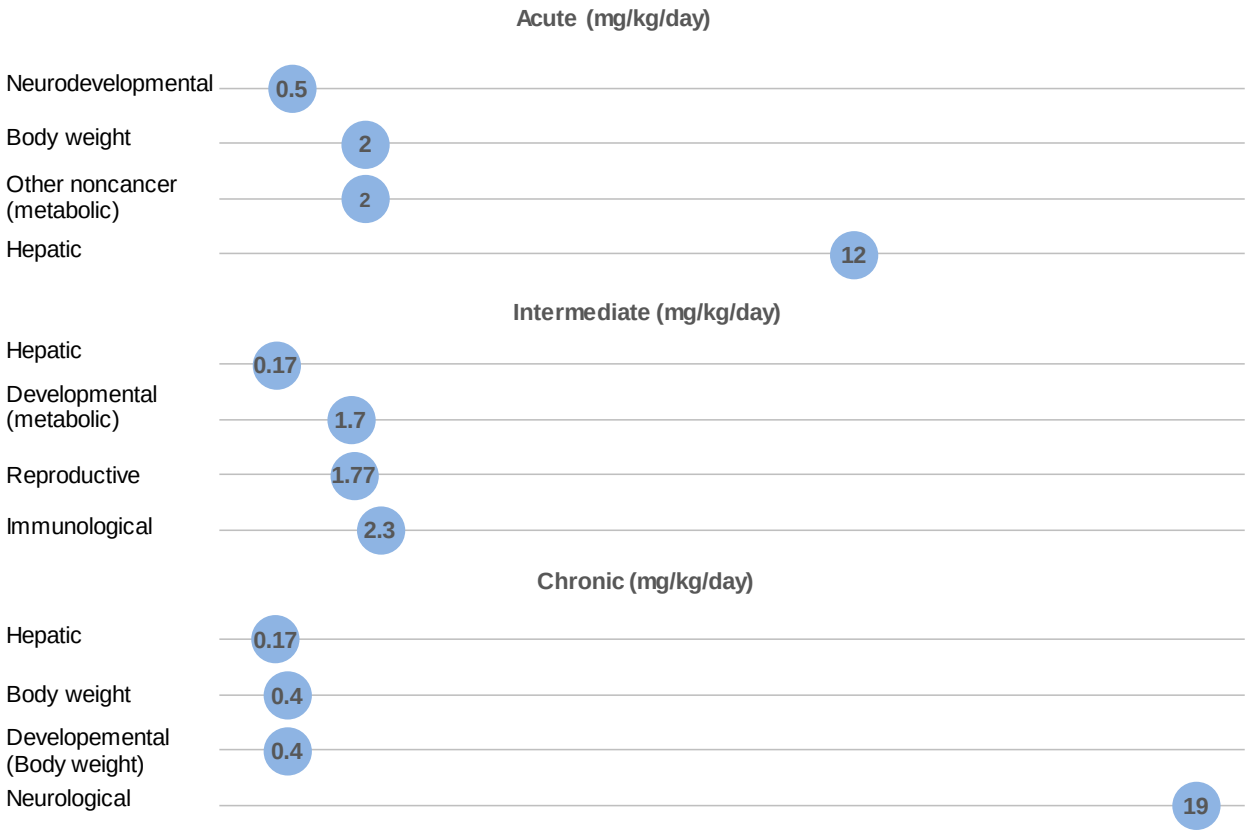


Table 1-1. Minimal Risk Levels (MRLs) for DDT, DDE, and DDD[a]

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

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of DDT, DDE, and DDD. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

While this document is specifically focused on the primary forms or isomers of DDT, DDE, and DDD (namely *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD), data for other isomers of these compounds will be discussed when available and appropriate. In some cases, the generic term DDT is used to refer to the collective forms of DDT, DDE, and DDD. However, for all quantitative studies, the term ΣDDT (Σ is used to mean sum of) will be used to indicate the total sum of DDT, DDE, and DDD.

Typically, people are not exposed to DDT, DDE, or DDD individually, but rather to a mixture of all three compounds since DDE and DDD are degradation and metabolic products of DDT. In addition, DDT, DDE, and DDD each can exist in three isomeric forms based on the relative position of the chlorine substitutions on the two chlorophenyl rings (Chapter 4). The most prevalent isomer of DDT, DDE, or DDD in the environment is the *p,p'*- isomer. Technical-grade DDT contains 65–80% *p,p'*-DDT, 15–21% *o,p'*-DDT, and up to 4% of *p,p'*-DDD (Metcalf 1995), and DDE is the principal metabolite of DDT (Chapter 3). When the toxicity of the isomers of DDT, DDE, or DDD reported in the experimental data differ in an organ system, such as the reproductive or developmental systems, isomer-specific results are presented, when available. Therefore, the data presented in this document include some relevant toxicity information on the *o,p'*- and *p,p'*- isomers of DDT and technical-grade DDT.

2. HEALTH EFFECTS

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to DDT, DDE, and DDD, but may not be inclusive of the entire body of literature.

Most laboratory animal toxicity studies of DDT, DDE, or DDD have involved oral exposure; there are only a small number of available inhalation or dermal contact studies (see Figure 2-1). The most widely studied health effects examined in human and animal studies were reproductive, neurological, and developmental effects, and cancer (Figure 2-1). Considerable focus also has been given to effects on body weight and the liver in animal studies, endocrine, and immunological effects in human and animal studies, and human studies of risk for DMT2 (Figure 2-1). The human study counts in Figure 2-1 are principally for epidemiological studies examining possible associations between adverse health outcomes and levels of DDT, DDE, or DDD in samples of tissues or body fluids. Oral exposure through food and drinking water is the assumed principal route of exposure of the subjects in these studies. Studies that looked for associations between adverse health outcomes and more subjective measures of exposure (e.g., self-reported exposure history or work history records) were not included in the analyses described in this chapter. This chapter also discusses the small number of controlled-exposure human studies principally conducted in the 1940s through the 1950s, in which human subjects ingested, inhaled, or were dermally exposed to measured doses of DDT for acute or intermediate durations (most studies used technical DDT).

Levels of significant exposure (LSEs) for each route and duration of animals orally exposed are presented in Table 2-1 and illustrated in Figure 2-2. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less

serious" effects and "serious" effects is considered to be important because it helps the users of the profiles identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

The early controlled-exposure studies of human adult subjects given acute- or intermediate-duration exposure to oral doses of technical DDT provide adequate descriptions of exposure-response relationships for self-reported neurological symptoms and NOAELs for liver effects assayed by serum enzyme levels. In contrast, none of the epidemiological studies provide adequate evidence to describe LSEs to DDT, DDE, or DDD. For most of the health outcomes evaluated in multiple epidemiological studies, inconsistent evidence is available for associations with levels of DDT, DDE, or DDD in tissues or biological fluids, with the exception of consistent evidence for associations with: increased risk for abortions or preterm births (see Section 2.16); increased prevalence for wheeze in infant or child offspring (see Section 2.14); increased prevalence of DMT2 (see Section 2.18); and increased risk for liver cancer (see Section 2.19). In addition, consistent evidence for no associations was found in studies of breast cancer in women, pancreatic cancer, and endometrial cancer (see Section 2.19). Although epidemiological studies provide consistent evidence of associations (or no associations) between DDT and some health outcomes, these data do not establish causality. Other factors, particularly co-exposure to other highly lipophilic compounds (e.g., PCBs, CDDs, CDFs), may have influenced the study results. Some of the epidemiological studies have statistically adjusted for exposure to one or more non-DDT compounds to decrease the uncertainty; however, most studies did not include this adjustment.

Health effects of DDT, DDE, DDD, and their related isomers have been evaluated in many animal studies (see Figure 2-1). Nearly all of the studies evaluated were oral exposure studies; no animal inhalation studies were identified. The most examined noncancer endpoints were reproductive, neurological, developmental, body weight, and hepatic effects. The most reliable health effects data come from oral studies of animals administered DDT (metabolites or isomers). Limited animal data for dermal exposure studies indicated that DDT and related compounds are not dermal irritants. Results from the oral animal studies identify the following targets of DDT, DDE, and DDD toxicity.

- **Hepatic effects:** Acute-, intermediate-, and chronic-duration oral exposures of laboratory animals to DDT, DDE, or DDD have been associated with mild-to-severe hepatic effects, such as induction of microsomal CYP450 xenobiotic metabolizing enzymes, liver hypertrophy, hepatocellular eosinophilic foci, and, less frequently, hepatocellular necrosis.

- **Neurological and neurodevelopmental effects:** Tremors, convulsions, and intermittent myoclonic movements have been observed in mature laboratory animals after acute-, intermediate- and chronic-duration exposures to technical DDT, *p,p'*-DDT, or *p,p'*-DDE at relatively high exposure levels. Young laboratory mice appear to be particularly sensitive to brain neurochemical changes and associated neurobehavioral changes from acute-duration exposure to low doses of technical DDT during critical windows of neurodevelopment (PND 10, but not PND 3 or 18).

- **Reproductive and developmental reproductive effects:** Reproductive effects of DDT and related compounds in laboratory animals have been observed at relatively high dose levels. The observed effects include decreased male reproductive tissue weight or increased weight of the uterus after acute-duration exposures and decreased fertility after intermediate- or chronic-duration exposures. Gestational exposure to *p,p'*-DDT or *p,p'*-DDE has been associated with decreased prostate weight and decreased AGD in male offspring, decreased fertility in male and female offspring, and increased resorptions in female offspring after impregnation. Gestational exposure to *o,p'*-DDD or *p,p'*-DDT has been associated with delayed vaginal opening and increased ovary weight in female offspring. Exposure during gestation and lactation was associated with decreased fertility in female offspring at a high dose level of *o,p'*-DDT, but not at 5–6-fold lower doses of *o,p'*-DDT or *p,p'*-DDT.

- **Body weight effects:** Decreased body weight or body weight gain have been observed in laboratory animals orally exposed to DDT and related compounds after acute-, intermediate-, or chronic-duration exposures at relatively high dose levels.

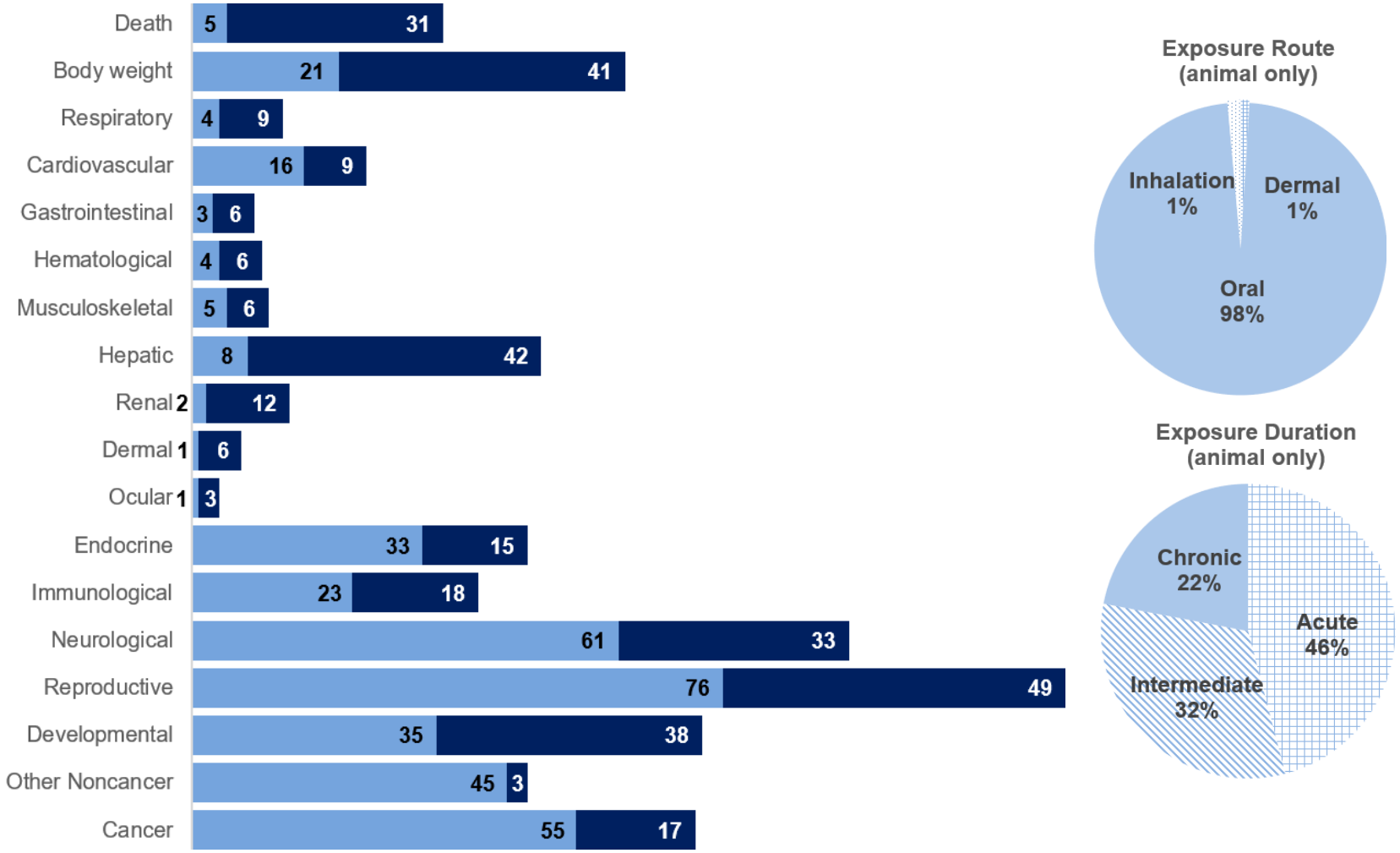
- **Immunological effects:** Suppression or stimulation of various immune system responses have been observed in rats and mice exposed to dietary doses of technical DDT, *p,p'*-DDT, *p,p'*-DDE, *p,p'*-DDD, or *o,p'*-DDD, but evidence is weak for weight changes or histological changes in immune system organs or tissues in laboratory animals after intermediate- or chronic-duration exposures.

- **Cancer:** The liver appears to the primary cancer target for isomers of DDT, DDE, and DDD in laboratory animals.

Figure 2-1. Overview of the Number of Studies Examining DDT, DDE, and DDD Health Effects*

Most studies examined the potential reproductive, developmental, and cancer effects of DDT, DDE, and DDD

More studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 636 studies (including those finding no effect) have examined toxicity; most animal studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	Human 7 M, 4 F	Once (F)	5.1–120.5	CS	Neuro	10.3		16	Convulsions
DDT (NS) Hsieh 1954									
2	Monkey (Rhesus) 4 NS	Once (G)	0, 150	OW GN BC BI	Hepatic		150		Increased serum LDH, ALP, and aminotransferases
DDT (NS) Agarwal et al. 1978									
3	Monkey (Rhesus) NS M	Once (G)	0, 150	BW GN HP BI	Neuro		150		Decreased CNS total lipids, phospholipids, and cholesterol
DDT, technical grade Sanyal et al. 1986									
4	Rat (Sprague-Dawley) 5–6 F	GD 13.5–17.5 (G)	0, 50, 100	CS BW DX	Bd wt	100 F			
					Develop	50 M	100 M		Fetal alterations of steroidogenic cells; histological and ultrastructural alterations in fetal-type Leydig cells on ED 19.5 (vacuolated and reduced number of lipid droplets in Leydig cells), partially degenerated mitochondria in adrenal cortex
***p,p'*-DDE Adamsson et al. 2009**									
5	Rat (NS) NS	Once (NS)	NS	LE	Death			400	LD_{50}
DDD (NS) Ben-Dyke et al. 1970									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
6	Rat (NS) NS	Once (NS)	NS	LE	Death			300	LD_{50}
DDT (NS) Ben-Dyke et al. 1970									
7	Rat (NS) 5 NS	Once (G)	NS	LE	Death			800	LD_{50}
DDT (NS) Cameron and Burgess 1945									
8	Rat (Wistar) 20 F	7 days, PNDs 23–30 (F)	0, 50, 100, 200, 300	DX	Develop	50 F	100 F		Increased uterus weight; premature vaginal opening
***o,p'*-DDT Clement and Okey 1972**									
9	Rat (Wistar) NS	5 or 12 days (G)	0, 40	GN OW BI	Hepatic		40		18% increase in relative liver weight; increased liver GSH and AHH enzyme activities
DDT (NS) de Waziers and Azais 1987									
10	Rat (DA/Han) 6 F	3 days (G)	0, 10, 100, 500	OW BI	Repro	10	100		Significant increase in wet uterine weight
***o,p'*-DDT Diel et al. 2000**									
11	Rat (Sherman) NS B	Once (G)	NS	LE	Death			4,000	LD_{50}
DDD, technical grade Gaines 1969									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
12	Rat (Sherman) B	Once (G)	NS	LE	Death			880 M 1,240 F	LD_{50}
DDT, technical grade Gaines 1969									
13	Rat (Sherman) B	Once	NS	LE	Death			113	LD_{50}
***p,p'*-DDT Gaines 1969**									
14	Rat (Sprague-Dawley) 15 F	5 days GDs 15–19 (G)	0, 28	DX	Develop		28 F		Delayed vaginal opening (2 days)
***o,p'*-DDD Gellert and Heinrichs 1975**									
15	Rat (Sprague-Dawley) 15 F	5 days GDs 15–19 (G)	0, 28	DX	Develop		28 F		11.9% increase in body weight
***o,p'*-DDE Gellert and Heinrichs 1975**									
16	Rat (Sprague-Dawley) 15 F	5 days GDs 15–19 (G)	0, 28	DX	Develop		28 F		13% increase in body weight
***o,p*'-DDT Gellert and Heinrichs 1975**									
17	Rat (Sprague-Dawley) 15 F	5 days GDs 15–19 (G)	0, 28	DX	Develop		28 F		9% increase body weight and 26% decrease in ovary weight in offspring
***p,p'*-DDT Gellert and Heinrichs 1975**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
18	Rat (Sprague-Dawley) 10 M	Once (GO)	0, 25, 50, 100, 200	CS OF	Endocr	25	50		Reduced capacity to concentrate iodine in thyroid
DDT, technical grade Goldman 1981									
19	Rat (Long-Evans) 8 F	5 days GDs 14–18 (GO)	0, 100	DX	Develop		100 M		At 10 months of age, significant decrease in ventral prostate weight; percent of animals with areolas; and mean number of retained nipples
***p,p′*-DDE Gray et al. 1999**									
20	Rat (Sprague-Dawley) 11 F	5 days GDs 14–18 (GO)	0, 100	DX	Develop		100 M		At 15 months of age, decreased weight of glans penis, epididymis, and ventral prostate; reduced AGD; increased percent with areolas and number with retained nipples
***p,p′*-DDE Gray et al. 1999**									
21	Rat 32 M	Once (G)	0, 75	CS	Neuro			75	Tremors
DDT (NS) Herr and Tilson 1987									
22	Rat 12 M	Once (G)	0, 50, 75, 100	CS	Neuro			50	Tremors
DDT (NS) Herr et al. 1985									
23	Rat (Wistar) 40 M	Once (GO)	160	GN HP BI CS	Neuro			160	Tremors
DDT (NS) Hietanen and Vainio 1976									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
24	Rat (Fischer-344) 4 M	Once (G)	0, 25, 50, 75, 100	BI CS	Neuro	25	50		Tremors, more severe at 75 and 100 mg/kg/day; increased brain 5-HIAA, aspartate, and glutamate
***p,p'*-DDT** **Hong et al. 1986; Hudson et al. 1985**									
25	Rat (Albino Sprague-Dawley) 18 M	Once (G)	0, 100-600	GN BI CS	Neuro		100	200	LOAEL: Intermittent myoclonic movement Serious LOAEL: Severe myoclonus, tremors, seizures; increased brain 5-HIAA
***p,p'*-DDT** **Hwang and Van Woert 1978**									
26	Rat (Sprague-Dawley) 6 M	10 days (G)	0, 25, 50, 100	CS OW BC BW	Bd wt	100			
					Hepatic		25		Increased absolute liver weight (42%)
					Renal	100			
					Repro	25	50		Inhibited regrowth of TP-inhibited accessory sex organs; decreased seminal vesicle weight (34%)
***p,p'*-DDE** **Kang et al. 2004**									
27	Rat (Long-Evans) 8 F	5 days GDs 14–18 (GO)	0, 100	DX	Develop		100 M		Males: reduced AGD at birth; PND 13 retained thoracic nipples
***p,p'*-DDE** **Kelce et al. 1995**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
28	Rat (Long-Evans) 6 M	4 days (GO)	0, 200	CS OW BC BW	Bd wt		200		Decreased body weight (29.8%)
					Repro		200		Reduced seminal vesicle and ventral prostate weight
***p,p'*-DDE** **Kelce et al. 1995**									
29	Rat (Sprague-Dawley) 10 M	5 days (GO)	0, 200	CS OW BC	Repro		200		Reduced seminal vesicle and ventral prostate weight
***p,p'*-DDE** **Kelce et al. 1997**									
30	Rat (Wistar) 6 M	14 days (GO)	0, 12	BI HP OW	Hepatic		12		Increased relative liver weight; necrotic changes; increased cell proliferation peaked at exposure day 3
DDT, technical grade **Kostka et al. 2000**									
31	Rat 6 M	2 days, PNDs 4 and 5 (G)	0, 500	BW OW HP RX	Repro		500		Decreased number of fetuses and implantations in non-exposed dams mated with exposed males
DDT (NS) **Krause et al. 1975**									
32	Rat (Long-Evans) 5 M	4 days (G)	0, 5, 12.5, 25, 50, 100	CS OW BI BW	Hepatic	12.5	25		Increased relative liver weight (32%)
					Repro	100			
***p,p'*-DDE** **Leavens et al. 2002**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
33	Rat (Sprague-Dawley) 8 M	14 days PNDs 28-41 (GO)	0, 2	BC	Other noncancer		2		Altered glucose homeostasis (increased fasting glucose and fasting insulin, insulin resistance, impaired glucose tolerance)
***p,p'*-DDE Liang et al. 2020**									
34	Rat (Sprague-Dawley) 6 M	Once or 5 days (GO)	50	OW HP RX	Repro	50			
***p,p'*-DDT Linder et al. 1992**									
35	Rat (Sprague-Dawley) 6 M	Once (GO)	100	OW HP RX	Repro	100			
***p,p'*-DDT Linder et al. 1992**									
36	Rat (Holtzman) 3–6 F	5 days GDs 14–18 (GO)	0, 1, 10, 50, 100, 200	DX	Develop	10 M	50 M		Reduced AGD on PND 1 and relative ventral and dorsolateral prostate weights on PND 21; increased nipple retention starting at 100 mg/kg/day; delayed age at preputial separation at 200 mg/kg/day
***p,p'*-DDE Loeffler and Peterson 1999**									
37	Rat (NS) 10 B	Once (G)	346.3–553.9	LE	Death			437.8	
DDT, technical grade Lu et al. 1965									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
38	Rat (NS) 10 B	4 days (G)	216.8–359.2	LE	Death			279.2	4-Day LD_{50}, preweanling; cumulative dose
DDT, technical grade Lu et al. 1965									
39	Rat (NS) 10 B	Once (G)	4,000	LE	Death			4000	
DDT, technical grade Lu et al. 1965									
40	Rat (NS) 10 B	Once (G)	317.2–397.8	LE	Death			355.2	LD_{50}, weanling rats
DDT, technical grade Lu et al. 1965									
41	Rat (NS) 10 B	4 days (G)	225.6–364.8	LE	Death			285.6	4-Day adult LD_{50}; cumulative dose
DDT, technical grade Lu et al. 1965									
42	Rat (NS) 10 B	Once (G)	158.7–238.3	LE	Death			194.5	LD_{50}, adult rats
DDT, technical grade Lu et al. 1965									
43	Rat (Fischer-344) 3/dose M	2 weeks (F)	0, 0.85, 2.6, 7.7, 23, 69, 200	BC BW BI GN NX	Bd wt Hepatic Neuro	200 69 200	200		Increased relative liver weight
***p,p'*-DDD Nims et al. 1998**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
44	Rat (Fischer-344) 3/dose M	2 weeks (F)	0, 0.85, 2.5, 7.6, 23, 69, 200	BC BW BI GN NX	Bd wt Hepatic Neuro	200 7.6 200	23		Increased relative liver weight
***p,p'*-DDE** **Nims et al. 1998**									
45	Rat (Fischer-344) 3/dose M	2 weeks (F)	0, 0.94, 2.8, 8.5, 25, 76, 200	BC BW BI GN NX	Bd wt Hepatic Neuro	200 8.5 200	25		Increased relative liver weight
***p,p'*-DDT** **Nims et al. 1998**									
46	Rat 8 M	Once (GO)	200, 600, 1,000	CS BI	Neuro	200		600	Convulsions, myoclonus
***p,p'*-DDT** **Pranzatelli and Tkach 1992**									
47	Rat NS M	Once (G)	0, 50, 100, 200, 400, 600	CS	Neuro	50	200	400	LOAEL: Intermittent myoclonus Serious LOAEL: Continuous myoclonus
***p,p'*-DDT** **Pratt et al. 1986**									
48	Rat (Sprague-Dawley) NS F	8 days GDs 8–15 (GO)	0, 100	DX	Develop		100		≥10% increased body weight in F3 offspring body weight; altered glucose homeostasis in F1, F2, and F3 males and F1 females; ultrastructural changes to pancreatic β-cells in F1, F2 and F3 offspring
***p,p'*-DDE** **Song and Yang 2017** [Direct exposure to F0 dams only; endpoints evaluated in F1, F2, and F3 offspring.]									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
49	Rat	8 days GDs 8–15 (GO)	0, 100	DX	Develop		100		20% decrease in F1 and F2 fertility, 25-40% decrease in F3 fertility (traced to male germline); decreased motile sperm and area of the seminiferous tubules in all generations
***p,p'*-DDE** **Song and Yang 2018** [Direct exposure to F0 dams only; endpoints evaluated in F1, F2, and F3 offspring]									
50	Rat (Fischer-344, Albino) 6 M	Once (G)	0, 75	CS BI NX	Neuro		75		Tremors and increased brain 5-HIAA
***p,p'*-DDT** **Tilson et al. 1986**									
51	Rat (Fischer-344) M	Once (G)	0, 25, 50, 100	CS NX	Neuro	25	50	100	LOAEL: Hyperirritability and tremors Serious LOAEL: Severe tremors and death in some rats
***p,p'*-DDT** **Tilson et al. 1987**									
52	Rat (Fischer-344) 5–6 M	2 weeks (F)	0, 0.5, 5.0, 50	HE HP BC	Hemato	0.5	5		Increase in total iron binding capacity
***p,p'*-DDT** **Tomita et al. 2013**									
53	Rat (Fischer-344) 33 M	7 days (F)	0, 106	BI BC OW CS	Hepatic		106		Increased absolute and relative liver weight
***p,p'*-DDT** **Tomiyama et al. 2003**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
54	Rat (Fischer-344) 36 M	Once (G)	0, 106	CS	Neuro			106	Tremors and convulsions, hyperactivity
***p,p'*-DDT** **Tomiyama et al. 2003**									
55	Rat (Fischer-344) 5 M	14 days (F)	0, 5, 16, 50		Hepatic		5		Increased relative liver weight
***p,p'*-DDT** **Tomiyama et al. 2004**									
56	Rat (Sprague-Dawley) 8–11 F	5 days GDs 14–18 (GO)	0, 10, 100	DX	Develop	100 F	10 M		Nipple retention in PND 13 males
***p,p'*-DDE** **You et al. 1998**									
57	Rat (Long-Evans) 8–11 F	5 days GDs 14–18 (GO)	0, 10, 100	DX	Develop	100 F 10 M	100 M		Reduced anogenital distance on PND 2; retained thoracic nipples on PND 13
***p,p'*-DDE** **You et al. 1998**									
58	Rat (Long-Evans) 5–8 M	4 days (F)	0, 70	BW OW BC	Bd wt Renal Repro	70 70	70		Decreased ventral prostate weight (30%); epididymis (12.7%), and seminal vesicle (47%) weights
***p,p'*-DDE** **You et al. 1999a**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
59	Mouse (NMRI) 12 M	Once PND 10 (GO)	0, 0.5	DX	Develop		0.5[b]		7 days after exposure: increased muscarinic receptor binding, decreased high affinity, and increased low affinity binding
DDT (NS) Eriksson and Nordberg 1986									
60	Mouse (NMRI) 12 M	Once PND 10 (GO)	0, 0.5	DX	Develop		0.5[b]		Delayed habituation observed as increased motor activity
DDT (NS) Eriksson et al. 1990a									
61	Mouse (NMRI) 12 B	Once PND 10 (GO)	0, 0.5	DX	Develop		0.5 M[b]		Increased motor activity (reduced habituation) at 4 months; increased potassium evoked Ach release; reduced density of muscarinic receptors in cerebral cortex at 3 months
DDT (NS) Eriksson et al. 1990b									
62	Mouse (NMRI) 12 M	Once at either PND 3, 10, or 19 (GO)	0, 0.5	DX	Develop		0.5[b]		At 4 months of age in males dosed at 10 days: decrease in cerebral cortex muscarinic acetylcholine receptor binding; delayed habituation
DDT, technical grade Eriksson et al. 1992									
63	Mouse (NMRI) 5–8 M	Once PND 10 (GO)	0, 0.5	DX	Develop		0.5 M[b]		At 5 months of age: delayed habituation (increased motor activity); decrease in cortical muscarinic acetylcholine receptors
DDT (NS) Eriksson et al. 1993									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
64	Mouse (albino) 15 M	Once (GO)	0, 160	CS	Neuro			160	Tremors
***p,p'*-DDT** **Hietanen and Vainio 1976**									
65	Mouse (C57BL/6H) 10 M	5 days (G)	0, 0.4, 2	BC BW	Bd wt Other noncancer	2 M 0.4 M	 2 M		 Fasting hyperglycemia 7 days after last exposure
***p,p'*-DDE** **Howell et al. 2014**									
66	Mouse (NMRI) NS M	Once PND 10 (GO)	0, 0.5	DX	Develop		0.5[b]		Decreased muscarinic receptors in cerebral cortex; increased spontaneous activity at 5 months
DDT, technical grade **Johansson et al. 1995**									
67	Mouse (NMRI) NS M	Once PND 10 (GO)	0, 0.5	DX	Develop		0.5[b]		Decreased muscarinic receptors in cerebral cortex; increased spontaneous activity at 5 and 7 months
DDT, technical grade **Johansson et al. 1996**									
68	Mouse (Inbred Swiss) NS M	Once (G)	NS	LE	Death			300	LD_{50}
DDT, technical grade **Kashyap et al. 1977**									
69	Mouse (Albino) 10 M	Once (G)	0, 200, 400, 600	CS BI	Neuro			200	Convulsions
***p,p'*-DDT** **Matin et al. 1981**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
70	Mouse (C3H) NS B	6 days (F)	M: 87.5 F: 85.7	LE	Death			85.7 F	50% of mice died after a 6-day feeding period
***p,p'*-DDT Okey and Page 1974**									
71	Mouse (CD-1) 15 F	7 days GDs 11–17 (GO)	0, 0.018, 0.18	DX	Develop	0.018 M			
***o,p'*-DDT Palanza et al. 1999**									
72	Mouse (CF-1) 6–10 F	GDs 11–17 (G)	0, 0.02, 0.2, 2, 20, 100	BW DX	Bd wt Develop	100 100			
***o,p'*-DDT Palanza et al. 2001**									
73	Mouse (CF1) 8 NS	1 week (F)	0, 42.9	BW BI OW	Hepatic	42			29% increase in absolute liver weight; increased cytochrome-c reductase and P-450
DDE (NS) Pasha 1981									
74	Mouse (CF1) 4 M, 4 F	Once (G)	NS	LE	Death			251.3 F 237 M	LD_{50}
DDT, technical grade Tomatis et al. 1972									
75	Mouse (CF1) 8 B	Once (G)	NS	LE	Death			810	LD_{50}
***o,p'*-DDE Tomatis et al. 1972**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
76	Mouse (CF1) 8 B	Once (G)	NS	LE	Death			1466	LD_{50}
***p,p'*-DDD** **Tomatis et al. 1972**									
77	Guinea pig (NS) 5 NS	Once (G)	NS	LE	Death			400	LD_{50}
DDT (NS) **Cameron and Burgess 1945**									
78	Guinea pig (NS) 10 M	Once (G)	0, 160	CS GN HP BI	Neuro			160	Paralysis of hind legs
DDT (NS) **Hietanen and Vainio 1976**									
79	Hamster (NS) 8 F	Once (G)	0, 160	CS GN HP BI	Neuro	160			
DDT (NS) **Hietanen and Vainio 1976**									
80	Dog (NS) NS	14 days (IN)	0, 50	BW HP CS	Cardio			50	Decrease in contractile force
					Endocr		50		Decreased plasma glucocorticoids
***o,p'*-DDD** **Cueto 1970**									
81	Dog (NS) NS	10 days (C)	0, 138.5	HP BC	Endocr			138.5	Adrenal hemorrhage
***o,p'*-DDD** **Kirk et al. 1974**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
82	Dog (mongrels and beagles) 10 NS	Once (C)	0, 200	OW HP	Endocr		200		Adrenal vacuolization and necrosis
***p,p'*-DDD** **Powers et al. 1974**									
83	Rabbit (NS) 5 NS	Once (G)	NS	LE	Death			300	LD_{50}
DDT (NS) **Cameron and Burgess 1945**									
84	Rabbit (New Zealand) 10 F	4 days GDs 4–7 (G)	0, 1.0	DX	Develop		1		On GD 28, 33% decreased fetal weight; decreased fetal brain and kidney weights
DDT (NS) **Fabro et al. 1984**									
85	Rabbit (New Zealand) 6–15 F	3 days GDs 7–9 or 21–23 (GO)	0, 10, 50	RX DX	Repro			10	Exposure on GDs 7–9: increased resorptions, 1.3% in controls, 9.5% in treated; increased incidence of prematurity 22%
					Develop		10	50	LOAEL: 11% decreased fetal weight on day 28 Serious LOAEL: GDs 7–9 exposure: 19% decreased fetal weight on day 28; 40% deliveries premature; GDs 21–23 exposure
***p,p'*-DDT** **Hart et al. 1972**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
86	Rabbit (New Zealand) 6–15 F	GDs 7–9 (GO)	0, 50	RX DX	Repro			50	Increased resorptions, 1.8% in controls, 25% in treated
					Develop			50	22% decreased offspring weight
***p,p'*-DDT** **Hart et al. 1971**									
87	Rabbit (New Zealand) 30 M	10 days (G)	0, 4.3	BC IX	Immuno	4.3			
DDT (NS) **Shiplov et al. 1972**									
INTERMEDIATE EXPOSURE									
88	Monkey (Squirrel) 5–6 B	2, 4, or 6 months (G)	0, 0.05, 0.5, 5, 50	LE CS BC BI	Death			50	Death of 6/6 in 14 weeks
					Hemato	50			
					Hepatic	5			
					Neuro	5		50	Staggering, weakness, loss of equilibrium
***p,p'*-DDT** **Cranmer et al. 1972** [Liver endpoints not assessed at 50 mg/kg/day.]									
89	Monkey (Rhesus) NS M	100 days (G)	0, 10	GN HP BI	Neuro		10		15–20% decrease in brain lipids, CNS phospholipids, and cholesterol
DDT, technical grade **Sanyal et al. 1986**									
90	Rat (albino) 10–12 M	8–22 weeks (F)	0, 2.2, 5.5, 11	BW FI BC CS IX	Bd wt	11			
					Immuno	2.2	5.5		Decreased relative spleen weight (17%) at 22 weeks; increased serum albumin/globulin ratio and reduced IgG titers after tetanus toxoid stimulation
***p,p'*-DDT** **Banerjee 1987b**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
91	Rat (Wistar) 10–12 M	4 weeks (F)	0, 2.3, 5.7, 11.4	BW CS FI OW LE IX	Bd wt	11.4			
					Immuno	2.3 M	5.7 M		Decreased IgG and IgM, increased albumin/globulin ratio
***p,p'*-DDT** **Banerjee et al. 1995**									
92	Rat (Wistar) 8–12 M	6 weeks (F)	0, 20.2	LE FI BW OW IX	Bd wt	20.2			
					Hepatic	20.2			
					Immuno		20.2		After ovalbumin immunization: decreased serum IgG and IgM, and ovalbumin antibody titre; increased % migration of leucocytes and macrophages; decreased footpad thickness; decreased relative spleen weight
***p,p'*-DDD** **Banerjee et al. 1996**									
93	Rat (Wistar) 8–12 M	6 weeks (F)	0, 20.2	LE FI BW OW IX	Bd wt	20.2			
					Hepatic		20.2		Increased relative liver weight (17.1%)
					Immuno		20.2		After ovalbumin immunization: decreased serum IgG and IgM, ovalbumin antibody titre and increased serum albumin/globulin ratio; increased % migration of leucocytes and macrophages and decreased footpad thickness
***p,p'*-DDE** **Banerjee et al. 1996**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
94	Rat (Wistar) 8–12 M	6 weeks (F)	0, 20.2	LE FI BW OW IX	Bd wt	20.2			
					Hepatic		20.2		Increased relative liver weight (14.2% increase)
					Immuno		20.2		After ovalbumin immunization: decreased serum IgG and IgM, ovalbumin antibody titre; increased % migration of leucocytes and macrophages; decreased footpad thickness
***p,p'*-DDT** **Banerjee et al. 1996**									
95	Rat (Wistar) NS B	7 months (F)	0, 2.6, 26, 128	RX	Repro	26 F		128 F	Decreased fertility in F1 females bred with nonexposed males
***o,p'*-DDT** **Clement and Okey 1974**									
96	Rat (Wistar) NS B	Through breeding GDs 1–21 LDs 1–21 (F)	0, 1.7, 16.8, 84	DX	Develop	16.8	84		Decreased body weights and growth of nursing pups 17% less body weight than controls at age 21 days; reduced fertility in F1 females (25% produced litters versus 100% in control)
***o,p'*-DDT** **Clement and Okey 1974**									
97	Rat (Wistar) NS B	Through breeding, GDs 1–21 LDs 1–21 (F)	0, 1.7, 16.8, 42.1	LE RX DX	Repro	16.8 F			
					Develop	1.7	16.8	42.1	LOAEL: Decreased body weights and growth of nursing pups Serious LOAEL: All F1 offspring dead by 10 days after birth
***p,p'*-DDT** **Clement and Okey 1974**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
98	Rat (albino) 5 F	31 days 24 hours/day (F)	0, 2.3, 23	GN BC IX	Immuno		2.3		Decreased severity of anaphylactic shock, decreased mast cells response to diphtheria toxoid
DDT (NS) Gabliks et al. 1975									
99	Rat (Wistar) 12 M	3 weeks (GO)	0, 15	BW BI OW	Hepatic		15		Increase in liver weight and in cytochrome P450 enzymes
***p,p'*-DDT Gupta et al. 1989**									
100	Rat (F344/ DuCrj) 20 M, 20 F	26 weeks (F)	Male: 0, 0.17, 1.7, and 19.1; females: 0, 0.21, 2.2, 25.2	HP BW FI CS	Hepatic	0.21 F	2.2 F 0.17 M		Hepatocellular hypertrophy Hepatocellular hypertrophy
***p,p'*-DDT Harada et al. 2003, 2006**									
101	Rat (F344/ DuCrj) 30 M	4 weeks (F)	0, 4.8, 15.4, 45.7	HP BW FI CS	Bd wt Hepatic	45.7	4.8		Increased absolute and relative liver weight; decreased gap junctional intercellular communication protein Cx32; increased hepatocyte proliferation (% PCNA labeling index) at ≥15.4 mg/kg/day
***p,p'*-DDT Harada et al. 2003; Tomiyama et al. 2004**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
102	Rat (Sprague-Dawley) P and F1, each 24 M, 24 F/dose	2-generation P generation: 10 weeks from before mating, through lactation. F1 generation: during rearing for 10 weeks, through mating, gestation, and lactation F2 generation: through weaning (F)	P- males: 0, 0.343, 3.44, 25; P- females: 0.73, 3.75, 27.7	CS BW OW DX OF HP GN FX FI BC	Bd wt	25 M	27.7 F		P and F1 females: decreased body weight
					Hepatic	0.73 F	3.75 F		Centrilobular hypertrophy and increased relative liver weights in P and F1 females
						0.343 M	3.44 M		Centrilobular hypertrophy, fatty change of hepatocytes; increased absolute and relative liver weight in P and F1 males.
					Renal	3.44	25		Parental males and females and F1 females: increased kidney weight (no histopathology)
					Neuro	25 M	27.7 F		Increased incidence of tremors in P and F1 parental females
					Repro	25 M			
						0.73 F	3.75 F		F0 females: decreased estradiol levels at 3.75 and 27.7 mg/kg/day; increased progesterone at 27.7 mg/kg/day
					Develop	3.75	27.7		Decreased pup viability index on PND 21 in F1 pups; Delayed preputial separation in F1 males and decreased body weight; increased kidney weight (no histopathology) in F1 females
***p,p'*-DDT Hojo et al. 2006**									
103	Rat (Sprague-Dawley) 6 F	36 weeks 7 days/week (F)	0, 6.6, 13.2	GN HP BC	Hepatic		6.6		Focal necrosis/regeneration
DDT (NS) Jonsson et al. 1981									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
104	Rat (Sprague-Dawley) 6 F	36 weeks (F)	0, 6, 12	RX	Repro	6		12	Decreased fertility
DDT, technical grade Jonsson et al. 1976									
105	Rat (Long-Evans) 12 M	37 days PNDs 21–57 (GO)	0, 100	CS BW BC RX	Bd wt		100		Increased body weight (18%)
					Repro			100	Delayed onset of puberty by 5 days
***p,p'*-DDE Kelce et al. 1995**									
106	Rat (Wistar) 8–10 M	8 weeks (F)	0, 10.3, 20.6	IX	Immuno	10.3	20.6		Decreased serum antibody titer to SRBC
DDT, technical grade Koner et al. 1998									
107	Rat (Sprague-Dawley) 110 F	5 weeks premating, 5 days/week (G)	0, 10	RX	Repro	10			
***p,p'*-DDE Kornbrust et al. 1986**									
108	Rat (Wistar) 6 M	3 weeks 3 times/week (GO)	0, 100, 200	BW OW HP BC BI	Bd wt	100			
					Repro		100		Marginal, but significant decrease in testosterone in the testis
DDT (NS) Krause 1977									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
109	Rat (NS) 6 M	20 days PNDs 4–23 (G)	0, 200	BW OW HP	Bd wt	200			
					Repro		200		Decreased absolute testis weight; decreased tubular diameter; reduced number of Sertoli cells, A-spermatogonia, and Leydig cells 6–12 days after exposure; significant reduction in number of fetuses and implants after two matings
DDT (NS) Krause et al. 1975									
110	Rat (Osborne-Mendel) 15 M, 15 F	15–27 weeks (F)	0, 0.05, 0.25, 0.5, 2.5	OW GN HP	Hepatic	0.05	0.25		Minimal centrilobular hypertrophy, cytoplasmic oxyphilia
DDT, technical grade Laug et al. 1950									
111	Rat (Sprague-Dawley) 8 M	21 days PNDs 28–48 (GO)	0, 2	OW BW BC	Bd wt		2		Increased terminal body weight (16%)
					Other noncancer		2		Metabolic syndrome (increased fat pad weight and percent body fat, altered plasma lipid profile)
***p,p'*-DDE Liang et al. 2020**									
112	Rat (Fischer-344) 6 M	42 days (F)	0, 10	OW BW HP BC BI FI	Bd wt	10			
					Hepatic	10			
					Renal	10			
					Immuno	10			
					Repro	10			
***p,p'*-DDE Makita et al. 2003a**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
113	Rat (Osborne-Mendel) 5 M, 5 F	6 weeks (F)	M: 49, 88, 160, 280, 490; F: 54, 96, 170, 300, 540	BW	Bd wt		160 M	170 F	39% reduction in body weight in females 10% reduction in body weight in males
DDD-technical NCI 1978									
114	Rat (Osborne-Mendel) 5 M, 5 F	6 weeks (F)	M: 0, 16, 28, 50, 88, 157; F: 0, 17, 31, 54, 97, 172	LE BW	Bd wt		50 M	97 F	45% reduction in body weight in females 16% reduction in body weight in males
DDT, technical grade NCI 1978									
115	Rat (Osborne-Mendel) 20–50 F	26 weeks (GO)	F: 0, 30, 61	CS	Neuro			30 F	By week 26, tremors in 8% at 30 mg/kg/day and 90% at 61 mg/kg/day; hunched appearance by week 6 at 61 mg/kg/day; tremors also observed in males, but accurate doses could not be determined
DDT, technical grade NCI 1978									
116	Rat (Osborne-Mendel) 5 M, 5 F	6 weeks (F)	M: 0, 28, 49, 88, 160, 280; F: 30, 50, 96, 170, 300	LE BW	Death			300 F	All female rats died by 6 weeks
					Bd wt	300 F	49 M		11% body weight depression in males
***p,p'*-DDE NCI 1978**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
117	Rat (Sherman) 4–20 B	2–6 months (F)	0, 0.5, 1.7, 5, 20, 40	GN HP BI	Hepatic	5 F	20 F		Mild hepatocellular hypertrophy, more severe in males than females
						0.5 M	1.7 M		More severe effects at 5 mg/kg/day in males; no quantitative data provided
DDT, technical grade Ortega 1956									
118	Rat (Sprague-Dawley) 11 M (treated); 24 M (control)	104 days; 14 days *in utero*, 20 lactational days, 70 days directly (G)	0, 35	DX	Develop		35		Increased liver mass, relative liver weight; testicular mass and relative testis weight. Decreased seminiferous tubule diameter, epithelium thickness, and lumen diameter; increased serum testosterone
DDE (NS) Patrick et al. 2016									
119	Rat (Sprague-Dawley) 27 M (treated); 24 M (control)	104 days; 14 days *in utero*, 20 lactational days, 70 days directly (G)	0, 35	DX	Develop		35		Increased liver mass, increased relative liver weight; Decreased seminiferous tubule diameter, epithelium thickness, and lumen diameter; increased testicular mass
DDT (NS) Patrick et al. 2016									
120	Rat (Wistar) 36 M, 36 F	9 weeks (F)	M: 0, 34.1; F: 0, 37	BW FI WI GN HP CS	Neuro			34.1 F	Tremors in 80% of females after 9 weeks of treatment
DDT, technical grade Rossi et al. 1977									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
121	Rat (Fischer-344) 7 M	13 and 26 weeks (F)	0, 0.17, 1.7, 19.1	HE HP BC	Hemato	1.7	19.1		Significantly decreased hematocrit and hemoglobin levels (at 13 and 26 weeks) and erythrocyte counts (at 13 weeks only) coupled with increased bone marrow hematopoiesis on week 26
***p,p'*-DDT** **Tomita et al. 2013**									
122	Rat (Fischer-344) 45 M	28 days (F)	0, 5, 16, 50	HP BI BC	Hepatic		5		Increased absolute and relative liver weight
***p,p'*-DDT** **Tomiyama et al. 2004**									
123	Rat (Wistar) 46 F	20 weeks (F)	0, 0.1, 1.0, 2.0, 4.0	BW OW RX	Bd wt Repro	4 4			
***o,p'*-DDT** **Wrenn et al. 1971**									
124	Rat (Sprague-Dawley) 10 F	GD 6–PND 20 (G)	0, 5, 15, and 50	BW DX CS OW	Bd wt Hepatic Develop	50 15 15	 50 50		 Increased relative liver weight (20%) in dams Reduced weaning index and number of pups live on PND 21; prolonged preputial separation and early vaginal opening
***p,p'*-DDE** **Yamasaki et al. 2009**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
125	Mouse (Hissar) 12–15 M	3–12 weeks (F)	0, 4.2, 10.5, 21	FI GN BC CS BI IX	Immuno	4.2	10.5		Decreased splenic PFC response to T-antigen independent LPS at weeks 6–12; decreased IgM antibody titer at 21 mg/kg/day
DDT (NS) Banerjee 1987a									
126	Mouse (Rockfeller) 8–12 M	24 weeks (F)	0, 4.3, 10.7, 21.4	IX	Immuno	4.3	10.7		Increased growth of Mycobacterium leprae in footpad
***p,p′*-DDT Banerjee et al. 1997a**									
127	Mouse (Hissar albino) 25–30 M	3–12 weeks (F)	0, 4, 10, 20	BW FI BC CS OW IX	Bd wt	20			
					Hepatic	4	10		Increased relative liver weight (14.7%)
					Immuno	10	20		Reduced relative spleen weight, decreased secondary haemagglutination titres, and decreased splenic PFC response to LPS
***p,p′*-DDT Banerjee et al. 1986**									
128	Mouse (Hissar) 8–10 M	4 weeks (F)	0, 4.1, 10.1, 20.3	LE BW FI OW IX	Bd wt	20.3			
					Immuno	10.1	20.3		Decreased splenic PFC response to SRBC (in restraint-stressed mice only)
***p,p′*-DDT Banerjee et al. 1997b**									
129	Mouse (C-57) 9 B	60–90 days (F)	0, 34.3, 51.4	RX	Repro	34.3		51.4	78% decreased fertility
DDT, technical grade Bernard and Gaertner 1964									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
130	Mouse (CF1) NS F	GDs 1–21 LDs 1–21 (F)	0, 34.3	DX	Develop		34.3		Decreased maze performance learning at 1 and 2 months in survivors
DDT, technical grade Craig and Ogilvie 1974									
131	Mouse (C57BL/6J) 14–15 F	15 days, GD 12–PND 5 (G)	0, 1.7	DX	Develop	1.7 M	1.7 F		In female offspring on high fat diets for 12 weeks: Metabolic syndrome (impaired glucose tolerance, hyperinsulinemia, dyslipidemia), impaired cold tolerance, altered bile acid metabolism
***p,p'*-DDT; prepared mixture of 77.2% p,p'-DDT and 22.8% o,p'-DDT La Merrill et al. 2014a, 2014b**									
132	Mouse (C57BL/6J) 14–15 F	15 days, GD 12–PND 5 (G)	0, 1.7	DX	Develop		1.7		Increased systolic and diastolic blood pressure in male offspring at 5 months; increased systolic in males and females at 7 months; cardiac hypertrophy (increased left ventricular wall thickness) in females, but not in males
***p,p'*-DDT; prepared Mixture of 77.2% p,p'-DDT and 22.8% o,p'-DDT La Merrill et al. 2016**									
133	Mouse (B6C3F1) 20 M, 20 F	86–130 days (F)	0, 0.86, 1.7, 3.4, 5.1,10.2,20.4	RX	Repro	3.4	5.1		Decreased number of pups/litter at birth or PND 1, decreased fertility
DDT, technical grade Ledoux et al. 1977									
134	Mouse (NMRI) 13 F	72–74 days 7 days/week (F)	0, 2.0	BI RX	Repro		2		Prolonged length of estrus cycle; decreased number of implants (223 versus 250 in controls)
***p,p'*-DDT Lundberg 1973**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
135	Mouse (NMRI) 10–14 F	28 days (G)	0, 1.77	GN BI RX	Repro		1.77		Decreased corpora lutea 17.2%
***p,p'*-DDT** **Lundberg 1974**									
136	Mouse (B6C3F1) 5 M, 5 F	6 weeks (F)	M: 0, 45, 72, 114, 180, 287; F: 0, 49, 78, 123, 195, 310	BW LE	Bd wt	310 F 287 M			
DDD-technical **NCI 1978**									
137	Mouse (B6C3F1) 5 M, 5 F	6 weeks (F)	M: 0, 3, 6, 10, 18, 32; F: 0, 4, 6, 11, 20, 35	BW LE	Death Bd wt	 35 F 32 M		35 F	4 out of 5 died
DDT, technical grade **NCI 1978**									
138	Mouse (B6C3F1) 5 M, 5 F	6 weeks (F)	M: 0, 25, 35, 49, 66, 94; F: 0, 27, 38, 53, 71, 101		Death Bd wt	 101 F 94 M		66	Death of 4/5 males and 2/5 females
***p,p'*-DDE** **NCI 1978**									
139	Mouse (NMRI) 10–15 M	28 days (G)	0, 6.25	BW OW GN BI	Hepatic Repro		6.25 6.25		Increased absolute and relative liver weight Reduced seminal vesicle weight (28%) in castrated males only
***p,p'*-DDT** **Orberg and Lundberg 1974**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
140	Mouse (CF1) 60 B	15–30 weeks (F)	0, 42.8	BW OW GN HP	Cancer			42.8	CEL: Liver hepatomas
***p,p'*-DDT** **Tomatis et al. 1974b**									
141	Mouse (BALB/c) 53 M, 53 F	120 days (F)	0, 1.3	RX	Repro	1.3			
DDT, technical grade **Ware and Good 1967**									
142	Dog (NS) 14 M	36-150 days (C)	0, 50	OW HP CS	Endocr			50	Adrenocortical necrosis
***p,p'*-DDD** **Kirk and Jensen 1975**									
143	Rabbit (New Zealand) 5 F	3 times/week 12 weeks (GO)	0, 3	RX HP	Repro		3		Reduced ovulation rate and slight decrease circulating progesterone post-insemination
DDT, technical grade **Lindenau et al. 1994**									
144	Rabbit (New Zealand) 5 F	12–15 weeks 3 days/week (GO)	0, 3	RX	Repro	3			
DDT, technical grade **Seiler et al. 1994**									
145	Rabbit 8 M	8 weeks (F)	0, 0.184, 0.92, 2.1, 6.54	BW HP BC IX	Immuno	2.1			
***p,p'*-DDT** **Street and Sharma 1975**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
CHRONIC EXPOSURE									
146	Human 51 M	12–18 months (F)	0, 0.05, 0.5	BC CS BW	Bd wt	0.5			
					Cardio	0.5			
					Hemato	0.5			
					Hepatic	0.5			
					Neuro	0.5			
DDT, technical grade **Hayes et al. 1956**									
147	Monkey (Rhesus) 22 B	3.5–7 years (F)	0, 0.1, 1, 3.9, 98	GN CS	Hepatic		3.9		N=3 at 3.9 mg/kg/day; slight variation in liver cell size and mild hydropic changes histopathology (n=1); severe hydropic and hyaline changes of liver cytoplasm with focal acute hepatitis (n=1)
DDT (NS) **Durham et al. 1963**									
148	Monkey (Cynomolgus) 13 M, 11 F	130 months (F)	0, 6.4-15.5	HP OW CS BW HE GN	Death			6.9 F	
					Hepatic		6.4 F		Fatty changes in the liver
					Neuro			6.9 F	Severe tremors
***p,p'*-DDT** **Takayama et al. 1999**									
149	Rat (MRC Porton) 30–38 B	Life (F)	0, 6, 12, 24	BW GN HP CS	Bd wt	24			
					Resp	24			
					Neuro	24			
					Cancer			12 F	CEL: Liver-cell tumors (6.6 and 18.4% at 12 and 24 mg/kg/day)
DDT, technical grade **Cabral et al. 1982b**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
150	Rat (Osborne Mendel) 30 B	27 months (F)	0, 20	BW HP GN	Resp	20			
					Hemato		20		Hemolysis in spleen
					Hepatic		20		Focal hepato-cellular necrosis
					Renal			20	Some tubular epithelial necrosis and polycystic degeneration; small hemorrhages
DDT (NS) Deichmann et al. 1967									
151	Rat (Sprague-Dawley) F1, 5 M, 10 F	2-generation (F)	0, 0.5, 1.5	RX	Repro	1.5			
DDT, technical grade Duby et al. 1971									
152	Rat (Sprague-Dawley) F1, 5 M, 10 F	2-generation (F)	0, 0.1, 0.3	RX	Repro	0.3			
***o,p'*-DDT Duby et al. 1971**									
153	Rat (Sprague-Dawley) F1, 5 M, 10 F	2-generation (F)	0, 0.4, 1.2	RX	Repro	1.2			
***p,p'*-DDT Duby et al. 1971**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
154	Rat (Osborne-Mendel) 12 M, 12 F	2 years (F)	0, 7, 14, 28, 42, 56	GN	Hepatic		7		Focal hepatocellular necrosis
DDT, technical grade Fitzhugh and Nelson 1947									
155	Rat (F344/DuCrj) 40 M, 40 F	1–2 years (52, 78, and 104 weeks) (F)	Male: 0, 0.17, 1.7, and 19.1; females: 0, 0.21, 2.2, 25.2	HP BW FI CS BI	Bd wt	2.2 F		25.2 F	25% decreased mean body weight in females
						1.7 M	19.1 M		12% decreased mean body weight in males
					Hepatic	0.21 F	2.2 F		Increased incidence of hepatocellular hypertrophy (close to 100% from week 26 to 104)
							0.17[c] M		Increased incidence of hepatocellular hypertrophy (close to 100% from week 52 to 104) $BMDL_{10}$ of 0.05 mg/kg/day
					Neuro	2.2 F	25.2 F		Whole body tremors weeks 70–104
						1.7 M	19.1 M		
					Cancer			1.7 M	CEL: Hepatocellular adenoma in males at ≥1.7 mg/kg/day and in females at 25.2 mg/kg/day; hepatocellular carcinomas in males (19.1 mg/kg/day)
***p,p'*-DDT Harada et al. 2003, 2006**									
156	Rat (Osborne-Mendel) 20–50 M, 20–50 F	78 weeks (F)	M: 0, 116, 231; F: 0, 66, 131	BW CS GN HP	Bd wt			66 F 116 M	26–28% decrease in body weight gain
					Resp	131 F 231 M			
					Cardio	131 F 231 M			

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Gastro	131 F 231 M			
					Musc/skel	131 F 231 M			
					Hepatic	131 F 231 M			
					Renal	231 M	66 F		Chronic inflammation of the kidney
					Dermal	131 F 231 M			
					Endocr	131 F 231 M			
					Immuno	131 F 231 M			
					Neuro	131 F 231 M			
					Repro	131 F 231 M			
					Cancer			116 M	CEL: thyroid follicular cell adenoma and carcinoma
DDD, technical grade NCI 1978									
157	Rat (Osborne-Mendel) 20–50 M, 20–50 F	78 weeks (F)	M: 0, 23, 45; F: 0, 16, 32	BW CS GN HP	Bd wt		32 F 45 M		20% decrease in body weight gain
					Resp	32 F 45 M			
					Cardio	32 F 45 M			
					Gastro	32 F 45 M			
					Musc/skel	32 F 45 M			

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hepatic	32 F	23 M		Fatty metamorphosis
					Renal	32 F 45 M			
					Dermal	32 F 45 M			
					Endocr	32 F 45 M			
					Immuno	32 F 45 M			
					Repro	32 F 45 M			
DDT, technical grade NCI 1978									
158	Rat (Osborne-Mendel) 20–50 M, 20–50 F	78 weeks (F)	M: 0, 31, 59; F: 0, 19, 36	BW CS GN HP LE	Death			19 F	16% death rate compared to 0% in controls
					Bd wt		31 M	19 F	16% decrease in body weight gain in males 21% decrease in body weight gain in females
					Resp	36 F 59 M			
					Cardio	36 F 59 M			
					Gastro	36 F 59 M			
					Musc/skel	36 F 59 M			
					Hepatic	36 F	31 M		Fatty metamorphosis
					Renal	36 F 59 M			
					Dermal	36 F 59 M			

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Endocr	36 F 59 M			
					Immuno	36 F 59 M			
					Repro	36 F 59 M			
***p,p'*-DDE** **NCI 1978**									
159	Rat (Sprague-Dawley) 6 M, 12 F	2-generation (F)	0, 1, 10	RX	Repro	10			
DDT, technical grade **Ottoboni 1969**									
160	Rat (Sprague-Dawley) 6 M, 12 F	2-generation (F)	0, 1.9, 18.6	RX DX	Repro	18.6			
					Develop	1.9	18.6		Tail abnormalities, constriction rings in 13.2–25.5%; no effect on birth weights or body weights at weaning
DDT, technical grade **Ottoboni 1969**									
161	Rat (Sprague-Dawley) 12 M, 12 F	7 days/week life (F)	0, 1.6	RX	Repro	1.6			
DDT, technical grade **Ottoboni 1972**									
162	Rat (Wistar) 36 M, 36 F	120 weeks (F)	M: 0, 34.1; F: 0, 37	BW FI WI GN HP CS	Cancer			34.1 M	CEL: Liver cell tumors (33.3%)
DDT, technical grade **Rossi et al. 1977**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
163	Rat (Fischer-344) 5–10 M	Up to 104 weeks (F)	0, 0.17, 1.7, 19.1	HE HP BC	Hemato	0.17	1.7		Reduced hemoglobin, mean corpuscular volume and mean corpuscular hemoglobin and increased hematopoiesis in bone marrow at week 78
***p,p'*-DDT** **Tomita et al. 2013**									
164	Rat (Sprague-Dawley) F0 12 B	3 generations (F)	0, 0.13, 0.63, 1.25	RX	Repro	1.25			
DDT, technical grade **Treon et al. 1954**									
165	Mouse (ICR) 400 F	70 weeks (conception through death); multi-generation (F)	0, 16.5	GN DX	Resp	16.5			
					Cardio	16.5			
					Hepatic		16.5		Acute congestion in the liver
					Renal	16.5			
					Develop	16.5			Increased neonatal death (lactation index only), but decreased relative risk of postweaning death compared to controls
DDT, technical grade **Del Pup et al. 1978**									
166	Mouse (C57BL/6N) 36 M, 36 F	81 weeks (F)	0, 28	GN HP	Cancer			28	CEL: Liver tumors - primarily in males
***p,p'*-DDT** **Innes et al. 1969**									
167	Mouse (Swiss) 30 M, 30 F	80 weeks (F)	0, 16.5	BW GN HP CS	Neuro			16.5	Tremors
					Cancer			16.5	Lymphomas; lung and liver tumors NS

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
DDT, technical grade Kashyap et al. 1977									
168	Mouse (Swiss) 30 B	80 weeks (F)	0, 13	HP CS	Ocular		13		Unilateral and bilateral corneal opacity
DDT, technical grade Kashyap et al. 1977									
169	Mouse (Swiss-Webster) 4 M, 14 F/ generation	3 generations (F)	0, 5, 20, 50	RX	Repro			20	Decreased fertility
DDT (NS) Keplinger et al. 1970									
170	Mouse (B6C3F1) 20–50 M, 20–50 F	78 weeks (F)	M: 0, 71, 141; F: 0, 71, 142	BW CS GN HP	Bd wt		71 F	142 F	LOAEL: 17% decrease in body weight gain Serious LOAEL: 28% decrease in body weight gain
						141 M			
					Resp	142			
					Cardio	142			
					Gastro	142			
					Musc/skel	142			
					Hepatic	142			
					Renal	142			
					Dermal	142			
					Ocular	142			
					Endocr	142			
					Immuno	142			

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro	142			
					Repro	142			
DDD, technical grade NCI 1978									
171	Mouse (B6C3F1) 20–50 M, 20–50 F	78 weeks (F)	M: 0, 3.7, 7.4; F: 0, 15.0, 30.2	BW CS GN HP LE	Death			15 F	10% mortality compared to 0% in controls
					Bd wt	7.4 M 30.2 F			
					Resp	7.4 M 30.2 F			
					Cardio	7.4 M 30.2 F			
					Gastro	7.4 M 30.2 F			
					Musc/skel	7.4 M 30.2 F			
					Hepatic	7.4 M 30.2 F			
					Hepatic	30.2 F	3.7 M		Amyloidosis
					Renal	7.4 M 30.2 F			
					Dermal	7.4 M 30.2 F			
					Endocr	7.4 M 30.2 F			
					Immuno	7.4 M 30.2 F			
					Neuro	7.4 M 30.2 F			
					Repro	7.4 M 30.2 F			
DDT, technical grade NCI 1978									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
172	Mouse (B6C3F1) 20–50 M, 20–50 F	78 weeks (F)	M: 0, 27, 47; F: 0, 28, 49	BW CS GN HP LE	Death			49 F	40% death rate compared to 5% in controls
					Bd wt			28 F	29% decrease in body weight gain
						47 M			
					Resp	49			
					Cardio	49			
					Gastro	49			
					Musc/skel	49			
					Hepatic	49			
					Renal	49 F	27 M		Chronic inflammation of the kidney
					Dermal	49			
					Ocular	49			
					Endocr	49			
					Immuno	49			
					Repro	47 M 49 F			
					Cancer			28 F	CEL: hepatocellular carcinomas; 0/19, 19/47, 34/48
								27 M	CEL: hepatocellular carcinomas; 0/19, 7/41, 17/47
***p,p'*-DDE** **NCI 1978**									
173	Mouse (A strain) NS	5 generations (G)	0, 1.7, 8.7	LE GN HP	Death			8.7 F	F0 dams: 14 out of 30 animals died before 6 months (lung adenomas in 3/14)
					Cancer			1.7	Lung tumors, NS, lung adenomas
DDT, technical grade **Shabad et al. 1973**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
174	Mouse (BALB/c) 683 B	Life 6 generations (F)	0, 0.4, 0.7	BW GN HP BC CS LE	Cancer			0.4	Lung adeno-carcinomas in F2, leukemia in F3
***p,p'*-DDT** **Tarjan and Kemeny 1969**									
175	Mouse (BALB/c) 60 M, 60 F	Life 2-generation (F)	0, 0.4, 4, 50	BW GN HP	Cancer			50 F	Liver tumors in F0 and F1
DDT, technical grade **Terracini et al. 1973**									
176	Mouse (CF1) 30 B	2 years (F)	0, 15.8	GN HP CS	Cancer			15.8	Liver tumors, NS
***p,p'*-DDT** **Thorpe and Walker 1973**									
177	Mouse (CF1) 50 M, 50 F	Life multi-generation (F)	M: 0, 0.38, 1.91, 9.5, 47.6; F: 0, 0.36, 1.82, 9.1, 45.5	BW GN HP	Cancer			45.5 F 0.38 M	Liver tumors in F0 and F1 Liver tumors in F0 and F1
DDT, technical grade **Tomatis et al. 1972**									
178	Mouse (CF-1) 20 M, 20 F	2-generation (F)	0, 0.4, 2, 10, 50	DX	Develop	10		50	Increased preweanling death at 50 mg/kg/day; increased tremors, convulsions
***p,p'*-DDT** **Tomatis et al. 1972**									
179	Mouse (CF1) 60 M, 60 F	130 weeks (F)	M: 0, 42.6; F: 0, 45.8	BW GN HP CS	Cancer			42.6 M	CEL: lung and liver tumors
***p,p'*-DDD** **Tomatis et al. 1974a**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
180	Mouse (CF1) 60 M, 60 F	130 weeks (F)	M: 0, 42.6; F: 0, 45.8	BW OW GN HP LE	Cancer			42.6	CEL: liver tumors (males: 74 versus 35% in controls; females: 98 versus 1% in controls)
***p,p'*-DDE** **Tomatis et al. 1974a**									
181	Mouse (CF1) 60 NS	6 generations (F)	0, 0.33, 1.7, 8.3, 41.3	BW GN HP	Cancer			0.33	Liver tumors, NS
DDT, technical grade **Turusov et al. 1973**									
182	Mouse (CF1) 60 B	life (F)	0, 0.33, 1.65, 8.26, 41.32	GN HP CS	Develop	8.3		41.3	Increased in preweanling death
DDT, technical grade **Turusov et al. 1973**									
183	Mouse (CF1) 60 B	130-140 weeks (F)	0, 0.33, 1.7, 8.3, 41.3	GN HP CS	Neuro	1.7		8.3	Tremors
DDT, technical grade **Turusov et al. 1973**									
184	Mouse (NS) 12 M, 12 F	15 months (F)	0, 0.24, 2.4	RX LE	Repro	2.4			
DDT, technical grade **Wolfe et al. 1979**									
185	Hamster (Syrian) 30-40 B	Life (F)	0, 10, 20, 40	BW GN HP	Bd wt	40			
					Hepatic	20 F	40 F		Hepatocyte hypertrophy; fatty change
						10 M	20 M		Focal necrosis, hepatocyte hypertrophy
DDT, technical grade **Cabral et al. 1982a**									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
186	Hamster (NS) 60 B	Life (F)	0, 33, 67, 133	GN BI OW	Hepatic		67		50% increase in relative liver weight
DDT, technical grade Graillot et al. 1975									
187	Hamster (Syrian) 48 M, 48 F	128 weeks (F)	0, 95	BW LE HP CS	Bd wt		95		Decreased body weight gain
					Neuro	95			
					Cancer			95	CEL: adrenal neoplasms; 14% in controls, 34% in treated
DDT, technical grade Rossi et al. 1983									
188	Hamster (Syrian) 87 M, 88 F	128 weeks (F)	0, 47.5, 95	BW LE HP CS	Bd wt		95 M		11% decrease in body weight gain
					Hepatic		47.5		Liver necrosis
					Neuro	95			
					Cancer			47.5	CEL: hepatocellular tumors; 0/73, 11/69, 14/78
***p,p′*-DDE Rossi et al. 1983**									
189	Dog (NS) 1–10 NS	39–40 months (F)	0, 16, 80, 160	GN HP BI	Hepatic	16	80	160	LOAEL: Focal or diffuse liver alterations Serious LOAEL: Severe liver damage
DDT, technical grade Lehman 1965									

Table 2-1. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
190	Dog (Beagle) 4 M, 7–8 F	7 days/week, F2 generation (F)	0, 1, 5, 10	BW OW GN HP RX	Repro	10			
DDT, technical grade Ottoboni et al. 1977									

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented, with the exception of the neurological and developmental endpoints for which levels of effect for both males and females are presented.
[b]Used to derive an acute-duration oral minimal risk level (MRL) for DDT, DDE, or DDD of 0.0005 mg/kg/day based on the LOAEL of 0.5 mg technical DDT/kg on PND 10 for neurodevelopmental effects and an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL for DDT, DDE, or DDD of 0.0005 mg/kg/day based on a $BMDL_{10}$ of 0.05 mg *p,p'*-DDT /kg/day for hepatocyte hypertrophy and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). This value was also adopted as the intermediate-duration oral MRL for DDT, DDE, or DDD.

Principal studies for the MRLs

5-HIAA = 5-hydroxy-indoleacetic acid; AGD = anogenital distance; AHH = aryl hydrocarbon hydroxylase; ALP = alkaline phosphatase; B = both male(s) and female(s); BC = serum (blood) chemistry; Bd Wt or BW = body weight; BI = biochemical changes; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; CNS = central nervous system; CS = clinical signs; DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; FX = fetal toxicity; (G) = gavage, not specified; GD = gestation day; gen = generation(s); GN = gross necropsy; (GO) = gavage, oil; GSH = glutathione; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; (IN) = ingestion; IX = immune function; LD = lactation day; LD_{50} = dose producing 50% death; LDH = lactate dehydrogenase; LE = lethality; LOAEL = lowest-observed-adverse-effect-level; LPS = lipopolysaccharide; M = male(s); Musc/skel = muscular/skeletal; Neuro = neurotoxicology; NOAEL = no-observed-adverse-effect-level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; PCNA = proliferating cell nuclear antigen; PFC = plaque forming cell; PND = postnatal day; Repro = reproductive; RX = reproductive function; SRBC = sheep red blood cell; WI = water intake

Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Acute (≤14 days)

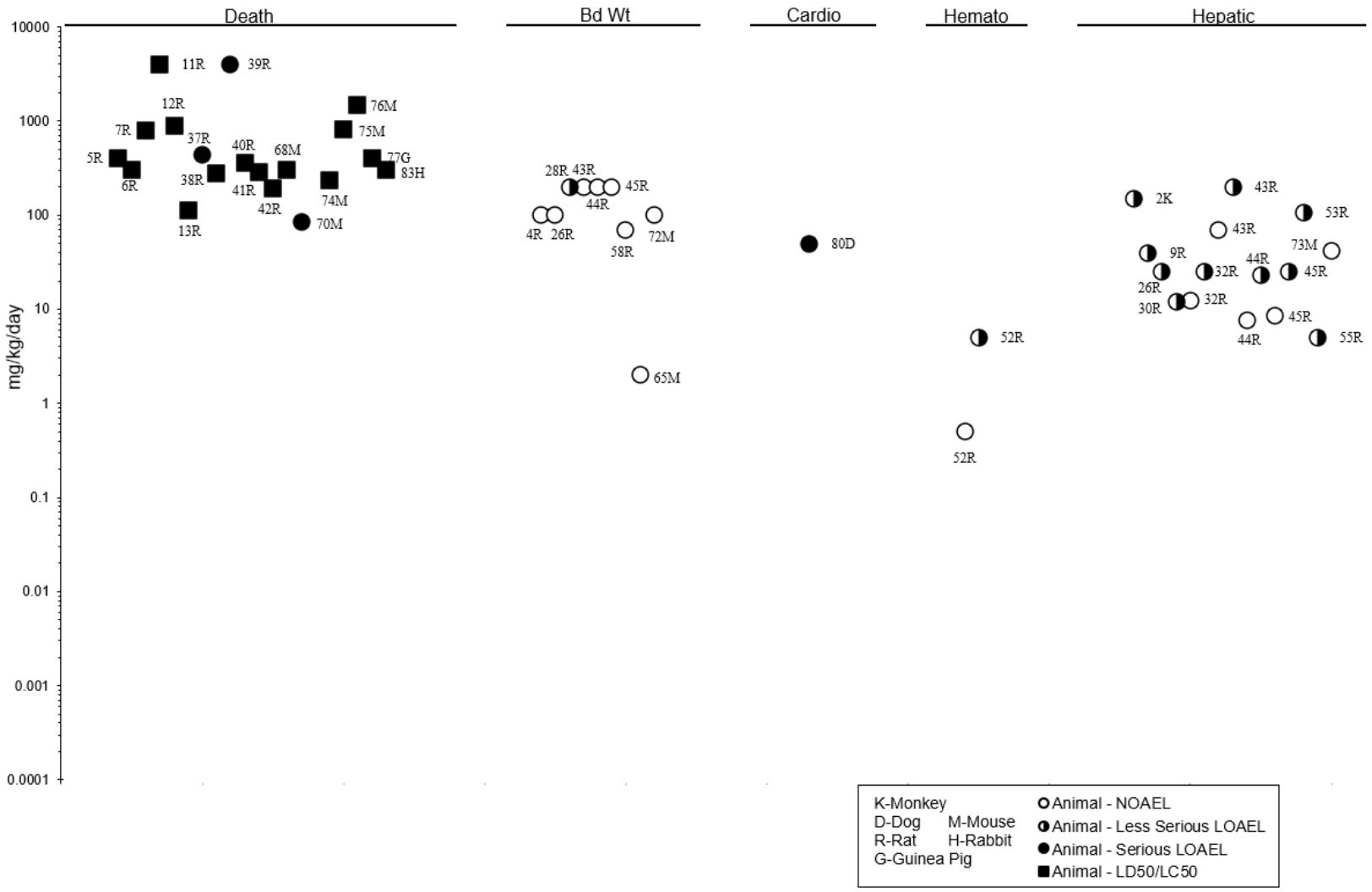


Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Acute (≤14 days)

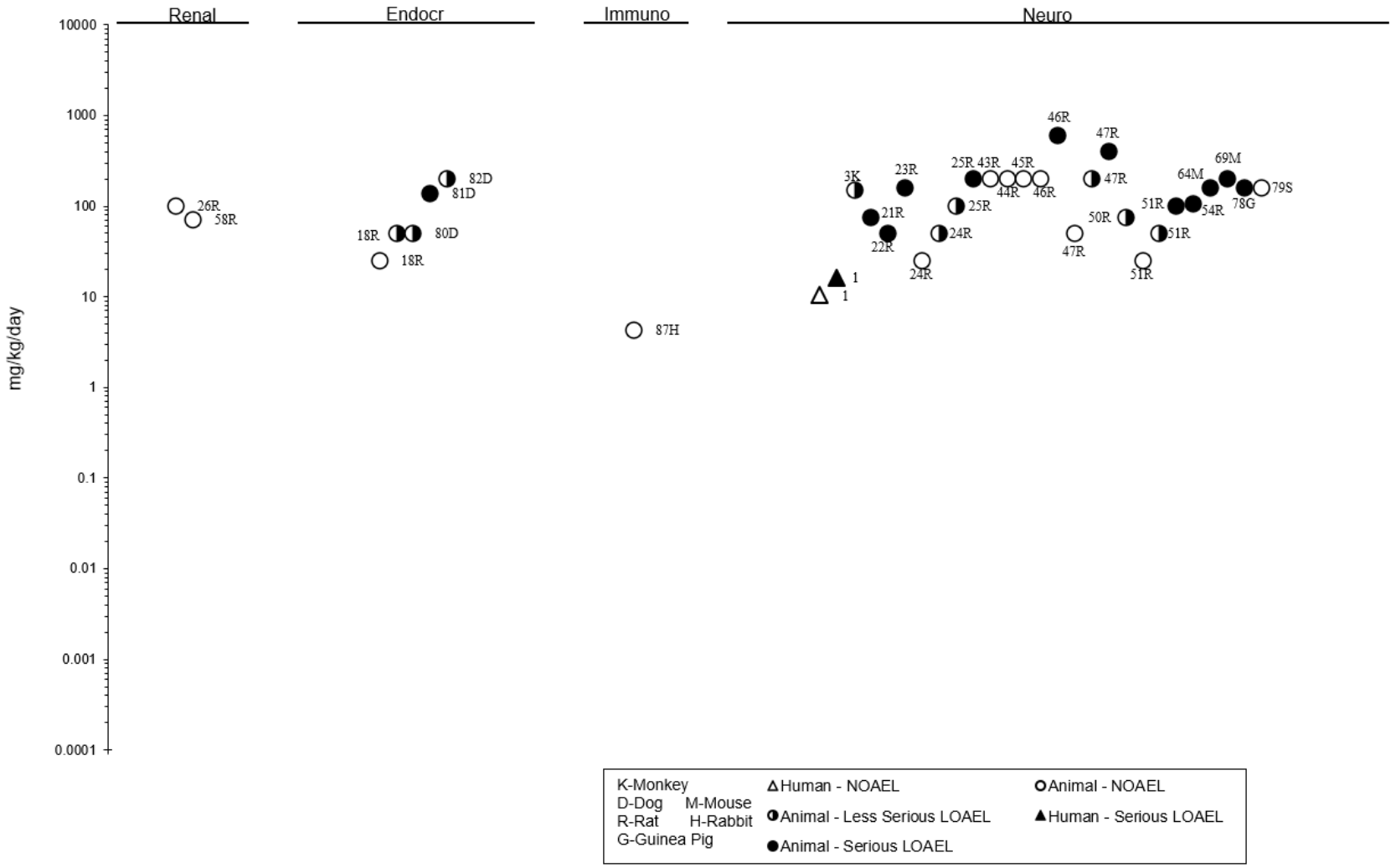


Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Acute (≤14 days)

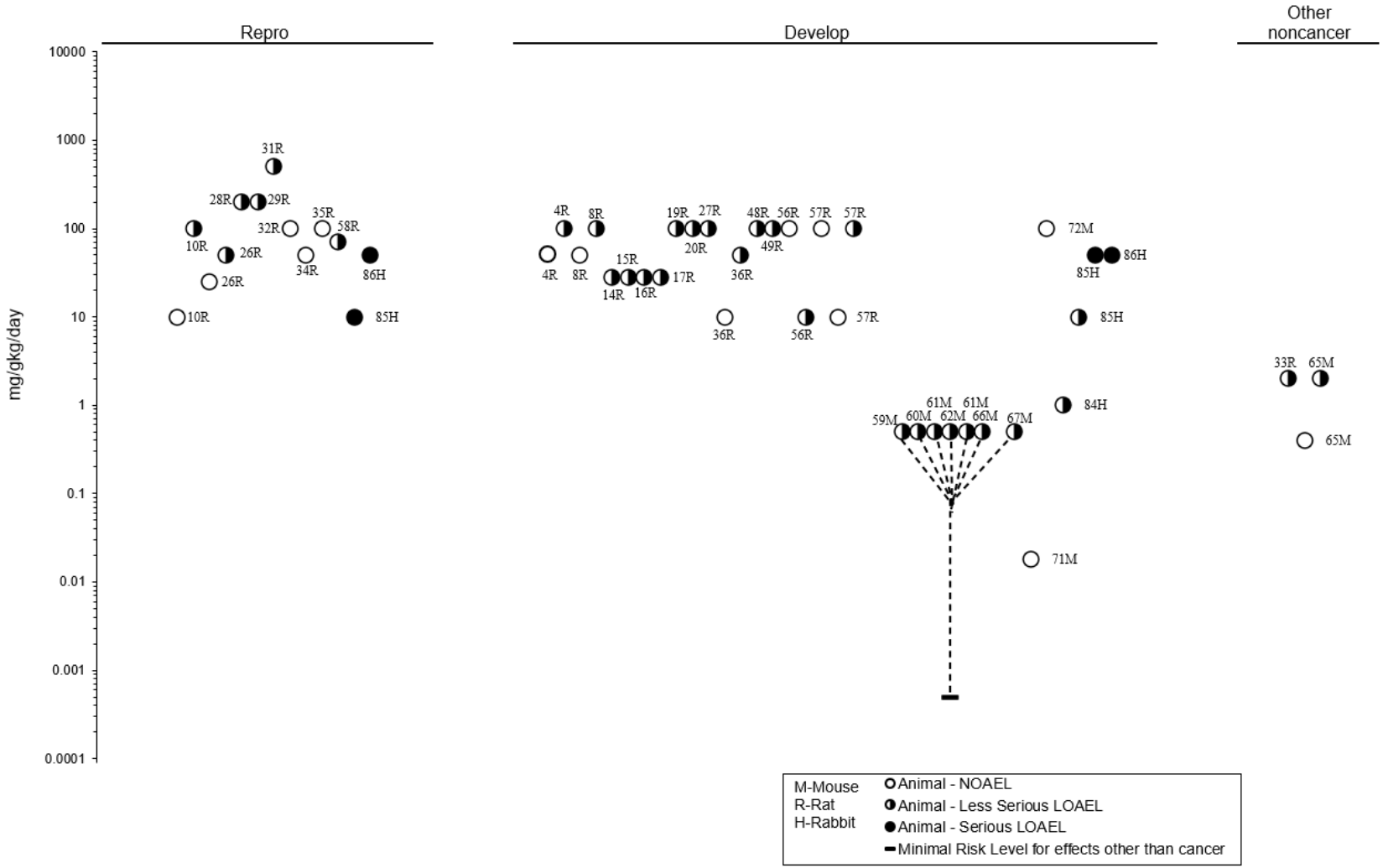


Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Intermediate (15-364 days)

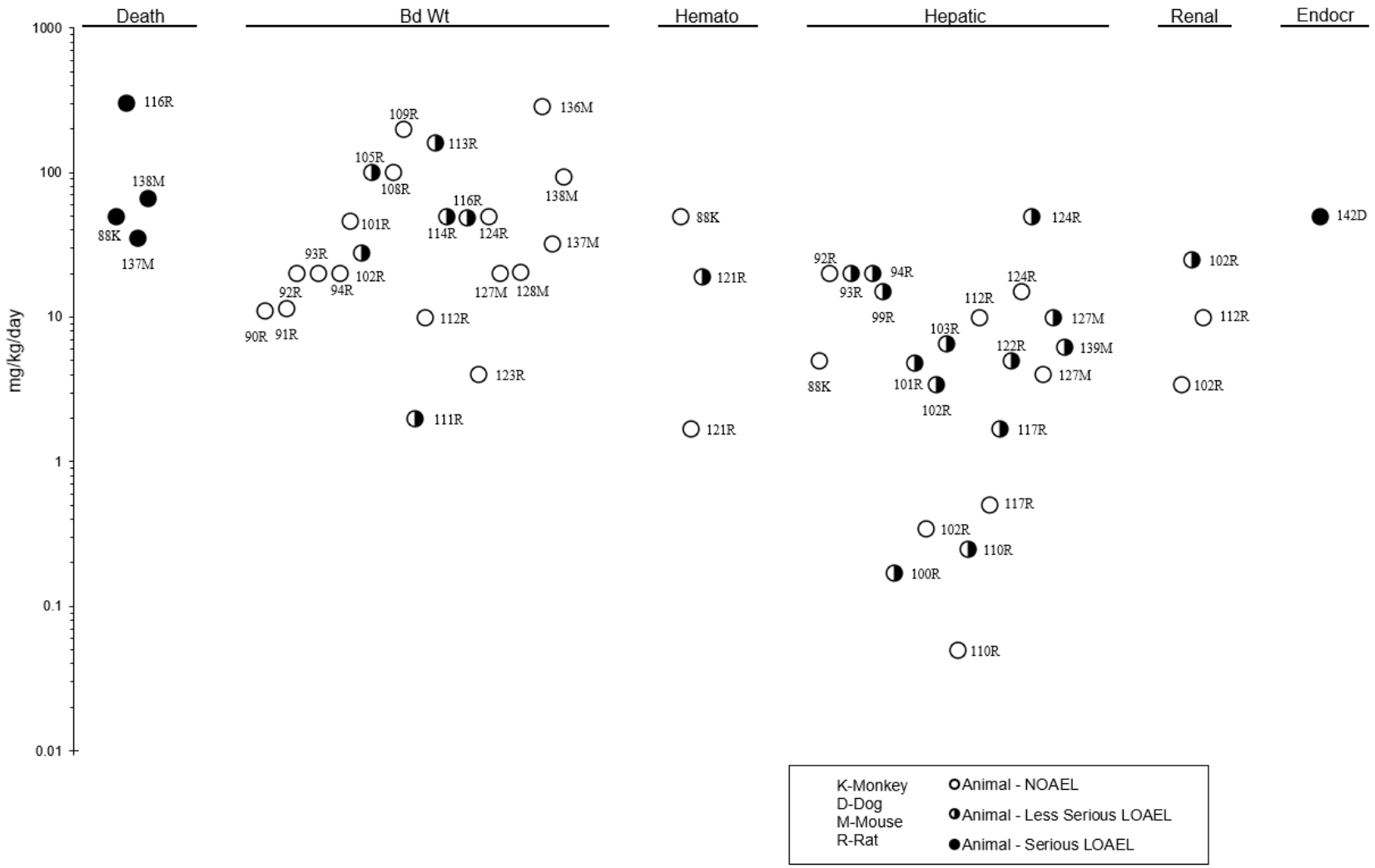


Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Intermediate (15-364 days)

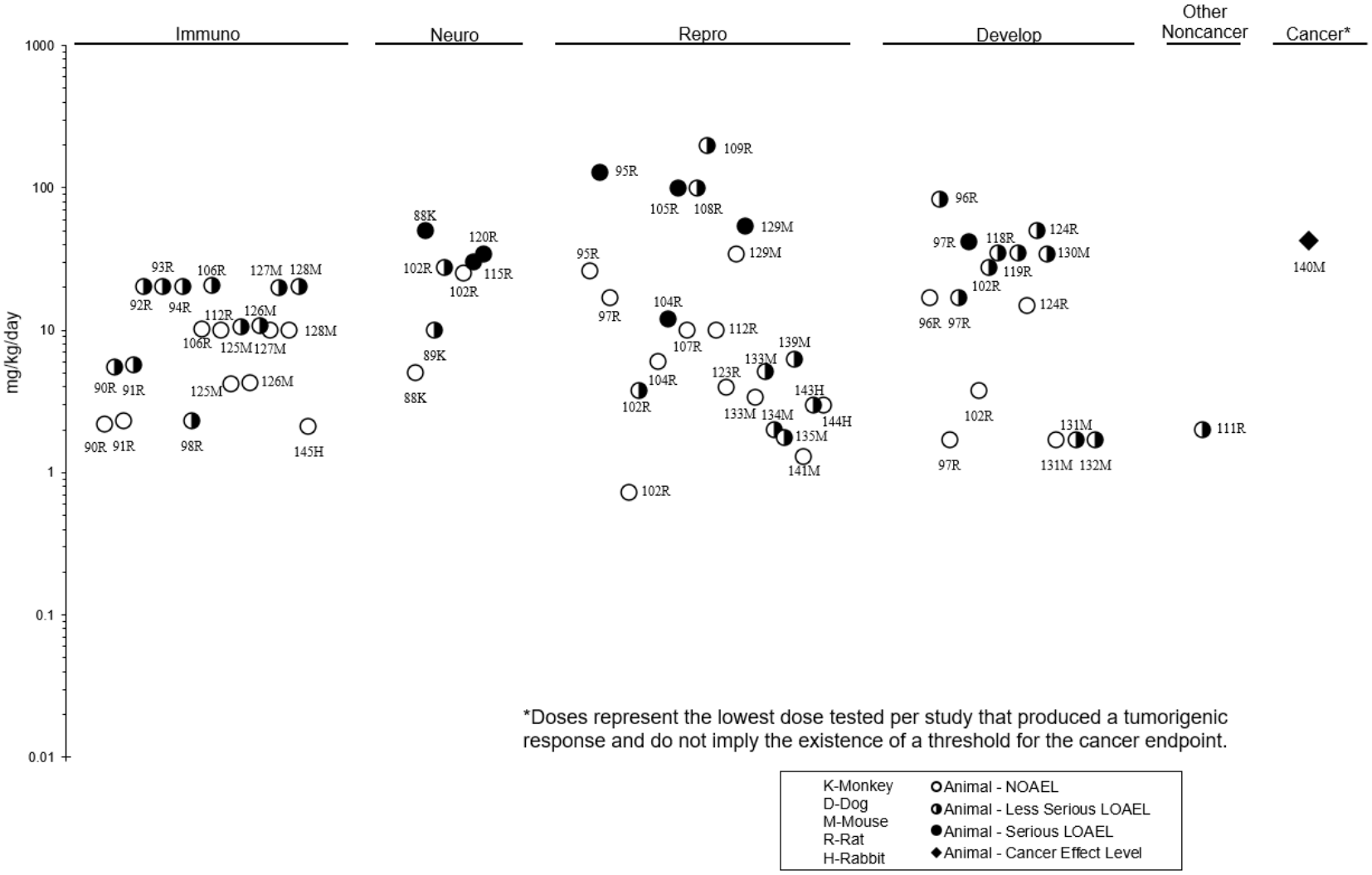


Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Chronic (≥365 days)

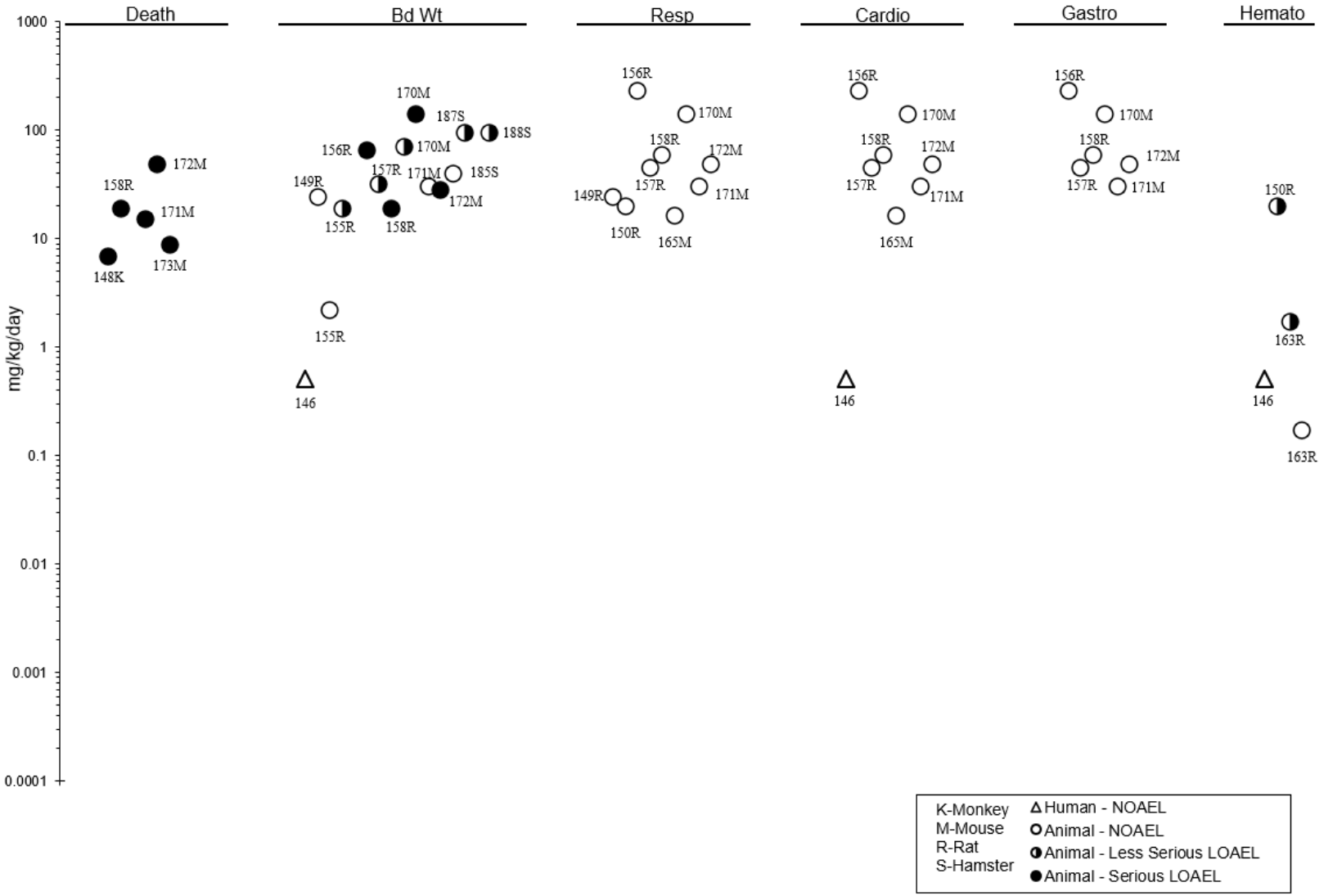


Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Chronic (≥365 days)

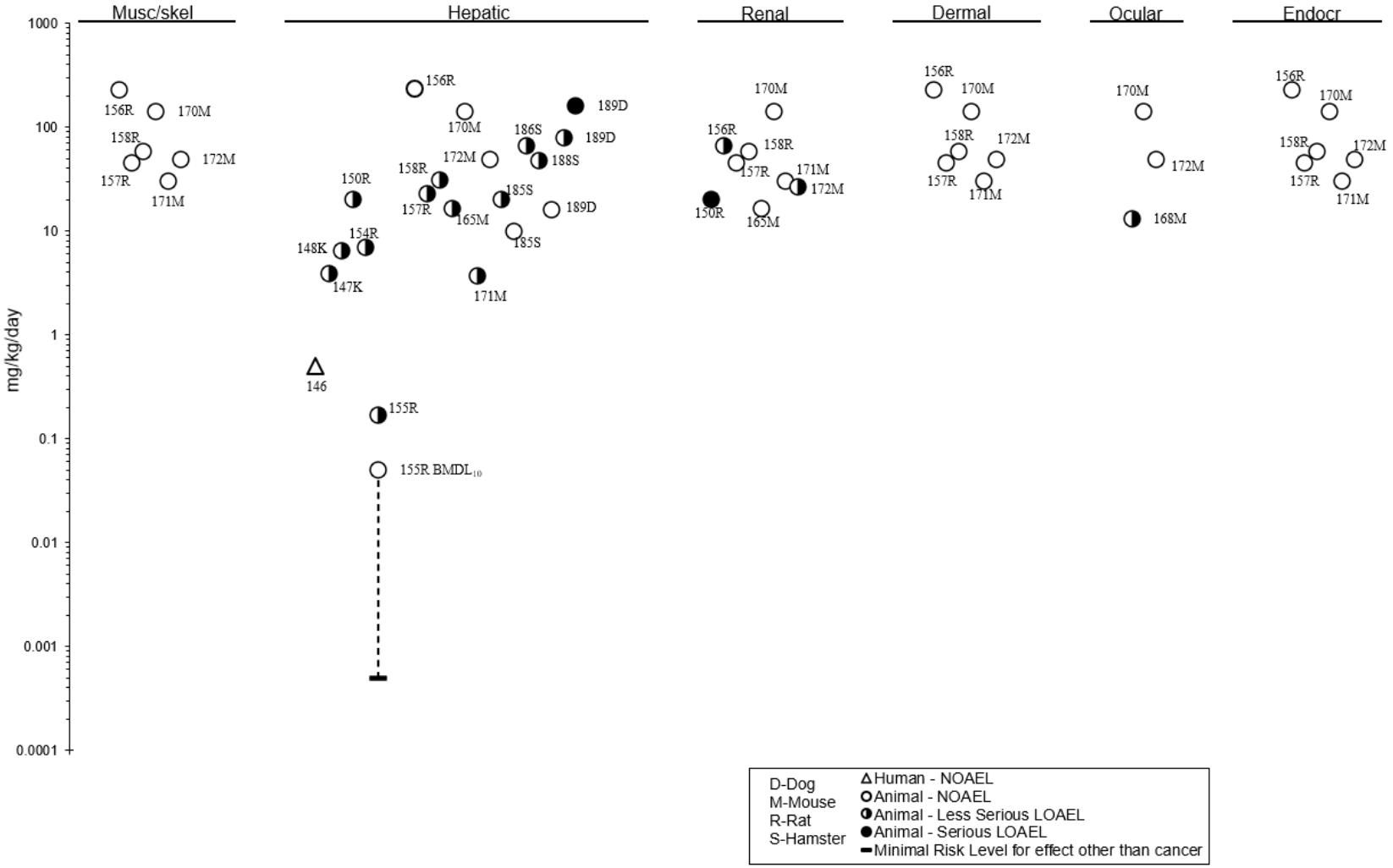
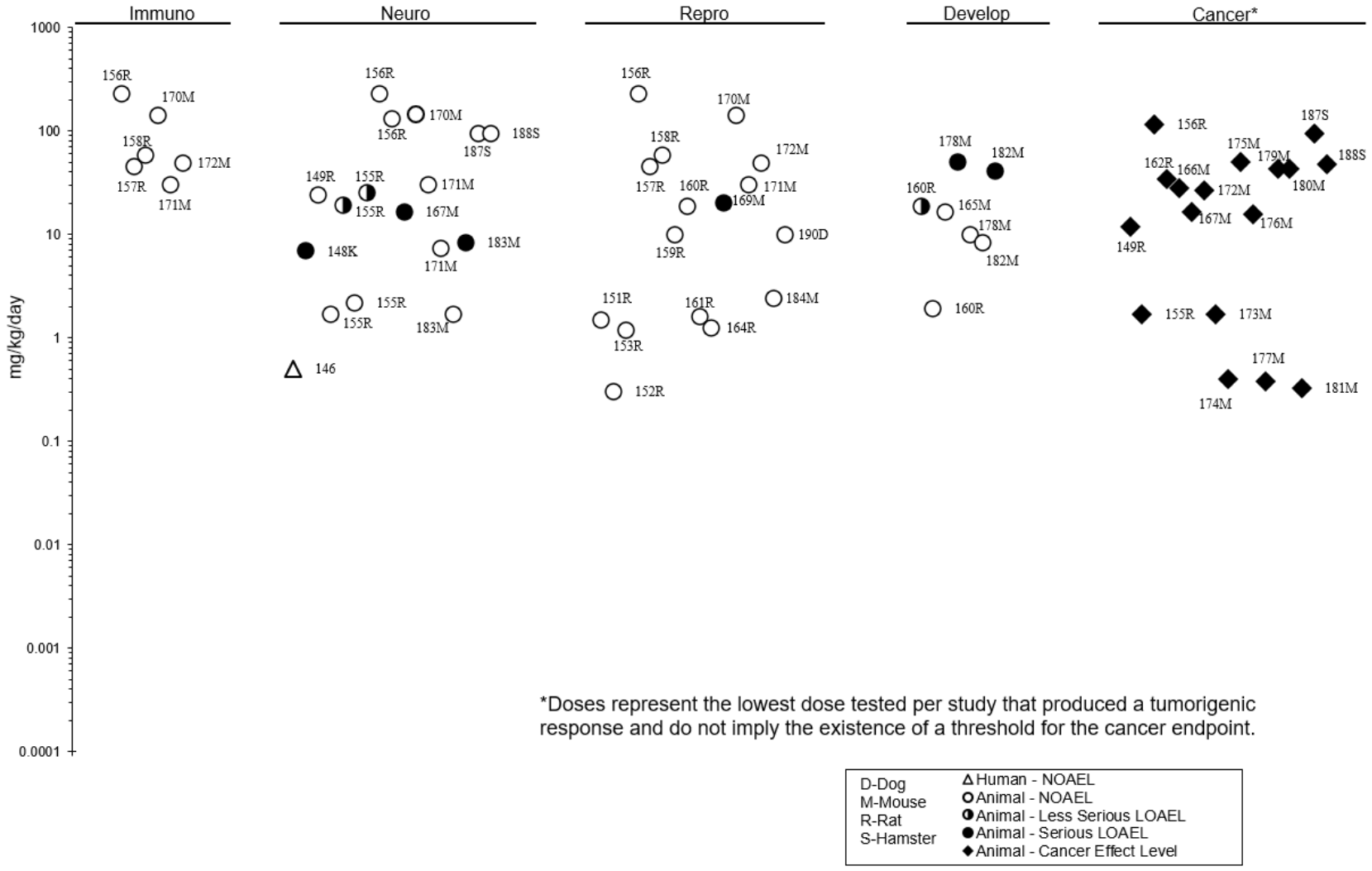


Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Chronic (≥365 days)



2.2 DEATH

Evidence of Death Effects of DDT, DDD, or DDE in Humans. Only one case of fatal poisoning in humans after accidental oral exposure to DDT has been documented (Hill and Robinson 1945). One ounce (approximately 30 mL) of 5% DDT in kerosene was ingested by a 1-year-old child. Clinical signs included coughing and vomiting followed by convulsions, which were characterized as generalized fine tremors. The child then became comatose and died 4 hours post-exposure; however, the contribution of the kerosene solvent to DDT toxicity was not addressed. In 1947, kerosene, not DDT, was determined to be the cause of death of a patient who fatally swallowed an approximate 150 mL solution of commercial DDT (~4% DDT, 4% lethane, and 92% kerosene) (Reingold and Lasky 1947). Doses as high as 285 mg DDT/kg body weight have been accidentally ingested by 28 men with no fatal results (Garrett 1947).

A few studies evaluated the risk of increased mortality in workers exposed to various compounds, including DDT (Beard et al. 2003; Brown 1992; Cocco et al. 2005; Wong et al. 1984). In general, these studies do not show clear evidence of increased mortality with occupational exposure to DDT.

A historical prospective mortality study was conducted on 3,600 white male workers employed between 1935 and 1976 in occupations that involved exposures to various brominated compounds, organic and inorganic bromides, and DDT (Wong et al. 1984). Among individuals exposed to DDT, overall mortality, expressed as the standardized mortality ratio (SMR), was not elevated over expected values. Similarly, a study of 4,552 male workers exposed to DDT and followed for 45 years reported no statistically significant increase in the relative risk of total mortality, or mortality due to various diseases or cancers in workers with estimated cumulative doses ranging from 0.01 to ≥2,755.1 mg DDT, between 1946 and 1950 (Cocco et al. 2005). Beard et al. (2003) also reported no significant increase in total mortality (SMRs) in occupationally exposed workers compared to the general population (Beard et al. 2003); in the exposed group, there were increases in mortality due to ischemic heart disease, respiratory disease, and pancreatic cancer. However, deaths from ischemic heart disease and respiratory disease were proposed to reflect smoking patterns, as comparisons with a control population of outdoor workers did not result in elevated deaths. This was not the case for pancreatic cancer; increases in deaths (SMR 5.27, 95% confidence interval [CI] 1.09–15.40) were found for workers with <3 years of DDT exposure, as compared the control population; no association was found in workers exposed to DDT for ≥3 years.

Brown (1992) conducted an update of a historical prospective mortality study of workers in five pesticide manufacturing plants. In the plant that manufactured DDT (230 persons and 90 deaths since 1964), there

was a significant excess of deaths (11) from cerebrovascular disease. The SMR was 2.38. The study is limited by insufficient exposure data (with the exception of DDT exposure information for 35 workers employed in 1967), possible confounding exposures, and relatively small numbers of deaths from stroke.

A limited number of general population studies do not show consistent evidence of increased risk of mortality with elevated DDT biomarker levels (Fry and Power 2017; Lind et al. 2019; Parada et al. 2016).

A study evaluating mortality in the general U.S. population (n=1,411) reported no statistically significant association between serum DDE levels from NHANES data and increased risk of all-cause mortality, cancer mortality, or mortality due to cardiovascular disease (Fry and Power 2017). However, a significant increase in risk of "other cause" mortality was observed; this included wide ranging causes of death other than cancer or cardiovascular disease. When evaluated by body mass index (BMI) and sex, the association was only observed at BMI ≥25 (hazard ratio [HR] 1.13, 95% CI 1.05, 1.22) and in males (HR 1.38, 95% CI 1.13, 1.69). In a general population study in Sweden, Lind et al. (2019) evaluated mortality in 992 men and women between 70 and 80 years of age. During that period 158 deaths occurred. There was no association between serum DDE levels and all-cause mortality (HR 1.01, 95% CI 0.85, 1.20).

Parada et al. (2016) evaluated a group of 633 women with breast cancer with available blood DDT (n=622), DDE (n=632), chlordane (n=622), and lipid levels; the women were followed for 15 years. At year 5, *p,p'*-DDT exposure was associated with all causes of mortality and breast cancer-specific mortality. The respective HRs and 95% CI for T2 (serum *p,p'*-DDT levels of ≥56.8–<91.2 ng/g) versus T1 (<56.8 ng/g) were 2.55 (1.20, 5.45) and 2.94 (1.12, 7.67). For T3 (serum *p,p'*-DDT levels of ≥91.2 ng/g) versus T1, the respective HRs and 95% CI were 2.19 (1.02, 4.67) and 2.72 (1.04, 7.13). At 15 years, there were no associations between serum DDT levels and breast cancer or all-cause mortality. For DDE, there were no associations with mortality at 5 years. However, at 15 years, the highest tertile of *p,p'*-DDE (≥1,058.2 ng/g) was inversely associated with all mortality (HR 0.66, 95% CI 0.44, 0.99), compared to T1 (<467.1 ng/g) (Parada et al. 2016). Although these data may indicate increased risk of mortality with increased serum DDT levels in these subjects, no comparisons were done with a control/non-breast cancer group, and data may not translate to risks to the general public.

Evidence of Death Effects of DDT, DDD, or DDE in Animals. The oral LD_{50} values for the various isomers and technical-grades of DDT, DDE, and DDD, as well as exposure levels associated with

decreased survival in repeated-dose toxicity animal studies, are recorded in Table 2-1 and plotted in Figure 2-2. No acute inhalation studies were identified.

The LD_{50} values reported in rats exposed to single oral gavage doses of *p,p'*-DDT ranged from 113 to 800 mg/kg (Ben-Dyke et al. 1970; Cameron and Burgess 1945; Gaines 1969). The LD_{50} values for guinea pigs and rabbits after oral exposure to *p,p'*-DDT were 400 and 300 mg/kg, respectively (Cameron and Burgess 1945). The LD_{50} for technical-grade DDT in male Sherman rats in one study was 217 mg/kg (Gaines 1969). Results from another study by Lu et al. (1965) revealed age-dependent LD_{50} values for technical-grade DDT in rats. The LD_{50} values in newborn, preweanling, weanling, and adult rats were >4,000, 438, 355, and 195 mg technical DDT/kg, respectively. However, when preweanling and adult rats were administered one-quarter of the LD_{50} daily for 4 days, there was no significant difference in the 4-day LD_{50} between the two age groups. Lu et al. (1965) suggested that the elimination mechanism in the pre-weanling rats is less well developed, thus making them more susceptible to repeated doses than adults. The age-dependent susceptibility to single high oral doses of DDT in rats was confirmed by others who suggested that seizures and hyperthermia, observed in the adults but not in young rats, as well as less resistance to hypoxia, contribute to the apparent higher sensitivity of the adult rat (Henderson and Woolley 1969, 1970). The LD_{50} values for single oral doses of technical-grade DDT in mice from two studies were 237 and 300 mg/kg (Kashyap et al. 1977; Tomatis et al. 1972). In a short-term feeding experiment, a daily dietary dose of about 85.7 mg *p,p'*-DDT/kg killed 50% of a group of mice after a 6-day feeding period (Okey and Page 1974).

In *p,p'*-DDE mortality studies, LD_{50} values of 880 and 1,240 mg/kg were reported for male and female Sherman rats, respectively (Gaines 1969). Death occurred in mice after single oral doses of *o,p'*-DDE ranging from 810 to 880 mg/kg (Tomatis et al. 1974a).

In *p,p'*-DDD mortality studies, reported LD_{50} values for rats and mice ranged from about 400 to >4,000 mg/kg/day (Ben-Dyke et al. 1970; Gaines 1969; Tomatis et al. 1974a).

In dermal exposure studies, the dermal LD_{50} of DDT in rats was reported by Ben-Dyke et al. (1970) and Cameron and Burgess (1945) as 2,500 and 3,000 mg DDT/kg, respectively. The LD_{50} was 2,510 mg of technical-grade DDT/kg in female Sherman rats (Gaines 1969). In guinea pigs, a single dermal dose of 1,000 mg DDT/kg resulted in death of 50% of the animals (Cameron and Burgess 1945). Dermal LD_{50} values in rabbits were 300 mg DDT/kg (Cameron and Burgess 1945) and 4,000–5,000 mg DDD/kg (Ben-Dyke et al. 1970). In the study by Cameron and Burgess (1945), the animals were dermally exposed to

various doses of DDT in solvents including kerosene, ether, dimethyl phthalate, or dibutyl phthalate. It is uncertain what contribution these solvents made to the toxic effects observed; the authors stated that kerosene itself may have caused some deaths.

After intermediate-duration oral exposure to *p,p'*-DDT or technical DDT, significantly increased mortality has been observed in animals exposed to doses ≥~25–35 mg/kg/day. Increased mortality occurred shortly after mating in F0 (3/24) and F1 (6/23) female rats (not observed in males) exposed to 27.7 mg *p,p'*-DDT/kg/day in the diet for 10 weeks prior to mating, and throughout mating, gestation, and lactation (Hojo et al. 2006). Four out of five female B6C3F1 mice fed a diet that provided ~35 mg technical DDT/kg/day for 6 weeks died (NCI 1978). Gavage exposure to 50 mg *p,p'*-DDT/kg/day produced deaths in four of six monkeys after 4 weeks of treatment; the remaining monkeys died during weeks 9 and 14 of treatment (Cranmer et al. 1972).

After chronic-duration exposure to *p,p'*-DDT, *p,p'*-DDE, or technical DDT, reduced survival has been observed in monkeys, rats, and mice. Mortality rates of 10% and 28% were observed in female B6C3F1 mice exposed to 15 and 30.2 mg technical DDT/kg/day, respectively, in the diet for 78 weeks (NCI 1978). Early mortalities were not observed in male mice exposed to the same dietary concentrations of technical DDT (NCI 1978). Following dietary exposure to 49 mg *p,p'*-DDE/kg/day in the diet for 78 weeks, female B6C3F1 mice had a 40% mortality rate (NCI 1978). A mortality rate of 16% was observed in female Osborne-Mendel rats exposed to 19 mg *p,p'*-DDE/kg/day in the diet for 78 weeks (NCI 1978). In a 130-month study that administered approximately 6.4–15.5 mg of *p,p'*-DDT/kg/day to Rhesus and Cynomolgus monkeys, there were 6/24 early deaths; the lowest dose associated with death was approximately 6.9 mg/kg/day (Takayama et al. 1999). Exposure-related reduced survival was not observed in male and female F344/DuCrj rats exposed for up to 104 weeks to 19.1 and 25.2 mg/kg/day *p,p'*-DDT, respectively, in the diet (Harada et al. 2003).

2.3 BODY WEIGHT

Evidence of Body Weight Effects of DDT, DDD, or DDE in Humans. A number of epidemiological studies have examined associations between serum or adipose levels of DDT, DDE, or total DDT and weight status markers including BMI, abdominal obesity, or measurements of visceral or subcutaneous abdominal tissue in various populations, including older adults (mean age ≥50 years of age), young adults (mean age 18–50 years old), pregnant and/or postpartum women, and children or adolescents (Table 2-2). Findings are inconsistent across studies, but generally suggest a positive association between DDT

metrics and body weight metrics in adults, with limited evidence of an inverse association in children and adolescents.

Table 2-2. Summary of Studies of Associations between DDT Exposure Biometrics and Body Weight Status[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Older adults (~50 years of age or older)			
Arrebola et al. 2014 Cross-sectional, 298 adults (145 men, 152 women), median age 52 years old (Spain)	Adipose DDE (IQR, ng/g lipid): 35.20–213.13	BMI	↑
De Roos et al. 2012 Cross-sectional, 109 sedentary and overweight/obese, post-menopausal women, 50–75 years old (United States, Washington)	Serum DDE (median (range), ng/g lipid): 488 (68.5–6,540)	BMI	↔
		Body weight	
		At 18 years	↔
		At 35 years	↔
		At 50 years	↑
		Current	↔
		Maximum	↔
		Weight loss episodes ≥20 pounds	↔
		Fat mass	↔
		Subcutaneous fat	↔
		Intra-abdominal fat	↑
		Waist circumference	↔
		Hip circumference	↔
		Waist:hip ratio	↔
Dhooge et al. 2010 1,583 adults (775 men, 808 women), 50–65 years old (Belgium)	Serum DDE (median (10^{th}–90^{th} percentile), ng/g fat): Men: 443 (123–1,398) Women: 556 (167–1,818)	BMI	
		Men	↑
		Women	↑
Lee et al. 2012a, 2012b Cohort/cross-sectional, 970 adults (49% men), 70 years old at study initiation (Sweden) Abdominal obesity defined as waist circumference >102 cm in men or >88 cm women	Serum DDE (quintiles, ng/mL) Q1: ≤0.902 Q2: 0.903–1.486 Q3: 1.487–2.304 Q4: 2.305–4.039 Q5: ≥4.040	Abdominal obesity at 70 years	
		Men	↑ (Q4, Q5)
		Women	↔
		Abdominal obesity developed between 70 and 75 years	
		Men	↔
		Women	↔

Table 2-2. Summary of Studies of Associations between DDT Exposure Biometrics and Body Weight Status[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
La Merrill et al. 2019 Cross-sectional, 147 Asian Indian adults, 45–84 years old (United States, California)	Plasma DDT metrics (median (range), ng/g lipid) DDE: 1,850 (85.1–27,900) DDT: 44.8 (8.67–2,880) *o,p'*-DDE: 1.70 (0.500–8.90) *o,p'*-DDT: 4.20 (<0.810–209)	BMI	↑ (*o,p'*-DDT, DDT) ↔(*o,p'*-DDE, DDE)
		Waist circumference	↑ (*o,p'*-DDT, DDT, DDE) ↔(*o,p'*-DDE)
La Merrill et al. 2018 Cohort, 988 elderly adults, 70 years old at the time of plasma collection, hypertension assessed at 70, 75, and 80 years old (Sweden)	Plasma DDE levels (IQR, ng/g lipid): 170–570	BMI	↑
Lim et al. 2011 Cross-sectional, 1,099 adults, mean age 60.2 years old (United States, NHANES 1999–2002)	Serum DDE (NR)	10-year changes in weight: Weight loss Weight gain	 ↑ ↓
Roos et al. 2013 Cross-sectional, 287 adults, 70 years old (Sweden) Adipose tissue measured by MRI	Serum DDE (IQR, ng/g lipid): 158.1–538.4	VAT	↑
		SAT	↑
		VAT/SAT	↔
Schildkraut et al. 1999 99 women (42 black, 57 white), mean age 57.4 years (United States, North Carolina)	Serum DDE (mean (SD), ppb): All: 10.5 (12.8) Black: 16.3 (16.0) White: 6.2 (7.2)	BMI All Black White	 ↑ ↔ ↔
		Waist:hip ratio	↔
		Weight loss in past year (>5 pounds)	↔
		Weight gain in past year (>5 pounds)	↔

Table 2-2. Summary of Studies of Associations between DDT Exposure Biometrics and Body Weight Status[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Younger adults (~18–50 years old)			
Elobeid et al. 2010 Cross-sectional, 2,464 subjects (1,140 males, 1,324 females) evaluated for BMI and 2,448 subjects (1,133 males, 1,315 females) evaluated for waist circumference, age 6–40+ years (United States, NHANES 1999–2002)	Serum DDT (NR)	BMI Overall Male Female Waist circumference Overall Male Female	 ↑ ↓ ↑ ↔ ↓ ↑
Lee et al. 2007b Cross-sectional, 721 non-diabetic adults including 175 adults with metabolic syndrome cases, ≥20 years old (United States, NHANES)	Serum DDE (NR)	WC	↔
Lee et al. 2011b Cohort, 5,115 adults (18–30 years old at initiation), BMI measured at 20-year follow-up (United States)	Serum DDE and DDT (NR)	BMI	↑ (DDE) ↔ (DDT)
Perry et al. 2005 Cohort, 466 nulliparous women, mean age 24.9 years, follow-up for 12 months or until a pregnancy was clinically confirmed (China)	Serum DDT (IQR, ng/g): 13.9–54.0	BMI	↓
Pregnant and postpartum women			
Bravo et al. 2017 Cross-sectional, 698 post-partum women from two regions (Argentina, Salta, and Ushuaia)	Serum DDT metrics (GM (95% CI), ng/g lipid): DDE Salta: 67 (59–75) Ushuaia: 33 (38-39) DDT Salta: 5.7 (5.2–6.2) Ushuaia: 2.7 (2.4–3.2)	BMI	↑ (DDE, DDT)

Table 2-2. Summary of Studies of Associations between DDT Exposure Biometrics and Body Weight Status[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Warner et al. 2018 Cohort, 468 women evaluated 3 times during 5-year period, mean age of 36.4 years and pregnant at first visit (United States, California)	Serum levels (IQR, ng/g lipid): DDE: 128.8–519.8 DDT: 1.9–7.2	BMI	↑ (DDT) ↔ (DDE)
		Waist circumference	↑ (DDT) ↔ (DDE)
		Body fat percent	↑ (DDT) ↔ (DDE)
		Obesity risk	↑ (DDT) ↔ (DDE)
Children and adolescents			
Balte et al. 2017 Cohort, 328 children, 8 years old at study initiation, annual follow-up for 3 years (Germany)	Serum DDE (median (IQR), ng/mL) 8 years: 0.3 (0.2) 9 years: 0.4 (0.2) 10 years: 0.3 (0.2)	Body weight	↓
		Height	↓
Burns et al. 2012 Cohort, 350 peri-pubertal boys, 8–9 years old at study initiation, annual follow-ups for 4 years (Russia)	Serum DDE 8–9 years old (10^{th}–90^{th} percentile, ng/g lipid): 122–866	BMI z-score	↓ (Q2–Q5)
		Height z-score	↓ (Q4–Q5)
		Change in height (over 4 years)	↓ (Q4–Q5)
Dhooge et al. 2010 1,679 adolescents (887 boys, 792 girls), 14–15 years old (Belgium)	Serum DDE (median (10^{th}–90^{th} percentile), ng/g fat): Boys: 103.6 (46.8–403.9) Girls: 84.0 (39.3–247.1)	BMI Boys Girls	 ↓ ↓
Kaur et al. 2020 Cohort, 87 diabetic youth (mean 14.2 years old at baseline); follow-up examination 5 years later (United States)	Serum DDE levels (quartile GM, ng/g lipid): Q1: 22.93 Q2: 39.23 Q3: 65.44 Q4: 127.32	BMI z-score	↔
Lee et al. 2016 Cohort, 214 children, 7–9 years old at baseline; follow-up 1 year later (n=158) (Korea)	Serum DDT metrics at baseline (IQR) ng/mL / ng/g lipid DDE: 0.16–0.41 / 26.74-71.24 DDT: 0.013–0.024 / 2.31–4.04	BMI	↔

Table 2-2. Summary of Studies of Associations between DDT Exposure Biometrics and Body Weight Status[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Tang-Peronard et al. 2015a Cohort, 509 children, 8–9 years old at study initiation (Denmark)	Serum DDE at study initiation (mean (range), ng/g): Boys: 40 (10–720) Girls: 40 (10–720)	BMI z-score	
		At 14–16 years	↔
		At 20–22 years	↑ (boys) ↓ (girls)
		Waist circumference	
		At 14–16 years	↔ (boys) ↓ (girls)
		At 20–22 years	↔
		Percent body fat	
		At 14–16 years	↔
		At 20–22 years	↔

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified.

↑ = positive association; ↓ = inverse association; ↔ = no association; BMI = body mass index; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; GM = geometric mean; IQR = interquartile range; MRI = magnetic resonance imaging; NHANES = National Health and Nutrition Examination Survey; NR = not reported; Q = quartile or quintile; SAT = subcutaneous adipose tissue; SD = standard deviation; VAT = visceral adipose tissue

Consistent evidence for significant positive associations between serum DDT metrics and body weight, BMI, and/or waist circumference was found in most studies of older adults ≥50 years of age (Arrebola et al. 2014; De Roos et al. 2012; Dhooge et al. 2010; La Merrill et al. 2018, 2019; Lee et al. 2012a; Schildkraut et al. 1999). Other studies of older adults have reported positive associations with measures of intra-abdominal fat (but not subcutaneous fat) in a group of postmenopausal women (De Roos et al. 2012) and with abdominal areas of visceral and subcutaneous adipose tissue (VAT and SAT) in a group of 70-year-old Swedish men and women (Roos et al. 2013). However, Lim et al. (2011) found an inverse relationship between weight change over a 10-year period and increased serum DDE in older adults.

Significant positive associations between serum DDT metrics and body weight metrics were also observed in two of three studies of U.S. adults <50 years old (Elobeid et al. 2010; Lee et al. 2007b, 2011b) and one study in U.S. women of childbearing age (Warner et al. 2018). Increased BMI was also observed with increased serum DDT metrics in Argentinian women 1–3 days postpartum (Bravo et al. 2017). In contrast, an inverse association for BMI was reported in a study of young (mean age ~25 years) Chinese women with very high serum levels of total DDT (32 ng/g) (Perry et al. 2005). It is possible that the apparent inverse association of very high serum levels on BMI in the group of Chinese women

(~10-fold >500 ng/g lipid) may be an entirely different response to DDT or DDE, than that inferred from the studies of people with serum total DDT or DDE levels <500 ng/g lipid, reflecting some non-monotonic response, but this possible explanation is based on very limited data.

Six studies evaluating DDT biometrics in children and adolescents provide inconsistent evidence for an inverse association between serum DDE and weight status markers (Balte et al. 2017; Burns et al. 2012; Dhooge et al. 2010; Kaur et al. 2020; Lee et al. 2016, Tang-Peronard et al. 2015a). Inverse associations were reported for BMI z-score in Russian boys (Burns et al. 2012), BMI in Belgian boys and girls (Dhooge et al. 2010), and body weight (and height) in German boys and girls (Balte et al. 2017). No significant associations for BMI z-scores were found in Danish or American children age 14–16 years of age (Kaur et al. 2020; Tang-Peronard et al. 2015a). At 20–22 years, the Danish study reported a positive association in the males and an inverse association in the females (Tang-Peronard et al. 2015a); no association was observed at ~19 years in the study from the United States (Kaur et al. 2020). Another study did not observe an association between serum DDT metrics and BMI in Korean children (Lee et al. 2016).

Inconsistent results were reported in studies evaluating sex differences in adults (Elobeid et al. 2010; Lee et al. 2012a) and children (Tang-Peronard et al. 2015a). For example, Elobeid et al. (2010) reported an inverse association between serum DDT and BMI in men and a positive association in women, and Lee et al. (2012a) reported no significant association with incidence of abdominal obesity at age 70 years in women and a significant positive association in men.

In a single controlled exposure study, no treatment-related effects on body weight were observed in a group of 51 male volunteers given daily doses of up to 0.5 mg technical DDT/kg for up to 18 months (Hayes et al. 1956).

Evidence of Body Weight Effects of DDT, DDT, or DDE in Animals. Effects on body weight have been observed in animals orally exposed to DDT and related compounds for acute, intermediate, and chronic durations of exposure.

Following acute-duration oral exposure of adult animals, reported body weight effects include transiently decreased body weight on GDs 17–21 (9–17 % decreased compared with controls; returned to control levels by postpartum day 1) in rat dams exposed to 200 mg *p,p'*-DDE/kg/day, but not 100 mg/kg/day, on GDs 14–18 (Loeffler and Peterson 1999), and in adult males treated for with 200 mg *p,p'*-DDE/kg/day for

4 days (Kelce et al. 1995). No significant exposure-related body weight changes were noted in rat dams exposed to gavage doses of 50 or 100 mg *p,p'*-DDT/kg/day during pregnancy on GDs 13.5–17.5 (Adamsson et al. 2009); mouse dams exposed by gavage to up to 100 mg *o,p'*-DDT/kg/day on GDs 11–17 (Palanza et al. 2001); castrated male rats exposed to up to 100 mg *p,p'*-DDE/kg/day for 10 days (Kang et al. 2004); or male mice exposed to up to 2 mg *p,p'*-DDE/kg/day for 5 days (Howell et al. 2014).

After intermediate duration exposure to technical DDT, *p,p'*-DDE, or technical DDD, decreased body weight or body weight gain have been observed in rats and mice. Significantly decreased body weight or body weight gain (≥10% decreased, compared with control values) were reported in male albino rats exposed by gavage to 0.2 mg technical DDT/kg/day for 120 days (Chowdhury et al. 1990); male and female Osborne-Mendel rats fed ≥50 or 97 mg technical DDT/kg/day, respectively, in the diet for 6 weeks (NCI 1978); male Osborne-Mendel rats fed ≥49 mg *p,p'*-DDE/kg/day in the diet for 6 weeks (NCI 1978); and female and male Osborne-Mendel rats exposed to 97 or 279 mg technical DDD/kg/day, respectively, in the diet for 6 weeks (NCI 1978). Increased body weight (16–18% increase) occurred in pubertal male Long-Evans rats dosed with 100 mg *p,p'*-DDE/kg/day from PNDs 21 to 57 (Kelce et al. 1995) and pubertal male Sprague-Dawley rats dosed with 2 *p,p'*-DDE/kg/day from PNDs 28 to 48 (Liang et al. 2020). No significant changes in body weight (compared with control values) were observed in male and female B6C3F1 mice fed 35 mg technical DDT/kg/day in the diet for 6 weeks (NCI 1978); male and female F344/DuCrj rats exposed to up to 45.7 mg *p,p'*-DDE/kg/day in the diet for 4 weeks (Harada et al. 2003); F0 and F1 parental female Sprague-Dawley rats exposed to up to 27.7 mg *p,p'*-DDE/kg/day for 10 weeks prior to mating and then throughout gestation and lactation (Hojo et al. 2006); Sprague-Dawley rat dams exposed to gavage doses as high 50 mg *p,p'*-DDE/kg/day from GD 6 to PND 20 (Yamasaki et al. 2009); or in prepubertal male F344/DuCrlCrlj rats receiving dietary doses of 10 mg *p,p'*-DDE/kg/day for 42 days (Makita et al. 2003a).

Following chronic-duration exposures to technical DDT, *p,p'*-DDT, *p,p'*-DDE, or technical DDD, decreases in body weight have been observed in rats, mice, and hamsters. After 78-week exposures, consistent decreases in body weight or body weight gain ≥20% were observed in female Osborne-Mendel rats exposed to 32 mg technical DDT/kg/day, 66 mg technical DDD/kg/day (lowest dose tested), and 19 mg *p,p'*-DDE/kg/day (lowest dose tested) (NCI 1978). Male rats exhibited a 16% decrease in weight gain at 45 mg technical DDT/kg/day (NCI 1978) and a 28% decrease with 116 mg technical DDD/kg/day (NCI 1978). The chronic 2-year study by Harada et al. (2003, 2006) reported a 12% decrease in body weight in F344/DuCrj male rats orally exposed to 19.1 mg *p,p'*-DDT/kg/day and a 25% decrease at 25.5 mg/kg/day in females. Female B6C3F1 mice exposed to 28 mg *p,p'*-DDE/kg/day or 71 mg technical

DDD/kg/day in their diets for 78 weeks had decreases in body weight gain of 29 and 17%, respectively (NCI 1978). Hamsters fed a diet that provided approximately 47.5 mg *p,p'*-DDE/kg/day for 128 weeks showed an unspecified reduction in body weight gain compared with controls (Rossi et al. 1983), but hamsters fed 40 mg technical DDT/kg/day for life were reported to have comparable body weights to control hamsters (Cabral et al. 1982a).

Mechanisms of Body Weight Effects of DDT, DDD, or DDE. The human epidemiological studies are consistent with the hypothesis that endocrine disrupting compounds (EDCs), including DDT, may act as obesogens that display non-monotonic dose-response relationships, leading to weight gain at lower exposure levels, but to growth restriction or weight loss at higher exposure levels (Tang-Peronard et al. 2011). Reduced body weights in the described animal studies are likely the result of high-dose exposure levels. Several studies focusing on potential mechanisms behind DDT-associated obesity and obesity-related diseases are discussed in Section 2.18. Further studies may increase understanding of the complexities between the timing of DDT exposure, differences between DDT metabolites, dose, and gender, as well as the influences of initial weight status and significant weight change on serum levels of DDT and DDT toxicity (La Merrill et al. 2013).

2.4 RESPIRATORY

Evidence of Respiratory Effects of DDT, DDD, or DDE in Humans. Epidemiological evidence of respiratory effects that are mediated by immunological function (e.g., asthma, wheezing, bronchitis, respiratory tract infections, and hypersensitivity) is discussed in detail in Section 2.14.

Three studies provide inconsistent evidence for associations between serum levels of *p,p'*-DDT or *p,p'*-DDE and measures of lung function (Balte et al. 2017; Hansen et al. 2016 [see Section 2.14]; Ye et al. 2015). In a study of 1,696 Canadian adults, serum levels of DDT and DDE were inversely associated with forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) in models adjusted for age, sex, ethnicity, height, smoking status, and daily energy expenditure; associations with FEV1/FVC and forced expiratory flow (FEF) at 25–75% were not statistically significant (Ye et al. 2015). No significant associations between serum DDE and lung function (FVC, FEV1, FEV1/FVC) were observed in a longitudinal study in 299–344 German children ages 8, 9, and 10 years after adjusting for height, weight, sex, breastfeeding duration, history of maternal smoking during pregnancy, and current environmental tobacco smoke exposure (Balte et al. 2017). In the other study, maternal serum levels of DDE showed no associations with reduced lung function (FEV1 percent of predicted value <90%), but a

positive association with airway obstruction (FEV1/FVC <75%) was noted in offspring at 20 years of age (Hansen et al. 2016).

In a single controlled exposure study, volunteers were exposed by inhalation of aerosols containing DDT at concentrations that left a white deposit on the nasal hair (Neal et al. 1944). Except for moderate irritation of the nose, throat, and eyes, which may have been related to the vehicle to disperse DDT in an aerosol, no significant changes were reported. The investigators provided some information on exposure levels, but noted that the DDT quickly settled, and thus, the actual exposure levels were lower than predicted.

Evidence of Respiratory Effects of DDT, DDD, or DDE in Animals. No studies were located regarding the respiratory effects in animals after acute or intermediate-duration oral exposure to DDT, DDD, or DDE.

In chronic-duration oral studies, rats fed a diet containing 20 mg commercial DDT/kg/day for 27 months did not develop adverse respiratory effects, with the exception of squamous bronchial metaplasia in one rat (Deichmann et al. 1967). In the 78-week chronic bioassay conducted by the National Cancer Institute (NCI 1978), no adverse effects on the respiratory system were observed in Osborne-Mendel rats treated in the diet with up to 45 mg technical DDT/kg/day, 59 mg *p,p'*-DDE/kg/day, or 231 mg technical DDD/kg/day, or in B6C3F1 mice treated with up to 30.2 mg technical DDT/kg/day, 49 mg *p,p'*-DDE/kg/day, or 142 mg technical DDD/kg/day (NCI 1978). No histopathological changes or tumors in the lung were noted at 55 weeks of age of ICR mice exposed from conception through death to 16.5 mg/technical-DDT/kg/day (Del Pup et al. 1978); however, development of lung tumors has been reported in other studies following oral exposure of mice to DDT isomers and is discussed in Section 2.19.

In rats, guinea pigs, and rabbits exposed to acute-duration dermal doses ranging from 50 to 200 mg DDT/kg, pulmonary edema and respiratory failure were reported (Cameron and Burgess 1945).

Mechanisms of Respiratory Effects of DDT, DDE, or DDD. There is inconsistent evidence supporting associations between exposures to DDT isomers and impaired lung function. However, some mechanistic studies have begun to evaluate the relationship between serum levels of DDT isomers and respiratory effects mediated by immunological dysfunction (see Section 2.14).

2.5 CARDIOVASCULAR

Evidence of Cardiovascular Effects of DDT, DDD, or DDE in Humans. A number of epidemiological studies have examined associations between serum or adipose levels of DDT, DDD, or DDE and cardiovascular outcomes, including general hypertension in adults, gestational hypertension, cardiovascular disease, and peripheral arterial disease (Table 2-3). The results provide inconsistent evidence for associations between serum or adipose levels of DDE or DDT and cardiovascular effects.

Table 2-3. Summary of Studies of Associations between DDT Exposure Biometrics and Cardiovascular Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Hypertension/blood pressure			
Arrebola et al. 2015b Cohort, 297 adults; median 48 years at recruitment, hypertension assessed at 10-year follow-up (Spain)	Adipose DDE (IQR, ng/g lipid): Total: 30.8–192.1 BMI ≤26.3: 17.1–149.5 BMI >26.3 46.4–239.5	Hypertension Total BMI ≤26.3 BMI >26.3	 ↔ ↔ ↔
Donat-Vargas et al. 2018 Cohort/Cross-sectional, 681 adults at baseline including both prediabetic and non-diabetic individuals (351 normotensive, 330 hypertensive) and 830 adults at 8–12-year follow-up (291 normotensive, 539 hypertensive) (Sweden)	Plasma DDE levels (mean±SD, ng/g lipid): Normotensive Prediabetics Baseline: 324±204 Follow-up: 241±198 Nondiabetics Baseline: 268±195 Follow-up: 157±139 Hypertensive Prediabetics Baseline: 371±263 Follow-up: 252±206 Nondiabetics Baseline: 313±252 Follow-up: 188±149	Hypertension All at baseline All at follow-Up All, longitudinal	 ↔ ↔ ↔
Goncharov et al. 2011 Cross-sectional, 394 adults (United States, Alabama)	Serum DDT, DDE, and *o,p'*-DDE (NR)	SBP	↔ (DDT) ↔ (DDE) ↔ (o,*p'*-DDE)
		DBP	↔ (DDT) ↔ (DDE) ↔ (o,*p'*-DDE)
Henriquez-Hernandez et al. 2014 Cross-sectional, 428 adults, (Canary Islands)	Plasma DDE (IQR, µg/L) 0.62–1.89	Hypertension	↔
		SBP	↔
		DBP	↔

Table 2-3. Summary of Studies of Associations between DDT Exposure Biometrics and Cardiovascular Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Lee et al. 2016 Cohort, 214 children, 7–9 years old at baseline; follow-up 1 year later (n=158) (Korea)	Serum DDT metrics at baseline (IQR) ng/mL ng/g lipid DDE 0.16–0.41 26.74-71.24 DDT 0.013–0.024 2.31–4.04	SBP	↔
		DBP	↔
Lee et al. 2007b Cross sectional, 721 adults NHANES 1999–2002 (United States)	Serum DDE (NR)	Blood pressure ≥130/85	↑
La Merrill et al. 2013 Cohort, 639 adult female offspring including 457 normotensive, 111 self-reporting hypertension, and 70 using hypertension medication (United States, California)	Maternal serum sampled during pregnancy (tertile boundaries, µg/L) DDT: 6.97–11.9 *o,p'*-DDT: 0.24–0.51 DDE: 37–54	Medicated hypertension	↑ (DDT) ↔ (*o,p'*-DDT) ↔ (DDE)
		Self-reported hypertension	↑ (T2 only) (DDT)
La Merrill et al. 2018 Cohort, 988 elderly adults, 70 years old at the time of plasma collection, hypertension assessed at 70, 75, and 80 years old (Sweden)	Plasma DDE levels (IQR, ng/g lipid): 170–570	Hypertension	↑
Lind et al. 2014 Cross-sectional, 1,016 elderly adults (70 years old) (Sweden)	Serum DDE (IQR, ng/g lipid) 158.1–538.4	Prevalent hypertension	↑
Valera et al. 2013a Cross-sectional, 315 Inuit adults (Canada)	Serum levels (GM (95% CI), µg/L) DDT: 0.20 (0.18–0.23) DDE: 6.41 (5.75–7.15)	Risk of hypertension	↓ (DDT) ↑ (DDE)
		SBP	↔ (DDT) ↔ (DDE)
		DBP	↔ (DDT) ↔ (DDE)

Table 2-3. Summary of Studies of Associations between DDT Exposure Biometrics and Cardiovascular Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Valera et al. 2013b Cross-sectional, 1,614 Inuit adults (Greenland)	Serum levels (GM (95% CI), µg/kg lipid) DDT: 25.5 (24.4–26.6) DDE: 1016.6 (968.9–1,066.7)	Hypertension All subjects 18–39 years ≥40 years SBP DBP	 ↔ (DDT) ↔ (DDE) ↑ (DDT) ↔ (DDE) ↔ (DDT) ↔ (DDE) ↔ (DDT) ↔ (DDE) ↔ (DDT) ↔ (DDE)
Gestational hypertension			
Savitz et al. 2014a, 2014b Cohort, 1,933 pregnant women including 364 with gestational hypertension and 151 with preeclampsia (United States)	Serum levels (IQR, µg/L) DDT: 6.22–14.19 DDE: 16.95–36.73	Gestational hypertension Preeclampsia	↓ (DDT) ↔ (DDE) ↔ (DDT) ↔ (DDE)
Other cardiovascular outcomes			
Ha et al. 2007 Cross-sectional, 889 adults NHANES 1999–2002 (United States)	Serum DDT (IQR, ng/g lipid): 189–2,440	Cardiovascular disease	↔
Lee et al. 2012b, 2012c Cohort, 898 adults (Sweden)	Serum DDE (µg/L) Q1: 0.011–1.019 Q2: 1.020–1.863 Q3: 1.864–3.493 Q4: 3.494–23.271	Incidence of stroke	↑
Min et al. 2011 Cross-sectional, 2,032 adults including 143 with peripheral artery disease (PAD) and 1,889 without PAD, NHANES 1999–2004 (United States)	Serum DDE (mean (95% CI), ng/g lipid) Subjects with PAD: Obese: 705.3 (539.7–921.9) Non-obese: 430.9 (296.7–625.9) Subjects without PAD: Obese: 434.0 (406.1–463.9) Non-obese: 373.5 (335.3–415.9)	Peripheral artery disease Obese Non-obese	 ↑ ↔

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified.

↑ = positive association; ↓ = inverse association; ↔ = no association; CI = confidence interval; DBP = diastolic blood pressure; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; GM = geometric mean; IQR = interquartile range; NHANES = National Health and Nutrition Examination Survey; NR = not reported; SBP = systolic blood pressure; SD = standard deviation; T = tertile

Four out of eight epidemiological studies on hypertension (La Merrill et al. 2018; Lee et al. 2007b; Lind et al. 2014; Valera et al. 2013a) reported some evidence for associations with serum or adipose levels of *p,p'*-DDE. *p,p'*-DDE levels were associated with increased risk of hypertension in U.S. adults (Lee et al. 2007b), an Inuit community in Quebec (Valera et al. 2013a), and elderly individuals in Sweden (La Merrill et al. 2018; Lind et al. 2014). Other studies did not observe an association between *p,p'*-DDE levels and risk of hypertension in adults (Arrebola et al. 2015b; Donat-Vargas et al. 2018; Henriquez-Hernandez et al. 2014; Valera et al. 2013b). Despite inconsistencies among individual studies, a meta-analysis of six of these studies (Arrebola et al. 2015b; Henriquez-Hernandez et al. 2014; Lee et al. 2007b; Lind et al. 2014; Valera et al. 2013a, 2013b) suggested that an overall small, but significant, association between DDE serum levels and hypertension may exist (Park et al. 2016).

Fewer studies have looked for associations with levels of DDT, and report both positive associations (in 18–39-year-old adults, but not in adults ≥40 years of age) (Valera et al. 2013b) and inverse associations (Valera et al. 2013a) between *p,p'*-DDT serum levels and hypertension. A single study examined possible associations between *p,p'*-DDT, *o,p'*-DDT, or DDE serum levels sampled from pregnant women in 1959–1967 and incidence of hypertension in adult daughters (as defined as medication for the treatment of hypertension) in 2005–2008 and found significant associations with *p,p'*-DDT, but not with *o,p'*-DDT or *p,p'*-DDE (La Merrill et al. 2013).

In other epidemiological studies, no statistically significant positive associations with gestational hypertension (Savitz et al. 2014a), cardiovascular disease (Ha et al. 2007), or systolic or diastolic blood pressure levels (Goncharov et al. 2011; Henriquez-Hernandez et al. 2014; Lee et al. 2016; Valera et al. 2013a, 2013b) were observed (Table 2-3). Significant associations were reported between serum DDT or DDE levels and incidences of stroke in elderly men (Lee et al. 2012b) and peripheral arterial disease in obese adults (Min et al. 2011). Another study (Mills et al. 2009) found a significant association between DDT pesticide use and incidence of nonfatal myocardial infarction, although DDT exposure was not measured; no associations were found for fatal myocardial infarction.

In a controlled exposure study, no clear effects on cardiovascular performance (resting and exercise heart rate, systolic blood pressure, and pulse pressure) were found in male volunteers orally administered 3.5 or 35 mg DDT/day by capsule for 12–18 months either as recrystallized DDT administered via a capsule or technical-grade DDT administered via a milk emulsion (about 0.05–0.063 or 0.36–0.5 mg/kg/day) (Hayes et al. 1956).

Evidence of Cardiovascular Effects of DDT, DDD, or DDE in Animals. In a developmental toxicity study, increased systolic blood pressure was measured at 5 and 7 months of age in the offspring of C57BL/6J mice exposed to 1.7 mg/kg/day of a mixture of *p,p'*-DDT (77.2%) and *o,p'*-DDT (22.8%) from GD 12 to PND 5 (La Merrill et al. 2016). Cardiac hypertrophy was also observed in 8.5-month-old mice. No other studies evaluating cardiovascular effects following acute- or intermediate-duration studies in rodents orally exposed to DDT, DDD, or DDE were identified. A 14-day study in dogs exposed to *o,p'*-DDD, resulted in decreased contractile force at a LOAEL of 50 mg/kg/day (Cueto 1970), but no effects were observed with *p,p'*- isomers in dogs at any exposure duration.

In chronic-duration oral exposure studies, no significant chemical-related adverse effects on the cardiovascular system were observed in Osborne-Mendel rats treated in the diet for up to 78 weeks with up to 45 mg technical DDT/kg/day, 59 mg *p,p'*-DDE/kg/day, or 231 mg technical DDD/kg/day or in B6C3F1 mice treated with up to 30.2 mg technical DDT/kg/day, 49 mg *p,p'*-DDE/kg/day, or 142 mg technical DDD/kg/day (NCI 1978). No histopathological changes in the heart were noted at 55 weeks of age of ICR mice exposed from conception through death to 16.5 mg/technical-DDT/kg/day (Del Pup et al. 1978).

Cameron and Burgess (1945) exposed rats, guinea pigs, and rabbits to acute-duration dermal doses ranging from 50 to 200 mg DDT/kg and reported an increased fat content in the muscle fibers of the heart in some animals.

Mechanisms of Cardiovascular Effects of DDT, DDD, or DDE. In men, DDT has known anti-androgenic effects and has been inversely associated with serum testosterone (Blanco-Muñoz et al. 2012). Low levels of testosterone have been linked to hypertension and is a known risk factor for the development of major cardiac events, supporting the hypothesis that the anti-androgenic effects of DDE may impact cardiac health (Lind et al. 2014); see Section 2.16 for discussion of anti-androgenic effects. Although plausible, more experimental studies are needed to elucidate potential mechanistic relationships between DDT anti-androgenic activity and cardiovascular effects.

In a mouse developmental toxicity study, DDT-induced increased systolic and diastolic blood pressure could be partially reversed with the angiotensin converting enzyme (ACE) inhibitor, captopril (La Merrill et al. 2016). The results are consistent with the idea that overactivation of ACE may be involved in DDT-induced hypertension (La Merrill et al. 2016). Biochemical studies on kidney tissue showed the

overactivation of the renin-angiotensin system to be associated with increased renal expression of sodium transporter messenger ribonucleic acid (mRNA) (La Merrill et al. 2016). Genes from the renin-angiotensin pathway were also altered in the liver of rats orally exposed to DDE for 12 weeks, including decreased aldosterone receptor expression (Sa et al. 2018). However, no significant changes were observed in angiotensinogen, ACE 2, or angiotensin II receptor gene expression in adipose or liver tissue. Microarray analysis indicated perturbations in other pathways relevant to hypertension, including the retinoid acid biosynthesis pathway, endothelial NO synthase (eNOS) activation, and regulation and urea cycle pathways. These pathways were more perturbed when DDE exposure was combined with a high-fat diet (Sa et al. 2018). Whether similar mechanisms may operate in humans is unknown.

2.6 GASTROINTESTINAL

Evidence of Gastrointestinal Effects of DDT, DDD, or DDE in Humans. Two cohort studies have evaluated potential associations between maternal DDT metrics and gastrointestinal infections and/or symptoms in infants (Table 2-4). A Mexican birth cohort study reported a positive association between maternal serum levels of DDE and mother-reported incidence of diarrhea over the first 2 years of life in urban families, but not rural families (Cupul-Uicab et al. 2017). No associations were observed between maternal DDT levels and incidence of diarrhea. The other cohort study did not observe significant associations between gastrointestinal infections in 6- or 12-month-old offspring and maternal serum levels of DDE in Inuit mother-infant pairs (Dallaire et al. 2004).

Table 2-4. Summary of Studies of Associations between DDT Exposure Biometrics and Gastrointestinal Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Dallaire et al. 2004 Cohort, 199 Inuit mother-infant pairs (Canada, Nunavik)	Maternal serum DDE (quartiles, ng/g lipid): Q1: <183 Q2: 183–281 Q3: 281–472 Q4: >472	Gastrointestinal infections at 6 or 12 months	↔

Table 2-4. Summary of Studies of Associations between DDT Exposure Biometrics and Gastrointestinal Endpoints[a]

Reference, study type, and population	Biomarker[b]			Outcome evaluated	Result
Cupul-Uicab et al. 2017	Maternal serum DDT metrics (median (IQR), ng/g lipid):			Mother-reported bouts of diarrhea over first 2 years	
Cohort, 747 mother-son pairs, including 448 urban and 299 rural families (Mexico)		DDT	DDE		
	All:	0.27 (0.67)	2.70 (4.50)	All	↔ (DDT, DDE)
	Urban:	0.19 (0.29)	2.21 (2.90)	Urban	↑ (DDE)
	Rural:	0.66 (1.48)	4.27 (6.95)		↔ (DDT)
				Rural	↔ (DDT, DDE)

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified.

↑ = positive association; ↓ = inverse association; ↔ = no association; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; IQR = interquartile range; Q = quartile

A study of 5,698 individuals from six cohorts in the Faroes Island reported an increased risk of inflammatory bowel disease (IBD) with increased blood DDT levels, but not DDE levels (Hammer et al. 2019). Results of this study are difficult to interpret due to the lack of adjustment for confounders (particularly other chemical exposures) in the statistical analysis. This specific population, which eats large quantities of fish and marine mammals, was evaluated due to the highest incidence of IBD in the world (81.5 per 100,000) and relatively high DDT and DDE levels (geometric means of 64 and 1,062 ng/g lipid, respectively).

Evidence of Gastrointestinal Effects of DDT, DDD, or DDE in Animals. No evaluation of gastrointestinal effects following acute or intermediate oral exposure studies have been reported.

In chronic-duration studies, no significant chemical-related adverse effects on the gastrointestinal system were observed in Osborne-Mendel rats treated for up to 78 weeks in the diet with up to 45 mg technical DDT/kg/day, 59 mg *p,p'*-DDE/kg/day, or 231 mg technical DDD/kg/day or in B6C3F1 mice treated with up to 30.2 mg technical DDT/kg/day, 49 mg *p,p'*-DDE/kg/day, or 142 mg technical DDD/kg/day (NCI 1978).

2.7 HEMATOLOGICAL

Evidence of Hematological Effects of DDT, DDD, or DDE in Humans. Epidemiological studies evaluating associations between hematological effects and DDT exposure biometrics are limited (Table 2-5). A Brazilian study of adults with markedly high levels of serum DDE (>10-fold higher than the general population) found no significant associations between serum DDE levels and risks for abnormal distributions of various blood cell types (Freire et al. 2015a, 2015b). Analysis of a general population NHANES cohort (2003–2004) found associations between serum DDT levels and increased number of lymphocytes and decreased number of segmented neutrophils (Serdar et al. 2014).

Table 2-5. Summary of Studies of Associations between DDT Exposure Biometrics and Hematological Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Freire et al. 2015a, 2015b Cross-sectional, 847 adults (415 males, 432 females) (Brazil)	Serum DDE (median (range), ug/g lipid): 1.80 (<LOD–136.5)	Anemia	↔
		Leukopenia	↔
		Leukocytosis	↔
		Neutropenia	↔
		Neutrophilia	↔
		Eosinophilia	↔
		Thrombocytopenia	↔
Serdar et al. 2014 Cross-sectional, 1,954 individuals (ages 12+ years), NHANES 2003–2004 (United States)	Serum DDT metrics (ng/g lipid)[c] DDT DDE 12–20 years: 3.1 105 21–40 years: 4.4 135 41–60 years: 5.5 305 >60 years: 7.3 570	Lymphocyte number	↑ (DDT) ↔ (DDE)
		Segmented neutrophils number	↓ (DDT)

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified.
[c]Estimated from graphically presented data using GrabIt! Software; study did not indicate if reported values represented means or medians.

↑ = positive association; ↓ = inverse association; ↔ = no association; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; LOE = limit of detection; NHANES = National Health and Nutrition Examination Survey

In a controlled exposure study, 51 male volunteers were exposed to 0.05–0.063 or 0.36–0.5 mg DDT/kg/day for 12–18 months (Hayes et al. 1956). Although some variation among individuals was noted for hemoglobin levels, red and white blood cell counts, and percentage of polymorphonuclear leukocytes, these variations did not correlate with increased dosage of DDT or with duration of exposure.

In a case-control study of patients with chronic debilitating fatigue, lasting at least 6 months, the mean concentration of *p,p'*-DDE in blood serum was significantly higher in case subjects (11.9 ppb; n=14) than in controls (5.2 ppb; n=23) (Dunstan et al. 1996). When the 37 subjects were pooled and then re-divided according to high serum DDE (>6 ppb) and low serum DDE (<6 ppb), the red blood cell distribution width (variation in erythrocyte cell width change) was significantly greater in the high-DDE group than in the low-DDE group; however, the changes were within the range of normal clinical values. No other differences were seen in other hematological parameters.

Evidence of Hematological Effects of DDT, DDD, or DDE in Animals. There is little evidence that hematological parameters are sensitive targets for DDT, DDE, or DDD toxicity.

Some evidence for microcytic anemia has been reported in rats fed *p,p'*-DDT in the diet at 19.1 mg/kg/day (highest dose tested) for 13 or 26 weeks and doses ≥1.7 mg/kg/day for 78 weeks (Tomita et al. 2013). The changes in hematocrit, hemoglobin, and red blood cell counts were small (approximately 3% lower than controls), but statistically significant. The magnitude of these decreases did not markedly change with longer durations of exposure and some were not significant at all time points. Additionally, no significant effects were observed after exposure for 104 weeks. When exposure was only for 2 weeks, anemic changes were not observed. However, small (<5%), statistically significant decreases were found at 50 mg/kg/day (highest dose tested), compared with control, including decreased hemoglobin content of reticulocytes, mature erythrocytes, and transferrin saturation (in the absence of altered plasma iron levels). There was, however, a marked increase in unsaturated iron binding capacity (115% increase at 50 mg/kg/day) and total iron binding capacity (5 and 53% at 5 and 50 mg/kg/day, respectively) after a 2-week exposure (Tomita et al. 2013).

In other intermediate- to chronic-duration studies, rats exposed to commercial DDT at 20 mg/kg/day for 27 months had congestion and hemolysis of the spleen (Deichmann et al. 1967). No hematological changes were observed in squirrel monkeys exposed orally to doses of 0.05–50 mg *p,p'*-DDT/kg/day for up to 6 months; however, all monkeys in the highest dose group (six animals) died by week 14 (Cranmer et al. 1972); the cause of death was not determined.

Cameron and Burgess (1945) exposed rats, guinea pigs, and rabbits to acute-duration dermal doses ranging from 50 to 200 mg technical DDT/kg. A decrease in hemoglobin and leukocytosis was reported.

Mechanisms of Hematological Effects of DDT, DDD, or DDE. Due to the lack of strong evidence that DDT exposure is associated with consistent hematological effects, mechanistic investigations are limited. Tomita et al. (2013) hypothesized that microcytic anemia from repeated dietary DDT exposure in rats may be due to impaired iron utility.

Several *in vitro* incubation studies indicated that DDT isomers can induce apoptosis in multiple blood cell-types including human primary peripheral blood mononuclear cells (PBMCs) (Alegria-Torres et al. 2009; Perez-Maldonado et al. 2004, 2005, 2006). In a preliminary study, exposed children in Chiapas, Mexico, had an increased percentage of PBMC apoptotic cells compared to a non-exposed group of controls (Perez-Maldonado et al. 2004). In a follow-up study with more participants, significant correlations between DDT or DDE exposure and DNA damage were reported; however, no significant associations between DDT or DDE exposure and oxidative DNA damage were observed (Perez-Maldonado et al. 2011). A correlation between DDE exposure and PBMC apoptosis was also reported.

2.8 MUSCULOSKELETAL

Evidence of Musculoskeletal Effects of DDT, DDD, or DDE in Humans. Inconsistent evidence is provided by a limited number of epidemiological studies for associations between serum levels of DDT, DDD, or DDE and bone mineral density in men (Glynn et al. 2000; Wallin et al. 2005) (Table 2-6) and peri- or post-menopausal women (Beard et al. 2000; Bohannon et al. 2000; Rignell-Hydbom et al. 2009a; Wallin et al. 2005) (Table 2-6). No clear evidence for associations with DDE serum levels were found in two studies of Swedish men (Glynn et al. 2000; Wallin et al. 2005), despite the known anti-androgenic effects of DDT and the association between androgen deprivation and bone loss and osteoporosis in men (Taylor et al. 2009). In studies of post-menopausal women, a significant association with decreased bone mineral density was found in one study (Beard et al. 2000), another study found an association with increased bone mineral density (Rignell-Hydbom et al. 2009a), and two studies found no associations with bone mineral density (Bohannon et al. 2000; Wallin et al. 2005).

Table 2-6. Summary of Studies of Associations between DDT Exposure Biometrics and Musculoskeletal Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Beard et al. 2000 Cross-sectional, 68 sedentary women (Australia)	Serum DDE (median (range), ppb): 3.9 (<LOD–44.8)	Bone mineral density	↓
Bohannon et al. 2000 Cross-sectional, 103 peri- and post-menopausal women, 50 black, 53 white (United States)	Serum DDE (mean±SD; ng/mL) Blacks: 13.9±10 Whites: 8.4±6	Bone mineral density (baseline/rate of change) in lumbar spine and radius: Whites Blacks All	 ↔ ↔ ↔
Glynn et al. 2000 Cross-sectional, 115 men (Sweden)	Serum DDT metrics (mean±SD, ng/g lipid) DDE: 738.8±684.8 DDT: 19.8±13.5 DDD: 2.8±2	Bone mineral density (femoral, lumbar spine, whole body)	↔
		Ultrasound bone endpoints (BUA and SOS)	↓ (DDE)
Rignell-Hydbom et al. 2009a Cross-sectional, 908 women (Sweden)	Serum DDE (median (5^{th}–95^{th} percentiles, ng/mL) Low BMD: 4.6 (0.77–17) Medium BMD: 4.6 (1.4–19) High BMD: 5.4 (1.5–18)	Osteocalcin	↔
		Bone mineral density	↑
Wallin et al. 2005 Cross-sectional, 196 men and 184 women (Sweden)	Serum DDE (median (5^{th}–95^{th} percentiles), ng/g lipid) Men: 580 (110, 2,140) Women: 600 (110, 2,310)	Bone mineral density Men Women	 ↔ ↔

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified, DDD = *p,p'*-DDD, unless otherwise specified.

↑ = positive association; ↓ = inverse association; ↔ = no association; BMD = bone mineral density; BUA = broad-band attenuation; DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; LOD = limit of detection; SD = standard deviation; SOS = speed of sound in os calcis

Evidence of Musculoskeletal Effects of DDT, DDD, or DDE in Animals. Limited information exists from studies in animals. In chronic-duration oral exposure studies, no significant chemical-related adverse musculoskeletal effects were observed in Osborne-Mendel rats treated in the diet with up to 45 mg technical DDT/kg/day, 59 mg *p,p'*-DDE/kg/day, or 231 mg technical DDD/kg/day, or in B6C3F1 mice treated with up to 30.2 mg technical DDT/kg/day, 49 mg *p,p'*-DDE/kg/day, or 142 mg technical

DDD/kg/day (NCI 1978). Fisher 344 rats treated for 104 weeks to 19.1 mg/kg/day DDT showed no histopathology of the femur and sternum (Tomita et al. 2013).

2.9 HEPATIC

Evidence of Hepatic Effects of DDT, DDT, or DDE in Humans. Inconsistent evidence is provided by four studies examining serum or cord blood levels of DDT or DDE and serum or urinary markers of liver damage or dysfunction (Table 2-7). No clearly significant associations were found with serum enzymes or chemicals indicative of liver damage (e.g., increased AST, ALT, or bilirubin) in subjects residing in a heavily contaminated region in Brazil (Freire et al. 2015a, 2015b) or in U.S. workers exposed to pesticides and monitored between 1969 and 1973 (Morgan and Lin 1978), but an analysis of NHANES data from 2003 to 2004 reported increased adjusted mean serum levels of ALT, gamma-glutamyl transferase (GGT), AST, and bilirubin in higher exposure quartiles, compared with the lowest exposure quartile (Serdar et al. 2014; see Table 2-7); however, the changes do not appear to be dose-related. Significant associations between cord blood DDE or DDT levels and urinary levels of total porphyrins, coproporphyrin I, and coproporphyrin III (indicators of altered hepatic heme synthesis in the liver) were reported in a group of 52 4-year-old children from Ribera D'Ebre Spain (Sunyer et al. 2008).

Table 2-7. Summary of Studies of Associations between DDT Exposure Biometrics and Hepatic Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Freire et al. 2015a, 2015b Cross-sectional, 847 adults (415 men, 432 women) (Brazil)	Serum DDE (median (range), ug/g lipid): All: 1.80 (<LOD–136.5) Men: 1.72 (<LOD–136.5) Women: 1.95 (<LOD–89.94)	Serum bilirubin (indirect)	↑ (women only)
		Serum bilirubin (total and direct)	↔
		Serum AST	↔
		Serum ALT	↔
		Serum GGT	↔
La Merrill et al. 2019 Cross-sectional, 147 Asian Indian adults, 45–84 years old (United States, California)	Plasma DDT metrics (median (range), ng/g lipid) DDE: 1,850 (85.1–27,900) DDT: 44.8 (8.67–2,880) *o,p'*-DDE: 1.70 (0.500–8.90) *o,p'*-DDT: 4.20 (<0.810–209)	Fatty liver	↑ (ΣDDT)

Table 2-7. Summary of Studies of Associations between DDT Exposure Biometrics and Hepatic Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Morgan and Lin 1978 Cross-sectional, 2,620 male pesticide-exposed workers and 1,049 unexposed controls (United States)	Serum DDT metrics (median, ppb) DDE DDT Control: 32 4.5 Possibly exposed: 34 5.2 Pest control operators: 33 5.8 Ag-chemical handlers: 41 6.5	Serum AP	↑ (weak)
		Serum AST	↔
		Serum ALT	↔
		Serum LDH	↑ (weak)
Serdar et al. 2014 Cross-sectional, 1,954 individuals (ages 12+) (United States; NHANES 2003–2004)	Serum DDT metrics (ng/g lipid)[c] DDT DDE 12–20 years: 3.1 105 21–40 years: 4.4 135 41–60 years: 5.5 305 >60 years: 7.3 570	Serum ALT Q3, Q4 Q2–Q4	 ↑ (DDE) ↑ (DDT)
		Serum GGT (Q2) (Q2, Q3)	 ↑ (DDE) ↑ (DDT)
		Serum AST	↑ (DDT)
		Serum total bilirubin Q3, Q4	↑ (DDE)
Sunyer et al. 2008 Cross-sectional, 52 4-year-old children (Spain)	Serum DDT metrics (IQR, ng/mL) DDE: 0.39-1.32 DDT: <LOD	Urinary porphyrins: Total Uroporphyrin I Coproporphyrin I Coproporphyrin III	 ↑ (DDE, DDT) ↔ ↑ (DDE, DDT) ↑ (DDE, DDT)

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified.
[c]Estimated from graphically presented data using GrabIt! software

↑ = positive association; ↓ = inverse association; ↔ = no association; AP = alkaline phosphatase; AST = aspartate amino transferase (formerly known as glutamic oxaloacetic transaminase); ALT = alanine aminotransferase (formerly known as glutamic pyruvic transaminase); DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; GGT = gamma-glutamyl transferase; IQR = interquartile range; LDH = lactate dehydrogenase; LOD = limit of detection; NHANES = National Health and Nutrition Examination Survey; Q = quartile

In a cross-sectional study, the odds of fatty liver were increased in Asian Indian adults with increased levels of plasma DDT and metabolites (La Merrill et al. 2019) (see Table 2-7). Studies of workers involved in the manufacture and formulation of DDT for many years found no evidence of hepatotoxicity, hepatic enlargement, or dysfunction (as measured by the bromsulphalein test, also known as sulfobromophthalein sodium) in one group (Laws et al. 1973) or hepatic metabolism of phenylbutazone or cortisol in another group (Poland et al. 1970).

In a single controlled-exposure study, Hayes et al. (1956) exposed 51 male volunteers to about 0.05–0.063 or 0.36–0.5 mg DDT/kg/day administered via a capsule for 12–18 months. The background dose

from concentration measured in food of both controls and test subjects was 0.0021–0.0038 mg DDT/kg/day. No signs of illness or adverse hepatic effects (as measured by liver function tests) reported were considered to be related to DDT exposure to humans.

Evidence of Hepatic Effects of DDT, DDD, or DDE in Animals. In animals, the liver appears to be one of the primary targets of toxicity for DDT and related compounds. Acute-, intermediate-, and chronic-duration oral exposures have been shown to cause dose-related mild-to-severe hepatic effects in numerous animal studies, with chronic exposure leading to the development of liver tumors in some animals (see Section 2.19). After acute oral exposure to technical DDT or unspecified DDT, *p,p'*-DDT, *p,p'*-DDE or unspecified DDE, or unspecified DDD, a number of liver effects in animals 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), changes in the appearance of the liver, and necrosis. Increased liver activities of various microsomal enzymes (e.g., CYP2B, CYP2B1, CYP3A1, CYP3A2, GGT, glutathione-S-transferase) have been observed after acute-duration oral exposure in rats given 200 mg *p,p'*-DDT/kg (Garcia and Mourelle 1984). Increases in relative liver weights >10% were observed in rats given 5–50 mg *p,p'*-DDT/kg/day for up to 14 days (Tomiyama et al. 2004); rats given 40 mg DDT/kg/day for 12 days (de Waziers and Azais 1987); rats given ≥4.2 mg DDT/kg/day, but not 0.17 mg/kg/day, for 14 days (Nims et al. 1998); and mice given 42.9 mg DDT(NS) or DDE(NS)/kg/day for 1 week, but not 42.9 mg DDD(NS)/kg/day (Pasha 1981). Increased liver weight was also reported in rats given 25 mg *p,p'*-DDE/kg/day for 4 days (Leavens et al. 2002) or 10 days (Kang et al. 2004), and rats given 106 mg *p,p'*-DDT/kg once or for 7 days (Tomiyama et al. 2003). Rhesus monkeys exposed once to 150 mg *p,p'*-DDT/kg had increased alkaline phosphatase (AP), lactate dehydrogenase (LDH), AST, and ALT activities in serum, indicative of liver damage (Agarwal et al. 1978). Necrotic liver changes, accompanied with increased liver weight, were observed in rats exposed to 12 mg *p,p'*-DDT/kg/day for 14 days (Kostka et al. 2000).

After intermediate-duration exposure to technical DDT, *p,p'*-DDT, or *p,p'*-DDE, an array of liver effects, similar to those observed after acute-duration exposure, have been observed in rats and mice. The lowest reliable intermediate-duration LOAEL for liver effects is 0.17 mg technical DDT/kg/day in the diet based on cellular hypertrophy observed in F344/DuCrj rats exposed for 26 weeks (Harada et al. 2003, 2006). Observations of liver effects include increased liver weight and induction of CYP enzymes in Wistar rats exposed by gavage to 15 mg *p,p'*-DDT/kg/day for 3 weeks (Gupta et al. 1989) and NMRI mice exposed to 6.25 mg *p,p'*-DDT/kg/day for 28 days (Orberg and Lundberg 1974); hepatic focal necrosis and regeneration in Sprague-Dawley rats exposed to 6.6 mg DDT/kg/day in the diet for 36 weeks (Jonsson et

al. 1981); minor vacuolation, hypertrophy and cell margination in livers of Sherman rats exposed to technical DDT in food for 2–18 months at 5 mg/kg/day in males and 20 mg/kg/day in females (Ortega 1956); increased relative liver weight (20% increase compared with control) in Sprague-Dawley rat dams exposed by gavage to 50 mg *p,p'*-DDE/kg/day (but not 15 mg/kg/day) between GD 6 and PND 20 (Yamasaki et al. 2009); centrilobular hypertrophy, fatty hepatocytes, and increased liver weight in F1 and F2 Sprague-Dawley rats exposed to 3.44 (males) or 3.75 (females) mg *p,p'*-DDT/kg/day in the diet in a 2-generation reproductive toxicity study (NOAELs of 0.34 and 0.73 mg/kg/day), and enlarged and darkened livers in F0 rats at 25 (males) or 27.7 (females) mg/kg/day, but not at 3.44 or 3.75 mg/kg/day (Hojo et al. 2006); and increased absolute and relative liver weight and liver levels of CYP2B1 and decreased levels of liver GJIC protein in male F344/DuCrj rats exposed to ≥5 mg *p,p'*-DDT/kg/day for 28 days (Harada et al. 2003, 2006; Tomiyama et al. 2004). Cellular hypertrophy and cytoplasmic eosinophilia were also reported in livers of Osborne-Mendel rats exposed to 0.25 mg technical DDT/kg/day (but not 0.05 mg/kg/day) in the diet for 15–27 weeks (Laug et al. 1950). Laug et al. (1950) however, 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." It is unknown, therefore, whether hepatic changes at this level would have reached statistical significance; the LOAEL for this study was therefore considered to be unreliable. Minor microscopic changes in hepatocytes (cytoplasmic vacuolation, mitochondrial changes, and lipid droplets) were described in male C57BL/6N mice treated by gavage with *p,p'*-DDT for 8 weeks, but only qualitative data were provided (Liu et al. 2017a, 2017b). No exposure-related changes in liver weight, liver histology, or serum levels of AST and ALT were reported in immature, prepubertal F344/DuCrl male rats exposed to 10 mg *p,p'*-DDE/kg/day in the diet for 42 days (Makita et al. 2003a).

Nonneoplastic liver lesions, and in some cases liver tumors, have been observed in rats, mice, hamsters, monkeys, and dogs after chronic oral exposure to DDT and related compounds. LSEs in the liver from chronic oral exposure are summarized in Table 2-1 and Figure 2-2, and the following three paragraphs, which first present the results for rats, followed by results for mice and then other laboratory animal species.

Chronic-duration exposure to DDT and related compounds has been associated with liver necrosis, centrilobular hypertrophy, hyperplasia, and fatty metamorphosis in rats (Deichmann et al. 1967; Fitzhugh and Nelson 1947; Harada et al. 2003, 2006; NCI 1978), including effects in F1 males and females in a 2-generation study (Hojo et al. 2006). In rats, the lowest reliable chronic-duration LOAELs for nonneoplastic histological changes in the liver are 0.17 mg *p,p'*-DDT/kg/day for hepatocellular

hypertrophy in male F344/DuCrj rats exposed in the diet for 2 years (the lowest dose tested by Harada et al. 2003, 2006) and 7 mg technical DDT/kg/day for focal hepatocellular necrosis in Osborne-Mendel rats exposed in the diet for 2 years (the lowest dose tested by Fitzhugh and Nelson 1947) (see Table 2-1 and Figure 2-2). Similar to intermediate exposure durations, increased CYP-450 content and microsomal activities and decreased GJIC protein Cx32 were observed in rats (Harada et al. 2003, 2006), as well as indicators of oxidative stress including increased lipid peroxide at ≥1.7 mg/kg/day, and 8-hydroxydeoxy-guanosine (8-OHdG) levels at 19.1 mg *p,p'*-DDT/kg/day in males (Harada et al. 2003, 2006). Increased incidences of liver tumors have been reported in rats (see Section 2.19).

Noncancer liver effects have been less consistently observed in chronically exposed mice. Liver effects in B6C3F1 mice exposed for 78 weeks were restricted to amyloidosis at dietary doses ≥3.7 mg technical DDT/kg/day (NCI 1978); however, NOAELs for noncancer liver histological changes of 49 mg *p,p'*-DDE/kg/day and 142 mg technical DDD/kg/day were reported for mice exposed for 78 weeks (NCI 1978). Increased incidences of liver tumors have been observed in mice (see Section 2.19).

Nonneoplastic changes in the liver have also been reported in monkeys, hamsters, and dogs chronically exposed to DDT and related compounds. In Rhesus and Cynomolgus monkeys exposed to *p,p'*-DDT in the diet for up to 130 months, fatty changes in the liver were observed at doses as low as 6.4 mg *p,p'*-DDT/kg/day (Takayama et al. 1999), mild to severe hydropic changes in liver cells, assessed by periodic biopsies, occurred in two of three Rhesus monkeys, but no functional liver changes, assessed by bromosulfalein retention, were observed when exposed to 3.9 mg technical DDT/kg/day in the diet for 3.5–7 years (Durham et al. 1963). Reported nonneoplastic liver effects in hamsters include focal necrosis after lifetime dietary exposure to 40, but not 20, mg technical DDT/kg/day (Cabral et al. 1982a); increased relative liver weight (with no increase in serum ALT, lactate dehydrogenase [LDH], or AP) after exposure to 67–133 mg technical DDT/kg/day in the diet for life (Graillot et al. 1975), and liver necrosis after 128-week dietary exposure to 47.5 mg *p,p'*-DDE/kg/day (Rossi et al. 1983). Rossi et al. (1983) also observed increased incidences of liver tumors at levels ≥47.5 mg *p,p'*-DDE/kg/day, but increased incidences of liver tumors were not observed in the other hamster chronic-duration studies. In dogs given technical DDT in the diet for 39–40 months, focal or diffuse liver changes occurred at 80 mg/kg/day and severe liver damage at 160 mg/kg/day; no liver changes were seen at 16 mg/kg/day (Lehman 1965).

Cameron and Burgess (1945) exposed rats, rabbits, and guinea pigs to acute-duration dermal doses of 10, 50, or 100 mg DDT/kg and reported fatty degeneration, calcification, and necrosis of the liver.

Mechanisms of Hepatic Effects of DDT, DDD, or DDE. DDT is considered to be an animal liver carcinogen with a nongenotoxic mitogenic mechanism of action (see Section 2.19). Studies in animals indicate that initial inductions of microsomal liver xenobiotic metabolizing enzymes (e.g., CYP monooxygenases) and transient bursts in DNA synthesis and cell proliferation are key initial hepatic responses to DDT exposure (Harada et al. 2003, 2006). Increased liver weights, particularly in acutely exposed animals, likely reflects this increased mitogenic, proliferative activity. Although cell proliferation generally ceases within days, it has been hypothesized that these initiated cells may contribute to the generation of eosinophilic abnormal hepatic foci (AHF) whose number and size correlate with dose and time of exposure (Harada et al. 2003). An observed decrease in the GJIC protein Cx32, which plays an important role in cell-cell communication, may contribute to the isolation of AHF cells from growth regulatory signals from neighboring cells (Harada et al. 2003). Additionally, increases in 8-OHdG and LPO are indicative of hepatic oxidative stress and damage to DNA, which may contribute to liver nonneoplastic changes and eventual tumor formation.

In *in vitro* studies, increased oxidative stress and reactive oxygen species (ROS) due to DDT exposure in Hep2 cells is thought to activate the Jak/STAT3 pathway, ultimately resulting in impaired expression of E-cadherin; loss of this adhesion molecule is associated with hepatocellular carcinogenesis and poor prognosis in humans (Nakagawa et al. 2014). The induction of microsomal liver xenobiotic metabolizing enzymes may be involved in proliferation of smooth-surfaced endoplasmic reticulum that are observed with longer durations of exposure, contributing to hypertrophy (Harada et al. 2006). In addition to CYP induction, DDT has been shown to activate both the constitutive androgen receptor (*CAR*) and *ERα* transcription factors, which increase transcription of target genes related to hepatocyte proliferation, cell-cycle progression, and apoptosis inhibition in the mouse liver (Kazantseva et al. 2013). Several animal and *in vitro* studies have demonstrated activation of microsomal enzymes in response to DDT-isomer exposure, presumably through activation of the *CAR* (Harada et al. 2016). Aberrant expression of genes within these functional categories were observed in micro-dissected tissues including hypertrophic tissue, eosinophilic AHF, and tumors in rats, from DDT-treated animals versus controls (Harada et al. 2016). *In vitro* studies in isolated hepatocytes also showed increases in expression of genes associated with hepatic estrogen, lipid, and sugar metabolism (Jellali et al. 2018).

2.10 RENAL

Evidence of Renal Effects of DDT, DDD, or DDE in Humans. In a case-control study of 270 chronic kidney disease patients and 270 age- and sex-matched controls from a hospital in Delhi India, serum levels of DDE, but not DDT, were significantly associated with risk for chronic kidney disease (Siddarth et al. 2014). However, no association was found once adjusted for serum levels of other pesticides including endosulfan, dieldrin, aldrin, and hexachlorocyclohexanes and glutathione-S-transferase (GST) genotype. In a prospective cohort study of 1,016 elderly Swedish adults aged 70–80 years, age-related decline in glomerular filtration was significantly greater in subjects with serum DDT levels in the third tertile, compared to the first (Jayasinghe et al. 2018).

No other epidemiological studies were located that examined possible associations between serum levels of DDT, DDD, or DDE and kidney outcomes.

Evidence of Renal Effects of DDT, DDD, or DDE in Laboratory Animals. Limited evidence is available for kidney effects in laboratory animals after acute- or intermediate-duration oral exposure to DDT and related compounds. In a two-generation study of Wistar rats exposed to *p,p'*-DDT in the diet before mating and during mating, gestation, and lactation, increased kidney weight was observed in F0 parental and F1 female rats at 25 mg/kg/day, but not at 3.44 mg/kg/day (Hojo et al. 2006). No significant changes in kidney weight or serum levels of creatinine or urea nitrogen were found in sexually immature male Wistar rats (6 weeks old) fed 10 mg *p,p'*-DDE/kg/day in the diet for 42 days (Makita et al. 2003a). Significant decreases (~36%) in kidney weights were observed in the offspring of pregnant rabbits given gavage doses of 1 mg DDT(NS)/kg/day on GDs 4–7 (Fabro et al. 1984). No significant changes in kidney weights were observed in Sprague-Dawley offspring, or their dams, exposed during GD 6–PND 20 to up to 50 mg *p,p'*-DDE/kg/day (Yamasaki et al. 2009), or in male rat offspring exposed during GDs 14–18 and then on PNDs 80–83 to 100 mg *p,p'*-DDE/kg/day (You et al. 1999a); no histological changes were observed in kidneys of offspring from C57BL/6J mouse dams treated with DDT (77.2% *p,p'*-DDT and 22.8% *o,p'*-DDT) during GD 12–PND 5 (La Merrill et al. 2016). No changes to kidney weight were found in castrated male Sprague-Dawley rats (Hershberger Assay) given gavage doses of *p,p'*-DDE up to 100 mg/kg/day for 10 days after castration, compared with control rats (Kang et al. 2004). Histology of the kidney was not examined in this study.

The kidney does not appear to be a sensitive target for histological changes in laboratory animals chronically exposed to DDT and related compounds. Histological kidney lesions were observed in

Osborne-Mendel rats exposed to 20 mg DDT(NS)/kg/day in the diet for up to 27 months (tubular epithelial necrosis and polycystic degeneration; Deichmann et al. 1967) and 66 mg technical DDD/kg/day in the diet for 78 weeks (chronic inflammation; NCI 1978), but no histological changes in the kidney were reported in Osborne-Mendel rats exposed to up to 45 mg technical DDT/kg/day or 59 mg *p,p'*-DDE for 78 weeks (NCI 1978). After 78-week exposures, chronic inflammation of the kidney was observed in male B6C3F1 mice exposed to ≥27 mg *p,p'*-DDE/kg/day, but no histological kidney changes were observed in female B6C3F1 mice exposed to up to 49 mg *p,p'*-DDE/kg/day or male or female B6C3F1 mice exposed to up to 30.2 mg technical DDT/kg/day or 142 mg technical DDD/kg/day (NCI 1978). No histopathological changes in the kidney were noted at 55 weeks of age in ICR mice exposed from conception through death to 16.5 mg/technical-DDT/kg/day (Del Pup et al. 1978).

Cameron and Burgess (1945) exposed rats, rabbits, and guinea pigs to acute-duration dermal doses ranging from 50 to 100 mg DDT/kg and reported fat deposits, tubular changes, calcification, and necrosis of the kidneys.

2.11 DERMAL

Evidence of Dermal Effects of DDT, DDD, or DDE in Humans. No correlation was found between DDT exposure in clinical laboratory workers, via dermal or inhalation routes, and the frequency and distribution of skin abnormalities, except for a few cases of minor skin irritation (Ortelee 1958).

Cameron and Burgess (1945) conducted a series of experiments on volunteers wearing clothing and undergarments impregnated with 1% DDT for 18–26 days in order to determine whether this treatment would protect soldiers against body lice. Several individuals had transient dermatitis, but no other symptoms were observed; however, the investigators did not attribute the dermatitis to DDT exposure.

Evidence of Dermal Effects of DDT, DDD, or DDE in Animals. No studies were located indicating adverse dermal effects in animals after oral exposure to DDT, DDE, or DDD.

Cameron and Burgess (1945) exposed rats, rabbits, and guinea pigs to acute-duration dermal doses of 10, 50, or 100 mg DDT/kg and reported inflammation, edema, and destruction of the epidermis. Guinea pigs were dermally dosed 5 days/week for 3 weeks with 322–400 mg DDT/kg (Kar and Dikshith 1970). A decrease in skin amino acids, disruption and degeneration of the basal cell layer, and morphologic changes in the cells were reported.

2.12 OCULAR

Evidence of Ocular Effects of DDT, DDD, or DDE in Humans. Reports of ocular effects in humans exposed to DDT in the air are limited to the studies by Neal et al. (1944) and Ortelee (1958). In the Neal et al. (1944) study, moderate, nonspecific eye irritation was reported by two volunteers exposed to an aerosol containing DDT. This effect is assumed to have been caused by direct contact of the aerosol with the eye and not by inhalation of the aerosol. The investigators provided limited information on exposure levels, but noted that the DDT quickly settled; thus, the actual exposure levels were lower than predicted. The ocular effects were only observed at the higher of the two tested concentrations. Red, itching, and inflamed eyes and/or excessive tearing was reported in 8 workers involved in the manufacture and/or formulation of DDT and exposed to "heavy" concentrations of dust; DDT air concentrations associated with these effects were not reported (Ortelee 1958). The study examined 40 workers, although DDT exposure was limited for 30 of the workers; it is unclear from the paper whether any of the cases of eye irritation were in the limited exposure group of workers.

Evidence of Ocular Effects of DDT, DDD, or DDE in Animals. Unilateral (11 exposed versus 1 control) and bilateral (9 exposed versus 2 controls) corneal opacity was described in a single study in mice exposed to 13 mg technical-DDT/kg/day in the diet for 80 weeks (Kashyap et al. 1977). In a second oral exposure study, minute darkened areas were observed during the ophthalmologic examination of the retina of 5 of 10 dogs administered capsules containing 50 mg/kg *o,p'*-DDD for 120–147 days; vision did not appear to be affected (Kirk and Jensen 1975). No evidence of vascular or cellular changes were observed during the histologic examination of the retina, and the darkened areas were not evident.

2.13. ENDOCRINE

Reported endocrine effects related to thyroid hormone dysregulation in humans and effects on endocrine-related tissues (pituitary, adrenals, thyroid, parathyroid) in laboratory animals are discussed in this section. Other possible hormonal effects of DDT, DDD, or DDE in humans and laboratory animals are described in Sections 2.14 (immunological effects), 2.15 (neurological effects), 2.16 (reproductive effects), 2.17 (developmental effects), and 2.18 (other noncancer effects).

Thyroid Hormone Dysregulation, Human Studies. Epidemiological studies provide inconsistent evidence for associations between levels of DDT, DDE, or DDD in biological fluids or tissues and changes in serum levels of thyroid hormone levels in humans (Tables 2-8 and 2-9). Table 2-8 describes

summary results from epidemiological studies that examined possible associations between DDT exposure biometrics in adolescents or adults and changes in serum levels of thyroid hormones (thyroid stimulating hormone [TSH]; triiodothyronine [T3]; thyroxine [T4]). An additional study in Table 2-8 only examined a possible association between serum DDE levels and serum levels for thyroid peroxidase antibody, TPOAb (Schell et al. 2009). Table 2-9 describes results from epidemiological studies looking for associations between maternal serum, cord blood, or breast milk DDT exposure metrics and levels of thyroid hormones in offspring.

Table 2-8. Summary of Studies of Associations Between DDT Exposure Biometrics in Adolescents or Adults and Serum Thyroid Hormone Levels[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Abdelouahab et al. 2008 Cross-sectional, 211 adults, (124 males, 87 females); mean age 49.2 years (Canada)	Serum DDE (IQR, ng/g lipid) Men: 139–387 Women: 157–459	TT3	↔ (men) ↓ (women)
		TT4	↔ (men) ↔ (women)
		TSH	↑ (men) ↔ (women)
Alvarez-Pedrerol et al. 2009 Cross-sectional, 1,090 pregnant women from two regions (Spain, Sabadell and Gipuzkoa)	Serum DDE (IQR, ng/g lipid) Sabadell: 69.8–174.8 Gipuzkoa: 59.9–139.4 Serum DDT <LOD	TSH	↔
		TT3	↔
		fT4	↔
Alvarez-Pedrerol et al. 2008 Cross-sectional, 259 children, 4 years of age (Spain)	Serum DDT metrics (quartile ranges, ng/mL) DDE / DDT Q2 0.436–0.807 / 0.026–0.049 Q3 0.808–1.75 / 0.050–0.103 Q4 1.76–43.9 / 0.104–0.657	TT3 Q2 versus Q1 Q3 versus Q1 Q4 versus Q1 Overall	 ↓ (DDT) ↔ (DDE) ↓ (DDT) ↔ (DDE) ↔ (DDT) ↔ (DDE) ↓ (DDT) ↔ (DDE)
		fT4	↔ (DDE) ↔ (DDT)
		TSH	↔ (DDE) ↔ (DDT)

Table 2-8. Summary of Studies of Associations Between DDT Exposure Biometrics in Adolescents or Adults and Serum Thyroid Hormone Levels[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Blanco-Muñoz et al. 2016 Cohort, 84 male floriculture workers, blood sampled during rainy season with high pesticide use (July–October 2004) and dry season with lower pesticide use (December 2004–May 2005) (Mexico)	Serum DDE (tertiles, ng/mL) Tertile 1: <0.37 Tertile 2: 0.37–7.96 Tertile 3: >7.96	TT3 Overall Tertile 2 versus 1 Tertile 3 versus 1	 ↔ ↔ ↑
		TT4 Overall Tertile 2 versus 1 Tertile 3 versus 1	 ↑ ↔ ↑
		TSH	↔
Bloom et al. 2014 Cross-sectional, 114 adults (66 males, 48 females), mean age 63.2 years (United States, New York)	Serum ΣDDT (DDE + DDT) (mean±SD, ng/mL) Men: 4.50±4.14 Women: 3.59±2.99	TSH	↔ (men) ↔ (women)
		fT4	↔ (men) ↔ (women)
		TT4	↔ (men) ↑ (women)
		TT3	↔ (men) ↑ (women)
Chevrier et al. 2008 Cross-sectional, 334 pregnant women ≥18 years old (United States, California)	Serum DDT metrics at 26 weeks gestation or before delivery (GM (95% CI), ng/g lipid): DDE: 1,302.1 (1,140.2–1,487.0) DDT: 18.8 (15.7–22.5) *o,p'*-DDT: 1.7 (1.5–2.0)	TSH	↔
		TT3	↔
		fT4	↔
		TT4	↔
Croes et al. 2015 Cross-sectional, 1,889 adolescents from two cohorts, 14–15 years old; FLEHS I cohort (n=1,679) and FLEHS-II cohort (n=210) (Belgium)	Serum DDE (GM (95% CI), ng/g lipid): FLEHS I: 94 (89–99) FLEHS II: 70 (63–78)	TSH	↔
		fT3	↔
		fT4	↑
Dallaire et al. 2009 Cross-sectional, 623 Inuit adults, mean age 36.8 years (Canada, Nunavik)	Serum DDE (GM (95% CI), ng/g lipid): 477.78 (441.70–516.81)	TSH	↔
		TT3	↔
		fT4	↔
Freire et al. 2012 Cross-sectional, 193 children, mean age 6.5 years (Brazil)	Serum DDT metrics (20th–80th percentile, ng/mL): *o,p'*-DDT: <LOD–2.20 DDT: 1.14–17.7 DDD: 0.25–2.63 DDE: 2.03–35.7	TSH	↔ (all DDT metrics)
		TT3	↑ (all DDT metrics)
		fT4	↑ (DDD) ↔ (*o,p'*-DDT, DDT, DDE)

Table 2-8. Summary of Studies of Associations Between DDT Exposure Biometrics in Adolescents or Adults and Serum Thyroid Hormone Levels[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Freire et al. 2013 Cross-sectional, 608 adults (303 males, 305 females) (Brazil)	Serum DDT metrics (IQR, ng/mL): Men / Women DDE 2.86–21.9 / 3.45– 28.9 *o,p'*-DDT <LOD–0.89 / <LOD–1.10 DDT 0.94–6.96 / 1.03–7.59 DDD 0.19–1.34 / 0.21–1.41	TSH Male and female	↔ (all DDT metrics)
		TT3 Male Female	↔ (all DDT metrics) ↑ (DDE) ↔ (*o,p'*-DDT DDD, DDT)
		fT4 Female Male	↑ (DDT) ↑ (*o,p'*-DDT) ↔ (DDD, DDE) ↓ (DDT) ↔ (*o,p'*-DDT DDD, DDE)
Hagmar et al. 2001 Cross-sectional, 110 men, 23–79 years old (Latvia, Sweden)	Plasma DDT metrics (percentiles, ng/g lipid) DDE / DDT 10th 197 / 10 50th 828 / 50 90th 3,152 / 185	TSH	↔
		TT3	↔
		fT3	↔
		TT4	↔
		fT4	↔
Kim et al. 2013 Cross-sectional, 105 pregnant women, mean age 33 years (Korea)	Serum DDT metrics before delivery (IQR, ng/g lipid): DDE: 38.85–78.87 DDT: 2.94–8.99 ΣDDT: 42.15–92.35	TSH	↔
		TT3	↔ (DDE) ↔ (DDT) ↓ (ΣDDT)
		fT3	↔ (DDE) ↔ (DDT) ↓ (ΣDDT)
		TT4	↔
		fT4	↔
Lopez-Espinosa et al. 2009 Cross-sectional, 157 pregnant women, mean age 30 years (Spain)	Serum DDE in first trimester (GM±GSD): 1.3±2.3 ng/mL 200±2.3 ng/g lipid	TSH ≥2.5 mIU/L	↔ ↑
		TT3	↔
		fT4	↓
Meeker et al. 2007 Cross-sectional, 341 male partners of subfertile couples, ages 20–54 years (United States, Massachusetts)	Serum DDE (5th–95th percentile,): 0.38–5.94 ng/mL 87.7–1,230 ng/g lipid	TSH	↓
		TT3	↑
		fT4	↑

Table 2-8. Summary of Studies of Associations Between DDT Exposure Biometrics in Adolescents or Adults and Serum Thyroid Hormone Levels[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Pelletier et al. 2002 Cohort, 16 obese men in a 15-week weight loss program; DDT metrics and thyroid hormones measured before and after weight loss program (Canada)	Serum DDT metrics (mean±SD, ng/g lipid): Before / After DDE 430±170.5 / 547.2±230.3 DDT 8.4±3.7 / 9.2±3.7	TT3	↔ (DDE) ↔ (DDT)
Rylander et al. 2006 Cross-sectional, 196 fishermen, median age 59 years (Sweden)	Serum DDE (quartiles, ng/g lipid): Q1: 300 Q2: >300–600 Q3: >600–1,100 Q4: >1,100	TSH per 100 ng/g Q2–Q4	 ↑ ↔
		fT3	↔
Schell et al. 2009 Cross-sectional, 115 youth (61 males, 57 females) including 47 breastfed and 68 non-breastfed subjects, median age 17.6 years (United States, Akwesasne Mohawk Nation)	Serum DDE (GM, ng/mL): Breastfed: 0.37 Non-breastfed: 0.28	TPOAb Breastfed Non-breastfed	 ↑ ↔
Takser et al. 2005 Cross-sectional, 101 pregnant women (Canada)	Serum DDT metrics at delivery (5^{th}–95^{th} percentile, ng/mL) DDE: 0.20–1.20 DDT: <LOD–0.07	TSH	↔ (DDE) ↔ (DDT)
		TT3	↔ (DDE) ↓ (DDT)
		fT4	↔ (DDE) ↔ (DDT)
Turyk et al. 2006 Cross-sectional, 56 male adults including 25–29 sport-caught fish eaters and 23–27 referents (United States, Great Lakes region)	Serum DDE (mean (range), ng/g lipid): Fish eaters: 602 (99–9,499) Referents: 290 (43–4,554)	TSH	↔
		TT3	↔
		fT4	↔
		TT4	↓

Table 2-8. Summary of Studies of Associations Between DDT Exposure Biometrics in Adolescents or Adults and Serum Thyroid Hormone Levels[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Turyk et al. 2007 Cross-sectional, 1,761 adults (1,021 men, 740 women), including subjects from NHANES 1999–2000 (454 males, 350 females) and NHANES 2001–2002 (667 males, 490 females) (United States)	Serum DDE (GM (95% CI), ng/mL): 1999–2000 1.82 (1.53–2.17) 2001–2002 2.12 (1.91–2.35) Serum DDE (GM (95% CI), ng/g lipid): 1999–2000 293.0 (248.0–346.1) 2001–2002 337.0 (304.3–373.1)	TSH 1999–2000 2001–2002 TT4 1999–2000 F <60 years F >60 years 2001–2002	 ↔ ↔ ↔ (all M & F) ↑ ↓ ↔ (all M & F)

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified; DDD = *p,p'*-DDD, unless otherwise specified

↑ = positive association; ↓ = inverse association; ↔ = no association; CI = confidence interval; DDD = dichloro-diphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; F = female(s); FLEHS = Flemish Environment and Health studies; fT3 = free triiodothyronine; fT4 = free thyroxine; GM = geometric mean; GSD = geometric standard deviation; IQR = interquartile range; LOD = limit of detection; M = male(s); Q = quartile; SD = standard deviation; TPOAb = thyroid peroxidase antibody; TSH = thyroid stimulating hormone; TT3 = total triiodothyronine; TT4 = total thyroxine

Table 2-9. Summary of Studies of Associations Between Maternal Serum, Cord Blood, or Milk DDT Exposure Metrics and Thyroid-Related Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Arrebola et al. 2016 Cohort, 200 mother-infant pairs (Bolivia)	Cord blood DDT metrics (IQR, ng/mL) DDE: 0.26–2.52 *o,p'*-DDT: 0.10–0.37	TSH (serum)	↔ (DDE) ↔ (*o,p'*-DDT)

Table 2-9. Summary of Studies of Associations Between Maternal Serum, Cord Blood, or Milk DDT Exposure Metrics and Thyroid-Related Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Chevrier et al. 2019 Cross-sectional, 720 mother-infant pairs including 371 male and 349 female infants (South Africa) TSH and T4 measured in newborn blood spot 7–10 days after birth	Maternal serum DDT metrics (IQR, ng/g lipid) DDT: 18.6–261.1 DDE: 92.3–878.3 *o,p'*-DDT: 3.4–22.8 *o,p'*-DDE: 2.3–6.9 *o,p'*-DDE was not included in the analysis	TSH (blood spot) (boys, girls, all)	↔ (DDT) ↔ (DDE) ↔ (*o,p'*-DDT)
		T4 (blood spot) <u>Boys</u> per 10-fold increase	↓ (DDT) ↔ (DDE) ↓ (*o,p'*-DDT)
		<u>Girls and all</u> 10-fold increase	↔ (DDT) ↔ (DDE) ↔ (*o,p'*-DDT)
Darnerud et al. 2010 Cohort, 150 mother-infant pairs (3 weeks) and 115 mother-infant pairs (3 months) (Sweden)	Maternal serum, milk, and infant serum DDE (median (range), ng/g lipid): Maternal serum: 91 (21–622) Milk: 113 (24–649) Infant serum: 95 (21–622) Calculated postnatal exposure levels of DDE (quartiles, ng/g x days) Q1: 0–190 Q2: 191–329 Q3: 330–503 Q4: 504–2,199	TT3, TSH, or fT4 (serum) 3 weeks 3 months Q2–Q4 versus Q1	 ↔ ↔ ↔
de Cock et al. 2017 Cross-sectional, 1,700 mother-child pairs data pooled from 3 studies (FLEHS-I cohort, Belgium; HUMIS cohort, Norway; PCB cohort, Slovakia) TSH measured in newborn blood spot 4-6 days of birth	Cord blood DDE (median (range), ng/L) FLEHS-I: 220 (14–3,740) HUMIS: 49 (7–462) PCB: 1,030 (2–6,652) Pooled: 240 (2–6,652) Pooled DDE (quartiles, ng/L) Q1: <108.43 Q2: 108.43–239.99 Q3: 240–574.49 Q4: ≥574.49	TSH (blood spot) Q2 versus Q1 (pooled) Q3 versus Q1 (pooled) Q4 versus Q1 (pooled)	 ↔ ↓ ↔

Table 2-9. Summary of Studies of Associations Between Maternal Serum, Cord Blood, or Milk DDT Exposure Metrics and Thyroid-Related Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
de Cock et al. 2014 Cohort, 83 mother-infant pairs including 53 male and 31 female children (Netherlands) T4 measured in newborn blood spot 4–7 days of birth	Cord blood and milk DDE (median (range), ng/g lipid) Cord blood: 81.87 (28.83–580.25) Milk: 44.10 (12.11–277.80) Total DDE (cord blood + milk; quartiles, ng/g lipid) Q1: <41.8 Q2: 41.8–74.5 Q3: 74.51–107.5 Q4: >107.5	T4 (blood spot) <u>Boys</u> Q2, Q3 and Q4 <u>Girls</u> Q2 and Q3 Q4	 ↔ ↔ ↑
Freire et al. 2011 Cross-sectional, 220 mother-infant pairs (Spain)	Placental DDT metrics (IQR, ng/g placenta) DDE: 0.84–3.37 DDT: <LOD–0.91 *o,p'*-DDT: <LOD–0.73 *o,p'*-DDD: <LOD–1.86 ΣDDT: 1.99–7.89	TSH ≥5 mU/L (cord blood)	↔ (DDE) ↔ (DDT) ↔ (*o,p'*-DDT) ↔ (*o,p'*-DDD) ↔ (ΣDDT)
Kim et al. 2015d Cohort, 102 mother-infant pairs (Korea) All hormones measured in cord blood; TSH also measured in infant bloodspot within 2 days after birth	Maternal serum and cord blood DDE (IQR, ng/g lipid) Serum: 38.7–73.9 Cord blood: 44.0–91.5	fT3 (cord blood) Cord blood Maternal serum TT3 (cord blood) Cord blood Maternal serum fT4 (cord blood) Cord blood Maternal serum TT4 (cord blood) Cord blood Maternal serum TSH (cord blood) Cord blood Maternal serum TSH (bloodspot) Cord blood Maternal serum	 ↔ ↓ ↓ ↔ ↔ ↓ ↔ ↓ ↔ ↔ ↑ ↑
Li et al. 2014 Cohort, 247 mother-infant pairs (China)	Maternal serum and cord blood DDT metrics (median, ng/g lipid) Maternal / Cord blood DDE: 333.951 / 193.513 DDT: 7.456 / <LOD	TSH (cord blood)	↔ (DDE)

Table 2-9. Summary of Studies of Associations Between Maternal Serum, Cord Blood, or Milk DDT Exposure Metrics and Thyroid-Related Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Lopez-Espinosa et al. 2010 Cross-sectional, 453 mother-infant pairs (Spain)	Cord blood DDT metrics (GM (95% CI), ng/g lipid) DDE: 197 (181–213) DDT: 8.0 (7.0–9.3) Analysis groups (DDE) Group 1: <50th percentile Group 2: ≥50th –90th percentile Group 3: ≥90th percentile	TSH (cord blood) Group 2 versus 1 Group 3 versus 1 10-fold increase	 ↔ (DDT) ↔ (DDE) ↔(DDT) ↔ (DDE) ↔(DDT) ↔ (DDE
Maervoet et al. 2007 Cross-sectional, 198 mother-infant pairs (Belgium)	Cord blood DDE (median (5th–95th percentile), ng/g lipid) 134 (25.3–628)	In cord blood fT3 fT4 TSH	 ↔ ↓ ↔
Ribas-Fito et al. 2003b Cohort, 98 mother-infant pairs (Spain) TSH measured in newborn plasma 3 days after birth	Cord serum DDE (median, ng/mL) 0.85	TSH (plasma) ≥10 mU/L per doubling of DDE	 ↔

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified; DDD = *p,p'*-DDD, unless otherwise specified

↑ = positive association; ↓ = inverse association; ↔ = no association; CI = confidence interval; DDD = dichloro-diphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; FLEHS = Flemish Environment and Health Studies; fT3 = free triiodothyronine; fT4 = free thyroxine; GM = geometric mean; HUMIS = Norwegian Human Milk Study; IQR = interquartile range; LOD = limit of detection; PCB = polychlorinated biphenyl; Q = quartile; T4 = thyroxine; TSH = thyroid stimulating hormone; TT3 = total triiodothyronine; TT4 = total thyroxine

Associations with any DDT metric in studies of adults and adolescents (Table 2-8) were found in:

- 9/18 studies for T3 (4 with inverse associations and 5 with positive associations; 9 with no associations);
- 9/17 studies with T4 (2 with inverse associations, 5 with positive associations, and 2 with age- or sex-dependent inverse or positive associations; 8 with no associations);
- 4/18 studies with TSH (1 with an inverse association and 3 with positive associations; 14 with no associations).

Evidence for possible associations between DDT serum biometrics and serum thyroid hormone levels in adolescent and adult humans is considered to be inconsistent due to: (1) the inconsistency of finding associations across studies; (2) the variable direction of association across those studies finding an association (some found increasing, and others found decreasing, levels of thyroid hormone levels with increasing DDT biometric level); and (3) the variability across studies in the DDT metric showing an association with serum thyroid hormone levels (some found associations with DDE, others with DDT).

Two studies summarized in Table 2-8 used multiple logistic regression analyses to examine possible associations with thyroid hormone dysregulation in adults (Freire et al. 2013; Lopez-Espinosa et al. 2009), but this statistical technique did not provide information that clarified inconsistencies in the available data. No associations were found between several DDT biometrics (DDT, DDD, and DDE) and prevalences of adult subjects with serum levels of TPOAb ≥10 U/mL (Freire et al. 2013), but an elevated risk was found for DDE in pregnant subjects with TSH levels ≥2.5 mIU/L (Lopez-Espinosa et al. 2009). However, the Lopez-Espinosa et al. (2009) study did not find an association between DDE and TSH levels.

The inconsistent evidence for associations between DDT, DDD, or DDE in maternal serum, cord blood, or breast milk and levels of thyroid hormones in offspring is presented in Table 2-9. Associations with any maternal DDT metric were found in:

- 1/3 studies for T3 (1 inverse, 0 positive, and 2 with no association);
- 4/5 studies for T4 (3 inverse, 1 positive, and 1 with no association); and
- 1/10 studies for TSH (0 inverse, 1 positive, and 9 with no association).

The inconsistency of the evidence is emphasized by the observations that: (1) one study reported no associations between changes in children's serum DDE levels at 3 weeks or 3 months with changes in children's serum levels of TSH, total T3, or free T4 (Darnerud et al. 2010) and (2) another study reported no associations between cord blood DDE and cord blood TSH and T4 levels, an inverse association with total T3 levels, and associations for increased levels of TSH in newborn infants' blood with increasing levels of DDE in cord blood or maternal serum (Kim et al. 2015d).

Effects on Non-Sexual, Endocrine-Related Organs in Laboratory Animals. Non-sexual endocrine system organs (e.g., pituitary, adrenal glands, thyroid) do not appear to be sensitive toxicity targets in laboratory animals orally exposed to DDT and related compounds.

No exposure-related nonneoplastic histological changes were found in three non-sexual endocrine system organs in the NCI (1978) studies of rats and mice exposed to technical DDT, *p,p'*-DDE, or technical DDD: pituitary, thyroid, and parathyroids. In male and female offspring of Sprague-Dawley rats exposed to gavage doses of 5, 15, or 50 mg *p,p'*-DDE/kg/day on GD 6–PND 20, relative weights of the pituitary and thyroid gland were not significantly different from control values; a 13% increase in relative adrenal weight in 50-mg/kg/day female offspring was observed (Yamasaki et al. 2009). Histology of the pituitary and thyroid glands were reported to be normal, but the adrenals were not examined histologically (Yamasaki et al. 2009). Adrenal gland changes were reported in dogs after administration of single oral doses of 200 mg technical DDD/kg via a capsule; the alterations consisted of vacuolation, inflammation, and necrosis (Powers et al. 1974). In some dogs, adrenal gland biopsies were taken prior to the terminal sacrifice. No histological alterations were observed 6 hours post-exposure, but were observed as early as 26 hours post-exposure. Powers et al. (1974) also conducted a repeated exposure study in which dogs were administered capsules containing 100 mg technical DDD/kg/day for 6 days or 200 mg/kg/day DDD every other day for 30 days. Although the study reported vacuolation, atrophy, and necrosis of the adrenal gland, conclusions cannot be drawn from this repeated exposure study due to the poor reporting of the study design (it appears that some of the dogs received two or three 6-day exposures) and the long recovery period (up to 32 weeks for some animals). Necrosis of the adrenal cortex was observed in dogs exposed to 138.5 mg *o,p'*-DDD/kg/day for 10 days (Kirk et al. 1974); adrenocortical necrosis, degeneration, and vacuolation also was reported in dogs exposed to 50 mg *o,p'*-DDD/kg/day for 120–156 days (Kirk and Jensen 1975).

In a series of reports by Yaglova and Yaglov (2014, 2015a, 2015b, 2017) and Yaglova et al. (2016), very low doses of *o,p'*-DDT administered to male Wistar rats in drinking water for 6 or 10 weeks (0.0019–0.004 mg *o,p'*-DDT/kg/day) was reported to increase serum levels of total T4, free total T4, T3, and free T3, decrease serum TSH levels, and produce histological changes in the thyroid (e.g., enlarged follicles, increased resorption of thyroglobulin, and decreased height of thyrocytes in peripheral lobes of the thyroid). The toxicological significance of these reports is uncertain because of the small magnitude of the changes in serum thyroid hormone levels and the absence of reporting of incidence data for the histological changes; thus, the apparent LOAEL of 0.0019 *o,p'*-DDE/kg/day was excluded from Table 2-1 and Figure 2-2. The only other study of thyroid effects in orally exposed laboratory animals reported reduced iodine concentrating capacity in Sprague-Dawley rats given single doses ≥50 mg/kg technical DDT (Goldman 1981).

Similarly, Yaglova et al. (2017, 2018) reported alterations in serum corticosterone, epinephrine, and norepinephrine in male rats exposed to low doses of *o,p'*-DDT for 6 or 10 weeks, with or without prenatal exposure via dam (estimated doses of 0.004 mg *o,p'*-DDT/kg/day). However, the direction of change altered with exposure paradigm and timepoint evaluated. Significant changes in adrenal histology were also reported (reduced area of zona fasciculata cells and nuclei, and enlarged mitochondria); however, incidence data are not reported. As with thyroid data, the toxicological significance of these reports is uncertain due to inconsistent findings and the absence of reporting of incidence data for the histological changes; thus, the apparent LOAEL of 0.004 *o,p'*-DDE/kg/day was excluded from Table 2-1 and Figure 2-2.

Mechanisms of Endocrine Effects of DDT, DDE, or DDD. Although available studies of thyroid histology in laboratory animals orally exposed to DDT and related compounds do not clearly identify the thyroid as a sensitive toxicity target, the potential disruption of thyroid hormone homeostasis by environmentally persistent organochlorine chemicals, such as PCBs and DDT compounds, is an active area of *in vitro*, cell biology, and epidemiological research (for reviews of mechanistic hypotheses, see Liu et al. 2014; Rossi et al. 2017; Yaglova and Yaglov 2015b). To explain the observation of decreased serum levels of T4, T3, and TSH measured in Sprague-Dawley rats after 5 days of intraperitoneal co-exposure to PCB153 and *p,p'*-DDE (32 mg PCB153 + 20, 60 or 100 mg *p,p'*-DDE/kg/day), Liu et al. (2014) proposed that disruptive mechanisms could include decreasing levels of thyroglobulin, deiodinase 2, and serum transthyretin (TTR), inducing hepatic enzymes that metabolize thyroid hormones, and increasing levels of hormone receptors. Placental gene expression in Korean mothers supports a potential association between alterations in these pathways and DDE exposure, as maternal serum DDE was positively associated with increased methylation levels of placental deiodinase type 3 and mono-carboxylate transporter 8 genes (Kim et al. 2019). TTR gene methylation was not associated with serum DDE levels. Rossi et al. (2017) proposed that DDT may disrupt thyroid hormone homeostasis via inhibitory action on the TSH receptor via internalization of the TSH receptor from the plasma membrane by altering the structure of membrane lipid subdomains and that autoimmune responses to extracellular vesicles containing the TSH receptor could develop (Rossi et al. 2017). Yaglova and Yaglov (2015b) proposed that *o,p'*-DDT interferes with iodine anion transport into follicular thyrocytes, evidenced by decreased levels of the Na+/I- symporter (NIS) and increased thyroperoxidase (TPO) observed in exposed rats.

2.14. IMMUNOLOGICAL

Evidence of Immunological Effects of DDT, DDD, or DDE in Humans. Several epidemiological studies have examined associations between serum DDE levels 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) in adults (Table 2-10) and children (Table 2-11). These studies provide inconsistent evidence for associations between DDE serum levels and immune function biomarkers or immune-related conditions in adults or children. Additional epidemiological studies have examined associations between DDE levels in cord blood, maternal serum, or breast milk and levels of immune function markers or prevalence of immune-related conditions in offspring (Table 2-12). These studies provide consistent evidence for 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. Evidence for associations other immune-related endpoints in offspring (asthma, infections) was inconsistent.

Table 2-10. Summary of Studies of Associations Between DDT Exposure Biometrics in Adults and Immunological Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Cooper et al. 2004 Cross-sectional, 137 African-American male adult farmers (United States, North Carolina)	Serum DDE (quartiles, ng/mL): Q1: <3.0 Q2: 3.0–5.9 Q3: 6.0–11.9 Q4: ≥12.0	Serum IgA	↔
		Serum IgG Q2 versus Q1 Q3–Q4 Overall	 ↔ ↓ ↔
		Anti-nuclear antibodies	↔
Miyake et al. 2011 Cross-sectional, 124 post-partum women (Japan) Samples collected 1 month after delivery; prevalence of allergic disorders self-reported for past 12 months	Milk DDE (IQR, ng/g lipid): 47.5–97.0	Wheeze	↔
		Asthma	↔
		Eczema	↔
		Rhinoconjunctivitis	↔
Ryu et al. 2018 Cross-sectional, 95 adults, mean age 44.8 years (Korea)	Serum DDT metrics (IQR, ng/g lipid): DDT / DDE Q1: 1.7 / 19.9 Q2: 3.8 / 45.9 Q3: 5.1 / 70.0 Q4: 8.4 / 127	T Lymphocytes $CD8^+CD57^+$ $CD8^+CD28^-$ $CD4^+CD57^+$ $CD4^+CD28^-$	 ↔ ↔ ↔ ↓ (DDE) ↔ (DDT)

Table 2-10. Summary of Studies of Associations Between DDT Exposure Biometrics in Adults and Immunological Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Vine et al. 2001 Cross-sectional, 302 adults including 151 Aberdeen residents (living near a pesticides dump site) and 151 control adults living in a community outside of Aberdeen (United States, North Carolina)	Serum DDE (quintiles, ng/mL): Q1: ≤1.0 Q2: >1.0–2.0 Q3: >2.0–4.3 Q4: >4.3–7.6 Q5: >7.6	Cell counts	
		WBC	↔
		Total lymphocytes	↑
		CD3	↑
		CD4	↔
		CD56	↑
		Mitogen induced lymphoproliferative activity	
		PHA	↔
		ConA	↓
		PKW	↔
		Serum	
		IgA	↑
		IgG	↔
		IgM	↔
		Cell mediated immune function (skin test)	↔

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified.

↑ = positive association; ↓ = inverse association; ↔ = no association; ConA = concanavalin A; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; Ig(X) = immunoglobin X; IQR = interquartile range; PHA = phytohemagglutinin; PKW = pokeweed mitogen; Q = quartile or quintile; WBC = white blood cell

Table 2-11. Summary of Studies of Associations between DDT Exposure Biometrics in Children and Immunological Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Karmaus et al. 2001 Cross-sectional, 343 school-aged (second grade) (Germany)	Serum DDE (quartiles, ng/mL): Q1: ≤0.2 Q2: 0.21–0.29 Q3: 0.30–0.43 Q4: 0.44–4.02	Otitis media	↔
		Pneumonia	↔
		Whooping cough	↔
		Asthma	↑
		IgE ≥200	↑
		Change in IgE	
		Q2–Q3	↔
		Q4 versus Q1	↑

Table 2-11. Summary of Studies of Associations between DDT Exposure Biometrics in Children and Immunological Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Karmaus et al. 2003 Cross-sectional, 323 school-age children (second grade) including 134 that were breastfed 1–12 weeks, 142 that were breastfed >12 weeks, and 47 that were not breastfed (Germany)	Serum DDE (quartiles, ng/mL): Q1: <0.21 Q2: 0.21–0.29 Q3: 0.29–0.44 Q4: ≥0.44	Asthma, bronchiolar hyperactivity, atopic eczema, hay fever	↔
		IgE >200 kU/L Q2–Q3 Q4 versus Q1	 ↔ ↑
		IgE aeroallergen Q2–Q3 Q4 versus Q1	 ↔ ↑
Karmaus et al. 2005a, 2005b Cross-sectional, 331 children aged 7–10 years (Germany)	Serum DDE (quartiles, ng/mL): Q1: ≤0.2 Q2: 0.21–0.29 Q3: 0.30–0.43 Q4: >0.43	Serum IgG Q2–Q3 Q4 versus Q1	 ↔ ↑
		Serum IgA Q2 versus Q1 Q3–Q4	 ↔ ↑
		Serum IgM Q2–Q4	 ↔
		Serum IgE Q2–Q3 Q4 versus Q1	 ↔ ↑
		WBC Q2–Q3 Q4 versus Q1	 ↔ ↑
		Eosinophilic granula content Q2–Q3 Q4 versus Q1	 ↔ ↓
		Basophilic surface IgE Q2 versus Q1 Q3 versus Q1 Q4 versus Q1	 ↔ ↑ ↔
		No associations were observed for lymphocyte counts/subpopulations	
Meng et al. 2016 Case-control, 620 children with asthma and 218 controls, ages 3–6 years; cases and controls combined for analysis (China)	Serum DDT metrics (mean, ng/g lipid): Controls / Cases DDE 36.9 / 166.52 DDT 10.13 / 12.13 DDD 42.06 / 33.71 *o,p'*-DDT 69.42 / 38.32	Asthma	↑ (DDE) ↔ (DDT) ↔ (DDD) ↔ (*o,p'*-DDT)
		Severe asthma	↔

Table 2-11. Summary of Studies of Associations between DDT Exposure Biometrics in Children and Immunological Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Perla et al. 2015 Cross-sectional, 962 children, ages 12–15 years (United States; NHANES)	Serum DDE (GM (95% CI), ng/g): 105 (93.0–1,185) Tertiles T1: <40th percentile T2: 40th–80th percentiles T3: >80th percentile	Asthma prevalence (current wheeze or ever asthma) T2 versus T1 T3 versus T1 p-trend	 ↔ ↔ ↔

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified; DDD = *p,p'*-DDD, unless otherwise specified

↑ = positive association; ↓ = inverse association; ↔ = no association; CI = confidence interval; DDD = dichloro-diphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; GM = geometric mean; Ig(X) = immunoglobin X; NHANES = National Health and Nutrition Examination Survey; Q = quartile; T = tertile

Table 2-12. Summary of Studies of Associations Between Maternal Serum, Cord Blood, or Milk DDT Exposure Metrics and Immunological Endpoints in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Ashley-Martin et al. 2015 Cohort, 1,258 mother-infant pairs (Canada) Immunological parameters measured in cord blood.	First trimester maternal serum DDE (tertiles, ng/mL): T1: ≤0.23 (referent) T2: 0.24–0.39 T3: >0.39	IgE (≥1.2 ng/mL) Ig33/TSLP ratio (≥80%) Per doubling DDE T2–T3	↔ ↓ ↔
Bilrha et al. 2003 Cross-sectional, 112 mother-infant pairs including 47 from a fish-eating population and 65 from a non-fish-eating population (Canada)	Cord blood DDE (GM (95% CI), ng/g lipid): Fish-eaters: 144 (114–182) Non-fish eaters: 84 (73–96)	Cytokines in mitogen (PHA) induced cord blood mononuclear cells: IL-10 TNF-α	 ↔ ↓
Cupul-Uicab et al. 2014 Cohort, 747 mother-male infant pairs (Mexico) Occurrence of LRTI in infants assessed through mean age of 21.4 months	Maternal serum DDT metrics at birth (quartiles, ng/g lipid): DDE / DDT Q1 ≤3.0 / ≤0.25 Q2 3.01–6.00 / 0.26–0.75 Q3 6.01–9.00 / 0.76–1.99 Q4 >9.00 / ≥2.00	LRTI	↔ (DDE) ↔ (DDT)

Table 2-12. Summary of Studies of Associations Between Maternal Serum, Cord Blood, or Milk DDT Exposure Metrics and Immunological Endpoints in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Dallaire et al. 2004 Cohort/Cross-sectional, 199 Inuit mother-infant pairs (Canada, Nunavik) Maternal and infant serum collected at birth and 7 months of age, respectively	Maternal and infant serum DDE (quartiles, ng/g lipid): Maternal / Infant Q1 <183 / <100 Q2 183–281 / 100–355 Q3 281–472 / 355–618 Q4 >472 / >618	URTI 6 or 12 months Q2 versus Q1 Q3–Q4	 ↑ ↔
		Otitis 6 months Q2 versus Q1 Q3 versus Q1 Q4 versus Q1 12 months	 ↔ ↑ ↔ ↔
		GI infections 6 months 12 months Q2 versus Q1 Q3–Q4	 ↔ ↑ ↔
		LRTIs 6 or 12 months	 ↔
		All Infections 6 months Q2–Q3 Q4 versus Q1 12 months	 ↑ ↔ ↔
Dewailly et al. 2000 Cohort, 98 Inuit mother-infant pairs (Canada, Nunavik) Maternal milk collected 3 days post-birth	Maternal milk DDE (tertiles, ng/g lipid): T1: <730 T2: 730–1,320 T3: >1,320	Acute otitis media 0–3 months T2–T3	 ↔
		4–7 months T2 versus T1 T3 versus T1	 ↔ ↑
		8–12 months T2 versus T1 T3 versus T1	 ↑ ↔
		1 year ≥1 episode T2–T3	 ↑
		1 year ≥3 episode T2 versus T1 T3 versus T1	 ↑ ↔
Gascon et al. 2012 Cohort, 1,421 mother-infant pairs including 1,342 Spanish mothers and 79 Latin-American mothers (Spain)	Spanish maternal serum DDE (quartiles, ng/g lipid): Q1: <72.6 Q2: 72.6–115.9 Q3: 115.9–191.7 Q4: >191.7	LRTI <u>Spanish</u> Q2 versus Q1 Q3–Q4 Continuous <u>Latin-American</u> T2–T3 Continuous	 ↔ ↑ ↑ ↑ ↔

Table 2-12. Summary of Studies of Associations Between Maternal Serum, Cord Blood, or Milk DDT Exposure Metrics and Immunological Endpoints in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Maternal serum collected at a median of 12.9 weeks gestation. Respiratory tract infections (LRTIs) and wheeze assessed at 12–24 months in offspring	Latin maternal serum DDE (tertiles, ng/g lipid): T1: <197.9 T2: 197.9–595.9 T3: >595.9	Wheezing Spanish Q2 versus Q1 Q3 versus Q1 Q4 versus Q1 Continuous Latin-American T2 versus T1 T3 versus T1 Continuous	 ↔ ↑ ↔ ↑ ↔ ↑ ↔
Gascon et al. 2014 Meta-analysis, multi-site, mother-infant cohorts: Duisburg (n=204) FLEHS I (n=133) HUMIS (n=386) PCB cohort (n=720) Rhea (n=996) INMA, Menorca (n=395) INMA, Gipuzkoa (n=540) INMA, Sabadell (n=543) INMA, Valencia (n=505) PELAGIE (n=186)	Estimated cord-serum levels of DDE (GM, ng/mL) Duisburg: 0.201 FLEHS I: 0.285 HUMIS: 0.052 PCB: 0.934 Rhea: 0.641 INMA, Menorca: 1.067 INMA, Gipuzkoa: 0.208 INMA, Sabadell: 0.229 INMA, Valencia: 0.503 PELAGIE: 0.165 Tertile levels not reported: T1, T2, and T3 = low, medium, and high exposure levels	<18 months Bronchitis or wheezing Continuous T2 versus T1 T3 versus T1	 ↑ ↔ ↑
		<18 months Bronchitis Continuous T2–T3	 ↑ ↔
		<18 months Wheeze Continuous T2 versus T1 T3 versus T1	 ↔ ↔ ↑
		>18 months Wheeze Continuous T2–T3	 ↔ ↔
Glynn et al. 2008 Cohort, mother-infant pairs including 81 for WBC counts, 52 for lymphocyte profile, and 190 for respiratory infections (Sweden) Maternal serum collected during late pregnancy and mild was collected 3 weeks post-delivery; infant endpoints assessed at 3 months of age	Maternal serum and milk DDE (median, ng/g lipid): Serum / Milk WBC: 85 / 289 Lymphocyte: 83 / 306 Infection: 88 / 311 Quartile levels not reported	WBC count	↔ (serum)
		Eosinophil count	↔ (serum)
		Eosinophil %	↓ (serum)
		Neutrophil, lymphocyte, or monocyte (count, %)	↔ (serum)
		All lymphocyte subsets	↔ (serum)
		Respiratory infections Q2 versus Q1 Q3–Q4 Q2–Q4	 ↓ (milk) ↔ (milk) ↔ (serum)

Table 2-12. Summary of Studies of Associations Between Maternal Serum, Cord Blood, or Milk DDT Exposure Metrics and Immunological Endpoints in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Hansen et al. 2014 Cohort, 872 mother-offspring pairs, offspring follow-up at 20 years of age (Denmark)	Maternal serum DDE (tertiles, ng/mL) T1: 0.20–1.86 T2: >1.86–3.24 T3: >3.25–38.77	Asthma Self-reported Current medicine use Hospital diagnosis 20-year medicine use	 ↔ ↔ ↔ ↔
Hansen et al. 2016 Cohort, 421 mother-offspring pairs, offspring follow-up at 20 years of age (Finland)	Maternal serum DDE (tertiles, ng/mL) T1: 0.2–1.9 T2: 1.9–3.2 T3: 3.2–38.8	Allergic sensitization	↔
		Airway obstruction T2 versus T1 T3 versus T1 p-trend	 ↔ ↑ ↑
		Reduced lung function	↔
Huang et al. 2018 Cohort, 674 mother-child pairs, offspring follow-up at 2 years of age (South Africa)	Maternal serum (GM, µg/L) DDE: 292.95 DDT: 70.04 *o,p'*-DDT: 9.18	Persistent fever	↑ (DDE) ↔ (DDT) ↔ (*o,p'*-DDT)
		Ear infections	↔
		Severe sore throat	↔
Jusko et al. 2016a, 2016b Cohort/Cross-sectional, 541 mother-infant pairs (Slovakia) Infant response to tuberculosis (BCG) vaccination measured at 6 months	Maternal serum, cord blood, and estimated 6-month DDE (IQR, ng/g lipid): Maternal: 265–723 Cord blood: 259–706 Estimate at 6 months: 115–847	BCG-IgG	↔ (serum) ↔ (cord) ↓ (6-months)
		BCG-IA	↔ (serum) ↔ (cord) ↓ (6-months)
Sunyer et al. 2005 Cohort, 405 mother-child pairs (Spain) Serum collected at 4 years of age for presence of IgE specific to house dust mite, cat, and grass; positive value defined as atopy	Cord blood DDE (quartiles, ng/mL): Q1: <0.57 Q2: 0.57–1.03 Q3: 1.03–1.90 Q4: >1.90	Wheezing All children Q2–Q3 Q4 versus Q1 Non-atopic Q2–Q3 Q4 versus Q1	 ↔ ↑ ↔ ↑

Table 2-12. Summary of Studies of Associations Between Maternal Serum, Cord Blood, or Milk DDT Exposure Metrics and Immunological Endpoints in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Sunyer et al. 2006 Cohort, 402 mother-infant pairs; serum samples from children at 4 years (n=285); Atopic status evaluated at 6 years (Spain)	Cord blood and child serum DDT metrics (range, ng/mL) : DDE DDT Cord 0.043–19.54 0.008–2.283 Serum 0.088–43.88 0.038–0.658	Asthma at 6.5 years All children Non-atopic >1 wheeze event/year All children Years 1, 2, and 3 Year 4 Year 6.5 Persistent wheeze at 6.5 years Non-atopic Year 1, 2, 3, 4, 6.5 Persistent wheeze at 6.5 years *No associations with DDT found*	 ↑ (DDE) ↑ (DDE) ↔ (DDE) ↑ (DDE) ↔ (DDE) ↔ (DDE) ↔ (DDE) ↔ (DDE)
Sunyer et al. 2010 Cohort, 520 mother-infant pairs (Spain)	Maternal serum DDE (tertiles, ng/g lipid): T1: <83.0 T2: 83.0–149.5 T3: >149.5 DDT was not detected	LRTIs At 6 months T2 versus T1 T3 versus T1 Log↑ At 14 months T2–T3 Log↑ Recurrent T2–T3 Log↑	 ↑ ↔ ↑ ↑ ↑ ↑ ↑

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified.

↑ = positive association; ↓ = inverse association; ↔ = no association; BCG = *Mycobacterium bovis* bacilli Calmette-Guerin; CI = confidence interval; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; FLEHS = Flemish Environment and Health Studies; GI = gastrointestinal; GM = geometric mean; HUMIS = Norwegian Human Milk Study; Ig(X) = immunoglobin X; IL-(X) = interleukin-(x); INMA = Infancia y Medio Ambiente; IQR = inter quartile range; LRTI = lower respiratory tract infection; med.= medicine; PCB = polychlorinated biphenyl; PELAGIE = Perturbateurs endocriniens, Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance; PHA = phytohemagglutinin; Q = quartile; T = tertile; TNF-α = tumor necrosis factor-alpha; TSLP = thymic stromal lymphopoietin; URTI = upper respiratory tract infection; WBC = white blood cell

Results from studies of adults and children. In cross-sectional studies of adults (Table 2-10), various associations were observed with increasing DDE serum levels; however, the few overlapping endpoints were inconsistent between studies. One study in American adults reported decreased serum levels of IgG with increasing serum DDE, but no associations were observed with serum IgA or anti-nuclear antibodies

(Cooper et al. 2004). Another study from the United States reported increased total lymphocytes, CD3s, CD56s, and serum IgA with increasing serum DDE, with no associations for white blood cells, CD4s, or serum IgG or IgM (Vine et al. 2001). Decreased lymphoproliferation in response to a T-cell mitogen (concanavalin A) was also associated with increased serum DDE; no change in response to other mitogens or cell mediated immune functions were observed (Vine et al. 2001). In Korean adults, CD4+/CD28- T-cells were decreased with increased serum DDE levels; no changes were observed in other T-cell subpopulations (Ryu et al. 2018). In adult Japanese women, no significant associations were found between DDE levels in their breast milk and prevalence of asthma, wheeze, rhino-conjunctivitis, or eczema (Miyake et al. 2011).

Studies examining possible associations between serum DDE levels in children and immunological outcomes also provide inconsistent evidence across studies (Table 2-11). Associations between increasing serum DDE levels and prevalence of asthma and serum IgE >200 kU/L were found in a group of German children, but the association was not apparent when the data were stratified by gender, breastfeeding status, or age, or when the logistic regression models included other organochlorine compounds analyzed in the children's serum (Karmaus et al. 2001). In a second analysis to examine the protective effects of breastfeeding and detrimental effects of DDE, no associations were found for increasing prevalences for several atopic outcomes (asthma, bronchial hyper-reactivity, atopic eczema, or hay fever), except for increased prevalence of children with serum IgE >200 kU/L (Karmaus et al. 2003). In a third analysis, elevated serum levels of IgG, IgA, and IgE, were associated with high serum DDE levels (Karmaus et al. 2005a, 2005b). Additional findings in children with high serum DDE levels, compared to low serum DDE levels, included elevated white blood cell counts and IgE counts on basophils, but decreased eosinophilic granula content. A small, but elevated, increased risk for asthma was observed with increasing serum DDE was found in children ages 3–6 years in one study (Meng et al. 2016), but no association with asthma prevalence was found in another study of children ages 12–15 years (Perla et al. 2015).

Results relating maternal exposure and immunological outcomes in offspring. Consistent evidence for associations between levels of DDE in maternal serum and prevalence of wheeze (or airway obstruction) in infant or child offspring have been reported in five studies (Gascon et al. 2012, 2014; Hansen et al. 2016; Sunyer et al. 2005, 2006; Table 2-12). Each of these European cohort studies reported elevated risk for this condition in infants of mothers with high DDE serum levels, compared with infants of mothers with low DDE levels, or increasing risk for this condition in infants with increasing maternal serum DDE levels. For example, the Gascon et al. (2014) meta-analysis of 4,608 mother-infant pairs from 10 birth

cohorts from 7 European countries reported elevated RRs of 1.14 for bronchitis or wheeze and 1.16 for wheeze in young (<18 months old) infants of mothers with the highest category of DDE serum levels, compared with referent infants of mothers in the low DDE serum level category (Table 2-12). This association was not significant with offspring older than 18 months (Gascon et al. 2014).

Inconsistent evidence comes from studies examining associations between maternal serum or cord blood DDE levels and prevalence for asthma or changes in blood immune function markers associated with wheezing or asthma. Hansen et al. (2014) found no association for asthma in 20-year-old offspring with maternal serum DDE levels at birth, but Sunyer et al. (2006) reported increased risk for asthma in 6.5-year-old children with increasing cord blood DDE levels. One study (Ashley-Martin et al. 2015) reported an association between increased maternal serum DDE levels and decreased ratio of interleukin-33 and thymic stromal lymphopoietin (IL-33/TSLP) in cord blood, but no associations with cord blood levels of IL-33 or IgE; elevated levels of each of these individual immune function markers have been associated with wheezing or asthma in other studies. In other studies, associations were found between increasing cord blood DDE levels and decreased cord blood levels of tumor necrosis factor-alpha (TNF-α), but not IL-10, in 111 Canadian mother-infant pairs (Bilrha et al. 2003) and between increasing infant serum DDE levels and decreased IgG and IgA responses to vaccination, but no associations with maternal or cord blood DDE levels (Jusko et al. 2016a, 2016b).

Inconsistent evidence comes from five studies examining associations between maternal serum or breast milk levels of DDE and prevalence of infections in offspring (Table 2-12). No associations were found with increased prevalence of lower respiratory tract infections in a group of 747 Mexican <2-year-old children (Cupul-Uicab et al. 2014) or respiratory tract infections during the first 3 months after birth in a group of 190 Swedish infants (Glynn et al. 2008), but associations were found for increased prevalence for all infections (respiratory, ear, and gastrointestinal) during the first 6 months, but not 12 months, after birth in a group of 199 Canadian children (Dallaire et al. 2004), ear infections between 4 and 12 months, but not 0–3 months, after birth in 98 Inuit infants (Dewailly et al. 2000), lower respiratory tract infections between 6 and 14 months after birth in a group of 520 children from Catalonia Spain (Sunyer et al. 2010); lower respiratory tract infections between birth and 14 months in a group of 1,342 children from Gipuzkoa, Sabadell, and Valencia Spain (Gascon et al. 2012); and elevated rates of persistent fever between 1 and 2 months were associated with *p,p'*-DDE, but not *o,p'*-DDT or *p,p'*-DDT and no associations were found for the number of ear infections or severe sore throats (Huang et al. 2018).

Evidence of Immunological Effects of DDT, DDE, or DDD in Laboratory Animals

Summary. Studies of laboratory animals have provided evidence for suppression or stimulation of various immune system responses in rats and mice exposed to dietary doses of technical DDT, *p,p'*-DDT, *p,p'*-DDE, *p,p'*-DDD, or *o,p'*-DDD as low as 2–20 mg/kg/day, but evidence is weak for weight changes or histological changes in immune system organs or tissues in laboratory animals after intermediate- or chronic-duration exposures.

Acute-duration evidence. Information on possible immunological effects in laboratory animals after acute-duration oral exposure to DDT and related compounds is restricted to a study in New Zealand rabbits that reported that gavage administration of 4.3 mg DDT(NS)/kg/day for 10 days produced no effects on serum antibody titers to *Salmonella typhi* infection (Shiplov et al. 1972). Additionally, a study in male NOD mice administered *p,p'*-DDE via intraperitoneal injection every other day for 10 days found increases in splenocyte proliferation in response to Concanavalin A exposure in mice exposed to 100 mg/kg DDE, but not at 1 mg/kg; increases in IL-6, tumor necrosis factor-α, and interferon-γ were also observed at 100 mg/kg (Cetkovic-Cvrlje et al. 2016). There were no effects on splenocyte viability or splenocyte immunophenotype.

Intermediate-duration evidence. 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 immune responses has been examined in rats (Banerjee 1987b; Banerjee et al. 1995, 1996; Gabliks et al. 1975; Hamid et al. 1974; Koner et al. 1998), mice (Banerjee 1987a; Banerjee et al. 1986, 1997a, 1997b; Rehana and Rao 1992), and rabbits (Street and Sharma 1975). As shown in Table 2-1, Figure 2-2, and the following text, the lowest doses associated with immune system perturbations in intermediate-duration studies of laboratory animals ranged from about 2 to 20 mg/kg/day, and *p,p'*-DDT was the most widely used test material.

Evidence of immunosuppression comes from studies evaluating the response to various antigens:

- Response to sheep red blood cells (SRBC)
    - decreased splenic plaque forming cell (PFC) response and thymic rosette-forming cell response in Sprague-Dawley rats exposed to 121 mg *o,p'*-DDD/kg/day for 16–24 days (no statistical analysis performed) (Hamid et al. 1974);
    - decreased serum antibody titer response in Wistar rats exposed to 20.6 mg *p,p'*-DDT/kg/day, but not 10.3 mg/kg/day, in the diet for 8 weeks (Koner et al. 1998);

  - decreased splenic PFC response in Hissar mice fed 20 mg *p,p'*-DDT/kg/day, but not 4 or 10 mg/kg/day, for 12 weeks (Banerjee et al. 1986); and
  - decreased splenic PFC response in restraint-stressed Hissar mice fed 20.3 mg *p,p'*-DDT/kg/day, but not 4.1 or 10.1 mg/kg/day, for 4 weeks (Banerjee et al. 1997b).
- Response to tetanus or diphtheria toxoids
  - decreased antibody response to tetanus toxoid in Wistar rats exposed for 22 weeks to 11 mg *p,p'*-DDT/kg/day in the diet, but not doses ≤5.5 mg/kg/day, and decreased serum IgG levels and decreased relative spleen weight (17–20% decreased) and increased serum albumin/globulin ratio resulting from decreased IgG titers in tetanus toxoid-immunized rats exposed to ≥5.5 mg/kg/day, but not 2.2 mg/kg/day (Banerjee 1987b);
  - decreased serum levels of IgG and IgM and antibody titers in response to tetanus toxoid and increased serum albumin/globulin ratio in Wistar rats fed 5.7 mg *p,p'*-DDT/kg/day (but not 2.3 mg/kg/day) in a low (3%) protein diet for 4 weeks; these effects were not seen in similarly exposed rats fed diets containing 12 or 20% protein (Banerjee et al. 1995);
  - decreased severity of anaphylactic shock and number of mast cells in mesenteries in response to diphtheria toxoid (without effects on serum antitoxin titers) in albino rats exposed to 2.3 or 23 mg technical DDT/kg/day in the diet for 31 days (Gabliks et al. 1975).
- Response to *Escherichia coli* lipopolysaccharide
  - decreased splenic PFC response and reduced secondary haemagglutination titres in Hissar mice fed 10.5 or 21 mg *p,p'*-DDT/kg/day, but not 4.2 mg/kg/day, for 6–12 weeks (Banerjee 1987a).
- Response to ovalbumin
  - decreased serum levels of IgM, IgG and ovalbumin antibodies in Wistar rats exposed to 20.2 mg *p,p'*-DDT, *p,p'*-DDE, or *p,p'*-DDD/kg/day in the diet for 6 weeks and increased serum albumin/globulin ratio in *p,p'*-DDT and *p,p'*-DDE exposed animals (Banerjee et al. 1996).
- Resistance to leprosy bacilli
  - increased susceptibility to leprosy bacilli infections in Rockfeller mice exposed to 10.7 or 21.4 mg *p,p'*-DDT/kg/day, but not 4.3 mg/kg/day, in the diet for 24 weeks (Banerjee et al. 1997a).

- Response to tuberculin
    - decreased skin reactivity to tuberculin challenge in New Zealand rabbits exposed for 8 weeks to 6.54 mg *p,p'*-DDT/kg/day, but not to doses ≤2.10 mg/kg/day, in the diet (Street and Sharma 1975).

Possible effects on weights or histology of immune system organs have also been examined in laboratory animals after intermediate-duration oral exposure to technical DDT, *p,p'*-DDT, *p,p'*-DDE, *p,p'*-DDD, *o,p'*-DDT, or *o,p'*-DDD, but the evidence from these studies for these types of immune effects is weak. Hamid et al. (1974) observed decreased absolute weights of the thymus and spleen, along with decreased body weight and atrophy of the thymus and adrenal glands, in Sprague-Dawley rats exposed to 121 mg *o,p'*-DDD/kg/day for 16–24 weeks. Yaglova et al. (2013, 2020) reported changes in thymus morphology, such as increased counts of Hassall's corpuscles in the thymic medulla and increased width of the subcapsular layer, and increased ^{3}H-thymidine incorporation rates in the thymus of Wistar rats exposed to 0.0019–0.0078 mg *o,p'*-DDT/kg/day in drinking water for up to 10 weeks. Observations from both studies were not included in Table 2-1 or Figure 2-2 due to lack of incidence data and statistical analysis (Hamid et al. 1974), or the lack of corroborating evidence for immune system effects at such low exposure levels, unknown toxicological relevance of findings, and deficiencies in reporting of methodological details (Yaglova et al. 2013, 2020). No exposure-related changes in organ weight or histology in the spleen or thymus were reported in F344/DuCrl rats exposed to 10 mg *p,p'*-DDE/kg/day for 42 days (Makita et al. 2003a). In a study of rabbits exposed to *p,p'*-DDT in the diet for up to 8 weeks at doses ranging from 0.18 to 6.54 mg/kg/day, several effects were reported in all exposed groups that were of uncertain adversity: 23–36% increase in relative spleen weight; decreased counts of splenic germinal centers (about 12 centers/4-mm diameter in all exposed groups versus about 19/4-mm diameter in control); and increased mean severity score for thymic atrophy (means were about 0.5, 1.9, 0.7, 0.9, and 1.1 for control through high-dose groups) (Street and Sharma 1975).

Chronic-duration evidence. Studies of laboratory animals orally exposed to DDT, DDE, or DDD for chronic durations do not identify the immune system as a sensitive toxicity target, but the scope of these investigations did not include possible perturbations of immune system function. In the 78-week chronic bioassays, no treatment-related histological changes in the thymus, spleen, or lymph nodes were observed in Osborne-Mendel rats treated in the diet with up to 45 mg technical DDT/kg/day, 59 mg *p,p'*-DDE/kg/day, or 231 mg technical DDD/kg/day or in B6C3F1 mice exposed to dietary doses up to 30.2 mg technical DDT/kg/day, 49 mg *p,p'*-DDE/kg/day, or 142 mg technical DDD/kg/day (NCI 1978). Similarly, F344/DuCrl rats treated for 104 weeks to up to 19.1 mg *p,p'*-DDT/kg/day showed no

histopathology of the spleen (Tomita et al. 2013). In a 2-generation study, no exposure-related organ weight changes or histopathologies in the spleen or thymus were reported in Sprague-Dawley rats exposed to *p,p'*-DDT up to 25 mg/kg/day (males) or 27.7 mg/kg/day (females) (Hojo et al. 2006).

No studies were located regarding immunological effects in humans or animals after dermal exposure to DDT, DDE, or DDD.

Mechanisms of Immunological Effects of DDT, DDE, or DDD. Although several DDT exposure-related immunomodulatory effects have been reported, the mechanisms behind these effects are still under investigation. There is currently no clear understanding of the pathophysiological mechanisms of immune-mediated respiratory (e.g., asthma, wheezing, bronchitis) or other immunological effects associated with exposure to DDT, DDE, or DDD.

Disruptions to humoral and cell-mediated immune responses could be due to a variety of cellular and system responses that have been observed *in vitro*. Exposure to DDT or to related compounds has been shown to increase ROS, nitric oxide (NO), or TNF-α production (Perez-Maldonado et al. 2005; Dutta et al. 2008); induce pro-inflammatory responses (Gaspar-Ramirez et al. 2015; Kim et al. 2004); alter inflammatory mediator production (Mangum et al. 2016) and apoptotic pathways (Alegria-Torres et al. 2009; Perez-Maldonado et al. 2004, 2005); alter immune cell morphologies and activity (Dutta et al. 2008; Reed et al. 2004; Udoji et al. 2010); and lead to aberrant cytokine production (Alegria-Torres et al. 2009; Kim et al. 2004; Quaranta et al. 2006) and alterations in the complement system (Dutta et al. 2008). Microscopic observations of peripheral blood mononuclear cells (PBMCs) exposed to 10, 50, or 100 µg/mL technical DDT showed characteristic signs of cells undergoing apoptosis (cytoplasmic vacuolization, loss of pseudopodia, and presence of lipid bodies), as well as dose-related increases in the inflammatory cytokine, TNF-α and NO (51.7% increase at high dose) (Dutta et al. 2008). Other studies suggested that increased TNF-α, and pro-inflammatory responses following DDT exposure could be the result of activation of transcription factors including NF-κB and AP-1 (Kim et al. 2004); TNF-α in turn may regulate expression of the aryl hydrocarbon receptor (AhR), which can further mediate the inflammatory response (Gaspar-Ramirez et al. 2015).

Natural killer (NK) cells are an important first-line immune response against tumor cells and viral infection; correlations between plasma *p,p'*-DDT levels and reduction of NK cell numbers has been documented in fish eaters from southeast Sweden (Svensson et al. 1994). *In vitro,* NK lytic function was decreased by 55.4% 24 hours following exposure to 2.5 µM *p,p'*-DDT for 60 minutes in culture (Udoji et al. 2010); determinations of whether DDT can interfere with the essential involvement of mitogen-activated protein kinase (MAPK) signaling in NK cell lytic activity is under investigation (Udoji et al. 2010). In a follow-up study, Hurd-Brown et al. (2013) found 22, 35, and 36% decreases in binding function in NK cells exposed to 2.5 µM DDT for 24 hours, 48 hours, or 6 days, respectively. Exposure to 2.5 µM DDT for 24 or 48 hours also resulted in decreases in CD16 expression in NK cells; no alterations were observed in CD2, CD11a, CD18, or CD56 cell-surface protein expression.

Despite several studies attempting to uncover possible mechanisms of DDT-related immunological effects *in vitro,* it is unclear whether the responses observed in various cultured cell types would occur *in vivo,* or on a scale large enough to elicit an adverse immunotoxic response. This may be reflected in the inconsistencies observed in human epidemiological studies (see Tables 2-10, 2-11, and 2-12).

2.15 NEUROLOGICAL

Summary. Volunteers given single oral doses of DDT reported mild neurological symptoms like perspiration, headache, and nausea at doses as low as 6 mg DDT/kg and transient convulsions or tremors at doses ≥16 mg/kg/day (Hayes 1982; Hsieh 1954; Velbinger 1947a, 1947b), but no neurological effects were found in volunteers who ingested 0.05–0.063 or 0.36–0.5 mg/kg/day for 12–18 months (Hayes et al. 1956). In epidemiological studies, inconsistent evidence was provided for associations of serum levels of DDT, DDE, or DDD with deficits in cognitive or mental status tests or risks for neurological conditions, such as Alzheimer's, Parkinson's disease, or attention deficient disorder, in adults or adolescents or associations between DDT, DDE, or DDD levels in maternal serum at birth or during pregnancy, cord blood, placenta tissue, or breast milk with adverse neurodevelopmental effects of offspring (for references, see Tables 2-13 and 2-14 and following text).

Table 2-13. Summary of Neurological Perturbations in Adult or Adolescent Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Adult exposure			
Kim et al. 2015a Cross-sectional, 644 elderly adults, 60–85 years (United States, NHANES 1999-2002)	Serum DDT metrics (quartile medians, ng/g lipid) DDE / DDT Q1 280 / <LOD Q2 663 / <LOD Q3 1,290 / 12.9 Q4 2,660 / 36.3 Serum DDT metrics (quartile medians, ng/g serum) DDE / DDT Q1 1.73 / <LOD Q2 4.42 / <LOD Q3 8.28 / 0.09 Q4 18.3 / 0.23	Risk of low DSST scores (<25th percentile) Q2–Q3 Q4 versus Q1 p-trend	 ↔ (DDE, DDT) ↑ (DDE, DDT) ↑ (DDE, DDT)
Kim et al. 2015b Cross-sectional, 644 elderly adults, 60–85 years (United States, NHANES 1999-2002) Age quintiles: Q1: (60–63 years) (n=134) Q2: (64–67 years) (n=121) Q3: (68–72 years) (n=124) Q4: (73–39 years) (n=128) Q5: (80–85 years) (n=137)	Serum DDT metrics (tertile medians, ng/g lipid) DDE / DDT T1 324.5 / 5.7 T2 940.5 / 9.4 T3 2,200.0 / 25.6	Risk of low DSST scores (<25th percentile) in older adults (Q2–Q5) versus younger (Q1) within DDT/DDE tertiles Age Q2–Q4 (versus Q1) Age Q5 versus Q1 T1 and T2 T3 p-trend Q1–Q5 T1 and T2 T3	↔ (DDE, DDT) ↑ (DDE, DDT) ↔ (DDE, DDT) ↑ (DDE, DDT) ↔ (DDE, DDT)
Kim et al. 2015c Cross-sectional, 644 elderly adults including 437 hypertensive and 207 normotensive subjects, 60–85 years (United States; 1999–2002 NHANES)	Serum DDT metrics (tertile medians, ng/g lipid) DDE / DDT T1 324.5 / 5.7 T2 940.5 / 9.4 T3 2,200.0 / 25.6	Risk of low DSST scores (<25th percentile) in hypertensive versus normotensive (referent) subjects within DDT/DDE tertiles T1 and T2 T3	 ↔ (DDE, DDT) ↑ (DDE, DDT)
Lee et al. 2016a, 2016b Cohort, 989 adults, 70 years old at study initiation, follow-up at 75 and 80 years of age (Sweden)	Serum DDE (tertiles) ng/g lipid / ng/g serum T1 <162 / <1.0 T2 162–551 / 1.0–3.5 T3 >551 / >3.5	Risk of mild to overt Alzheimer's disease	↔

Table 2-13. Summary of Neurological Perturbations in Adult or Adolescent Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Medehouenou et al. 2014 Cross-sectional, 2,023 adults >65 years old, including 574 dementia cases 399 Alzheimer's disease cases, and 1,449 controls with normal cognition (Canada)	Serum DDT metrics (IQR, ng/mL): DDE / DDT Dementia 2.20–7.70 / 0.03–0.12 Alzheimer's disease 2.40–8.18 / 0.02–0.13 Control 1.80–7.80 / 0.03–0.12	Dementia	↔ (DDE) ↔ (DDT)
		Alzheimer's disease	↔ (DDE) ↔ (DDT)
Richardson et al. 2014 Case-control, 86 Alzheimer's disease patients (mean age 70.2 years) and 79 controls (mean age 74.1 years); cases and controls combined for analysis (United States)	Serum DDE (tertiles, ng/g cholesterol): T1: 90–260 T2: 270–1,640 T3: 1,660–18,750	Alzheimer's disease T2 versus T1 T3 versus T1	 ↔ ↑
		Mini mental status Exam score T3 versus T1	 ↓
Steenland et al. 2014 Cross-sectional, 89 adults, mean age 74 years (Costa Rica)	Serum DDT metrics (quartiles, ng/mL): DDE / DDT Q1 <0.27 / <0.09 Q2 ≥0.27–0.69 / ≥0.09–0.13 Q3 >0.69–1.26 / >0.13–0.17 Q4 >1.26 / >0.17	Mini mental status Exam score	↔ (DDE) ↔ (DDT)
		Tremor-at-rest	↔ (DDE) ↔ (DDT)
Weisskopf et al. 2010 Nested case-control, 101 confirmed cases of Parkinson's disease (mean age 49.7 years) and 349 matched controls (mean age 52.8 years); cases and controls combined for analysis (Finland)	Serum DDT metrics (IQR, ng/g lipid) DDE: 787–1,676 DDT: 191.8–359.4	Parkinson's disease Confirmed cases (all) Confirmed cases (never smokers)	 ↔ (DDE) ↔ (DDT) ↔ (DDE) ↔ (DDT)
Child/adolescent exposure			
Lee et al. 2007a Cross-sectional, 278 children, including 44 learning disability cases and 26 Attention Deficit Disorder cases, 12–15 years old (United States; NHANES 1999–2000)	Serum DDT (IQR by percentile, ng/g lipid) <50th: 49.0–98.4 ≥50th: 186–528	Learning disabilities	↔
		Attention deficit disorder	↔

Table 2-13. Summary of Neurological Perturbations in Adult or Adolescent Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Rocha-Amador et al. 2009 Cross-sectional, 73 children living in a region in which DDT was used for malaria control, 6–11 years old (Mexico)	Serum DDT metrics (GM±SD, ng/mL): DDE: 57.3±6.6 DDT: 5.5±6.4	Rey-Osterrieth complex figure test: Copy scores Immediate recall scores	 ↔ (DDE) ↔ (DDT) ↓ (DDE) ↔ (DDT)

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified.

↑ = positive association; ↓ = inverse association; ↔ = no association; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; DSST = Digit Symbol Substitution Test (to assess cognitive function); GM = geometric mean; IQR = interquartile range; LOD = limit of detection; NHANES = National Health and Nutrition Examination Survey; Q = quartile or quintile; SD = standard deviation; T = tertile

Table 2-14. Summary of Studies of Associations between Maternal Serum, Cord Blood, Breast Milk, or Placental DDT Exposure Biometrics and Neurological Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Early development assessments such as Bayley Scales of Infant Development (BSID), Brazleton Neonatal Behavior Assessment Scale (BNBAS), Mullen Scales of Early Learning (MSEL), or MacArthur Bates Communicative Development Index (CDI)			
Bahena-Medina et al. 2011 Cohort, 265 maternal-infant pairs (Mexico) BSID assessed at ~1 month	Maternal serum DDE (GM, ng/mL): 1st trimester: 6.33 3rd trimester: 7.27	Neurological soft signs	↔
		Abnormal reflexes	↔
		PDI	↔
		MDI	↔
Engel et al. 2007 Cohort, 151 mother-infant pairs (United States, New York) BNBAS assessed before hospital discharge	Maternal serum DDE (IQR, ng/L): 0.4–1.3	Habituation	↔
		Orientation	↔
		Motor	↔
		Range of state	↔
		Regulation of state	↔
		Autonomic stability	↔
		Abnormal reflexes	↔

Table 2-14. Summary of Studies of Associations between Maternal Serum, Cord Blood, Breast Milk, or Placental DDT Exposure Biometrics and Neurological Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Eskenazi et al. 2006 Cohort, 360 mother-infant pairs (United States, California) BSID assessed at 6 (n=330), 12 (n=327), and 24 (n=309) months	Maternal serum DDT metrics (GM, ng/g lipid): DDE: 1,436 DDT: 22.0 *o,p'*-DDT: 1.8	PDI 6 months 12 months 24 months MDI 6 months 12 or 24 months 	 ↓ (DDT, DDE) ↔ (*o,p'*-DDT) ↔ (DDE) ↓ (DDT) ↔ (*o,p'*-DDT) ↔ (DDE, DDT, *o,p'*-DDT) ↔ (DDE, DDT, *o,p'*-DDT) ↔ (DDE) ↓ (DDT) ↓ (*o,p'*-DDT)
Eskenazi et al. 2018 Cohort, 705 mother-child pairs (365 boys, 340 girls) (South Africa) BSID-III assessed at 1 and 2 years	Maternal serum metrics at birth (IQR, ng/g lipid): DDT: 18.6–254.0 DDE: 92.2–832.5	Cognitive 1 year All Boys Girls 2 years Fine motor 1 year 2 years All, boys Girls *No associations with receptive or expressive communication, gross motor, language or motor composite, or social-emotional metrics*	 ↔ (DDT) ↑ (DDE) ↑ (DDT, DDE) ↔ (DDT, DDE) ↔ (DDT, DDE) ↔ (DDT, DDE) ↔ (DDT, DDE) ↓ (DDT) ↔ (DDE)
Fenster et al. 2007 Cohort, 303 mother-infant pairs (United States, California) BNBAS assessed at ≤2 months	Maternal serum DDT metrics (GM (95% CI), ng/g lipid): DDE: 1,464.2 (1,268–1,691) DDT: 23.2 (19.2–28.2) *o,p'*-DDT: 1.8 (1.5–2.1)	Habituation Orientation Motor Range of state Regulation of state Autonomic stability Reflexes	↔ ↔ ↔ ↔ ↔ ↔ ↔
Forns et al. 2012b Cohort, 1,391 mother-child cohort (Spain) BSID assessed at 14 months	Maternal serum DDE (IQR, ng/g lipid): 74.44–200.26	PDI MDI	↔ ↔

Table 2-14. Summary of Studies of Associations between Maternal Serum, Cord Blood, Breast Milk, or Placental DDT Exposure Biometrics and Neurological Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Gascon et al. 2013 Cohort, 1,175 mother-infant pairs (Spain) BSID assessed at 14 months; postnatal estimates based on maternal serum exposure and PBPK modeling	Maternal serum DDE and postnatal estimates of exposure (IQR, ng/g lipid): Maternal: 76.61–204.57 Postnatal 1st 3 months: 107.16–356.48 2nd 3 months: 94.39–447.22 3rd 3 months: 72.86–463.17 4th 3 months: 61.27–417.79	PDI Maternal Postnatal MDI Maternal Postnatal	 ↔ ↔ ↔ ↔
Gladen et al. 1988 Cohort, 302 mother-child pairs (United States, North Carolina) BSID assessed at 6 and 12 months	Transplacental DDE exposure categories based on maternal milk at birth (ng/g lipid): 1. 0–0.9 5. 4–4.9 2. 1–1.9 6. 5–5.9 3. 2–2.9 7. 6+ 4. 3–3.9 Estimated DDE intake from breast milk from birth to age of test was also calculated (exposure levels not reported)	PDI Transplacental Milk intake MDI Transplacental 6 months 12 months Milk intake 6 months 12 months	 ↔ ↔ ↑ ↔ ↔ ↔
Hoyer et al. 2015 Cohort, 1,103 mother-child pairs from Ukraine (n=492), Poland (n=520), and Greenland (n=91) Assessment of early development milestones assessed by parental recall	Maternal serum DDE (tertiles, ng/g lipid): Greenland T1: 5–209 T2: 209–445 T3: 445–3,122 Ukraine T1: 147–488 T2: 88–791 T3: 791–4,834 Poland T1: 88–303 T2: 303–471 T3: 471–1,750	Crawl Stand-up Walking Developmental coordination disorder score	↔ ↔ ↔ ↔

Table 2-14. Summary of Studies of Associations between Maternal Serum, Cord Blood, Breast Milk, or Placental DDT Exposure Biometrics and Neurological Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Jeddy et al. 2018 Cohort, 400 mother-daughter pairs at study initiation (England) CDI assessed by mothers at 15 months and 38 months	15-month follow-up (n=375 for DDE; n=363 for DDT) Maternal serum DDT metrics at GW 15 (tertiles, ng/g lipid): DDE / DDT T1: ≤229.5 / ≤9.0 T2: 229.51–420.0 / 9.01–14.7 T3: >420.0 / >14.7	Verbal Comprehension T2–T3 p-trend Nonverbal communication, social development or vocabulary comprehension and production	 ↔ (DDE) ↑ (DDT) ↔ (DDE) ↑ (DDT) ↔ (DDT, DDE)
	For 38-month follow-up (n=339 for DDE; n=331 for DDT) Maternal serum DDT metrics at GW 15 (tertiles, ng/g lipid): DDE / DDT T1: ≤234 / ≤9.2 T2: 234.1–445 / 9.21–14.8 T3: >445 / >14.8 DDT analysis stratified by maternal depression score (EPDS).	Communicative All T2 versus T1 T3 versus T1 p-trend Maternal EPDS ≤6 Maternal EPDS >6 Language T2 versus T1 T3 versus T1 p-trend Intelligibility	 ↔ (DDT, DDE) ↓ (DDT) ↔ (DDE) ↓ (DDT) ↔ (DDE) ↓ (DDT) ↔ (DDT) ↔ (DDE, DDT) ↓ (DDE) ↔ (DDT) ↔ (DDE, DDT) ↔ (DDT, DDE)
Jusko et al. 2012 Cohort, 1,100 mother-infant pairs (United States) BSID assessed at 8 months, cognitive development (IQ) assessed at 7 years	Maternal DDT metrics (quintiles, ng/mL): DDE / DDT Q1 <15 / <5 Q2 15–29.9 / 5.0–9.9 Q3 30–44.9 / 10–14.9 Q4 45–59.9 / 15–19.9 Q5 >60 / >20	MDI PDI IQ	↔ (DDE) ↔ (DDT) ↔ (DDE) ↔ (DDT) ↔ (DDE) ↔ (DDT)

Table 2-14. Summary of Studies of Associations between Maternal Serum, Cord Blood, Breast Milk, or Placental DDT Exposure Biometrics and Neurological Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Pan et al. 2009 Cohort, 304 mother-infant pairs (United States, North Carolina) MSEL and CDI assessed at 12 months; breast milk was collected 3-months postpartum	Breast milk DDT metrics (median (range), ng/g lipid): DDE: 121 (1–2,140) DDT: 5 (<LOD–80) Estimated lactational exposure metric to 1 year (median (range), ng/g lipid): DDE: 871 (134–19,260) DDT: 33 (1–523)	Fine motor All	 ↔ (DDE) ↑ (DDT)
		Gross motor All Boys Girls	 ↔ (DDE, DDT) ↑ (DDE) ↔ (DDE)
		No associations with receptive or expressive language, visual reception, or CDI	
Ribas-Fito et al. 2003a Cohort, 92 mother-infant pairs (Spain) BSID assessed at 13 months	Cord blood DDE (median, ng/mL): 0.85	MDI	↓
		PDI	↓
		Griffith scales Locomotor Social Hearing/language Performance Eye-hand coordination	 ↓ ↓ ↔ ↓ ↔
Rogan and Gladen 1991 Cohort, 678 mother-child pairs (United States, North Carolina) BSID assessed at 18 and 24 months	Transplacental DDE exposure categories based on maternal milk at birth (ng/g lipid): 1. 0–0.9 5. 4–4.9 2. 1–1.9 6. 5–5.9 3. 2–2.9 7. 6+ 4. 3–3.9 Estimated DDE intake from breast milk from birth to age of test was also calculated (exposure levels not reported)	MDI Transplacental Milk intake	 ↔ ↔
		PDI Transplacental Milk intake	 ↔ ↔
Ruel et al. 2019 Cohort, 181 mother-child pairs (Netherlands) BSID assessed at 18 months	Maternal serum DDE level at GW 35 (IQR, ng/g lipid): 68.8–144.0	MDI	↔
		PDI	↔

Table 2-14. Summary of Studies of Associations between Maternal Serum, Cord Blood, Breast Milk, or Placental DDT Exposure Biometrics and Neurological Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Sagiv et al. 2008 Cohort, 542 mother, infant pairs (United States, Massachusetts) BNBAS assessed in 408 infants at 1–3 days following birth and at ~2 weeks	Cord blood DDE (mean±SD, ng/g serum): 0.48±0.85	Irritability	↑
		Never in state for orientation items	↑
		Alertness	↔
		Quality of alertness	↔
		Cost of attention	↔
		Consolability	↔
		Self-quieting	↔
		Hand-to-mouth	↔
		Elicited activity	↔
		Spontaneous activity	↔
		Motor maturity	↔
Stewart et al. 2000 Cohort, 293 mother-child pairs, including 141 fish-eaters and 152 non-fish-eaters (United States, New York) BNBAS assessed at 12–24 and 25–48 hours after birth	Cord blood DDE (IQR, ng/g): 0.06–0.18	Habituation	↔
		Autonomic	↔
		Abnormal reflexes	↔
		Percent poor NBAS scores	↔
Torres-Sanchez et al. 2007 Cohort, 244 mother-infant pairs (Mexico) BSID assessed at 1, 3, 6, and 12 months	Maternal serum DDE (GM±GSD, ng/mL) Pre-pregnancy: 6.8±2.8 1st trimester: 6.4±2.8 2nd trimester: 6.8±2.9 3rd trimester: 7.8±2.8	MDI	
		Pre-pregnancy	↔
		All trimesters	↔
		PDI	
		Pre-pregnancy	↔
		1st trimester	↓
		2nd trimester	↔
		3rd trimester	↔
Torres-Sanchez et al. 2009 Cohort, 270 mother-child pairs (Mexico) BSID assessed at 12, 18, 24, and 30 months	Maternal serum DDE (GM±GSD, ng/mL) 1st trimester: 6.3±3.1 2nd trimester: 6.5±3.0 3rd trimester: 7.9±2.8	MDI and PDI All trimesters	↔

Table 2-14. Summary of Studies of Associations between Maternal Serum, Cord Blood, Breast Milk, or Placental DDT Exposure Biometrics and Neurological Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Behavioral problems, attention and ADHD			
Berghuis et al. 2018 Cohort, 101 mother-child pairs (55 boys, 46 girls) (Holland) Attention assessed at 13–15 years using TEA-Ch	Maternal serum DDE (IQR, ng/g lipid) 64.2–127.9	Attention	↔
Forns et al. 2012a Cohort, 393 mother-child pairs (Spain) Child attention evaluated at 11 years using the CPT-II	Cord blood DDE and child serum DDE at 4 years (IQR, ng/mL) Cord blood: 0.56–1.85 Serum: 0.46–1.81	tHRT (speed of correct response)	↓
		Errors of omission or commission	↔
Forns et al. 2016 Cohort, 522 mother-infant pairs (Norway) Children evaluated for behavioral problems at 12 and 24 months using the ITSC	Breast milk DDT metrics (IQR, ng/g lipid) DDE: 33.33–76.00 DDT: 2.44–4.47	Behavioral problems 12 months 24 months	 ↔ (DDE) ↑ (DDT) ↔ (DDE, DDT)
Lenters et al. 2019a, 2019b Cohort, 1,199 mother-child pairs including 55 children with ADHD and 1,144 without (Norway) Children assessed for clinical ADHD diagnosis at 13 years	Milk DDT metrics at a median of 33 days postpartum (IQR, ng/g) DDE: 32.78–73.76 DDT: 1.400–2.936	ADHD	↔ (DDE) ↓ (DDT)
Rosenquist et al. 2017 Cohort, 1,018 mother-child pairs (Greenland [n=525] and Ukraine [n=493]) Children assessed between 5 to 9 years by SDQ completed by parents	Maternal serum DDE (median, ng/g lipids) Pooled: 465 Greenland: 299 Ukraine: 639 Estimated postnatal serum DDE from birth to 1 year (median, ng/g lipids) Pooled: 9,642 Greenland: 7,075 Ukraine: 12,459	Total difficulties Maternal or postnatal	 ↔ (pooled or Individual)
		Emotional symptoms Maternal or postnatal	 ↔ (pooled or Individual)
		Conduct problems Maternal Postnatal	 ↑ (pooled, Ukraine) ↔ (Greenland) ↑ (pooled) ↔ (Individual)

Table 2-14. Summary of Studies of Associations between Maternal Serum, Cord Blood, Breast Milk, or Placental DDT Exposure Biometrics and Neurological Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
		Hyperactivity	
		Maternal	↑ (pooled) ↔ (individual)
		Postnatal	↔ (pooled or individual)
		Peer problems	
		Maternal	↔ (pooled or individual)
		Postnatal	↑ (pooled, Ukraine) ↔ (Greenland)
		Prosocial behavior	
		Maternal	↔ (pooled or individual)
		Postnatal	↔ (pooled, Ukraine) ↑ (Greenland)
Sagiv et al. 2010 Cohort, 573 mother-child pairs (Massachusetts) ADHD measured in children at 7–11 years using Connors' Rating Scale for Teachers	Cord blood DDE (median (5^{th}–95^{th} percentile), ng/g serum): 0.31 (0.11–1.32) Quartile levels not provided	Conners' ADHD index	
		P95 versus P5	↔
		Q4 versus Q1	↑
		DSM-IV inattentive	
		P95 versus P5	↔
		Q4 versus Q1	↔
		DSM-IV hyperactive-impulse	
		P95 versus P5	↑
		Q4 versus Q1	↔
		DSM-IV total	
		P95 versus P5	↑
		Q4 versus Q1	↑
Sioen et al. 2013 Cohort, 270 mother-child pairs (130 boys,140 girls) (Belgium) Child behavioral problems assessed at 7–8 years; SDQ completed by parents	Cord blood DDE (IQR, ng/g fat) All: 67.2, 218.5 Boys: 67.6, 226.0 Girls: 66.7, 205.9	Emotional symptoms	↔
		Conduct problems	↔
		Hyperactivity	↔
		Total difficulties	
		All	↑
		Boys	↔
		Girls	↑

Table 2-14. Summary of Studies of Associations between Maternal Serum, Cord Blood, Breast Milk, or Placental DDT Exposure Biometrics and Neurological Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Strom et al. 2014 Cohort, 872 mother-offspring pairs (Denmark) 22-year prospective follow-up to assess ADHD (n=27), depression (n=104), and scholastic achievement below median on standardized written examinations in 9th grade (n=383)	Maternal serum DDE (tertiles, ng/mL) T1: 0.20–1.86 T2: >1.86–3.24 T3: >3.24–38.77	ADHD	↔
		Depression	↔
		Scholastic achievement below median	↔
McCarthy Scales of Children's Abilities (MSCA), Wide Range Assessment of Memory and Learning (WRAML), or Wechsler Intelligence Scale for Children (WISC)			
Berghuis et al. 2018 Cohort, 101 mother-child pairs (55 boys, 46 girls), (Holland) WISC, AVLT, TEA-Ch, and Movement-ABC assessed at 13-15 years	Maternal serum DDE (IQR, ng/g lipid) 64.2–127.9	Intelligence	↔
		Memory	↔
		Subclinical motor skills (total score)	
		All	↔
		Boys	↑
		Girls	↔
Gaspar et al. 2015a, 2015b Cohort, 619 mother-child pairs (United States, California) WISC assessed at 7 years (n=316) and 10.5 years (n=595)	Maternal serum DDT metrics (IQR, ng/g lipid) DDT: 7.0–34.9 DDE: 257.2–1,165	Working memory	
		All	↔ (DDT, DDE)
		Boys	↑ (DDE)
		Girls	↔ (DDE)
		Perceptual reasoning	
		All	↔ (DDT, DDE)
		Boys	↔ (DDE)
		Girls	↔ (DDE)
		Verbal comprehension	
		All	↔ (DDT/DDE)
		Boys	↔ (DDE)
		Girls	↓ (DDE)
		Processing speed	
		All	↓ (DDT) ↔ (DDE)
		Boys	↔ (DDE)
		Girls	↓ (DDE)
		Full-scale IQ	
		All	↔ (DDT, DDE)
		Boys	↔ (DDE)
		Girls	↓ (DDE)

Table 2-14. Summary of Studies of Associations between Maternal Serum, Cord Blood, Breast Milk, or Placental DDT Exposure Biometrics and Neurological Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Gladen and Rogan 1991 Cohort, 370 mother-child pairs (United States, North Carolina) MSCA assessed at 3, 4, and 5 years	Transplacental DDE exposure categories based on maternal milk at birth (ng/g lipid): 1. 0–0.9 2. 1–1.9 3. 2–2.9 4. 3–3.9 5. 4–4.9 6. 5–5.9 7. 6+ Estimated DDE intake from breast milk from birth to age of test (ng/g lipid) 1. 0–3 2. 3–7 3. 7-11 4. 11–17 5. 17+	MSCA at 3 years Transplacental	↔
		MSCA at 4 years Transplacental Postnatal	↔
		MSCA at 5 years Transplacental	↔
Kyriklaki et al. 2016 Cohort, 689 mother-child cohort (Greece) MSCA assessed at 4 years	Maternal serum DDE (IQR, ng/mL): 1.9559–3.5353	MSCA	↔
Lyall et al. 2016 Cohort, 1,144 mother-infant pairs (United States, California) ASD cases (n=545); intellectual disability cases (n=181); control (general population) (n=418)	Maternal serum DDE (quartiles, ng/g lipid): Q1: <121.7 Q2: 121.7–212.5 Q3: 212.5–<505.4 Q4: ≥505.4	ASD Q2–Q4 p-trend	 ↔ ↔
		Intellectual disability Q2 Q3 Q4 p-trend	 ↔ ↑ ↔ ↔
Orenstein et al. 2014 Cohort, 393 mother-child pairs living near New Bedford Harbor Superfund Site (United States, Massachusetts) Memory and learning assessed at 8 years using WRAML	Cord blood DDE (mean±SD, ng/g serum): 0.5±01.1	Visual memory	↔
		Verbal memory	↔
		Learning	↔

Table 2-14. Summary of Studies of Associations between Maternal Serum, Cord Blood, Breast Milk, or Placental DDT Exposure Biometrics and Neurological Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Osorio-Valencia et al. 2015 Cohort, 167 mother-child pairs (Mexico) MSCA assessed at 5 years for laterality and spatial orientation endpoints only	Maternal serum DDE by trimester (median (10^{th}–90^{th} percentiles), ng/g lipid): 1^{st}: 1,331.1 (260.8–4,253.9) 2^{nd}: 1,138.1 (152.7–2,983.4) 3^{rd}: 826.3 (149.0–2,767.6)	Laterality	↔
		Spatial orientation	↔
Ribas-Fito et al. 2006 Cohort, 475 mother-child pairs from the Ribera d'Ebre cohort (n=70) and the Menorca cohort (n=405) (Spain) MSCA assessed at 4 years	Cord blood DDT metrics (IQR, ng/mL): Ribera / Menorca DDT 0.01–0.05 / 0.04–0.21 DDE 0.50–1.70 / 0.57–1.94 DDT quartiles (ng/mL) Q1: ≤0.05 Q2: >0.051–0.10 Q3: >0.101–0.20 Q4: >0.20 Quartile analysis not conducted for DDE	GCI Continuous Q4 versus Q1 All Boy Girls	 ↓ (DDT) ↔ (DDE) ↓ (DDT) ↔ (DDT) ↓ (DDT)
		Memory Continuous Q4 versus Q1 All Boy Girls	 ↓ (DDT) ↓ (DDE) ↓ (DDT) ↔ (DDE) ↓ (DDT)
		Verbal Continuous Q4 versus Q1 All Boy Girls	 ↓ (DDT) ↔ (DDE) ↓ (DDT) ↔ (DDE) ↓ (DDT)
		Executive function Continuous	 ↓ (DDT) ↔ (DDE)
		Memory span Continuous	 ↓ (DDT) ↔ (DDE)
		Verbal memory Continuous	 ↓ (DDT) ↔ (DDE)

Table 2-14. Summary of Studies of Associations between Maternal Serum, Cord Blood, Breast Milk, or Placental DDT Exposure Biometrics and Neurological Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Ribas-Fito et al. 2007 Cohort, 391 mother-infant pairs (Spain) MSCA assessed at 4 years	Cord blood DDT by duration of breastfeeding (IQR, ng/mL): DDT DDE <2 weeks 0.04–0.27 0.49–1.94 2–20 weeks 0.04–0.23 0.56–2.02 >20 weeks 0.03–0.14 0.62–1.77	GCS 2–20 versus <2 weeks >20 versus <2 weeks	↔ (DDT, DDE) ↑ (all or high DDT exposure) ↔ (DDE)
		Verbal scale 2–20 versus <2 weeks >20 versus <2 weeks	↔ (DDT, DDE) ↔ (DDT, DDE)
		Memory scale 2–20 versus <2 weeks >20 versus <2 weeks	↔ (DDT, DDE) ↔ (DDT, DDE)
Companion study to Ribas-Fito et al. 2006	DDT exposure groups (ng/mL) Low (n=162): <0.05 Medium (n=138): 0.05–0.20 High (n=91): >0.20		
Sagiv et al. 2012 Cohort, 584 mother-child pairs (258 boys, 254 girls) (United States, Massachusetts) CPT (n=578) and WISC (n=584) assessed at 8 years	Cord serum DDE (mean±SD, ng/g): 0.50±1.03	CPT Reaction time and time variability Errors of omission or commission	↔ ↔
		WISC Processing speed Freedom from distractibility	↔ ↔
Torres-Sanchez et al. 2013 Cohort, 203 mother-child pairs (Mexico) MSCA assessed at 42, 48, 54, and 60 months	Maternal serum DDE (median (10^{th}–90^{th} percentile, ng/mL) 1^{st} trimester: 7.65 (1.84–23.05) 2^{nd} trimester: 8.22 (1.32–23.41) 3^{rd} trimester: 8.95 (1.7–29.20)	GCI 1^{st} or 2^{nd} trimester 3^{rd} trimester Average	↔ ↓ ↔
		GCI: perceptual performance	↔
		GCI: quantitative 1^{st} or 2^{nd} trimester 3^{rd} trimester Average	↔ ↓ ↓
		GCI: verbal 1^{st} or 2^{nd} trimester 3^{rd} trimester Average	↔ ↓ ↔
		Memory 1^{st} or 2^{nd} trimester 3^{rd} trimester Average	↔ ↓ ↔
		Motor	↔

Table 2-14. Summary of Studies of Associations between Maternal Serum, Cord Blood, Breast Milk, or Placental DDT Exposure Biometrics and Neurological Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Traglia et al. 2017 Nested case-control from two cohorts, 790 mother-child pairs (390 cases of ASD, 400 controls) and 764 infants (366 cases of ASD, 369 controls) (United States, California)	Maternal and neonatal serum DDE levels: NR	ASD	↔
Other			
Cartier et al. 2014 Cohort/Cross-sectional, 146 Inuit children (Canada, Nunavik) VEP evaluation at 11 years	Cord blood DDT metrics (mean±SD, ng/g lipids): DDE: 509.27±295.31 DDT: 24.45±23.20 Child serum DDT metrics at 5 years: NR Child serum DD metrics at 11 years (GM, ng/g lipids): DDE: 268.54±265.14 DDT: 6.93±5.68	N150 amplitude Cord blood 5-year serum 11-year serum N75 amplitude Cord blood 5-year serum 11-year serum P100 wave latency Cord blood 5-year serum 11-year serum	 ↑ (DDE) ↔ (DDT) ↔ (DDE, DDT) ↔ (DDE, DDT) ↔ (DDE, DDT) ↓ (DDE) ↔ (DDT) ↔ (DDE, DDT) ↔ (DDE, DDT) ↔ (DDE, DDT) ↔ (DDE, DDT)
Riva et al. 2004 Cohort, mother-infant pairs (n=25) (Italy) VEP evaluation at 12 months	Colostrum and milk levels (30- and 90-days postpartum) of DDT and DDE (NR)	P100 wave latency	↔ (DDE) ↔ (DDT)

Table 2-14. Summary of Studies of Associations between Maternal Serum, Cord Blood, Breast Milk, or Placental DDT Exposure Biometrics and Neurological Outcomes in Offspring[a]

Reference, study type, and population	Biomarker[b]			Outcome evaluated	Result
Ren et al. 2011	Placental DDT metrics (IQR, ng/g lipid)			Anencephaly	↑ (Σ*o,p'*-DDTs)
				Spina bifida	↑ (Σ*o,p'*-DDTs)
Case-control, 80 fetuses or newborns with neural tube defect and 50 healthy matched controls; cases and controls combined for analysis (China)		Cases	Controls	Any neural tube defects	↑ (Σ*o,p'*-DDTs)
	o,p'-DDT	0.47–2.2	0.25–1.0		
	o,p'-DDE	0.70–1.8	0.53–1.0		
	o,p'-DDD	0.84–3.0	0.76–1.9		
	Σ*o,p'*-DDTs	2.5–7.6	2.0–3.8		
	p,p'-DDT	0.40–2.0	0.30–1.1		
Neural tube defect cases (n=80 fetuses or newborns)	*p,p'*-DDE	26–79	37–76		
	p,p'-DDT	2.2–7.6	2.4–6.2		
Healthy matched controls (n=50 newborns)	Σ*p,p'*-DDTs	31–85	39–83		
	Σall DDTs	35–98	41–88		

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDD = *p,p'*-DDD, unless otherwise specified; DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified.

↑ = positive association; ↓ = inverse association; ↔ = no association; ADHD = attention deficit hyperactivity disorder; ADHD-DSM-IV = ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ASD = autism spectrum disorder; AVLT = Auditory Verbal Learning Test; BNBAS or NBAS = Brazelton Neonatal Behavioral Assessment Scale (two components for evaluating behavior and reflex); BSID = Bayley Scales of Infant Development (for mental and psychomotor development); CDI = MacArthur-Bates Communicative-Development Inventories (to measure language comprehension); CI = confidence interval; CPT = Continuous Performance Test; CPT-II = Cognitive Performance Test-II; DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloro-ethylene; DDT = dichlorodiphenyltrichloroethane; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EPDS = Edinburgh Postnatal Depression Scale; GCI = general cognitive index; GCS = General Cognitive Score; GM = geometric mean; GSD = geometric standard deviation; GW = gestation week; HRT = hit reaction time (measures speed of visual processing); IQ = intelligence quotient; IQR = interquartile range; ITSC = infant toddler symptom checklist; LOD = limit of detection; MDI = mental development index; Movement-ABC = Movement Assessment Battery for Children; MSCA = McCarthy Scales of Children's Abilities (to assess cognitive and motor development); MSEL = Mullen Scales of Early Learning; NBAS = Neonatal Behavioral Assessment Scale; NR = not reported; PBPK = physiologically based pharmacokinetic; PDI = psychomotor developmental index; Q = quartile or quintile; SD = standard deviation; SDQ = Strengths and Difficulties Questionnaire; T= tertile; TEA-Ch = Test of Everyday Attention for Children; VEP = visual evoked potential (to assess visual brain function/visual processing); WISC = Wechsler Intelligence Scale for Children; WRAML = Wide Range Assessment of Memory and Learning

In laboratory animals orally exposed to DDT or metabolites, tremors, convulsions, or myoclonus (abrupt, repeated involuntary contractions of skeletal muscles) and increases in brain biogenic amine and neurotransmitter levels have been observed at acute-duration doses ≥50 mg DDT/kg/day (see text below for references). Acute-duration oral administration of DDT and related compounds *in utero* or to neonates during sensitive periods of neurodevelopment also has been associated with behavioral and neurochemical changes in mice (see Section 2.17 for references and more details).

Tremors, hyperactivity, or hunched appearance have been observed in mature laboratory animals after intermediate- or chronic-duration oral exposure to *p,p'*-DDT, technical DDT, or *p,p'*-DDE at intermediate-duration doses as low as 27 mg *p,p'*-DDE/kg/day and chronic-duration doses as low as 6.9 mg *p,p'*-DDT/kg/day, but these signs of neurological dysfunction were not observed in laboratory rats or mice exposed chronically to doses as high as 231 mg technical DDD/kg/day (see text below for references).

Evidence for Neurological Effects in Controlled-Exposure Human Studies. The nervous system appears to be one of the primary target systems for DDT toxicity in humans after acute-duration, high level exposures. Several investigators conducted experimental studies on humans in the 1940s and 1950s at controlled high doses that produced neurological effects (e.g., Hayes et al. 1956; Velbinger 1947a, 1947b). Other data come from accidental poisonings where dose levels were crudely estimated. Persons exposed to 6 mg DDT/kg administered orally by capsule generally exhibited no illness, but perspiration, headache, and nausea were reported (Hayes 1982), and convulsions were reported at doses of 16 mg DDT/kg or higher (Hsieh 1954). In a controlled exposure study with volunteers given single oral doses of DDT suspended in oil, the reported symptoms included prickly sensation of the mouth at 250 or 500 mg; uncertain gait, malaise, cold moist skin, and hypersensitivity to dermal contact within 6 hours of dosing with 750 or 1,000 mg; and prickly tongue, mouth, and nose, dizziness, confusion, tremors, headache, fatigue, and vomiting within 10 hours of dosing with 1,500 mg (about 22 mg/kg) (Velbinger 1947a, 1947b). Symptoms disappeared within 24 hours of dosing. Similar symptoms were reported in persons after accidental or intentional ingestion of DDT (Francone et al. 1952; Garrett 1947; Hsieh 1954; Mulhens 1946). No neurological effects were noted in 51 volunteers who ingested 3.5 or 35 mg DDT/day (0.05–0.063 or 0.36–0.5 mg/kg/day) for 12–18 months (Hayes et al. 1956). The subjects displayed no loss of coordination and there was no indication of tremors. Other tests (over 20) conducted on the volunteers were negative and showed no peripheral neuropathy or central nervous system functional deficits. Background DDT levels in food of both controls and test subjects were 0.0021–0.0038 mg DDT/kg/day.

Neurological Adult or Adolescent Epidemiological Studies. Possible associations between serum levels of DDT, DDE, or DDD and deficits in cognitive or mental status tests or risks for neurological conditions, such as Alzheimer's, Parkinson's disease, or attention deficient disorder have been evaluated in studies described in Table 2-13. The studies provide inconsistent evidence for such associations. In adults, associations were found with low Digit Symbol Substitution Test scores in U.S. adults ages 60–85 years participating in the 1999–2002 NHANES (Kim et al. 2015a, 2015b, 2015c) and with increased risk for

Alzheimer's disease and decreased Mini Mental Status Exam (MMSE) scores in a U.S. case-control study (Richardson et al. 2014), but no significant associations were found between serum biometrics and increased risk for cognitive impairment in 70-year-old Swedish adults (Lee et al. 2016a, 2016b); increased risk for dementia or Alzheimer's disease in Canadian adults (Medehouenou et al. 2014); decreased MMSE scores or increased risk for at-rest tremors in Costa Rican adults ages >65 years (Steenland et al. 2014), or increased risk for Parkinson's disease in Finnish adults ages 20–70 years (Weisskopf et al. 2010). No significant associations were found between serum DDT or DDE levels and increased risks for learning disability or attention deficient disorder in U.S. adolescents ages 12–15 years participating in the NHANES (Lee et al. 2007a), but serum levels of DDE were associated with decreased scores for a test of visual memory in 6–11-year-olds living in a Mexican region in which DDT was used for malaria control (Rocha-Amador et al. 2009).

Neurodevelopmental Epidemiological Studies. Possible associations between DDT, DDE, or DDD levels in maternal serum at birth or during pregnancy, cord blood, placenta tissue, or breast milk with adverse neurodevelopmental effects in offspring have been examined in numerous epidemiological studies. To date, these studies (summarized in Table 2-14) provide inconsistent evidence for such associations. Studies in Table 2-14 are presented in four groups of studies evaluating associations with: (1) neurobehavioral endpoints in infants ≤2 years of age using the Bayley Scales of Infant Development (BSID), the Brazelton Neonatal Behavioral Assessment Scale (BNBAS), Mullen Scales of Early Learning (MSEL), or the MacArthur-Bates Communicative Development Inventories (CDI); (2) behavioral problems, attention and attention deficit hyperactivity disorder (ADHD) in offspring; (3) cognitive endpoints in older children using McCarthy Scales of Children's Abilities (MSCA), Wide Range Assessment of Memory and Learning (WRAML), Wechsler Intelligence Scale for Children (WISC), and related methods; and (4) other neurological endpoints in offspring. The following paragraphs summarize the inconsistency of the evidence relating maternal biometrics for DDT, DDE, or DDD with related neurological outcomes in offspring.

Early neurodevelopment epidemiological studies. Using the BSID, no associations between maternal DDT, DDE, or DDD biometrics and adverse early developmental scores in children up to about 30 months after birth were found in a North Carolina cohort (Gladen et al. 1988; Rogan and Gladen 1991), a U.S. 12-center cohort (Jusko et al. 2012), cohorts from Sabadell, Gipuzkoa, and Valencia, Spain (Forns et al. 2012b; Gascon et al. 2013), or a cohort from the Netherlands (Ruel et al. 2019). However, significant associations with age-dependent BSID deficits were reported for cohorts from Ribera d'Ebre and Menorca, Spain (Ribas-Fito et al. 2003a); Salinas, California (Eskenazi et al. 2006); Morelos, Mexico (Bahena-

Medina et al. 2011; Torres-Sanchez et al. 2007, 2013), and Limpopo, South Africa (Eskenazi et al. 2018). In another North Carolina birth cohort, significant associations were reported for MSEL motor deficits, but not for MSEL language scales or CDI scores, in 12-month-olds in a 2004–2006 North Carolina birth cohort (Pan et al. 2009). In a British birth cohort, decreased communication and language CDI scores were associated with maternal serum DDT metrics at 38 months; no associations were observed between maternal DDT metrics and CDI scores at 15 months (Jeddy et al. 2018). No significant associations were reported with time of achieving early development milestones (e.g., crawling or walking) in cohorts from Ukraine, Poland, and Greenland (Hoyer et al. 2015). No statistically significant associations with BNBAS deficits for infants <2 weeks of age were found in cohorts from New York City (Engel et al. 2007); Oswego, New York (Stewart et al. 2000); or Salinas, California (Fenster et al. 2007), but significant associations were reported for attention-related BNBAS deficits in a New Bedford, Massachusetts cohort (Sagiv et al. 2008).

Epidemiological studies of attention, behavioral problems, or ADHD in offspring. Diagnosis of ADHD and/or attention impairments were not associated with increased maternal or cord blood biometrics in a 22-year follow-up of offspring from a Danish cohort (Strom et al. 2014), 13-year-olds from a Norwegian cohort (Lenters et al. 2019a), 4-year-olds from a Greek cohort (Kyriklaki et al. 2016), 11-year-olds from a Spanish cohort (Forns et al. 2012a), or 13–15-year-olds from a Dutch cohort (Berghuis et al. 2018). However, a positive association was found between cord blood DDE and Connors' ADHD Index in children ages 7–11 years in a New Bedford Massachusetts cohort (Sagiv et al. 2010). A meta-analysis of 11 cohorts from 8 European countries did not observe a significant association between DDE levels (cord blood or maternal serum, blood, or breast milk) and ADHD in a pooled analysis (Forns et al. 2018).

General behavior problem scores at 12 months (assessed using the Infant Toddler Symptom Checklist) were associated with breast milk DDT levels in a Norwegian cohort, but not at 24 months (Forns et al. 2016). Strengths and Difficulties Questionnaire (SDQ) scores for total behavioral difficulties were also positively associated with maternal biometrics for children ages 7–8 years in a Flemish cohort (Sioen et al. 2013), but not children ages 5–9 years from Greenland or the Ukraine (Rosenquist et al. 2017). However, individual behavior (hyperactivity, conduct, or peer problems) scores in 5–9-year-old children from Greenland or the Ukraine were positively associated with maternal and/or prenatal serum DDE (Rosenquist et al. 2017).

Epidemiological studies of cognitive endpoints in non-infant children. No associations with maternal biometrics were found for MSCA-evaluated deficits in 3–5-year-old children in a North Carolina cohort

(Gladen and Rogan 1991); MSCA deficits in 4-year-old children in a Greek cohort (Kyriklaki et al. 2016), or WRAML deficits in 8-year-olds in a New Bedford, Massachusetts cohort (Orenstein et al. 2014), but associations were reported for MSCA cognitive deficits, but not spatial orientation deficits, in 42–60-month-old children in a Morelos, Mexico cohort (Osorio-Valencia et al. 2015; Torres-Sanchez et al. 2013) and MSCA general cognitive and memory deficits in 4-year-old children in cohorts from Ribera d'Ebre and Menorca, Spain (Ribas-Fito et al. 2006, 2007). In intelligence assessments, no associations were reported with IQ in 7-year-old children in a U.S. 12-center cohort (Jusko et al. 2012), 8-year-old children in a New Bedford, Massachusetts cohort (Sagiv et al. 2012), or 13–15-year-olds from a Dutch cohort (Berghuis et al. 2018). However, associations were reported with IQ deficits at 7 years of age, but not at 10.5 years of age, in children (especially girls) in a Salinas, California cohort (Gaspar et al. 2015a, 2015b) and for increased risk for intellectual disability, but not autism spectrum disorder (ASD), in a 2000–2003 Southern California birth cohort (Lyall et al. 2016). In a nested case-control study from a Californian birth cohort, ASD case status was not associated with maternal or neonatal serum DDE levels (Traglia et al. 2017).

Epidemiological studies of other neurodevelopmental endpoints in offspring. Associations between cord blood DDE levels and visual evoked potential (VEP) deficits were reported in a group of 150 11-year-old children (Cartier et al. 2014), but no significant associations were found for VEP deficits in a group of 25 12-month-old children (Riva et al. 2004). Placental levels of Σ*o,p'*-DDTs, but not *Σp,p'-DDTs*, were significantly associated with increased risk of neural tube defects in a study of 80 cases and 50 controls without neural tube defects (Ren et al. 2011).

Evidence for Neurological Effects in Laboratory Animals. The nervous system appears to be one of the primary targets in animals after acute-, intermediate-, and chronic-duration oral exposure to technical or *p,p'*-DDT. Several older acute- or intermediate-duration studies (Henderson and Woolley 1969; Hrdina and Singhal 1972; Hrdina et al. 1973; Khairy 1959; Sobotka 1971; Talts et al. 1998; vom Saal et al. 1995) are mentioned in the text below to reflect the breadth of supporting evidence, but were not included in Table 2-1 and Figure 2-2 for various reasons such as poor study design (e.g., low number of animals), lack of comprehensive endpoint evaluation, poor data reporting, outdated methodologies, or exposure levels well above exposure levels producing the most sensitive neurological endpoints. Clinical signs of neurological effects also have been observed in rats and mice after chronic-duration dietary exposure to *p,p'*-DDE, but were not observed in rats or mice after chronic-duration exposure to technical DDD (NCI 1978).

Acute-duration oral exposure to high doses of DDT has been associated with DDT-induced tremors or myoclonus (abrupt, repeated involuntary contractions of skeletal muscles), hyperexcitability, or tremors and convulsions in several species. These effects have been observed in rats after single high gavage doses of about 50–600 mg technical *p,p'*-DDT/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; supported by Henderson and Woolley 1969; Hrdina and Singhal 1972; Hrdina et al. 1973). Mice receiving single gavage doses of 160 mg DDT(NS)/kg had tremors (Hietanen and Vainio 1976), and single doses of 200–600 mg *p,p'*-DDT/kg/day induced convulsions (Matin et al. 1981). In guinea pigs and hamsters similarly dosed, no tremors were observed at 160 mg DDT(NS)/kg, but hind leg paralysis occurred in guinea pigs (Hietanen and Vainio 1976).

Acute-duration oral exposure of animals to DDT and related compounds also has been associated with increases in brain biogenic amine and neurotransmitter levels. Alterations in the metabolite 5-hydroxy-indoleacetic acid (5-HIAA), the degradation product of serotonin, have been reported to correlate with DDT-induced tremors; doses ≥50 mg *p,p'*-DDT/kg/day resulted in increases in the levels of 5-HIAA in the brain (Hong et al. 1986; Hudson et al. 1985; Hwang and Van Woert 1978; Tilson et al. 1986 supported by Hrdina et al. 1973). Alterations in the levels of other neurotransmitters have been found. The neurotransmitter changes observed are consistent with a mechanistic hypothesis that DDT and metabolites influence membrane ion fluxes and consequently potentiate neurotransmitter release. Acetylcholine and norepinephrine decreased in rats after acute-duration oral exposure to 400 mg/kg DDT (Hrdina et al. 1973), and aspartate and glutamate were statistically significantly increased in brain tissue of F344 rats after administration of single oral doses ≥50 mg *p,p'*-DDT/kg (Hong et al. 1986; Hudson et al. 1985; Tilson et al. 1986).

Acute-duration oral administration of DDT and related compounds *in utero* or to neonates during sensitive periods of neurodevelopment has been associated with behavioral and neurochemical changes in mice (see Section 2.17 for more details and references).

Behavioral effects have been examined in only a few studies of rodents exposed to DDT as adults. Administration of single oral doses as high as 100 mg *p,p'*-DDT/kg to male F344 rats did not markedly impair their ability to acquire a conditioned behavioral response, although ≥50 mg/kg doses produced tremors, and death occurred in some rats in the 100 mg/kg group (Tilson et al. 1987). Two earlier reports provided inconsistent evidence of DDT effects on behavioral endpoints, but they examined different

behavioral endpoints. Sobotka (1971) reported an impairment of habituation in open field activity in adult albino mice after administration of single oral doses of 25 mg DDT(NS)/kg, but not after 10 mg/kg. No statistically significant differences in tests of problem solving, locomotion speed, or reaction to stress were found between untreated rats and rats given oral doses up to 30 mg DDT (NS)/kg/day in food for 21 days (Khairy 1959). The doses in these adult animal studies were distinctly higher than the dose of technical DDT administered to neonates in the Eriksson et al. (1990a, 1990b, 1992, 1993) studies discussed in Section 2.17.

Other neurological effects have been reported in animal studies after intermediate-duration oral exposure to DDT or DDE isomers, including body tremors and/or hunched appearance in female Osborne-Mendel rats after 26 weeks of dietary exposure to 30 mg technical DDT/kg/day (NCI 1978), female Wistar rats after 9 weeks of dietary exposure to 34 mg technical DDT/kg/day (Rossi et al. 1977), male B6C3F1 mice after 22 weeks of dietary exposure to 27 *p,p'*-DDE/kg/day (NCI 1978); parental and F1 parental females (but not males) exposed to 27.7 mg/kg/day *p,p'*-DDT for 10 weeks before mating, through gestation and lactation in a 2-generation study (Hojo et al. 2006); and male Osborne-Mendel rats after 8 weeks of dietary exposure to 59 mg of *p,p'*-DDE/kg/day (NCI 1978). Other observed effects include decreased brain levels of total lipids and the relative amount of cholesterol to phospholipid after oral exposure of Rhesus monkeys to 10 mg technical DDT/kg/day for 100 days (Sanyal et al. 1986) and staggering, weakness, and loss of equilibrium in monkeys treated for up to 14 weeks with a lethal dose of 50 mg *p,p'*-DDT/kg/day, but not with exposure to 5 mg/kg/day (Cranmer et al. 1972).

Effects reported in animals after chronic-duration oral exposure include severe tremors in F344/DuCrj rats at doses of 19.1 (males) and 25.2 (females) mg *p,p'*-DDT/kg/d in the diet after 70–104 weeks of exposure (Harada et al. 2003, 2006); severe tremors in some Rhesus and Cynomolgus monkeys exposed in the diet to doses ≥6.9 mg of *p,p'*-DDT/kg/day in a 130-month study (Takayama et al. 1999); and hyperactivity and tremors in chronically exposed mice at dietary doses ≥8.3 mg technical DDT/kg/day (Kashyap et al. 1977; Turusov et al. 1973). In contrast, no clinical signs of neurotoxicity were observed in hamsters fed diets at doses up to 95 mg technical DDT or *p,p'*-DDE/kg/day for life (Rossi et al. 1983). In the 78-week NCI (1978) chronic bioassays, by week 26, tremors or hunched appearance were observed in about 8% of female Osborne-Mendel rats exposed to 30 mg technical DDT/kg/day and in 90% of females exposed to 61 mg technical DDT/kg/day. Tremors were also reported in male rats exposed to technical DDT and *p,p'*-DDE, but due to changes in dosing early in the studies, accurate exposure levels are unclear; tremors ceased when doses were lowered. No tremors were observed in female rats at up to 36 mg *p,p'*-DDE/kg/day or in male or female rats exposed to up to 231 mg technical DDD/kg/day. In

B6C3F1 mice, observations of tremors or hunched appearance in males and females were comparable to controls at dietary doses up to 30.2 mg technical DDT/kg/day and 142 mg technical DDD/kg/day. Male mice exposed to a time-weighted average dose of 47 mg *p,p'*-DDE/kg/day exhibited a hunched appearance in a cyclic fashion throughout the exposure period, but were comparable to controls during the last 12 weeks; no neurological effects were observed in female mice exposed to up to 49 mg *p,p'*-DDE/kg/day (NCI 1978).

Cameron and Burgess (1945) exposed rats, rabbits, and guinea pigs to acute-duration dermal doses ranging from 50 to 200 mg/kg DDT(NS) and reported tremors and nervousness.

Mechanisms of Neurological Effects of DDT, DDE, or DDD. There are several proposed mechanisms for the neurotoxic effects of DDT and its metabolites. DDT has been shown to disrupt nerve membrane ion fluxes through induced closure of sodium channels (Vijverberg et al. 1982), inhibition of potassium transport, and by targeting Na^+/K^+ and Ca^{2+}/Mg^{2+} ATPases (Janicki and Kinter 1971). There is also evidence that DDT can potentiate neurotransmitter release through interference with calcium calmodulin binding, which could then lead to central nervous system excitation and induction of tremors (Harada et al. 2016).

Evidence *in vitro* suggests DDT and its metabolites can also inhibit the plasma membrane dopamine transporter (DAT) and the vesicular monoamine transporter (VMAT2); these transporters are often disrupted in Parkinson's Disease patients (Hatcher et al. 2008). However, *in vivo,* mice exposed orally to 1, 3, or 6 mg DDT/kg every 3 days for 30 days demonstrated none of the expected nigrostriatal effects or evidence of neuronal dysfunction and DDT was not associated with Parkinson's Disease in a study in adults (Weisskopf et al. 2010). This suggests that the effects of DDT and its metabolites on the dopamine system *in vitro* may not translate into neurotoxicological outcomes in exposed individuals (Hatcher et al. 2008).

A study exploring potential mechanisms involved in DDT associations with Alzheimer's disease suggests that DDT may positively affect the amyloid-β (Aβ) synthesis pathway, and impair the clearance and degradation of Aβ peptides, potentially through impairment of the ATP-binding cassette transporter A1 (ABCA1) and insulin-degrading enzyme (IDE), both of which play roles in Aβ homeostasis (Li et al. 2015). Epigenetic changes, particularly alterations in methylation status of neuronal cells and tissues of the brain, are thought to contribute to various neuronal pathologies, including Alzheimer's disease (Shutoh et al. 2009). DNA from the hypothalamus of young rats dosed with 0.06 mg/kg DDT/day for

4 weeks was hypomethylated at CpG islands for six genes, including the estrogen-regulated neuropeptides *Gal, Sst,* and *Penk1*; mRNA levels of several genes including DNA methyltransferase, *Dnmt1*, were also significantly lower in exposed groups (Shutoh et al. 2009). Kajta et al. (2017) proposed that prenatal exposure to DDT may underly adult-onset of neuropsychiatric disorders based on their observation of global DNA hypomethylation following prenatal exposure to DDT in mice that showed depressive-like behaviors in the forced swim and tail suspension tests. Gene expression in the brain for the Htr1a/serotonin signaling pathway and the level of methylation in specific endocrine genes (ESR1, GPER1) were also altered. Whether these changes could contribute to any pathologies is unknown. Further neuro-specific studies looking at genetic and epigenetic changes related to DDT exposure could further our understanding of possible relationships with adverse neurological effects.

2.16 REPRODUCTIVE

Evidence of Reproductive Effects in Humans. Tables 2-15, 2-16, and 2-17 summarize results from epidemiological studies that examined possible associations between exposure to DDT (isomers and metabolites), as assessed by levels of DDT in biological media (mostly blood), and reproductive outcomes. In the majority of the studies, levels of other persistent chemicals also were examined, including PCBs and other organochlorine pesticides. These tables only describe studies that included measurements of DDT metrics in biological fluid in each subject and examined possible associations with reproductive outcomes using correlation, logistic regression, or linear regression statistical techniques.

Table 2-15. Summary of Reproductive Outcomes in Adult Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]			Outcome evaluated	Result
Time to pregnancy (TTP)					
Axmon et al. 2006	Serum DDE (median, ng/g lipid)			Fecundity	
		Men	Women	Women from Greenland	↓
Cross-sectional, 1,505 women and 716 men, age ≥18 years (Greenland, Poland, Ukraine, Sweden)	Greenland	600	300		
	Poland	520	360	Women from other countries	↔
	Ukraine	920	620		
	Sweden	240	820	Men from all countries	↔
	Exposure categories (ng/g lipid) Low: <370 Medium: 370–750 High: >750				

Table 2-15. Summary of Reproductive Outcomes in Adult Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Buck Louis et al. 2013 Cohort, 47 couples that achieved pregnancy (A) and 154 couples that withdrew or did not achieve pregnancy (B), mean age ~30 years old (United States)	Serum DDE in men (GM (95% CI), ng/g) (A): 0.766 (0.721–0.814) (B): 0.818 (0.737–0.980) Serum DDE <LOD in women	Fecundity Males	 ↓
Chen et al. 2018 Cross-sectional, 68 women who had normal duration of pregnancy, mean age 30.5 years (Taiwan)	Milk DDT metrics 3 weeks postpartum (GM±SD, ng/g lipid) DDT: 0.360±0.798 DDE: 8.07±6.53 DDD: 0.161±1.64 ΣDDT: 9.81±7.52	Received medical treatment for infertility	↔ (ΣDDT)
Chevrier et al. 2013 Cross-sectional, 332 pregnant women, mean age 29 years (France)	Cord blood DDE exposure groups (ng/mL) Low: <0.130 Medium: 0.130–0.249 High: >0.250	Fecundity Medium versus low High versus low p-trend	 ↔ ↓ ↓
Harley et al. 2008 Cross-sectional, 289 pregnant women, median age 25 years (United States)	Serum DDT metrics (GM (range), ng/g lipid) DDT: 24 (2–33,174) *o,p'*-DDT: 2 (0.1–1,878) DDE: 1,500 (49–159,303)	Fecundity	↔ (DDT) ↔ (DDE) ↔ (*o,p'*-DDT)
Law et al. 2005 Cross-sectional, 390 pregnant women, median age 23 years (United States)	Serum DDE (quintiles, ng/mL) Q1: 0–14 Q2:15–29 Q3: 30–44 Q4: 45–59 Q5: ≥60	Fecundity	↔
***In vitro* fertilization outcomes**			
Al-Saleh et al. 2009 Case-control, 619 women undergoing IVF treatment including 63 cases of unsuccessful fertilizations and 556 controls with successful fertilization (resulting in 203 successful and 321 unsuccessful pregnancies), mean age 31.8 years (Saudi Arabia)	DDE levels (IQR, ug/L) Serum: 0.180–1.750 Follicular fluid: <LOD–0.475 DDD and DDT levels <LOD	Pregnancy outcome Fertilization rate	↔ ↔

Table 2-15. Summary of Reproductive Outcomes in Adult Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Bloom et al. 2017 Cross-sectional, 32 women undergoing IVF treatment, mean age 36 (California, United States)	Follicular fluid DDT metrics (IQR, ng/mL) DDT: <LOD–0.02 DDE: 0.28–0.57	Antral follicle count (at baseline)	↔ (DDT) ↔ (DDE)
		<u>Intermediate IVF endpoints</u>	
		Oocyte maturity	↔ (DDT) ↓ (DDE)
		Oocyte fertilization or embryo quality	↔ (DDT) ↔ (DDE)
		<u>Clinical IVF outcomes</u>	
		Implantation or Live births	↔ (DDT) ↔ (DDE)
Menstrual cycle			
Chen et al. 2018 Cross-sectional, 68 women who had normal duration of pregnancy, mean age 30.5 years (Taiwan)	Milk DDT metrics 3 weeks postpartum (GM±SD, ng/g lipid) DDT: 0.360±0.798 DDE: 8.07±6.53 DDD: 0.161±1.64 ΣDDT: 9.81±7.52	Bleeding duration	↔ (ΣDDT)
		Cycle length	↔ (ΣDDT)
		Age menarche began	↔ (ΣDDT)
Cooper et al. 2005 Cross-sectional, 2,314 adult women, mean age 24 years (United States)	Serum DDE (quintiles, ng/g): Q1: <15 Q2: 15–29 Q3: 30–44 Q4: 45–59 Q5: >60	Bleeding duration	↔
		Cycle irregularity	↔
		Heavy bleeding	↔
		Dysmenorrhea	↔
		Cycle length	↔
Denham et al. 2005 Cross-sectional, 138 young women, 10–16.9 years old (Canada, United States)	Blood DDE (GM±GSD, ng/mL): 0.35±0.347	Presence or absence of menarche	↔
Gallo et al. 2016 Cross-sectional, 140 adult women, mean age 30.7 years (Canada, United States)	Serum DDE (GM±GSD, ng/mL): 0.30±0.29	Ovulatory status	↔
Ouyang et al. 2005 Cross-sectional, 466 adult women, mean age 24.9 years (China)	Serum ΣDDT (quartile means, ng/g serum): Q1: 13.5 Q2: 23.5 Q3: 34.0 Q4: 57.1 ΣDDT = DDT, DDE, DDD	Age at menarche	
		Q2–Q3	↔
		Q4	↓
		Linear (per 10 ng/g)	↓
		Short cycle	↔
		Long cycle	↔

Table 2-15. Summary of Reproductive Outcomes in Adult Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Toft et al. 2008 Cross-sectional, 1,494 adult women from Greenland (n=454), Ukraine (n=374), Poland (n=203), and Sweden (n=463)	Serum DDE (mean (95% CI), ng/g lipid): Greenland: 444 (406–482) Sweden: 2,147 (1,788–2,506) Ukraine: 800 (745–854) Poland: 430 (393–467) Serum DDE (tertiles, ng/g lipid) T1: <370 T2: 370–750 T3: >750	Menstrual cycle length Poland Other countries	 ↑ ↔
		Irregular cycles All countries	 ↔
		Short cycles All countries	 ↔
		Long cycle Greenland Poland Sweden or Ukraine	 ↓ ↑ ↔
Windham et al. 2005 Cross-sectional, 49 women, 18–40 years old (Laos-born, residing in United States)	Serum DDT metrics (quartiles, ng/mL): DDT DDE Q1: <0.5 <7 Q2: 0.5–0.69 7–12 Q3: 0.70–1.39 13–23 Q4: >1.4 >24	Menstrual cycle length	↔ (DDE) ↔ (DDT)
		Follicular phase	↔ (DDE) ↔ (DDT)
		Luteal phase Q2 versus Q1 Q3 versus Q1 Q4 versus Q1	 ↔ (DDT,DDE) ↓ (DDE) ↔ (DDT ↓ (DDT, DDE)
Uterine and ovarian alterations			
Cooney et al. 2010 Case-control, 29 women with endometriosis (cases) and 51 women without endometriosis (controls), 18–40 years old (United States)	Serum DDE (tertiles, ng/g): T1: <0.63 T2: 0.63–0.94 T3: >0.94	Endometriosis	↔
Porpora et al. 2009 Case-control, 80 women with endometriosis (cases; mean age 31.6 years) and 78 women without endometriosis (controls; mean age 29.5 years) (Italy)	Serum DDE (tertiles, ng/g lipid): T1: ≤231 T2: 232–492 T3: ≥493	Endometriosis	↔
Trabert et al. 2015 Case-control, 99 women with uterine fibroids (cases) and 374 women without uterine fibroids (controls), 18–44 years old (United States)	Serum DDT metrics (GM (95% CI), ng/g): Cases DDE: 36.95 (29.09–46.94) DDT: 1.20 (0.89–1.62) *o,p'*-DDE: 0.61 (0.47–0.8) Controls DDE: 16.90 (15.31–18.66) DDT: 1.22 (1.04–1.43) *o,p'*-DDE: 0.69 (0.59–0.79)	Uterine fibroids	↑ (DDE) ↔ (DDT) ↔ (*o,p'*-DDE)

Table 2-15. Summary of Reproductive Outcomes in Adult Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Upson et al. 2013 Case-control, 248 women with endometriosis (cases) and 538 women without endometriosis (controls), 18–49 years old (United States)	Serum DDT metrics (quartiles, ng/g serum): DDT / DDE Q1 ≤0.019 / ≤0.906 Q2 >0.019–0.028 / >0.906–1.56 Q3 >0.028–0.024 / >1.56–2.82 Q4 ≥0.024 / ≥2.82 Serum ΣDDT (quartiles, mol/g): Q1 ≤2.88 Q2 >2.88–5.03 Q3 >5.03–8.95 Q4 ≥8.95	Ovarian endometriosis All endometriosis	↔ (DDE) ↔ (DDT) ↔ (ΣDDT) ↔ (DDE) ↔ (DDT) ↔ (ΣDDT)
Spontaneous abortion and/or preterm birth			
Farhang et al. 2005 Cross-sectional, 420 pregnant women, median age 26 years, maternal blood samples collected during early postpartum (n=334), the third trimester (n=54), or the second trimester (n=32) (United States, California)	Serum DDT metrics (quartiles, ng/mL) DDE / DDT Q1 ≤31.5 / ≤8.1 Q2 31.7–42.5 / 8.2 – 11.0 Q3 42.6–54.7 / 11.1–16.2 Q4 ≥57.5 / ≥16.3	Preterm	↔ (DDE) ↔ (DDT)
Khanjani and Sim 2006 Cross-sectional, 815 women, mean age 27.8 years, breast milk collected 6–12 weeks postpartum (Victoria, Australia)	Milk DDT metrics (tertiles, ng/g fat) DDT / DDE T1: 0–39 / 0–400 T2: 39–66 / 400–730 T3: >66 / >730	Preterm birth Miscarriage or still birth	↔ (DDT) ↔ (DDE) ↔ (DDT) ↔ (DDE)
Korrick et al. 2001 Case-control, 15 women with spontaneous abortions (cases; mean age 25.3 years) and 15 women with normal term pregnancy (controls; mean age 25.0 years), maternal serum collected postpartum (mean 14.8 months in cases and 6.5 months in controls) (China)	Serum DDT metrics (IQR, ng/g serum) Cases / Controls DDT 0.5–0.8 / 0.3–0.6 DDE 11–31 / 8–16 DDD 0.07–0.11 / 0.06–0.12 *o,p'*-DDT 0.05–0.19 / 0.06–0.12 *o,p'*-DDE 0.05–0.10 / 0.04–0.06 ΣDDE 11–33 / 9–17	Spontaneous abortion	↑ (DDE) ↑ (*o,p'* -DDE) ↑ (ΣDDT) ↔ (DDT) ↔ (*o,p'* -DDT) ↔ (DDD)

Table 2-15. Summary of Reproductive Outcomes in Adult Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Longnecker et al. 2005 Cross-sectional, 1,717 women (5,215 pregnancies; mean age 25.4 years), serum collected during the third trimester (United States)	Serum DDE, (quintiles, ng/mL) Group 1: ≤15 Group 2: 15–29 Group 3: 30–44 Group 4: 45–59 Group 5: ≥60 Median (IQR): 24.5 (16.7–36.2)	Fetal loss Group 2 versus 1 Group 3 versus 1 Group 4 versus 1 Group 5 versus 1 Per 60 ng/mL	 ↔ ↑ ↑ ↔ ↑
Longnecker et al. 2001 Cross-sectional, 2,380 pregnant women, including 361 cases of preterm birth, serum collected during the third trimester (United States)	Serum DDE, (quintiles, ng/mL) Group 1: ≤15 Group 2: 15–29 Group 3: 30–44 Group 4: 45–59 Group 5: ≥60 Median (IQR): 25 (17–37)	Preterm birth Groups 2–5 p-trend	 ↑ ↑
Ouyang et al. 2014 Cohort, 291 newly married Chinese women (mean age 24.9 years), serum collected prior to pregnancy (China)	Serum ΣDDT (ng/g): Mean±SD: 34.4±17.9 Median: 30.7	Early pregnancy loss >median versus <median	 ↔
Torres-Arreola et al. 2003 Case-control, 100 women delivering preterm infants (cases) and 133 women delivering full-term infants (controls), ≥15 years old, maternal serum collected ≤24 hours after delivery (Mexico)	Serum DDE (IQR, ng/g lipid): Cases: 115.69–268.01 Controls: 82.39–284.04	Preterm birth	↔
Venners et al. 2005 Cohort, 388 newly married Chinese women (20–34 years old), serum collected prior to pregnancy (China)	Serum ΣDDT (tertiles, ng/g) T1: 5.5–22.9 T2: 23.0–36.5 T3: 36.6–113.3	Early pregnancy loss T2 versus T1 T3 versus T1 Total pregnancy loss T2 versus T1 T3 versus T1	 ↔ ↑ ↔ ↑
Wood et al. 2007 Case-control, 26 women delivering preterm infants (cases; mean age 29.2 years) and 52 women delivering full term infants (controls; mean age 29.7 years), maternal serum collected 1 day postpartum (Canada)	Serum DDE (median (range), ng/g lipid) Case: 67.02 (28.57–431.88) Control: 69.29 (15.79–618.52)	Premature delivery	↔

Table 2-15. Summary of Reproductive Outcomes in Adult Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Wojtyniak et al. 2010 Cohort, 1,322 mother-infant pairs, ≥18 years old, maternal serum collected at 24–33 weeks gestation (Greenland [n=572], Ukraine [n=611], Poland [n=258])	Serum DDE (GM, ng/g lipid) Greenland: 273.8 Ukraine: 653.3 Poland: 356.8	Preterm birth Greenland Ukraine Poland	 ↔ ↔ ↑
Menopause			
Cooper et al. 2002 Cross-sectional, 1,407 women (including 748 breast cancer cases and 659 controls; combined for analysis) (United States)	Serum DDE (percentiles, ng/g lipid): <50th: <620 50th–74th: 620–1,360 75th–89th: 1,370–2,760 ≥90th: ≥2,770	Early menopause 50th–75th versus <50th 75th–89th versus <50th ≥90th versus <50th Continuous	 ↔ ↔ ↔ ↑
Grindler et al. 2015 Cross-sectional, 1,442 menopausal women >30 years old (United States, NHANES 1999–2008)	Serum DDE (ng/g lipid): Median: 243 90th percentile: 1,430	Age at menopause >90th versus <90th Continuous	 ↓ ↓
Sex hormones			
Blanco-Muñoz et al. 2012 Cross-sectional, 84 men, 18–52 years old (Mexico)	Serum DDE (GM±SD, ng/g lipid): 864±2,578	Prolactin Inhibin B FSH LH Testosterone Estradiol	↓ ↑ ↔ ↔ ↔ ↔

Table 2-15. Summary of Reproductive Outcomes in Adult Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Bornman et al. 2018 Cross-sectional, 535 men (301 from indoor residual spraying [IRS] village; 234 from non-IRS village), median age 21 (South Africa)	Serum DDT metrics (ng/g lipid): DDE Group 1: <LOD Group 2: 500–2,600 Group 3: 2,700–17,200 Group 4: 17,300–99,700 DDT Group 1: <LOD Group 2: 30–4,000 Group 3: 5,000–73,000 Group 4: 74,000–519,000	Total testosterone Group 2 versus 1 Group 3 versus 1 Group 4 versus 1	 ↔ (DDE) ↓ (DDT) ↔(DDE, DDT) ↑ (DDE, DDT)
		Free testosterone Groups 2–3 Group 4 versus 1	 ↔(DDE, DDT) ↑ (DDE, DDT)
		Bioavailable testosterone Groups 2–3 Group 4 versus 1	 ↔(DDE, DDT) ↑ (DDE, DDT)
		Estradiol Group 2 versus 1 Group 3 versus 1 Group 4 versus 1	 ↔(DDE, DDT) ↑ (DDE, DDT) ↑ (DDE) ↔ (DDT)
		SHBG Group 2 versus 1 Group 3 versus 1 Group 4 versus 1	 ↓(DDE, DDT) ↔ (DDE) ↓ (DDT) ↔(DDE, DDT)
		FSH Group 2 versus 1 Group 3 versus 1	 ↔(DDE, DDT) ↓(DDE, DDT)
		LH Group 2 versus 1 Group 3 versus 1	 ↔ (DDE) ↓ (DDT) ↓(DDE, DDT)
Emeville et al. 2013 Cross-sectional, 277 adult men, 45–69 years old (French West Indies)	Serum DDE (IQR, ng/mL): 0.96–4.03	DHT	↓
		LH	↑
		Testosterone (total, free, and bioavailable)	↔
		Dehydroepi-androsterone	↔
		Androstenedione	↔
		Androstenediol	↔
		Estrone (and sulfate)	↔
		Estradiol	↔
		SHBG	↔
		FSH	↔

Table 2-15. Summary of Reproductive Outcomes in Adult Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Freire et al. 2014 Cross-sectional, 304 men (15–94 years old) and 300 women (17–92 years old; 223 premenopausal, 77 peri/post-menopausal) (Brazil)	Serum DDT metrics (IQR, ng/mL): Men DDE: 2.86–21.9 DDT: 0.94–6.96 DDD: 0.19–1.34 *o,p'*-DDT: <LOD–0.89 Premenopausal women DDE: 2.96–21.81 DDT: 1.02–7.30 DDD: 0.19–1.19 *o,p'*-DDT: <LOD–1.06 Peri-/post- menopausal women DDE: 6.21–65.60 DDT: 1.24–10.67 DDD: 0.31–1.79 *o,p'*-DDT: <LOD–1.23	Testosterone (men)	↓ (*o,p'*-DDT) ↔ (DDT, DDE, DDD)
		Estradiol (women) Premenopausal Peri-/post-menopausal	 ↔ ↔
		Progesterone (women) Premenopausal Peri-/post-menopausal	 ↔ ↔
		LH (women) Premenopausal Peri-/post-menopausal	 ↔ ↓ (DDT, DDD) ↔ (DDE) ↔ (*o,p'*-DDT)
		FSH (women) Premenopausal Peri-/post-menopausal	 ↔ ↓ (DDD) ↔ (*o,p'*-DDT, DDT, DDE)
Ferguson et al. 2012 Cross-sectional study, 341 men, 18–51 years old (United States)	Serum DDE (IQR, ng/g lipid) 141–329	FSH	↔
		LH	↔
		Inhibin B	↔
		Total testosterone	↔
		Free testosterone	↔
		Estradiol	↔
		SHBG	↔
		FAI	↔
		Testosterone/estradiol	↔
		Testosterone/LH	↔
Giwercman et al. 2006 Cross-sectional, 258 men from Greenland (18–50 years old), 198 men from Ukraine (19–45 years old), 113 men from Poland (20–46 years old), and 184 men from Sweden (24–68 years old) (Sweden, Greenland, Ukraine, Poland)	Serum DDE (median (range), ng/g lipid): Greenland: 500 (5.9–13,000) Ukraine: 1,000 (320–12,000) Poland: 509 (200–2,100) Sweden: 190 (40–2,300) All: 530 (5.9–13,000)	Free testosterone Greenland Ukraine Other countries All	 ↑ ↑ ↔ ↔
		SHBG Ukraine Other countries, all	 ↑ ↔
		LH Ukraine Other countries	 ↑ ↔

Table 2-15. Summary of Reproductive Outcomes in Adult Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
		Inhibin B	
		Ukraine	↓
		Other countries, all	↔
		FSH	
		Individual countries	↔
		All	↑
		Estradiol	
		Individual countries	↔
		All	↔
Goncharov et al. 2009 Cross-sectional, 257 Mohawk men (18–82 years old) and 436 Mohawk women (18–95 years old) (Canada, United States)	Serum DDE (mean (range), ng/g): 2.89 (0.14–14.98)	Total testosterone	↔
Hagmar et al. 2001 Cross-sectional, 110 men, 23–79 years old (Latvia, Sweden)	Plasma DDT metrics (percentiles, ng/g lipid) DDE DDT 10th 197 10 50th 828 50 90th 3,152 185	FSH	↑ (DDT) ↑ (DDE)
		Free testosterone	↑ (DDE) ↔ (DDE)
		LH	↔
		Prolactin	↔
Haugen et al. 2011 Cross-sectional, 172 men, 19–40 years old (Northern (n=77) or Southern (n=95) Norway)	Serum DDE (median (range), ng/g lipid) Northern: 57 (17–161) Southern: 64 (13–429)	Total testosterone	↓
		Free testosterone	↓
		SHBG	↔
		LH	↔
		Inhibin	↔
		FSH	↑
		E2	↔
Martin et al. 2002 Cross-sectional, 137 men, 30–88 years old (United States)	Serum DDE (IQR, ng/g lipid): 558–2,136	Total testosterone	↔
		Bioavailable testosterone	↔
		DHT	↔
		FAI	↔

Table 2-15. Summary of Reproductive Outcomes in Adult Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Perry et al. 2006 Cohort, 287 female textile workers trying to conceive (20–34 years old), major metabolites of progesterone and estrogen were collected in urine for 1 year or until pregnancy (China)	Serum DDT metrics (IQR, ng/g): DDT: 0.99–2.23 DDE: 19.30–39.58 DDD: 0.15–0.29 *o,p'*-DDT: 0.12–0.24 *o,p'*-DDE: 0.06–0.12 ΣDDT: 20.96–42.63 Associations analyzed based on menstrual cycle phase	PdG (progesterone metabolite) Follicular phase Periovulation Luteal phase E1C (estrogen metabolite) Follicular phase Pre-ovulation Luteal phase	 ↓ (DDD) ↔ (other metrics) ↓ (ΣDDT, DDE, DDD) ↔ (other metrics) ↓ (ΣDDT, DDT, DDE, *o,p'*-DDE, DDD) ↔ (*o,p'*-DDT) ↔ (all metrics) ↓ (all metrics) ↓ (ΣDDT, DDE, *o,p'*-DDE) ↔ (*o,p'*-DDT, DDT, DDD)
Rignell-Hydbom et al. 2004 Cross-sectional, 195 fishermen, mean age 50.6 years (Sweden)	Serum DDE (median (range), ng/g lipid): 240 (33.4–2,251)	FSH LH Estradiol Testosterone Inhibin B SHBG	↔ ↔ ↔ ↔ ↔ ↔
Rylander et al. 2006 Cross-sectional, 196 men, median age 59 years (Sweden)	Serum DDE (quartiles, ng/g lipid): Q1: 300 Q2: >300–600 Q3: >600–1,100 Q4: >1,100	Estradiol per 100 ng/g Q2 versus Q1 Q3–Q4 FSH LH Total testosterone SHBG FAI	 ↓ ↔ ↓ ↔ ↔ ↔ ↔ ↔
Schell et al. 2014 Cross-sectional, 127 young Mohawk men, 10–<17 years old (Canada, United States)	Serum DDE (mean±SD, ng/g): 0.45±0.35	Free testosterone	↔

Table 2-15. Summary of Reproductive Outcomes in Adult Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Turyk et al. 2006 Cross-sectional, 56 men including 25–29 sport-caught fish eaters and 23–27 referents, 27–70 years old (United States, Great Lakes Region)	Serum DDE (mean (range), ng/g lipid): Fish eaters: 602 (99–9,499) Referents: 290 (43–4,554)	Total testosterone	↔
		Free testosterone	↔
		SHBG	↔
		SHBG-T	↔
		LH	↔
		FSH	↔
		Estrone sulfate	↔
Windham et al. 2005 Cross-sectional, 49 women, 18–40 years old (Laos-born, residing in United States)	Serum DDT metrics (quartiles, ng/mL): DDT / DDE Q1: <0.5 / <7 Q2: 0.5–0.69 / 7–12 Q3: 0.70–1.39 / 13–23 Q4: >1.4 / >24	Progesterone Q2 Q3 Q4	 ↔ (DDE) ↓ (DDE) ↓ (DDE)
Semen parameters-sex organ function			
Aneck-Hahn et al. 2007 Cross-sectional, 311 adult males, 23–40 years old (South Africa)	Serum DDT metrics (median (range), ng/mL) DDE: 697 (<LOD–6,621) DDT: 249 (<LOD–2,644) Serum DDT metrics (median (range), ng/g lipid) DDE: 134 (<LOD–997) DDT: 46 (<LOD–519)	Sperm parameters	
		Volume	↓ (DDE) ↔ (DDT)
		Total count	↓ (DDE) ↔ (DDT)
		Beat cross frequency	↑ (DDE) ↑ (DDT)
		Straight-line velocity	↔ (DDE) ↓ (DDT)
		Mean motility	↓ (DDE) ↓ (DDT)
		Head displacement	↔ (DDE) ↓ (DDT)
		Tail defects	↔ (DDE) ↓ (DDT)
		Round cells	↑ (DDE) ↑ (DDT)
		Cytoplasmic droplets	↔ (DDE) ↑ (DDT)
		Oligozoospermia	↑(DDE)
		Asthenozoospermia	↑ (DDT)

Table 2-15. Summary of Reproductive Outcomes in Adult Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Charlier and Foidart 2005 Case-control, 83 subfertile/ unfertile men (cases, mean age 26 years) and 75 fertile men (controls, mean age 25 years) (Belgium)	Blood DDE (mean±SD, ng/g lipid) Cases: 1,050±550 Controls: 980±530	Sperm parameters	
		Concentration	↔
		Motility	↔
		Abnormal morphology	↔
Dallinga et al. 2002 Case-control, 34 men with poor sperm quality (cases, mean age 35 years) and 31 men with normal sperm (controls, mean age 37 years) (Belgium)	Serum DDE (mean±SD, ng/g blood) Cases: 0.31±0.42 Controls: 0.22±0.22	Sperm parameters	
		Sperm count	↔
		Progressive motility	↔
		Overall motility	↔
		Sperm morphology	↔
de Jager et al. 2006 Cross-sectional, 116 adult males, mean age 27 years old (Mexico)	Serum DDE (mean±SD, ng/g lipid): 45,000±31,000	Sperm parameters	
		Volume	↔
		Count	↔
		Concentration	↔
		Velocity	↔
		Mean motility	↓
		Tail abnormalities	↑
		Progressive motility	↓
		Chromatin integrity	↔
		Epididymal function	↔
Haugen et al. 2011 Cross-sectional, 172 men, 19–40 years old (Northern (n=77) or Southern (n=95) Norway)	Serum DDE (median (range), ng/g lipid) Northern: 57 (17–161) Southern: 64 (13–429)	Sperm parameters	
		Concentration	↔
		Count	↔
		Motility	↔
Hauser et al. 2003 Cross-sectional, 212 adult males (mean age 36 years) (United States)	Serum DDE (tertiles, ng/g lipid): T1:≤184.3 T2: 1.84.9–296.6 T3: ≥302.5	Sperm parameters	
		Concentration	↔
		Motility	↔
		Morphology	↔
Messaros et al. 2009 Cross-sectional, 336 adult males, 18–60 years old (United States)	Serum DDT metrics (median, ng/g lipid): DDT: 4.72 DDE: 290.4 High ΣDDT=DDT+DDE at or above the 75th percentile	Sperm parameters	
		Motility	↑ (high ΣDDT)
		Abnormal morphology	↑ (high ΣDDT)
		Concentration	↑ (high ΣDDT)

Table 2-15. Summary of Reproductive Outcomes in Adult Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Pant et al. 2007 Case-control, 50 infertile men (cases) and 50 fertile men (controls) (India)	Semen DDT metrics (mean±SE, ng/mL): Cases / Controls DDT 2.17±0.77 / 3.07±0.92 DDE 20.29±2.13 / 7.24±0.46 DDD 20.74±1.92 / 13.14±1.09 *o,p'*-DDT 2.92±1.27 / 0.12±0.06	Sperm parameters	
		Concentration	
		Cases	↓ (DDE, DDD)
		Controls	↔
		Motility	
		Cases	↔
		Controls	↔
Rignell-Hydbom et al. 2005a Cross-sectional, 157 adult men, mean age 47 years (Sweden)	Serum DDE (median (range), ng/g lipid): 231 (40 – 2252)	Markers of secondary sex organ function	
		PSA	↔
		Neutral α-glucosidase	↔
		Fructose	↔
		Zinc	↔
Toft et al. 2006 Cross-sectional, 763 adult men from Greenland (n=194), Ukraine (n=195), Poland (n=189), and Swedish fishermen (n=185), mean ages 28–47 years (Sweden, Greenland, Ukraine, Poland)	Serum DDE (mean±SD, ng/g lipid) Greenland: 890±1,160 Sweden: 240±310 Ukraine: 1,270±1,080 Poland: 580±310 Serum DDE (quintiles, ng/g lipid): Q1 0–250 Q2 251–500 Q3 501–1,000 Q4 1,001–1,500 Q5 >1,500	**Sperm parameters:**	
		Concentration	↔
		Motility	
		Greenland	↓
		All countries	↓
		Morphology	↔

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDD = *p,p'*-DDD, DDE = *p,p'*-DDE, and DDT = *p,p'*-DDT, unless otherwise specified.

↑ = positive association; ↓ = inverse association; ↔ = no association; CI =confidence interval; DDD = dichloro-diphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; DHT = 5α-dihydrotestosterone; E2 = estradiol; FAI = free androgen index; FSH = follicle-stimulating hormone; GSD = geometric standard deviation; GM = geometric mean; IVF = *in vitro* fertilization; IQR= interquartile range; IRS = indoor residual spraying; LH = luteinizing hormone; LOD = limit of detection; NHANES = National Health and Nutrition Examination Survey; PSA = prostate specific antigen; Q = quartile or quintile; SD = standard deviation; SHBG = sex hormone-binding globulin; SHBG-T = sex hormone-binding globulin bound testosterone; T = tertile; TTP = time to pregnancy

Table 2-16. Summary of Studies of Associations between Human DDT Exposure Metrics in Child and Adolescent Serum and Reproductive Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Croes et al. 2015 Cross-sectional, 1,889 adolescents from two cohorts, 14–15 years old; FLEHS I cohort (n=1,679) and FLEHS II cohort (n=210) (Belgium)	Serum DDE (GM (95% CI), ng/g lipid): FLEHS I: 94 (89–99) FLEHS II: 70 (63–78)	Breast development (girls)	↓
		Genital development, menarche (girls)	↔
		Genital development, pubic hair growth (boys)	↑ (FLEHS I) ↔ (FLEHS II)
		Reaching adult phase testosterone levels (boys)	↔
		E2 (total and free) (boys)	↔
		Testosterone (total and free) (boys)	↔
		LH (boys)	↔
		FSH (boys)	↔
Den Hond et al. 2011 Cross-sectional, 1,679 adolescents (887 males, 792 females), 14–15 years old (Belgium)	Serum DDE (median (10^{th}–90^{th} percentile), ng/g lipid): Boys: 104 (47–404) Girls: 84 (39–247)	Genital development	↑ (boys)
		Pubic hair growth	↑ (boys) ↔ (girls)
		Tanner breast development (reaching P4)	↔ (girls)
		Menarche later than median (12 years, 9 months)	↔ (girls)
Dhooge et al. 2011 Cross-sectional, 887 male adolescents, 14–15 years old (Belgium)	Serum DDE (median (10^{th}–90^{th} percentile), ng/g lipid): 103.6 (46.8–403.9)	E2 (total)	↑
		E2 (free)	↔
		LH	↔
		Testosterone (total and free)	↔
		FSH	↔
		SHBG	↔
		Aromatase index	↔
Eskenazi et al. 2017 Prospective birth cohort (CHAMACOS), 234 boys, 9 years old (California, United Stated) Hormone levels measured at 12 years	Serum DDT metrics at 9 years of age (IQR, ng/g lipid): DDE: 79.5–295.9 DDT: 1–2.6	FSH	↔
		LH	↔
		Testosterone	↔

Table 2-16. Summary of Studies of Associations between Human DDT Exposure Metrics in Child and Adolescent Serum and Reproductive Endpoints[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Lam et al. 2014, 2015	Serum DDE (ng/g serum) Q1: 0.261–0.907 Q2: 0.908–1.406 Q3: 1.407–2.237 Q4: 2.238–41.301	Genital development	↔
Prospective cohort, 350 boys, 8–9 years old (Russia)		Pubic hair growth Stage P2+ Stage P5	 ↔ ↔ (Q2–Q3) ↑ (Q4) ↑ (p-trend)
Onset of puberty evaluated through 16–17 years old	Median: 287 ng/g lipid; 1.41 ng/g serum	Testicular volume	↔

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified.

↑ = positive association; ↓ = inverse association; ↔ = no association; BMI = body mass index; CHAMACOS = Center for the Health Assessment of Mothers and Children of Salinas; CI = confidence interval; DDE = dichlorodiphenyl-dichloroethylene; DDT = dichlorodiphenyltrichloroethane; E2 = estradiol; FLEHS = Flemish Environment and Health Studies; FSH = follicle stimulating hormone; GM = geometric mean; IQR = interquartile range; LH = luteinizing hormone; P1–5 = Tanner pubic hair growth, stages 1–5; Q = quartile; SHBG = sex-hormone binding globulin

Table 2-17. Summary of Studies of Associations between Human DDT Exposure Metrics in Maternal Serum, Cord Blood, or Breast Milk and Reproductive Endpoints in Offspring Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Effects in neonates/infants			
Araki et al. 2018	Maternal serum DDT metrics (IQR, pg/g-wet) DDD: 0.98–2.54 *o,p'*-DDD: <LOD DDE: 409.79–968.05 *o,p*'-DDE: 0.72–1.78 DDT: 16.22–33.94 *o,p'*-DDT: 2.28–4.67	Cord blood hormones for which an association was found:	
Cohort, 232 mother-infant pairs, 106 boys and 126 girls (Japan)		Prolactin Boys Girls	 ↓ (DDE, DDT *o,p*'-DDE, *o,p'*-DDT) ↔ (DDD) ↔ (all)
Hormone levels measured in cord blood		DHEA Boys Girls	 ↔ (all) ↓ (DDD) ↔ (DDE, DDT *o,p*'-DDE, *o,p'*-DDT)

Table 2-17. Summary of Studies of Associations between Human DDT Exposure Metrics in Maternal Serum, Cord Blood, or Breast Milk and Reproductive Endpoints in Offspring Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
		No associations observed between other hormones evaluated and DDT metrics (progesterone, estradiol, testosterone, LH, FSH, Inhibin B, INSL3, androstenedione, SHBG)	
Bhatia et al. 2005 Nested case-control, 428 mother-child pairs, including 75 cryptorchidism cases, 66 hypospadias cases, 4 cryptorchidism and hypospadias cases, and 283 normal controls (United States) Infants followed at least 2 years from birth	Maternal serum DDT metrics (quartiles, ng/mL) DDE / DDT Q1 <27.0 / <10.0 Q2 27.0–43.9 / 10.0–14.9 Q3 44.0–60.9 / 15.0–19.9 Q4 ≥61.0 / ≥19.9	Cryptorchidism	↔ (DDE) ↔ (DDT)
		Hypospadias	↔ (DDE) ↔ (DDT)
		Both cryptorchidism and hypospadias	↔ (DDE) ↔ (DDT)
Brucker-Davis et al. 2008 Nested case-control, 164 mother-infant pairs including 78 infants with cryptorchidism and 86 normal control infants (France)	Cord blood DDE (IQR, ng/mL) Controls: 0.1–0.5 Cases: 0.1–0.7 Combined: 0.1–0.6 Milk DDE (IQR, ng/g lipid) Controls: 51.1–177.8 Cases: 58.4–232.3 Combined: 52.3–213.6	Cryptorchidism status At birth At 3 months	 ↔ ↔
Carmichael et al. 2010 Nested case-control, 48 mother-infant pairs including 20 hypospadias cases and 28 normal controls (United States, California)	Maternal serum DDT metrics (IQR, ng/g lipid) Controls DDE: 95.0–312.5 DDT: 0.8–5.0 Cases DDE: 113.6–226.5 DDT: 1.4–3.9	Hypospadias	↔ (DDT) ↔ (DDE)
Damgaard et al. 2006 Nested matched case-control, 130 mother-child pairs including cryptorchidism cases (n=29 Danish; n=33 Finnish) and controls (n=36 Danish; n=32 Finnish) (Finland, Norway)	Maternal serum DDT metrics (mean, ng/g lipid) Cases / Controls DDT 4.63 / 3.98 DDE 97.32 / 83.76 DDD 0.36 / 0.34 *o,p'*-DDT 0.35 / 0.34 *o,p'*-DDE 0.08 / 0.08 *o,p'*-DDD 0.03 / 0.03 DDE/DDT 17.88 / 19.31 ΣDDT 140.41 / 116.6	Cryptorchidism	↔ (All DDT metrics)

Table 2-17. Summary of Studies of Associations between Human DDT Exposure Metrics in Maternal Serum, Cord Blood, or Breast Milk and Reproductive Endpoints in Offspring Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Fernandez et al. 2007 Case-control, 48 boys with hypospadias and/or cryptorchidism at 1 month of age (cases) and 114 healthy control boys (Spain)	Placental DDT metrics (IQR, ng/g lipid) Cases / Controls *o,p'*-DDD: 1.0–52.4 / 1.0–62.4 DDE: 2.6–8.9 / 1.8–7.7 *o,p'*-DDT: 1.0–1.9 / 1.0–4.8 DDT: 1.0–1.0 / 1.0–2.7 ΣDDT: 4.4–29.6 / 2.9–34.9	Cryptorchidism and/or hypospadias	↔ (*o,p'*-DDT) ↔ (DDT)
Giordano et al. 2010 Case-control, 80 hypospadias cases and 80 healthy controls (Italy)	Maternal serum DDE (IQR, ng/g) Cases (n=37): 0.79–1.73 Controls (n=21): 0.56–120 All subjects (n=58): 0.66–1.41	Hypospadias	↔
Garcia-Villarino et al. 2018 Cohort, 43 mother-infant pairs (27males, 16 females) (Spain) Maternal blood collected during 1st trimester	Geometric mean in maternal serum DDT metrics (GM (95% CI), ng/mL) Male infants DDD: 1.41 (0.78–2.53) *o,p'*-DDD: 0.76 (0.67–0.86) Female infants DDD: 1.28 (0.69–2.34) *o,p'*-DDD: 0.75 (0.70–0.80)	AGI at 18 months Boys Girls	 ↔ ↔
Longnecker et al. 2002 Nested case-control, mother-child pairs including 219 cryptorchidism cases, 199 hypospadias cases, 167 polythelia cases, and 552 healthy controls (United States)	Maternal serum DDE exposure categories (ng/mL) (1) <15.0 (2) 15.0–29.9 (3) 30.0–44.9 (4) 45.0–59.9 (5) ≥60 Median (ng/mL) ranges in cases and controls: 23.6–31.9	Cryptorchidism Hypospadias Polythelia	↔ ↔ ↔
Longnecker et al. 2007 Cross-sectional, 781 mother-infant pairs (Mexico)	Postpartum maternal serum DDT metrics (median) ng/g lipid / ng/mL DDT 250 / 1.9 DDE 2,700 / 19.5 DDT:DDE 0.12	AGD1 AGD2 ASD Penis length Penis width	↔ ↔ ↔ ↔ ↔

Table 2-17. Summary of Studies of Associations between Human DDT Exposure Metrics in Maternal Serum, Cord Blood, or Breast Milk and Reproductive Endpoints in Offspring Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Loreto-Gomez et al. 2018 Cohort, 156 mother-infant pairs (82 girls, 74 boys) (Mexico) Maternal blood collected during the 3rd trimester. Anogenital distance evaluated at 1, 3, 6, and 12 months	Maternal serum DDT metrics (IQR, ng/g lipid) DDE: 140.7–689.2 DDT: 2.8–20.0 *o,p'*-DDT: >LOD–2.61	AGD measures in boys (corrected for height)	
		ASD (to posterior base of scrotum)	↔(all metrics)
		AGD1 (to anterior base of penis)	↑ (DDE) ↔ (DDT) ↔ (*o,p'*-DDT)
		AGD2 (to posterior base of penis)	↔ (all metrics)
		AGD measures in girls (corrected for height)	
		AFD (to posterior fourchette)	↔ (DDE) ↔ (DDT) ↑ (*o,p'*-DDT)
		ACD (to tip of clitoral hood)	↔ (all metrics)
		FCD (anterior to posterior fourchette)	↔ (all metrics)
Torres-Sanchez et al. 2008 Cohort, 71 mother-infant pairs (37 males and 34 females) (Mexico)	Maternal trimester serum DDE (median, ng/g lipid) Boys / Girls Baseline 2,456.6 / 1,688.2 1st 1,714.8 / 1,407.9 2nd 1,276.5 / 1,083.0 3rd 1,274.2 / 1,040.1 *p,p'*-DDT in both boys and girls at each sampling time point: 0.0123 ng/g lipid	API (boys)	
		Base	↔
		1st	↓
		2nd or 3rd	↔
		PA (boys) Base, 1st, 2nd or 3rd	↔
		PA/W (boys) Base, 1st, 2nd or 3rd	↔
		No significant associations were observed in girls	
Effects in adolescents			
Eskenzai et al. 2017 Prospective birth cohort (CHAMACOS), 232 mother-son pairs (California, United States) Serum hormones levels in boys at 12 years. Maternal DDT metrics were measured during pregnancy (n=83) or extrapolated (n=149) using prediction models when boys were recruited at 9 years of age	Measured maternal serum DDT metrics (IQR, ng/g lipid): DDE: 214.3–1622.2 DDT: 6.8–57.2 Measured and extrapolated maternal serum DDT metrics (IQR, ng/g lipid): DDE: 260.4–1621.6 DDT: 7.1–50.3	Serum hormones (adjusted for Tanner Stage):	
		Serum LH	↓(DDE) ↓ (DDT)
		Serum FSH	↔ (DDE) ↔ (DDT)
		Serum testosterone	↔ (DDE) ↓ (DDT)
		Results were similar for analysis using measured only or measured and extrapolated maternal exposure metrics	

Table 2-17. Summary of Studies of Associations between Human DDT Exposure Metrics in Maternal Serum, Cord Blood, or Breast Milk and Reproductive Endpoints in Offspring Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Effects in adults			
Cohn et al. 2003 Retrospective cohort, 289 mother-infant pairs; daughters born 1960–1963 (United States, California)	Maternal serum DDT metrics (median (range), ng/mL): *o,p'*-DDT: 0.49 (0.01–6.7) DDT: 13.05 (3.04–48.48) DDE: 48.19 (11.21–132.53)	Time to pregnancy in daughters (FR)	↑ (DDE) ↓ (DDT)
Han et al. 2016 Retrospective cohort study of 11 fish-eating communities, 151 mother-daughter pairs (aged 20–50 years), 288 daughter pregnancies (United States, Michigan)	Estimated birth serum DDE (tertiles, ng/mL) T1: 0–2.4 T2: 2.5–7.4 T3: ≥7.4	Time to pregnancy in daughters All time of UI TUI ≥1 month Planned baby	 ↔ ↔ ↔
Vasiliu et al. 2004 Retrospective cohort study of 11 fish-eating communities, 151 mother-daughter pairs (aged 20–50 years), (United States, Michigan)	Estimated maternal serum DDE at birth (median (95% CI), ng/mL): Age at menarche: 9–11 years: 7.0 (1.3–16.5) 12–14 years: 4.2 (0.4–15.0) 14–17 years: 3.8 (0–12.8)	Daughter's age at menarche	↔
Vested et al. 2014 Cohort, 166 mother-son pairs; follow-up with male offspring aged ~20 years (Denmark)	Maternal serum DDE (tertiles, nmol/mL) T1: 0.00073–0.00630 T2: >0.00630–0.01063 T3: >0.01063–0.05532	Sperm concentration	↔
		Total sperm count	↔
		Semen volume	↔
		Percent progressive spermatozoa	↔
		Percent motile spermatozoa	↔
		Percent morphologically normal spermatozoa	↔
		Mean testicular volume	↔
		Testosterone	↔
		Free testosterone	↔
		E2	↔
		LH	↔
		FSH	↔

Table 2-17. Summary of Studies of Associations between Human DDT Exposure Metrics in Maternal Serum, Cord Blood, or Breast Milk and Reproductive Endpoints in Offspring Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
		Inhibin B	↔
		SHBG	↔

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified, DDD= *p,p'*-DDD, unless otherwise specified

↑ = positive association; ↓ = inverse association; ↔ = no association; ACD= distance from center of anus to tip of clitoral hood; AFD = distance from center of anus to base of the posterior fourchette; AGD = anogenital distance; AGD1= distance from center of anus to anterior base of penis; AGD2 = distance from center of anus to posterior base of penis; AGI = anogenital index; ASD = distance from center of anus to the posterior base of scrotum; API = anal position index; CHAMACOS= Center for the Health Assessment of Mothers and Children of Salinas; CI = confidence interval; DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; DHEA = dehydroepiandrosterone; E2 = estradiol; FCD = fourchette length; FR = fecundability ratio; FSH = follicle stimulating hormone; GM = geometric mean; INSL3= insulin-like factor 3; IQR = interquartile range; LH = luteinizing hormone; LOD = limit of detection; PA = perineal distance; PA/W = perineal distance/weight; Q = quartile; SHBG = sex hormone-binding globulin; T = tertile; TUI = time of unprotected intercourse; UI = unprotected intercourse

Not included in these tables are studies that (although they conducted analyses such as those mentioned previously) presented the results only textually, without providing quantitative information. Finally, some studies in which the studied population was heavily exposed to DDT (i.e., areas of endemic malaria) and consequently had extremely high DDT body burdens were not included in the tables.

Summary of human evidence. In epidemiological studies examining possible association between levels of DDT, DDE, or DDD in tissues or biological fluids (e.g., serum), inconsistent evidence across studies of adults was provided for associations with time to pregnancy (fecundity), spontaneous abortion or preterm birth, menstrual cycle, uterine alterations, early menopause, levels of reproductive hormones in men or women, and semen parameters (Table 2-15). Inconsistent evidence across studies was provided for associations with puberty onset in preadolescents and adolescents (Table 2-16). Consistent evidence for no association was reported for maternal levels of DDT, DDE, or DDD in serum, cord blood, breast milk, or placenta with risks for male reproductive system birth defects (cryptorchidism [undescended testes] and hypospadias [condition in which the opening of the urethra is on the underside of the penis]) or adverse reproductive outcomes in adult offspring (Table 2-17).

Reproductive Effects in Adults (Table 2-15)

Time to pregnancy (TTP) (fecundity). Inconsistent evidence comes from five studies of the association between serum levels of DDT, DDD, or DDE and TTP (Table 2-15). Only one study reported an inverse association between serum DDE (in male partners) and longer TTP in models adjusted for potential confounders (Buck Louis et al. 2013). The geometric mean concentration of DDE was relatively low, 0.82 ng/g serum, compared with approximately 1.46 ng/g serum in contemporaneous surveys of U.S. adult males (CDC 2018). DDE levels in women were below the levels of detection. In two studies, inverse associations (found in preliminary analyses) lost statistical significance after models were adjusted for maternal age at conception (Axmon et al. 2006) or shellfish consumption and mercury in the women's hair (Chevrier et al. 2013). In other studies, DDT metrics in women's serum (Law et al. 2005) and of DDE and DDT (*p,p'*- and *o,p'*- isomers) (Harley et al. 2008) were not associated with TTP (Chen et al. 2018; Harley et al. 2008; Law et al. 2005). Recently, Buck Louis (2014) reviewed the issue of fecundity and environmental pollutants and noted that subtle changes in human fecundity may be easily missed without continued research specifically aimed at the preconception enrollment of couples for longitudinal measurement of sensitive outcomes such as TTP and pregnancy loss. The investigator also noted the necessity to consider male-mediated exposures when assessing couple-dependent outcomes because failure to do so may lead to the wrong conclusions, particularly in the absence of female exposures.

In vitro fertilization (IVF) outcomes. Two epidemiological studies have evaluated potential associations between DDT biometrics and IVF outcomes. Neither fertilization rate nor pregnancy outcome were associated with serum or ovarian follicular fluid DDE levels in a case-control study of successful and unsuccessful fertilizations in Saudi Arabian women undergoing IVF (Al-Saleh et al. 2009). Similarly, follicular fluid DDE and DDT levels were not associated with antral follicle count, oocyte fertilization, embryo quality, implantation, or number of live births in a small study of Californian women undergoing IVF (Bloom et al. 2017). However, oocyte maturity was negatively associated with follicular DDE levels in this study.

Menstrual cycle. Seven studies provide inconsistent evidence for associations between menstrual cycle changes and serum DDE or DDT levels: three reported associations and four reported no association (Table 2-15). High mean total DDT levels (~20–30 ng/g serum compared with <2 ng/g serum) reported in contemporaneous surveys of women from the U.S. general population [CDC 2018]) were associated with increased prevalence of short cycles and reduced age at menarche (Ouyang et al. 2005) and reduced

luteal phase length (Windham et al. 2005). However, in a larger study of women with similar mean serum DDE levels (30 ng/mL), no association was found between DDE and menstrual cycle parameters (Cooper et al. 2005). Evaluations of four different populations by Toft et al. (2008) also showed inconsistent results between studied groups. In Inuit women from Greenland, DDE was associated with decreased prevalence of long menstrual cycles, whereas in Polish women, DDE was associated with an increased risk for long cycles; both cohorts had similar mean serum DDE concentrations: 430 ng/g lipid in Polish women and 444 ng/g lipid in the Inuit group. In the same study, DDE was not associated with long cycles in a cohort of Swedish fishermen's wives who had a significantly higher mean serum DDE concentration (2,147 ng/g lipid) (Toft et al. 2008). No associations between DDE and menstrual cycle parameters were reported among women with low (≤0.35 ng/mL blood) DDE levels (i.e., Denham et al. 2005; Gallo et al. 2016). Additionally, no associations were observed between DDT biometrics in breast milk collected 3 weeks postpartum and historical menstrual cycle parameters (cycle length, bleeding duration, age at menarche) in Taiwanese women with normal pregnancies (Chen et al. 2018).

Uterine and ovarian alterations. Inconsistent evidence comes from four studies examining associations between serum DDE or DDT levels and uterine and/or ovarian alterations (Table 2-15). In one study, women with high serum levels of *p,p'*-DDE (36.95 ng/g serum) had an increased risk for uterine fibroids compared to women with lower levels of *p,p'*-DDE (16.9 ng/g serum); no association was found with *p,p'*-DDT (Trabert et al. 2015). A small study of only 18 endometriosis cases and 8 controls (not shown in Table 2-15) reported a higher concentration of DDE (and PCBs) in serum from cases (770 ng/g lipid) than in controls (310 ng/g lipid); no further analysis was conducted (Quaranta et al. 2006). Studies of women with relatively low serum levels of total DDT (DDT + DDE) did not find associations between serum levels of DDE or DDT and prevalence of endometriosis (Cooney et al. 2010; Porpora et al. 2009; Upson et al. 2013).

Spontaneous abortion and preterm birth. Inconsistent evidence comes from 10 studies examining associations between DDT biometrics and spontaneous abortion or preterm birth (Table 2-15). In large cross-sectional studies of women from the United States, significant positive associations were observed between serum DDE and preterm birth (Longnecker et al. 2001) and fetal loss (Longnecker et al. 2005). A smaller study in women from California did not observe an association between preterm birth and serum DDT metrics (Farhang et al. 2005). In China, spontaneous abortion was associated with increased serum *p,p'*-DDE, *o,p'*-DDE, and ΣDDT levels, but not *p,p'*-DDT, *o,p'*-DDT, or DDD levels (Korrick et al. 2001), and early and total pregnancy loss were associated with increased serum ΣDDT levels (Venners et al. 2005). A third study in China did not report an association between serum ΣDDT levels and early

pregnancy loss (Ouyang et al. 2014). Ouyang et al. (2014) noted that they classified the total DDT concentration as low and high by using a median split (30.7 ng/g serum), which may have influenced the results. In Poland, preterm birth was also positively associated with serum DDE levels during gestation (Wojtyniak et al. 2010). Additional studies in other countries reported no association between serum DDT metrics and spontaneous abortion and/or preterm birth, including Mexico (Torres-Arreola et al. 2003), Canada (Wood et al. 2007), Greenland (Wojtyniak et al. 2010), or the Ukraine (Wojtyniak et al. 2010). Neither DDT nor DDE in breast milk collected between 6 and 12 weeks postpartum was associated with preterm birth in a study of Australian women; no analysis of the pesticides in blood was conducted (Khanjani and Sim 2006).

Two studies from India reported higher levels of DDE in placental tissue from women who had preterm delivery compared with women who gave birth to full-term babies (Anand et al. 2015; Saxena et al. 1980); these studies are not in Table 2-15 because regression analysis was not conducted.

Menopause. Inconsistent evidence for an association between serum DDE levels and early age at menopause comes from two studies (Table 2-15). Cooper et al. (2002) found no association between serum DDE and early menopause in a study of 1,407 women when serum DDE was categorized into deciles. Analysis of DDE as a continuous variable, however, yielded a marginally higher risk for early menopause. In an evaluation of 1,442 women participants in NHANES 1999–2008, serum DDE was associated with early menopause in analyses of serum DDE categorized into deciles or when DDE was analyzed as a continuous variable (Grindler et al. 2015).

Reproductive sex hormones. Inconsistent evidence for associations between serum levels of DDT, DDD, or DDE and serum or urine levels of sex hormones or their metabolites is provided by 16 studies described in Table 2-15. Most of the studies (n=14) collected data from men, and only four studies collected data from women (Freire et al. 2014; Goncharov et al. 2009; Perry et al. 2006; Windham et al. 2005). A wide variety of sex hormones and related chemicals were measured across the studies, including testosterone (total, free, or bioavailable), sex-hormone-binding globulin (SHBG), estradiol (E2), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, progesterone, and inhibin B (IHB, which inhibits synthesis and secretion of FSH), as well as androgenic/estrogenic indices such as free androgen index (FAI, ratio of testosterone:SHBG), testosterone/estradiol ratio (marker of aromatase activity) and testosterone/LH ratio (marker of Leydig cell function). The inconsistency of the evidence is illustrated by Table 2-18 showing the number of studies reporting positive associations, inverse associations, and no associations for each examined sex hormone and related endpoints. For example,

among the 13 studies in men measuring serum levels of testosterone and related endpoints, 3 found positive associations (Bornman et al. 2018; Giwercman et al. 2006; Hagmar et al. 2001), 2 found inverse associations (Emeville et al. 2013; Freire et al. 2014), and 9 found no associations (Blanco-Muñoz et al. 2012; Ferguson et al. 2012; Goncharov et al. 2009; Haugen et al. 2011; Martin et al. 2002; Rignell-Hydbom et al. 2004; Rylander et al. 2006; Schell et al. 2014; Turyk et al. 2006).

Table 2-18. Number of Studies Finding Statistically Significant Associations and No Significant Associations Between Serum Levels of DDT, DDD, or DDE and Levels of Sex Hormones in Serum or Urine[a]

Men	Testosterone[b]	SHBG	E2[c]	LH	FSH	PL	IHB
	3 ↑	1 ↑	2 ↑	2 ↑	2 ↑	0 ↑	1 ↑
	2 ↓	0 ↓	0 ↓	1 ↓	1 ↓	1 ↓	1↓
	9 ↔	7 ↔	6 ↔	7 ↔	7 ↔	2 ↔	3 ↔

Women	Testosterone[b]	E2[c]	PG[d]	FSH	PL
	0 ↑	0 ↑	0 ↑	0 ↑	0 ↑
	0 ↓	1 ↓	2 ↓	0 ↓	0 ↓
	1 ↔	2 ↔	0 ↔	1 ↔	1 ↔

[a]Studies counted are from the 16 studies with results described in Table 2-15.
[b]Endpoints included in this count were serum testosterone (total, free, or bioavailable), FAI (free androgen index), and testosterone/LH ratio. Only one study evaluated testosterone levels in women (Goncharov et al. 2009).
[c]In all seven studies of men, serum levels of E2 were measured. In studies of E2 in women, Freire et al. (2014) measured serum E2 (association NS), and the major urinary metabolite of E2 was measured by Perry et al. (2006) (association NS) and Windham et al. (2005) (↓ association).
[d]Perry et al. (2006) and Windham et al. (2005) reported significant inverse associations with the major urinary metabolite of progesterone.

↑ = positive association; ↓ = inverse association; ↔ = no association; DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; E2 = estradiol; FAI = free androgen index; FSH = follicle-stimulating hormone; IHB = inhibin B; LH = luteinizing hormone; NS = not statistically significant; PG = progesterone; PL = prolactin; SHBG = sex hormone-binding globulin

The inconsistency of the evidence is further illustrated by stratification of the studies into high- (mean or median DDE or ΣDDT >5 ng/mL or >600 ng/g lipid) and low-level categories. Eight high-level studies collected data from men (Blanco-Muñoz et al. 2012; Bornman et al. 2018; Freire et al. 2014; Giwercman et al. 2006; Hagmar et al. 2001; Martin et al. 2002; Rylander et al. 2006; Turyk et al. 2006) and three collected data from women (Freire et al. 2014; Perry et al. 2006; Windham et al. 2005). All three high-level women studies evaluated E2 levels, but two found no association between serum DDE levels and E2 levels (Freire et al. 2014; Windham et al. 2005) and the third found an inverse association (Perry et al. 2006). In the eight high-level studies of men, six found associations with at least one sex hormone (Blanco-Muñoz et al. 2012; Bornman et al. 2018; Freire et al. 2014; Giwercman et al. 2006; Hagmar et al. 2001; Rylander et al. 2006), but sex hormones showing associations differed among the studies. For example, Blanco-Muñoz et al. (2012) found no association between DDE and serum testosterone, FSH,

LH, or E2, an inverse association with prolactin, and a positive association with inhibin B in a group of Mexican men, whereas Giwercman et al. (2006) reported positive associations with testosterone, SHBG, and LH, inverse associations with inhibin B, and no associations with FSH or E2 in a group of Ukrainian men. Two of seven high-level studies of men found no associations: Martin et al. (2002) evaluated several testosterone-related endpoints and Turyk et al. (2006) evaluated several testosterone-related endpoints, as well as SHBG, LH, FSH, and estrone sulfate. Contributing to the general inconsistency of the evidence, Emeville et al. (2013), in a low-level study of men, reported inverse associations between serum DDE and dihydrotestosterone and testosterone:LH ratio and a positive association with LH. Other low-exposure studies reported no associations between DDE and reproductive sex hormones (Ferguson et al. 2012; Goncharov et al. 2009; Haugen et al. 2011; Rignell-Hydbom et al. 2004, 2005a; Schell et al. 2014).

Semen parameters. Inconsistent evidence for associations between serum levels of DDT, DDD, or DDE and changes in semen parameters (e.g., sperm count or concentrations, sperm motility) comes from results of nine studies described in Table 2-15. Associations with changes in a number of sperm parameters were found in a study of men with high serum DDE levels (mean of 697 ng/mL) (Aneck-Hahn et al. 2007) and in a study of men with relatively low serum ΣDDT levels (mean of ~300 ng/g lipid) (Messaros et al. 2009). However, the risk for low sperm concentration was elevated in the low-level study, but not in the high-level study. Charlier and Foidart (2005) found no associations in sperm parameters at serum DDE levels 4–5 times higher than those associated with sperm alterations in the Messaros et al. (2009) study. Toft et al. (2006) reported associations with decreased sperm motility in a group of men with a mean serum DDE concentration of 890 ng/g lipid, but not in a group whose mean serum DDE was 1,270 ng/g lipid. de Jaeger et al. (2006) evaluated a wide range of sperm parameters in a Mexican population living in malaria endemic areas in which DDT was sprayed annually and found associations for decreasing sperm motility and increasing sperm tail abnormalities, but none for sperm count or concentration. The mean plasma concentration of DDE in the men was 45,000 ng/g lipid, which is approximately 200 times higher than levels reported in the most recent survey of men from the U.S. general population (CDC 2018). Other low-level studies (mean or median DDE or Σ DDT <5 ng/mL or <600 ng/g lipid) did not find associations between DDE and changes in sperm parameters (Dallinga et al. 2002; Haugen et al. 2011; Hauser et al. 2003) or secondary sex organ function (Rignell-Hydbom et al. 2005a). Associations between semen levels of DDE or DDD and sperm concentration, but not sperm motility, were reported in a single study using this biomarker of DDT exposure (Pant et al. 2007).

Reproductive Effects in Preadolescents/Adolescents (Table 2-16). Inconsistent evidence is provided by six studies examining possible associations between serum DDE levels and puberty onset outcomes in Russian or Californian preadolescent boys, ages 8–9 years (Eskenazi et al. 2017; Lam et al. 2014, 2015) and adolescent Belgian boys and girls, ages 14–15 years (Croes et al. 2015; Den Hond et al. 2011; Dhooge et al. 2011). Outcomes were Tanner indices of genitalia and pubic hair growth in males (Croes et al. 2015; Den Hond et al. 2011; Lam et al. 2014, 2015), Tanner indices of genitalia, public hair growth, and/or breast development and onset of menarche in females (Croes et al. 2015; Den Hon et al. 2011), and serum levels of sex hormones in male preadolescents (Eskenazi et al. 2017) or adolescents (Croes et al. 2015; Dhooge et al. 2011). Belgian and Californian subjects had relatively low levels of serum DDE, lower or comparable to those measured in the most recent survey of U.S. teenagers (CDC 2018), whereas the Russian boys had higher serum DDE levels (Table 2-16). In Russian boys, no associations were found for shifts in attaining early milestones for genitalia growth, testicular volume, or pubic hair growth (Lam et al. 2014), but at later stages of development, the highest DDE exposure quartile showed later attainment of Tanner pubic hair growth stage five (P5) than the first quartile (Lam et al. 2015). In contrast, data for Belgian boys showed associations between DDE serum levels and faster attainment of genitalia growth and pubic hair growth milestones (Croes et al. 2015; Den Hond et al. 2011). In Belgian boys, an association was found between DDE levels and increasing E2 levels, but no associations with other levels of reproductive sex hormones (Dhooge et al. 2011). In Belgian girls, an association between DDE levels and delayed development was observed in one study group (Croes et al. 2015), but not in another study group (Den Hond et al. 2011). In the California cohort, no associations were observed between serum DDT metrics and reproductive sex hormones in 9-year-old boys (Eskenazi et al. 2017).

Maternal Exposure and Effects in Offspring (Table 2-17).

Effects in neonates/infants. Results from seven studies described in Table 2-17 provide consistent evidence for no association between maternal DDT, DDE, or DDD levels in serum, cord blood, breast milk, or placenta and risk for the male cryptorchidism (undescended testes) or hypospadias (condition in which the opening of the urethra is on the underside of the penis) (Bhatia et al. 2005; Brucker-Davis et al. 2008; Carmichael et al. 2010; Damgaard et al. 2006; Fernandez et al. 2007; Giordano et al. 2010; Longnecker et al. 2002). Markers of androgen action in boys, such as decreased anogenital distance (AGD), were not associated with ΣDDT in four studies (Garcia-Villarino et al. 2018; Longnecker et al. 2007; Loreto-Gomez et al. 2018; Torres-Sanchez et al. 2008), except for a decrease in anal position index (a non-age-dependent measurement) in boys and DDE from maternal serum collected in the first trimester (but not 2nd or 3rd trimesters) in the Torres-Sanchez et al. (2008) study. Maternal DDT metrics were not

associated with penis length or width in one study (Longnecker et al. 2007). One study reported an inverse association between maternal serum DDT metrics and prolactin levels in cord blood from male infants; no associations were observed with other sex hormone levels in cord blood (Araki et al. 2018).

Epidemiological studies evaluating reproductive outcomes in female infants are limited (Table 2-17). One study reported an inverse association between maternal serum DDE and DHEA levels in cord blood from female infants; no associations were observed with other sex hormone levels in cord blood (Araki et al. 2018). One birth cohort reported a positive association between maternal serum *o,p'*-DDT and the anofourchette distance (AFD); AFD was not associated with other maternal DDT metrics and no associations were observed between maternal DDT metrics and anoclitoral distance or anterior-to-posterior fourchette distance (Loreto-Gomez et al. 2018). Two additional cohorts did not observe associations between AGD metrics and maternal serum DDT metrics in female infants (Garcia-Villarino et al. 2018; Torres-Sanchez et al. 2008).

Effects in adolescents. One study reported an inverse association between serum LH and testosterone in adolescent boys and maternal serum DDT levels; serum LH was also inversely associated with maternal serum DDE levels (Eskenzai et al. 2017). Serum FSH was not associated with maternal DDT metrics. No additional studies evaluating potential associations between maternal DDT exposure and reproductive endpoints in adolescents were identified.

Effects in adults. Four studies provided consistent evidence for no associations between maternal exposures to DDT and adverse reproductive outcomes in their adult offspring (Table 2-17). Two studies examined age at menarche and time to pregnancy (fecundity) in daughters from mothers exposed through consumption of Great Lakes fish (Han et al. 2016; Vasiliu et al. 2004); the other two studies measured sex hormones and menstrual cycle length in adult Danish daughters (Kristensen et al. 2016) and sperm parameters and sex hormones in adult Danish sons (Vested et al. 2014).

Evidence of Reproductive Effects of DDT, DDD, or DDE in Laboratory Animals

Overview. The principal reproductive effects of DDT and related compounds in laboratory animals have been observed at dose levels >1 mg/kg/day, and are thought to involve anti-androgenic activities (e.g., androgen-receptor binding and impaired male reproductive tissue development) of *p,p'* isomers of DDT, DDE, or DDD and estrogenic activities (e.g., estrogen-receptor binding and promotion of female

reproductive tissue development) of *o,p'*-DDT (see Harada et al. 2016; Hojo et al. 2006; Kelce et al. 1995, 1997; Yamasaki et al. 2009; You et al. 1998, 1999a).

Reliable acute-duration oral LOAELs for adverse effects on reproductive tissues or reproductive function in laboratory animals range from 50 to 200 mg/kg/day for decreased weights of male reproductive tissues from *p,p'*-DDT, technical DDT, technical DDD, or *p,p'*-DDE and from 100 to 500 mg/kg/day for increased uterine weight from *o,p'*-DDT (see Table 2-1, Figure 2-2, and text below).

After intermediate-duration exposure, decreased fertility has been observed in adult laboratory animals at doses ranging from 5.1 to 51.4 mg technical DDT/kg/day (Bernard and Gaertner 1964; Jonsson et al. 1976; Ledoux et al. 1977), but was not observed in other studies at dose levels up to 4 mg *o,p'*-DDT/kg/day (Wrenn et al. 1971), 10 mg *p,p'*-DDE/kg/day (Kornbrust et al. 1986), or 27.7 mg *p,p'*-DDT/kg/day (Hojo et al. 2006). The lowest apparent intermediate-duration LOAELs for other male and female reproductive effects are 3.75 mg/kg/day for decreased estradiol levels in female rats (Hojo et al. 2006), 6.25 mg *p,p'*-DDT/kg/day for decreased seminal weight in castrated mice (no effects were found in normal mice) (Orberg and Lundberg 1974), and 2 mg *p,p'*-DDT/kg/day in female mice exposed for 72–74 days before mating to nonexposed males for small decreases in the number of implants and decreased corpus luteum (Lundberg 1973, 1974).

No adverse effects on indices of reproduction in laboratory animals were observed in several chronic-duration oral multiple generation studies, which identified NOAELs of 0.5–18.6 mg technical DDT/kg/day in rats (Duby et al. 1971; Ottoboni 1969, 1972; Treon et al. 1954), 10 mg technical DDT/kg/day in dogs (Ottoboni et al. 1977), 0.3 mg *o,p'*-DDT/kg/day (Duby et al. 1971), and up to 27 mg *p,p'*-DDT/kg/day in rats (Duby et al. 1971; Hojo et al. 2006), but decreased fertility was observed in a multiple-generation study of mice at 20 mg technical DDT/kg/day (Keplinger et al. 1970). Histological examination revealed no exposure-related abnormalities in the ovaries, uterus, mammary glands, adrenals, or prostate of Osborne-Mendel rats or B6C3F1 mice fed dietary doses for 78 weeks up to 45 mg technical DDT/kg/day, 59 mg *p,p'*-DDE/kg/day, or 231 mg technical DDD/kg/day (rats) and 30.2 mg technical DDT/kg/day, 49 mg *p,p'*-DDE/kg/day, or 142 mg technical DDD/kg/day (mice) (NCI 1978).

Acute-duration studies. As shown in Table 2-1 and Figure 2-2, decreased weights of male reproductive tissues (e.g., seminal vesicles and ventral prostate) and decreased reproductive function have been observed after acute-duration exposure of male rats to DDT (NS), *p,p'*-DDT or *p,p'*-DDE, and increased uterine weights have been observed after acute-duration exposure of female rats to *o,p'*-DDT.

Decreases in weights of seminal vesicles or ventral prostate were observed in male adult Long-Evans or Sprague-Dawley rats given gavage doses of 200 mg *p,p'*-DDE/kg/day for 4 or 5 days, without changes in serum testosterone levels, but not at doses up to 100 mg *p,p'*-DDE/kg/day (Kelce et al. 1995, 1997; Leavens et al. 2002); castrated Sprague-Dawley 6-week-old rats supplemented with subcutaneous testosterone and co-exposed to gavage doses ≥50 mg *p,p'*-DDT/kg/day for 10 days (Kang et al. 2004); and adult male rats given gavage doses of 70 mg *p,p'*-DDE/kg/day for 4 days (You et al. 1999a). Other reported male reproductive effects include decreases in levator ani plus bulbocavernosus muscles and Cowper's gland in castrated rats supplemented with subcutaneous testosterone and administered 100 mg *p,p'*-DDT /kg/day via gavage for 10 days (Kang et al. 2004); decreased serum testosterone, but not LH or FSH, in male rats treated with 200 mg *p,p'*-DDE for 2 weeks by gavage (Krause 1977), and significantly decreased number of fetuses and implantations in non-exposed female rats mated with male rats given 500 mg DDT(NS)/kg/day on PNDs 4 and 5 (Krause et al. 1975). No significant changes in reproductive organ weights, histology of testis or epididymis, or sperm morphology or motility were observed in adult male Sprague-Dawley rats exposed once to 100 mg *p,p'*-DDT/kg, or to 50 mg *p,p'*-DDT/kg/day for 5 days (Linder et al. 1992).

Increased uterine weight as a result of *o,p'*-DDD exposure was observed in immature (23-day-old) female Wistar rats after 3 or 7 days exposure to dietary doses ≥100 mg *o,p'*-DDT/kg/day, accompanied by increased glycogen content and premature vaginal opening (Clement and Okey 1972) and in ovariectomized female DA/Han rats given 3 daily gavage doses ≥100 mg *o,p'*-DDT/kg/day, but not 10 mg/kg/day (Diel et al. 2000).

Acute-duration oral exposure of laboratory animals to *p,p'*-DDT, *p,p'*-DDE, *o,p'*-DDT, or *o,p'*-DDD during gestation has produced effects on developing reproductive tissues and reproductive functions in adults (see Section 2.17 for more details and references).

Intermediate-duration studies. Fertility has been assessed in adult laboratory animals after intermediate-duration exposures to technical DDT, *p,p'*-DDE, *p,p'*-DDT, or *o,p'*-DDT (see Table 2-1 and Figure 2-2). An early study (Green 1969) reported decreased fertility when parental male and female Sprague-Dawley rats were fed diets of approximately 0.56 mg DDT/kg/day (only level tested, presumably technical DDT) for 60 days before mating, but this apparent LOAEL for decreased fertility was not included in Table 2-1 and Figure 2-2 due to insufficient reporting of study details.

Decreased fertility after intermediate-duration exposure to technical DDT has been reported for female Sprague-Dawley rats exposed to 12 mg technical DDT/kg/day in food, but not to 6 mg/kg/day, for 36 weeks before mating to nonexposed males (Jonsson et al. 1976); female C-57 mice exposed to 51.4 mg technical DDT/kg/day in food, but not to 34.3 mg/kg/day, for up to 60–90 days before mating to non-exposed males (Bernard and Gaertner 1964); and pairs of male and female B6D2F1 mice exposed to ≥5.1 mg technical DDT/kg/day in food for 130 days before mating, but not in pairs exposed to up to 3.4 mg/kg/day for 86 days before mating (Ledoux et al. 1977).

Other studies reported no effects on fertility in female Sprague-Dawley rats exposed to up to 4 mg *o,p'*-DDT/kg/day in food for up to 20 weeks before mating to nonexposed males (Wrenn et al. 1971); female Sprague-Dawley rats given gavage doses of 10 mg *p,p'*-DDE/kg/day for 5 weeks before mating to nonexposed males (Kornbrust et al. 1986); pairs of male and female BALB/c mice exposed to 1.3 mg technical DDT/kg/day in food for 30 days before mating and 90 days beyond mating (Ware and Good 1967); New Zealand rabbits given gavage doses of 3 mg technical DDT/kg/day, 3 times/week for 12–15 weeks before artificial insemination, but a decreased ovulation rate and slight decrease in circulating progesterone levels (Lindenau et al. 1994; Seiler et al. 1994); and F0 parental male and female Sprague-Dawley rats exposed for 10 weeks before mating to dietary doses up to 25 or 27.7 mg *p,p'*-DDT/kg/day, respectively, but altered circulating levels of sex hormones in F0 females, but not in F0 males (Hojo et al. 2006).

Other findings for male reproductive effects after intermediate-duration exposure include decreased testis weight and Sertoli cell numbers in male rats exposed to gavage doses of 200 mg *p,p'*-DDT/kg/day on PNDs 4–23 and mated to nonexposed female rats on PND 60 or 90, as well as decreased number of fetuses and implants in the pregnant dams (Krause et al. 1975); and decreased seminal vesicle weight in castrated adult NMRI mice supplemented with testosterone and exposed to 6.25 mg *p,p'*-DDT/kg/day in food for 28 days, but not in similarly exposed nonsurgically modified mice (Orberg and Lundberg 1974). No significant changes in serum levels of sex hormones, sperm counts, and relative weights or histology of reproductive organs were observed in sexually immature male F344 rats exposed to 10 mg *p,p'*-DDE in food from 6 to 12 weeks of age (Makita et al. 2003a).

Other female reproductive effects include small (~12%) decreases in the number of implants and decreased number of corpus luteum in female NMRI mice exposed to 2 mg *p,p'*-DDT/kg/day for 72–74 days before mating to nonexposed males (Lundberg 1974) and decreased serum estradiol levels and increased progesterone (with no effects on fertility) in F0 female Sprague-Dawley rats fed dietary doses

≥3.75 or 27.7 mg *p,p'*-DDT/kg/day, respectively, for 10 weeks before mating with exposed males (Hojo et al. 2006).

Chronic-duration studies. 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 in the diet for 2 generations (Ottoboni 1969), 1.25 mg/kg/day for 3 generations (Treon et al. 1954), or 1.7 mg/kg/day for 11 breedings (Ottoboni 1972). Duby et al. (1971) found no reproductive effects in two successive generations of rats fed technical-grade DDT (0.5 mg/kg/day), *p,p'*-DDT (1.5 mg/kg/day) or *o,p'*-DDT (0.3 mg/kg/day). Hojo et al. (2006) found no effects on reproduction functions in F0 and F1 Sprague-Dawley rats exposed to dietary doses up to 25 (males) and 27.7 (females) mg *p,p'*-DDT/kg/day.

The results of a chronic-duration dietary study showed no treatment-related adverse effects on the ovaries, uterus, mammary glands, prostate, or adrenals of Osborne-Mendel rats treated in the diet with up to 45 mg technical DDT/kg/day, 59 mg *p,p'*-DDE/kg/day, or 231 mg technical DDD/kg/day (NCI 1978). The same findings were reported for B6C3F1 mice treated with up to 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 was not evaluated in the NCI (1978) study.

In mice, no adverse effects on reproduction were observed in field mice fed 2.4 mg technical DDT/kg/day in food for 15 months (Wolfe et al. 1979), but in multiple-generation studies of laboratory mice, decreased fertility was observed in Swiss Webster mice fed 20 mg technical DDT/kg/day, but not 5 mg/kg/day (Keplinger et al. 1970). No significant reproductive effects were reported in a 3-generation study in dogs dosed with up to 10 mg technical DDT/kg/day (Ottoboni et al. 1977).

Mechanisms of Reproductive Effects of DDT, DDD, or DDE. DDT and related compounds have been associated with altered reproductive outcomes in some epidemiological studies and laboratory animal studies. These effects are thought to involve anti-androgenic activities (e.g., androgen-receptor binding and impaired male reproductive tissue development) of *p,p'*-DDE, and estrogenic activities (e.g., estrogen-receptor binding and promotion of female reproductive tissue development) of *o,p'*-DDT (see Harada et al. 2016; Kelce et al. 1995, 1997; Yamasaki et al. 2009; You et al. 1998, 1999a).

Numerous studies have shown that *o,p'*-DDT has estrogenic activities, albeit relatively weak properties, compared with 17β-estradiol. For example, *o,p'*-DDT showed significantly stronger estrogenic activity for initiating implantation and in increasing uterine weight in young rats than *p,p'*-DDT (Johnson et al.

1992; Singhal et al. 1970). Welch et al. (1969) reported an estrogenic activity ranking of *o,p'*-DDT > technical DDT > *p,p'*-DDT in immature female rats treated intraperitoneally. In various *in vitro* assays for estrogenicity, however, *o,p'*-DDT gave positive estrogenic responses, but with a potency that was several orders of magnitude weaker than 17β-estradiol and diethylstilbestrol (DES, a synthetic form of estrogen) (Soto et al. 1997). In one assay, *o,p'*-DDT, *o,p'*-DDD, and *p,p'*-DDT were full estrogenic agonists, *p,p'*-DDE and *p,p'*-DDD were partial agonists, and technical DDT was a full agonist. In another study, it took 10^7 times more *o,p'*-DDT, *o,p'*-DDD, *p,p'*-DDT, *p,p'*-DDE, *p,p'*-DDD, and technical DDT to produce an estrogenic response comparable to that of 17β-estradiol (Soto et al. 1998). Additional assays that used gene expression and transcription mediated by estrogen receptor activation showed *o,p'*-DDT's estrogenic activity to be at least 10^5 less potent than 17β-estradiol in inducing estrogen-regulated gene transcription (Balaguer et al. 1999; Gaido et al. 1997; Sohoni and Sumpter 1998; Tully et al. 2000). Results from *in vitro* studies also have shown that *o,p'*- isomers can compete with estradiol for binding to the estrogen receptor, although with a binding affinity significantly lower than 17β-estradiol (Danzo 1997; Kelce et al. 1995). Experiments also showed that *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD were relatively ineffective in binding to the estrogen receptor (Kelce et al. 1995).

Other studies have shown that the environmentally persistent metabolite, *p,p'*-DDE, has anti-androgenic activity (Kelce et al. 1995, 1997; You et al. 1998, 1999a). In competitive androgen receptor binding assays of *p,p'*-DDT, *p,p'*-DDE, *o,p'*- DDT, and *p,p'*-DDD, the four chemicals showed dose-dependent competitive inhibition, but *p,p'*-DDE was the greatest competitor with an inhibition constant similar to that of DES and about 30 times weaker than 17β-estradiol (Kelce et al. 1995). The other three isomers were 12–20-fold less effective than *p,p'*-DDE. Experiments also showed that *p,p'*-DDT, *p,p'*-DDD, and *p,p'*-DDE bound the androgen receptor 14, 11, and 200 times more effectively than the estrogen receptor, respectively (Kelce et al. 1995). Maness et al. (1998) also showed that among DDT compounds, *p,p'*-DDE was the most potent for inhibiting androgen receptor regulated gene expression in a human cell line transiently transvected with the human androgen receptor and a reporter gene linked to an androgen responsive promoter. More recently, Tinwell et al. (2007) showed that the inhibitory action of *p,p'*-DDE on the weight of the ventral prostate of immature male rats was associated with a 4.4-fold increase in activity of L-amino oxidase, a protein associated with apoptosis and suggested that this protein has the potential to be a biomarker for endocrine disruption.

Results from several studies suggest that Sertoli cells may be involved in DDT (DDT, DDE, DDD)-induced alterations in sperm parameters. Sertoli cells facilitate the progression of germ cells to spermatozoa, are activated by FSH, and produce the protein complex inhibin, which inhibits FSH

synthesis and secretion. For example, *in vitro* incubation of Sertoli cells from immature rats with DDE resulted in decreased survival of the cells that appeared to be mediated by down-regulation of transferrin and up-regulation of androgen-binding protein (ABP) (Xiong et al. 2006). Both transferrin and ABP are glycoproteins produced and secreted by Sertoli cell into the lumen of the tubule and play an important role on differentiation and maturity of sperm. *In vitro* studies also have shown that DDT can reduce the number of FSH binding sites in Sertoli cells by triggering degradation of FSH receptors (Bernard et al. 2007), or by affecting intercellular junctions by altering the amount or inducing aberrant localizations of protein components of Sertoli cell tight junctions, specifically connexin 43 (Fiorini et al. 2004). Other studies have suggested that DDE can induce apoptotic Sertoli cell (and germ cell) death by mechanisms involving elevation of reactive oxygen species (ROS), reduction of mitochondrial membrane potential, and induction of apoptotic activating factors, ultimately leading to altered spermatogenesis (Mota et al. 2011; Quan et al. 2016; Shi et al. 2009, 2013; Song et al. 2008, 2011). Results from a study of *in vivo* exposure of rats to DDE as well as exposure of Sertoli cells to DDE *in vitro* showed that DDE can alter mRNA and protein expression of vimentin, N-cadherin, and FSH receptors (Yan et al. 2013). Vimentin protein is an important component of the Sertoli cell cytoskeleton and plays a key role in anchoring germ cells to the seminiferous epithelium. N-Cadherin play an important role in cell-cell adhesions and has been found in spermatogonia, primary spermatocytes, and Sertoli cells. FSH receptor expression controls the magnitude of FSH stimulatory action on Sertoli cells.

Results from a study of *in vitro* incubation of human sperm with DDE in a medium simulating exposure in the female reproductive tract showed that DDE increased intracellular levels of calcium in sperm cells, prematurely triggering acrosomal loss through acrosomal reaction or by damaging sperm membranes (Tavares et al. 2013). Results from a more recent study from the same group of investigators suggested that DDE promoted mitochondrial calcium overload that, in turn, induced mitochondrial malfunction affecting sperm motility and, ultimately, male fertility (Tavares et al. 2015).

Leydig cells have also been shown to be potential targets for DDT via the adrenal toxicant metabolite, 3-methylsulphonyl-DDE. LH stimulates Leydig cells to produce testosterone; prolactin increases the response of Leydig cells to stimulation by LH. Castellanos et al. (2013) reported that incubation of unstimulated primary neonatal porcine cells with 3-methylsulphonyl-DDE resulted in a concentration-dependent increased secretion of testosterone and estradiol; however, in LH-stimulated cells treated with 3-methylsulphonyl-DDE, there was decreased secretion of testosterone, estradiol, and progesterone. In addition, the expression of important steroidogenesis genes was down-regulated in LH-stimulated cells. These results suggested that the endocrine-disruptive activity of 3-methylsulphonyl-DDE is determined

by the physiological status of the Leydig cells. Proteomic analysis of unstimulated and LH-stimulated cells showed that 3-methylsulphonyl-DDE was acting on several pathways, including mitochondrial dysfunction, oxidative phosphorylation, EIF2-signaling, and glutathione-mediated detoxification (Kalayou et al. 2016).

Studies have also assessed ovarian function in relation to DDT exposure; most of the research has been conducted using *in vitro* cell populations. *p,p'*-DDE increased proliferation of porcine granulosa cells, decreased FSH-stimulated cAMP in these cells and in cultured Chinese hamster ovary cells, and decreased progesterone synthesis in granulosa cells (Chedrese and Feyles 2001). The fact that estradiol could not mimic the DDE-induced decrease in progesterone suggests that DDE also possess non-estrogenic endocrine disrupting properties. *p,p'*-DDE was also shown to increase the concentration of calcium in human granulosa-lutein cells in culture by rapid mobilization of calcium from extra- and intracellular sources, which could possibly affect the calcium response to FSH and human chorionic gonadotropin (Younglai et al. 2004a). Similar results were obtained when cells were incubated with *o,p'*-DDE; a mechanism involving a G-protein-coupled membrane receptor in the increase in cytoplasmic calcium was proposed (Wu et al. 2006). Further studies from the same group showed that *p,p'*-DDE can increase FSH stimulation of aromatase activity in human granulosa cells, which could result in overproduction of estradiol early in folliculogenesis and acceleration of oocyte maturation resulting ultimately in impaired fertilization (Younglai et al. 2004b). Incubation of human granulosa cells with *p,p'*-DDE also resulted in significant increases in the expression of the growth factors, vascular endothelial growth factor and insulin-like growth factor-1, both of which appear to play a key role in ovarian follicular development and corpus luteum function (Holloway et al. 2007). Similar results were obtained in ovarian tissue from young rats treated with a single dose of 100 µg *p,p'*-DDE/kg and sacrificed 20 days later (Holloway et al. 2007).

2.17 DEVELOPMENTAL

This section discusses human epidemiological evidence for effects on birth outcomes and subsequent postnatal growth patterns and evidence in laboratory animals exposed during gestation and/or early postnatal periods for fetotoxicity, birth weights and postnatal growth patterns, and developmental effects on neurological and reproductive systems.

Epidemiology Studies of Gestational or Early Life Exposures on Birth Outcomes and Subsequent Postnatal Growth Patterns

Gestational age. Evidence for associations between gestational age or length with maternal DDT exposure metrics was inconsistent across studies (Table 2-19). Of the 10 studies that evaluated gestational age or length, 3 found associations with decreased duration of gestation (Arrebola et al. 2016; Kezios et al. 2013; Wojtyniak et al. 2010) and the remaining 7 found no association with duration of gestation (see Table 2-19 for citations).

Table 2-19. Summary of Studies of Associations Between Human DDT Exposure Metrics and Gestational Age and Offspring Measures of Growth at Birth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Gestational age			
Arrebola et al. 2016 Cross-sectional, 200 mother-infant pairs (Bolivia)	Cord blood DDT metrics (IQR, ng/mL) DDE: 0.26–2.52 *o,p'*-DDT: 0.10–0.37	Gestational age	↓ (DDE) ↔ (*o,p'*-DDT)
Bjerregaard and Hansen 2000 Cross-sectional, 136 mother-infant pairs (Greenland) Maternal blood was collected "towards the end of pregnancy"	Maternal serum (GM (range), ng/mL) DDE: 3.7 (0.5–29.9) DDT: 0.1 (0.02–1.5) ΣDDT: 3.8 (0.5–30.8) Cord blood levels reported; correlations with maternal serum were 0.89 (DDE, ΣDDT) and 0.83 (DDT)	Gestation length Cord blood	↔ (all metrics)
Farhang et al. 2005 Cross-sectional, 420 mother-infant pairs (United States, California) Maternal blood samples collected early postpartum (n=334) or during the third (n=54) or the second (n=32) trimester	Maternal serum DDT metrics (quartiles, ng/mL) DDE DDT Q1 ≤31.5 ≤8.1 Q2 31.7–42.5 8.2 – 11.0 Q3 42.6–54.7 11.1–16.2 Q4 ≥57.5 ≥16.3	Gestational age	↔ (DDE) ↔ (DDT)

Table 2-19. Summary of Studies of Associations Between Human DDT Exposure Metrics and Gestational Age and Offspring Measures of Growth at Birth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Fenster et al. 2006 Cohort, 385 mother-infant pairs (United States, California) Maternal blood samples collected at 26±2.9 weeks of gestation	Maternal serum levels (GM (95% CI), ng/g lipid) DDE: 1,363.0 (1198.1–1551.0) DDT: 20.6 (17.3–24.5) *o,p'*-DDT: 1.6 (1.4–1.9)	Gestation length	↔ (all metrics)
Jusko et al. 2006 Cohort, 399 mother-infant pairs (United States, California) Maternal blood collected during 2nd or 3rd trimester	Maternal serum DDT metrics (IQR, ng/g lipid) DDE: 3,900–8,560 DDT: 1,110–2,300 *o,p'*-DDT: 120–350 ΣDDT: 5,680–11,150	Gestational age	↔ (all metrics)
Kezios et al**. 2013** Cohort, 600 mother-infant pairs (United States, California) Maternal blood collected during each trimester and postpartum	Maternal serum DDT metrics (IQR, ng/mL) DDE: 30.0–52.2 DDT: 7.9–15.1 *o,p'*-DDT: 0.28–0.68	Gestation length	↓ (DDE) ↔ (DDT) ↔ (*o,p'*-DDT)
Vafeiadi et al. 2014 Cohort, 1,117 mother-infant pairs (Greece) Maternal blood collected during the 1st trimester	Maternal serum DDE (IQR, ng/mL) 1.193–3.641	Gestational age	↔
Weisskopf et al. 2005 Retrospective cohort, 143 mother-infant pairs including 119 fish eaters and 24 non-fish-eaters (United States; Wisconsin, Illinois, Indiana, Ohio, and Michigan) Maternal blood collected at time of study (1–25 years postpartum) was used to estimate exposure	Maternal serum DDE (GM (range), ng/mL) Fish eaters: 2.03 (0.25–10) Non-fish-eaters: 1.0 (0.13–5.7)	Gestational age	↔

Table 2-19. Summary of Studies of Associations Between Human DDT Exposure Metrics and Gestational Age and Offspring Measures of Growth at Birth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Wojtyniak et al. 2010 Cohort, 1,322 mother-infant pairs (Greenland [n=572], Ukraine [n=611], Poland [n=258]) Maternal blood collected at 24–33 weeks of gestation	Maternal serum DDE (GM, ng/g lipid) Greenland: 273.8 Ukraine: 653.3 Poland: 356.8	Gestational age Greenland Ukraine Poland	 ↓ ↔ ↓
Wolff et al. 2007 Cross-sectional, 404 mother-infant pairs (United States, New York) Maternal blood collected during 3rd trimester	Maternal serum DDE (median (range), ng/mL): 0.64 (0–57.3)	Gestational age	↔
Offspring measures of growth at birth			
Al-Saleh et al. 2012 Cross-sectional, 1,571 mother-infant pairs (Saudi Arabia) Maternal blood collected at delivery	Maternal serum DDT metrics (mean±SD, ng/mL) DDE: 0.551±1.778 DDT: 0.008±0.113 DDD: 0.002±0.030 Placenta DDT metrics (mean±SD, ng/g dry weight) DDE: 10.167±18.850 DDT: 29.620±158.282 DDD: 7.042±18.030	Head circumference Serum Placenta	 ↓ (DDE) ↔ (DDE, DDT, DDE)
		Crown-heel length Serum Placenta	 ↓ (DDE) ↓ (DDE, DDT, DDD)
		Body weight Serum Placenta	 ↓ (DDE) ↓ (DDE) ↔ (DDT, DDD)
		Body length Serum Placenta	 ↓ (DDE) ↓ (DDE) ↔ (DDT, DDE)
		Ponderal index Serum Placenta	 ↔ (DDE) ↔ (DDE, DDT, DDD)
		Small for gestational age Serum Placenta	 ↑ (DDE) ↔ (DDE, DDT, DDD)

Table 2-19. Summary of Studies of Associations Between Human DDT Exposure Metrics and Gestational Age and Offspring Measures of Growth at Birth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Arrebola et al. 2016 Cross-sectional, 200 mother-infant pairs (Bolivia)	Cord blood DDT metrics (IQR, ng/mL) DDE: 0.26–2.52 *o,p'*-DDT: 0.10–0.37	Birth weight	↑ (DDE) ↔ (*o,p'*-DDT)
		Birth length	↔ (DDE) ↔ (*o,p'*-DDT)
		Head circumference	↔ (DDE) ↔ (*o,p'*-DDT)
		Ponderal Index	↔ (DDE) ↔ (*o,p'*-DDT)
Bergonzi et al. 2011 Cross-sectional, 70 mother-infant pairs; all deliveries via caesarean section (Italy) Biomarker levels reported in Bergonzi et al. (2009); maternal blood collected the day prior to scheduled caesarean section	Maternal DDT metrics (median (5^{th}–95^{th} percentile), ng/g lipid) Serum DDE: 112.3 (42–377) Placenta DDE: 62.5 (24–226) Adipose DDE: 202.0 (76–730) Adipose DDT: 7.0 (2.0–26.8) Cord blood DDT metrics (median (5^{th}–95^{th} percentile), ng/mL) Serum DDE: 0.25 (0.10–0.72)	Small weight for gestational age (all metrics)	↔ (DDE) ↔ (DDT)
		Small length for gestational age (all metrics)	↔ (DDE) ↔ (DDT)
		Birth weight (all metrics)	↔ (DDE) ↔ (DDT)
		Head circumference (all metrics)	↔ (DDE) ↔ (DDT)
		Birth length Adipose Other metrics	 ↔ (DDE) ↑ (DDT) ↔ (DDE)
Bjerregaard and Hansen 2000 Cross-sectional, 136 mother-infant pairs (Greenland) Maternal blood collected "towards the end of pregnancy"	Maternal serum (GM (range), ng/mL) DDE: 3.7 (0.5–29.9) DDT: 0.1 (0.02–1.5) ΣDDT: 3.8 (0.5–30.8) Cord blood levels not reported; correlations with maternal serum were 0.89 (DDE, ΣDDT) and 0.83 (DDT)	Birth weight Cord blood	 ↔ (all metrics)
Cabrera-Rodriguez et al. 2019 Cross-sectional, 447 mother-infant pairs (Canary Islands)	Cord blood DDE (median, ng/mL) 0.148	Birth weight Girls Boys All	 ↑ ↔ ↑

Table 2-19. Summary of Studies of Associations Between Human DDT Exposure Metrics and Gestational Age and Offspring Measures of Growth at Birth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
de Cock et al. 2016 Cross-sectional, 91 mother-infant pairs (58 males, 31 females) (Netherlands) Breast milk collected 2 months postpartum; for total DDE exposure, milk data were converted into cord plasma levels	DDE metrics (mean (range), ng/mL) Cord: 0.134 (0.029–0.47) Milk: 2.381 (0.400–11.39) Total: 0.1 (0.014–0.47) Exposure tertiles for total DDE (ng/mL) T1: <0.052 T2: 0.052–0.096 T3: >0.096	Birth weight Total (T3 versus T1)	↓ (Boys) ↔ (Girls)
Farhang et al. 2005 Cross-sectional, 420 mother-infant pairs (United States, California) Maternal blood samples collected early postpartum (n=334) or during the third (n=54) or the second (n=32) trimester	Maternal serum DDT metrics (quartiles, ng/mL) DDE / DDT Q1 ≤31.5 / ≤8.1 Q2 31.7–42.5 / 8.2 – 11.0 Q3 42.6–54.7 / 11.1–16.2 Q4 ≥57.5 / ≥16.3	Birth weight Small for gestational age	↔ (DDE) ↔ (DDT) ↔ (DDE) ↔ (DDT)
Fenster et al. 2006 Cohort, 385 mother-infant pairs (United States, California) Maternal blood samples collected at 26±2.9 weeks of gestation	Maternal serum levels (GM (95% CI), ng/g lipid) DDE: 1,363.0 (1,198.1–1,551.0) DDT: 20.6 (17.3–24.5) *o,p'*-DDT: 1.6 (1.4–1.9)	Birth weight Crown-heel length	↔ (all metrics) ↔ (all metrics)
Gladen et al. 2003 Cross-sectional, 197 mother-infant pairs (Ukraine) Breast milk collected 4–5 days postpartum	Milk DDT metrics (tertiles, ng/g lipid) DDE / DDT T1 1,900 / 257 T2 2,457 / 336 T3 3,250 / 425	Birth weight Relative weight (ratio of birth weight to mean weight for gestational age)	↔ (DDE) ↔ (DDT) ↔ (DDE) ↔ (DDT)
Guo et al. 2014 Cross-sectional, 81 mother-infant pairs (China) Maternal blood collected at birth	Maternal serum and cord blood DDT metrics (GM, ng/g lipid) Serum / Cord blood DDE 203.54 / 116.14 DDT 14.68 / 5.41 *o,p'*-DDE 0.62 / 0.85 *o,p'*-DDT 2.51 / 3.39 DDD 1.07 / 0.66 ΣDDT 245.82 / 146.03	Birth weight Serum Cord blood	 ↔ (all metrics) ↔ (all metrics)

Table 2-19. Summary of Studies of Associations Between Human DDT Exposure Metrics and Gestational Age and Offspring Measures of Growth at Birth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Jusko et al. 2006 Cohort, 399 mother-infant pairs (United States, California) Maternal blood collected during 2nd or 3rd trimester	Maternal serum DDT metrics (IQR, ng/g lipid) DDE: 3,900–8,560 DDT: 1,110–2,300 *o,p'*-DDT: 120–350 ΣDDT: 5,680–11,150	Birth weight	↔ (all metrics)
		Birth weight z-score	↔ (all metrics)
		Birth length	↔ (all metrics)
		Head circumference	↔ (all metrics)
Karmaus and Zhu 2004 Retrospective cohort, 168 mother-infant pairs (United States, Michigan) Maternal exposure based on historical blood measurements closest to the date of delivery	Maternal serum DDE (quartiles, ng/mL) Q1: <5.0 Q2: 5.0–15.0 Q3: 15–<25 Q4: ≥25	Birth weight	↔
		Small for gestational age	↔
Kezios et al**. 2013** Cohort, 600 mother-infant pairs (United States, California) Maternal blood collected during each trimester and postpartum	Maternal serum DDT metrics (IQR, ng/mL) DDE: 30.0–52.2 DDT: 7.9–15.1 *o,p'*-DDT: 0.28–0.68	Birth weight	↓ (DDE) ↑ (DDT) ↔ (*o,p'*-DDT)
		Small for gestational age	↔ (all metrics)
Khanjani and Sim 2006 Cross-sectional, 815 mother-infant pairs (Australia) Breast milk collected 6–12 weeks postpartum	Milk DDT metric exposure categories (ng/g lipid) DDE / DDT Low: 0–400 / 0–39 Medium: >400–730 / >39–66 High: >730 / >66	Low birth weight	↔ (DDE) ↔ (DDT)
		Small for gestational age	↔ (DDE) ↔ (DDT)
		Head circumference	↔ (DDE) ↔ (DDT)
Lenters et al. 2016 Cohort, 1,250 maternal-infant pairs (Greenland, Poland, Ukraine) Maternal blood collected during 2nd or 3rd trimester	Maternal serum DDE (pooled median, ng/mL): 3.39	Birth weight	↓
Longnecker et al. 2001 Cross-sectional, 2,380 mother-infant pairs (United States) Maternal blood collected during late pregnancy	Maternal serum DDE exposure groups (ng/mL) Group 1: ≤15 Group 2: 15–29 Group 3: 30–44 Group 4: 45–59 Group 5: ≥60	Small for gestational age Groups 2–5 (versus 1)	↑
		Birth length	↔
		Head circumference	↔

Table 2-19. Summary of Studies of Associations Between Human DDT Exposure Metrics and Gestational Age and Offspring Measures of Growth at Birth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Lopez-Espinosa et al. 2011 Cross-sectional, 494 mother-infant pairs (Spain)	Cord blood DDT metrics (IQR, ng/mL) DDE: 0.296–0.770 DDT: <LOD–0.074	Birth weight	↓ (DDE) ↓ (DDT)
		Birth length	↔ (DDE) ↔ (DDT)
		Head circumference	↔ (DDE) ↔ (DDT)
Müller et al. 2017 Cross-sectional, 95 mother-infant pairs (Tanzania) Breast milk collected <10 days postpartum	Milk DDT metrics (IQR, ng/g lipid) DDE: 95.5–580 DDD: 0.28–1.03 DDT: 1.09–10.6 ΣDDT: 95.7–619	Birth weight	↔ (all metrics)
		Birth length	↔ (all metrics)
		Head circumference Girls Boys	 ↓ (DDE) ↔ (DDD, DDT, ΣDDT) ↔
Ouidir et al. 2020a, 2020b Cohort, 2,284 mother-infant pairs (1,187 boys, 1,097 girls) (United States) Maternal blood collected during the 1st trimester	Maternal serum DDT metrics (IQR, ng/g) DDE: 52.34–170.68 DDD: 0–0.50 DDT: 0–2.17	Head circumference All, boys, girls	 ↓ (DDE) ↔ (DDD, DDT)
		Abdominal circumference All, boys Girls	 ↑ (DDD) ↔ (DDE, DDT) ↔ (all metrics)
		Fetal growth Boys All, girls	 ↑ (DDD) ↔ (DDE, DDT) ↔ (all metrics)
Ribas-Fito et al. 2002 Cross-sectional, 70 mother-infant pairs (Spain)	Cord blood DDE (IQR, ng/mL) 0.49–1.69	Birth weight	↔
		Crown-heel length	↔
		Small weight for gestational age	↔
		Small length for gestational age	↔

Table 2-19. Summary of Studies of Associations Between Human DDT Exposure Metrics and Gestational Age and Offspring Measures of Growth at Birth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Robledo et al. 2015 Cohort, 234 parental-infant pairs (99–113 males. 91–117 females) (United States, Michigan and Texas) Maternal and paternal blood collected prior to conception	Maternal preconception serum DDT metrics (GM (95% CI), ng/g) DDE: 0.580 (0.534–0.630) DDT: 0.012 (0.011–0.013) *o,p'*-DDT: 0.002 (0.002–0.003)	Birth weight Males Females	 ↔ (all metrics) ↓ (*o,p'*-DDT) ↔ (DDE, DDT)
		Head circumference Males Females	 ↔ (all metrics) ↓ (*o,p'*-DDT) ↔ (DDE, DDT)
		Length Males Females	 ↔ (all metrics) ↔ (all metrics)
		Ponderal Index Males Females	 ↔ (all metrics) ↔ (all metrics)
	Paternal preconception serum DDT metrics (GM (95% CI), ng/g) DDE: 0.752 (0.700–0.808) DDT: 0.014 (0.013–0.015) *o,p'*-DDT: 0.003 (0.003–0.003)	Birth weight Males Females	 ↔ (all metrics) ↔ (all metrics)
		Head circumference Males Females	 ↔ (all metrics) ↔ (all metrics)
		Length Males Females	 ↔ (all metrics) ↔ (all metrics)
		Ponderal Index Males Females	 ↔ (all metrics) ↑ (DDE) ↔ (*o,p'*-DDT, DDT)
Sagiv et al. 2007 Cross-sectional, 722 mother-infant pairs (United States, Massachusetts)	Cord blood DDE (quartiles, ng/g) Q1: 0–0.20 Q2: 0.20–0.30 Q3: 0.30–0.46 Q4: 0.47–14.93	Birth weight	↔
		Crown-heel length	↔
		Head circumference	↔
Sharma et al. 2012 Cross-sectional, 100 mother-infant pairs including 50 fetal growth restriction (FGR) cases and 50 normal controls (India) Maternal blood collected prior to delivery	Maternal serum DDT metrics (mean±SD, ng/mL) Control FGR DDE 2.58±2.3 2.68±1.4 DDT 0.73±1.1 1.67±1.4 Cord blood DDT metrics (mean±SD, ng/mL) Control FGR DDE 1.31±1.14 1.95±2.3 DDT 0.36±0.64 0.83±0.71	FGR Maternal serum Cord blood	 ↔ (DDE) ↑ (DDT) ↔ (DDE) ↑ (DDT)

Table 2-19. Summary of Studies of Associations Between Human DDT Exposure Metrics and Gestational Age and Offspring Measures of Growth at Birth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Siddiqui et al. 2003 Cross-sectional, 54 mother-infant pairs including 30 cases of intrauterine growth restriction (IUGR) and 24 normal controls (India) Maternal blood collected prior to delivery	Maternal serum DDT metrics (mean±SD, ng/mL) Control / IUGR DDE 6.32±2.95 / 8.79±4.19 DDD 12.1±10.2 / 12.8±11.5 DDT 0.26±1.25 / 0.55±1.75 o,p'-DDT 1.37±2.36 / 1.32±2.47 ΣDDT 20.0±14.3 / 23.4±13.7 Placental tissue DDT metrics (mean±SD, ng/mL) Control / IUGR DDE 8.89±5.22 / 11.2±6.32 DDD 22.1±19.3 / 25.4±19.9 DDT 0.48±1.65 / 0.29±1.09 o,p'-DDT 2.47±2.85 / 3.23±3.49 ΣDDT 33.9±25.3 / 40.2±23.7 Cord blood DDT metrics (mean±SD, ng/mL) Control / IUGR DDE 5.33±4.33 / 7.81±7.12 DDD 17.8±18.1 / 21.0±16.1 DDT 0.22±1.08 / 1.19±4.06 o,p'-DDT 2.34±4.03 / 3.38±4.04 ΣDDT 25.7±24.0 / 33.3±21.9	IUGR Maternal serum Placental tissue Cord blood	↑ (DDE) ↔ (all other metrics) ↔ (all metrics) ↔ (all metrics)
Tan et al. 2009 Cross-sectional, 41 mother-infant pairs (Singapore)	Cord blood DDT metrics (mean±SD, ng/g lipid) DDE: 402±455 DDT: 34.5±38.4 DDD: 3.83±5.78	Birth length Birth weight Head circumference	↑ (DDD, DDT) ↔ (DDE) ↑ (DDD, DDT) ↔ (DDE) ↑ (DDD, DDT) ↔ (DDE)
Vafeiadi et al. 2014 Cohort, 1,117 mother-infant pairs (Greece) Maternal blood collected during the 1st trimester	Maternal serum DDE (IQR, ng/mL) 1.193–3.641	Birth weight Head circumference	↔ ↔

Table 2-19. Summary of Studies of Associations Between Human DDT Exposure Metrics and Gestational Age and Offspring Measures of Growth at Birth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Valvi et al. 2017 Cross-sectional, 604 mother-infant pairs, including 49 mothers with gestational diabetes mellitus (GDM) and 555 mothers without GDM (Denmark) Maternal blood collected during 3rd trimester	Maternal serum DDE (IQR, ng/g lipid) No GDM: 330–920 GDM: 410–1,200 Combined: 330–940	Birth weight	↔
		Birth length	↔
		Head circumference	↔
Weihe et al. 2003 Cross-sectional, 500 mother-infant pairs (267 males, 233 females) (Faroe Islands) Maternal blood collected during 3rd trimester	Maternal serum DDT metrics (mean±SD, ng/mL) DDT: 0.175±0.251 DDE: 5.534±6.051	Birth weight	
		All	↔ (DDE, DDT)
		Males	↔ (DDE) ↑ (DDT)
		Females	↔ (DDE, DDT)
		Birth length	
		All	↓ (DDE, DDT)
		Males	↓ (DDE) ↔ (DDT)
		Females	↔ (DDE) ↓ (DDT)
		Head circumference	
		All, males, and females	↔ (DDE, DDT)
Weisskopf et al. 2005 Retrospective cohort, 143 mother-infant pairs including 119 fish eaters and 24 non-fish-eaters (United States; Wisconsin, Illinois, Indiana, Ohio, and Michigan) Maternal blood collected at time of study (1–25 years post-partum) was used to estimate exposure	Maternal serum DDE (GM (range), ng/mL) Fish eaters: 2.03 (0.25–10) Non-fish-eaters: 1.0 (0.13–5.7)	Birth weight	↓

Table 2-19. Summary of Studies of Associations Between Human DDT Exposure Metrics and Gestational Age and Offspring Measures of Growth at Birth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Wojtyniak et al. 2010 Cohort, 1,322 mother-infant pairs (Greenland [n=572], Ukraine [n=611], Poland [n=258]) Maternal blood collected at 24–33 weeks of gestation	Maternal serum DDE (GM, ng/g lipid) Greenland: 273.8 Ukraine: 653.3 Poland: 356.8	Birth weight Greenland Ukraine Poland	 ↓ ↔ ↓
Wolff et al. 2007 Cross-sectional, 404 mother-infant pairs (United States, New York) Maternal blood collected during 3rd trimester	Maternal serum DDE (median (range), ng/mL): 0.64 (0–57.3)	Birth weight Birth length Ponderal Index Head circumference Gestational age	↔ ↔ ↔ ↓ ↔

[a]Studies in this table were selected because they: (1) measured DDT-related metrics for each subject in biological fluids or tissues (maternal, paternal, cord, placental, and/or breast milk), and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified; DDD= p,p'-DDD unless otherwise specified

↑ = positive association; ↓ = inverse association; ↔ = no association; CI = confidence interval; DDD = dichloro-diphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; FGR = fetal growth restriction; GDM = gestational diabetes mellitus; GM = geometric mean; H= height; IUGR = intrauterine growth retardation; IQR = interquartile range; LOD = limit of detection; Q = quartile; SD = standard deviation; T = tertile

Offspring Measures of Growth at Birth. Epidemiological studies evaluating developmental DDT exposure metrics and measures of offspring growth at or before birth are shown in Table 2-19. This table only describes studies that included measurements of maternal, parenteral, or cord DDT metrics for each subject and examined possible associations with measures of growth at birth using correlation, logistic regression, or linear regression statistical techniques.

Inconsistent evidence is provided by 30 epidemiological studies examining possible associations between maternal serum or cord blood levels of DDT, DDD, or DDE and birth weight, birth weight status (e.g., small for gestational age or low birth weight), and/or fetal growth (e.g., intrauterine growth restriction [IUGR]): 10 studies reported associations with decreased birth weight, birth weight status, or IUGR; 5 studies reported associations with increased birth weight or fetal growth; 1 study reported an association of decreased birth weight with maternal serum DDE but increased birth weight with maternal serum

DDT; and 15 studies found no associations with birth weight or birth weight status (see Table 2-19 for citations). One study also reported no association between preconception paternal DDT metrics and birth weight (Robledo et al. 2015). Three meta-analyses evaluated potential associations between developmental exposure to DDT and birth weight or birth weight status from study populations in European birth cohorts comprising 8,825, 7,530, and 5,447 mother-infant pairs, respectively (Casas et al. 2015; Govarts et al. 2012, 2018). None of the meta-analyses found an association between maternal DDT-related biometrics and decreased infant weight at birth or small for gestational age in the combined datasets using multiple linear regression techniques.

Some studies in Table 2-19 also included other birth measures such as birth length, length status [including crown-heel length (CHL), ponderal index (weight relative to height), and small length for gestational age (SLGA)], and head circumference. Evidence for associations of these birth parameters with maternal DDT-related biometrics also was inconsistent across studies. Fifteen studies evaluated infant body length measures: 2 reported associations with decreased length (Al-Saleh et al. 2012; Weihe et al. 2003); 2 reported an association with increased length (Bergonzi et al. 2011; Tan et al. 2009); and 11 reported no association with body length or length status (see Table 2-19 for citations). Sixteen studies evaluated infant head circumference at birth: 5 reported associations with decreased head circumference (Al-Saleh et al. 2012; Muller et al. 2017; Ouidir et al. 2020a; Robledo et al. 2015; Wolff et al. 2007); 1 reported an association with increased head circumference (Tan et al. 2009); and 10 reported no associations with infant head circumference (see Table 2-19 for citations). One study also reported no association between preconception paternal DDT metrics and birth length or head circumference, but there was an association with increased ponderal index (Robledo et al. 2015).

Subsequent growth patterns. Inconsistent evidence is provided by 26 epidemiological studies examining possible associations between maternal or child serum, cord blood, or breast milk levels of DDT, DDD, or DDE and changes in growth patterns of offspring (Table 2-20). Among the 24 studies examining body weight endpoints in offspring (e.g., BMI, BMI z-score, overweight or obese status, rapid infant growth), 13 found associations of maternal DDT biometrics with increased weight or weight status and 11 found no associations of maternal biometrics and offspring weight or weight status (see Table 2-20 for citations). Offspring height status was assessed in 11 studies: two studies found associations with decreased height in offspring (Karmaus et al. 2002; Ribas-Fito et al. 2006), but no associations were found in the other 9 studies assessing offspring height or length (see Table 2-20 for citations).

Table 2-20. Summary of Studies of Associations between Human DDT Exposure Metrics and Measures of Post-Birth Offspring Body Weight and Growth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Agay-Shay et al. 2015 Cohort, 470 mother-child pairs, child growth measurements at 7 years (Spain)	Maternal serum DDE (GM (range), ng/g lipid): 126.3 (7.7–17,263.4) Tertiles not reported.	Overweight T2–T3	 ↑
		BMI z-score T2–T3	 ↔
Coker et al. 2018 Cohort, 708 mother-child pairs (365 males, 343 females), child growth assessed at 1 and 2 years (South Africa)	Maternal serum DDT metrics (GM±GSD, ng/g lipid): DDT: 68.94±6.65 DDE: 285.52±4.82	Weight-for-age All and males Females	 ↔ (DDT, DDE) ↑ (DDT) ↔ (DDE)
		BMI-for-age All and males Females	 ↔ (DDT, DDE) ↑ (DDT) ↔ (DDE)
		Weight-for-height All and males Females	 ↔ (DDT, DDE) ↑ (DDT) ↔ (DDE)
Cupul-Uicab et al. 2013 Cohort, 1,915 mother-child pairs at initiation, child growth assessed at 7 years (United States)	Maternal serum DDT metrics (IQR, ng/mL): DDE: 16.93–36.35 DDT: 6.46–14.16	Overweight or Obese	↔
		Obese	↔
		BMI	↔
Cupul-Uicab et al. 2010 Cohort, 788 mother-child pairs, child growth assessed from birth through ~2 years (Mexico)	Maternal serum DDT metrics (quartiles, ng/g lipid): DDE / DDT Q1 ≤3,000 / ≤250 Q2 3,010–6,000 / 260–750 Q3 6,010–9,000 / 760–1,990 Q4 ≥9,000 / ≥2,000	Height	↔
		BMI	↔
		Weight	↔
Delvaux et al. 2014 Cohort, 110 mother-child pairs (54 males, 56 females), child growth measurements at 7–9 years (Belgium)	Cord plasma DDE (IQR, ng/mL): Males: 0.14–0.44 Females: 0.12–0.44	Height	↔
		Weight	↔
		Skinfold thickness	↔
		BMI z-score	↔
		WC	↔ (males) ↑ (females)
		Waist/height	↔ (males) ↑ (females)
Garced et al. 2012 Cohort, 253 mother-child pairs, child growth assessed from birth through 12 months (Mexico)	Maternal serum DDE (GM±GSD, ng/mL): 1st trimester: 6.3±2.8 2nd trimester: 6.6±2.9 3rd trimester: 7.6±2.9	Weight-for-age	↔
		Length-for age	↔
		BMI-for-age	↔
		Head circumference	↔
		Weight-for-length	↔

Table 2-20. Summary of Studies of Associations between Human DDT Exposure Metrics and Measures of Post-Birth Offspring Body Weight and Growth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Gladen et al. 2004 Cohort, 304 mother-child pairs, child growth from 10 to 20 years (United States, Pennsylvania)	Maternal serum DDT metrics (quintiles, ng/g lipid) DDE / DDT Q1: <3,000 / <1,000 Q2: 3,000–5,900 / 1,000–1,900 Q3: 6,000–8,900 / 2,000–2,900 Q4: 9,000–11,900 / 3,000–3,900 Q5: ≥12,000 / ≥4,000 *o,p'*-DDT / ΣDDT Q1: <70 / <4,000 Q2: 80–150 / 4,000–7,900 Q3: 160–230 / 8,000–11,900 Q4: 240–310 / 12,000–15,900 *Q5: ≥320* / ≥16,000	Height	↔
		Height ratio	↔
		BMI	↔
		Skinfold thickness	↔
		Central adiposity	↔
		Skeletal age	↔
Gladen et al. 2000 Cohort, 594 mother-child pairs (316 females, 278 males), child growth measurements at 14 years (United States; North Carolina)	Maternal serum, milk, cord blood, and placenta DDE used to calculation transplacental exposure (ng/g fat): Group 1: 1: 0–1,000 Group 2: 1,000–2,000 Group 3: 2,000–3,000 Group 4: 3,000–4,000 Group 5: ≥4,000	Height	↔
		Weight	↑ (males) ↔ (females)
Heggeseth et al. 2015 Cohort, 249 mother-child pairs at initiation (113 females, 136 males), child growth development pattern assessed between 2 and 9 years (n=233) (United States, California)	Maternal serum DDT metrics (GM±GSD, ng/g lipid): DDE: 1,428±3.4 DDT: 21.2±5.3 *o,p'*-DDT: 1.7±4.3	Growth pattern showing increasing BMI (as opposed to stable growth)	↔
Hoyer et al. 2014 Cohort, 1,109 mother-child pairs, child growth assessed at 5–9 years (Greenland [n=525], Poland [n=92], Ukraine [n=492])	Maternal serum and estimated postnatal exposure of DDE (median, ng/g lipid) Maternal / Postnatal Greenland 300 / 7,075 Poland 385 / 11,627 Ukraine 639 / 12,535	BMI z-score	
		Maternal	↔
		Postnatal	↔
		Overweight	
		Maternal	↔
		Postnatal	↔

Table 2-20. Summary of Studies of Associations between Human DDT Exposure Metrics and Measures of Post-Birth Offspring Body Weight and Growth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Iszatt et al. 2015 Pooled cohort study of 2,487 mother-child pairs, child growth assessed from birth to 24 months (Europe) Duisburg cohort (n=222) FLEHS cohort (n=134) HUMIS cohort (n=399) Michalovce cohort (n=938) PELAGIE cohort (n=171)	Cord blood or milk DDE (mean, ng/g lipid): Prenatal / Postnatal Duisburg 141.4 / 255.3 FLEHS 214.7 / 272.6 HUMIS 63.4 / 177.3 Michalovce 540.5 / 954.3 PELAGIE 73.5 / 75.7	Weight for age Duisburg FLEHS HUMIS Michalovce PELAGIE Pooled prenatal Pooled postnatal	 ↑ ↔ ↔ ↔ ↔ ↑ ↔
Jusko et al. 2006 Cohort, 399 mother-child pairs, child growth assessed at birth and 5 years (United States, California)	Maternal serum DDT metrics (IQR, ng/g lipid): DDE: 3,900–8,560 DDT: 1,110–2,300 *o,p'*-DDT: 120–350 ΣDDT: 5,680–11,150	Sitting height Standing height Height z-score Weight z-score	↔ ↔ ↔ ↔
Karlsen et al. 2017 Cohort/Cross-sectional, 371 mother-child pairs, child growth assessed at 18 months and 5 years (Faroe Islands)	Maternal serum DDE and child serum DDE at 5 years (tertile, ng/g lipid) Maternal / Child T1 <90 / <130 T2 90–220 / 130–310 T3 >220 / >310	BMI z-score 18 months 5 years Overweight 18 months 5 years	 ↔ (all metrics) ↔ (all metrics) ↔ (all metrics) ↔ (all metrics)
Karmaus et al. 2009 Cohort, 259 women and their adult daughters at 2001–2002 (n=151) and 2006-2007 (n=129) (United States, Michigan)	Maternal serum DDE (quintiles, ng/mL): Q1: 0–1.502 Q2: 1.503–2.9 Q3: 2.9–6.1 Q4: 6.1–9.4 Q5: >9.4	Height Weight BMI	↔ ↑ ↑
Karmaus et al. 2002 Cohort/cross-sectional, 343 children, child's height from birth-48 months obtained from parents' records and measured at 8, 9, and 10 years (Germany)	Child serum DDE levels at 8 years of age (quartiles, ng/mL): Q1: 80–200 Q2: 210–290 Q3: 300–430 Q4: >440	Height 4–6 weeks, 3–4 months, 6–7 months, and 8 years 9 years *No significant trend at 10–12, 12–24, 43–48 months or at 10 years*	 ↔ (males) ↓ (females) ↓ (males) ↔ (females)

Table 2-20. Summary of Studies of Associations between Human DDT Exposure Metrics and Measures of Post-Birth Offspring Body Weight and Growth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Mendez et al. 2011 Cohort, 518 mother-child pairs including 374 normal weight mothers (NW) and 144 overweight (OW) mothers and 125 rapid growth children and 393 average/slow growth children; child growth assessed from birth to 14 months (Spain)	Maternal serum DDE (quartiles, ng/g lipid): Q1: ≤71.71 Q2: 71.71–116.92 Q3: 116.92–186.17 Q4: >186.17	Rapid infant growth NW mothers OW mothers	 ↑ (Q2–Q4) ↔
		BMI z-score at 14 months All mothers NW mothers OW mothers	 ↔ ↑ ↔
Pan et al. 2010 Cohort, 210 mother-child pairs, child growth assessed from birth to 12 months; all infants were breastfed for at least 6 months (United States, North Carolina)	Milk DDT metrics at 3 months (range, ng/g lipid) DDE: 113 (15–2,140) DDT: 5 (<LOD–36) Calculated lactational exposure metric (LEM) at 12 months (median (range), ng/g lipid-months) DDE: 880 (134–19,260) DDT: 34 (1–326)	Weight Milk LEM	 ↔ ↔
		Length Milk LEM	 ↔ ↔
Ribas-Fito et al. 2006 Cohort, 1,712 mother-child pairs at study initiation; child growth assessed at 1 year (n=1,540), 4 years (n=1,371), and 7 years (n=1,371) (United States)	Maternal serum DDE (quintiles, ng/mL): Q1: <15 Q2: 15–29 Q3: 30–44 Q4: 45–59 Q5: ≥60	Height 1 year (Q5 versus Q1) 4 year (Q5 versus Q1) 7 year (Q5 versus Q1)	 ↓ ↓ ↓
Tang-Peronard et al. 2014 Cohort, 585 mother-child pairs including 390 NW mothers and 195 OW mothers (305 males, 280 females); child growth assessed at 5 years (n=561) and 7 years (n=539) (Faroe Islands)	Maternal serum and milk DDE (quartiles, ng/g lipid): Q1: <340 Q2: 340–560 Q3: 570–920 Q4: ≥920	BMI at 5 or 7 years old with NW or OW mothers	↔ (males) ↔ (females)
		BMI change from 5–7 with NW mothers	↔ (males) ↔ (females)
		BMI change from 5–7 with OW mothers Q2–Q3 Q4 or per 10x ↑ DDE	 ↔ (males) ↔ (females) ↔ (males) ↑ (females)
		WC at 5 years old with NW or OW mothers	↔ (males) ↔ (females)
		WC at 7 years old with NW mothers	↔ (males) ↔ (females)

Table 2-20. Summary of Studies of Associations between Human DDT Exposure Metrics and Measures of Post-Birth Offspring Body Weight and Growth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
		WC at 7 years old with OW mothers	
		Q2	↔ (males) ↔ (females)
		Q3–Q4 or 10x ↑ DDE	↔ (males) ↑ (females)
Vafeiadi et al. 2015 Cohort, 698 mother-child pairs, child growth assessed at birth, 6 months, and 4 years (Greece)	Maternal serum DDE (IQR, ng/mL): 1.1876–3.5141	Rapid growth (0–6 months)	↔
		BMI z-score (4 years)	↑
		Obesity (4 years)	↑
		WC ≥58.6 cm (4 years)	↑
		Skinfold sum (4 years)	↔
Valvi et al. 2012 Cohort, 344 mother-child pairs (178 females, 166 males; 252 NW, 92 OW); child growth assessed at 6.5 years (Spain)	Cord blood DDT metrics (tertiles, ng/mL) DDE / DDT T1 <0.7 / <0.06 T2 0.7–1.5 / 0.06–0.18 T3 >1.5 / >0.18	Overweight at 6.5 years	
		DDE	
		T2 versus T1	↔ (males) ↑ (females) ↑ (total)
		T3 versus T1	↔ (males) ↔ (females) ↔ (total)
		DDT	
		T2–T3	↑ (males) ↔ (females) ↔ (total)
Valvi et al. 2014 Cohort, 1,285 mother-child pairs including 790 pairs from the Valencia and Gipuzkoa subcohort; child growth assessed from birth to 14 months (Spain)	Maternal first trimester serum DDE (quartiles, ng/g lipid): Q1: ≤73.6 Q2: >73.6–118.8 Q3: >118.8–203.1 Q4: >203.1	Overweight at 14 months	
		Q2–Q3	↔ (total) ↔ (subcohort)
		Q4 or 10x↑ DDE	↑ (total) ↑ (subcohort)
		Early Rapid Growth (0-6 months)	
		Q2–Q4	↔ (total) ↔ (subcohort)
		10x↑ DDE	↑ (total) ↔ (subcohort)
Verhulst et al. 2009 Cohort, 138 mother-child pairs, child growth assessed from 1 to 3 years (Belgium)	Cord blood DDE (mean (range), ng/g lipid): 212 (24–1,816)	Weight	↔
		Length	↔
		BMI	↔

Table 2-20. Summary of Studies of Associations between Human DDT Exposure Metrics and Measures of Post-Birth Offspring Body Weight and Growth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Warner et al. 2013 Cohort, 270 mother-child pairs, child growth assessed at 7 years (United States, California)	Maternal serum DDT metrics (GM±GSD, ng/g lipid): DDE: 1,422±3.3 DDT: 20.45±5.1 *o,p'*-DDT: 1.66±4.2	Obese	↔
		OW or obese	↔
		WC	↔
		BMI z-score	↔
Warner et al. 2014 Cohort, 261 mother-child pairs (118 males, 143 females), child growth assessed at 9 years (United States, California)	Maternal serum DDT metrics (mean±SD, ng/g serum): DDE: 1,500±800 DDT: 1,300±700 *o,p'*-DDT: 2,900±1,500	BMI z-score	
		Males	↔ (DDE) ↑ (DDT) ↑ (*o,p'*-DDT)
		Females	↔ (all metrics)
		WC z-score	
		Males	↔ (DDE) ↑ (DDT) ↑ (*o,p'*-DDT)
		Females	↔ (all metrics)
		Overweight/obese	
		Males	↔ (DDE) ↑ (DDT) ↑ (*o,p'*-DDT)
		Females	↔ (all metrics)
		WC	
		Males	↔ (DDE) ↑ (DDT) ↔(*o,p'*-DDT)
		Females	↔ (all metrics)
Warner et al. 2017 Cohort, 240 mother-child pairs (101 males, 139 females), child growth assessed at 12 years (United States, California)	Maternal serum DDT metrics (IQR, ng/g lipid): DDE: 606.9–2,837.4 DDT: 7.4–47.4 *o,p'*-DDT: 0.7–3.3	BMI z-score	
		All and Females	↔ (all metrics)
		Males	↑ (all metrics)
		WC z-score	
		All and Females	↔ (all metrics)
		Males	↑ (all metrics)
		Percent body fat	
		All, Females and Males	↔ (all metrics)
		Overweight/obese	
		All	↑ (DDE) ↔ (DDT) ↔ (*o,p'*-DDT)
		Females	↔ (all metrics)
		Males	↑ (all metrics)
		Obese	
		All and females	↔ (all metrics)
		Males	↔ (DDE) ↑ (DDT) ↑ (*o,p'*-DDT)

Table 2-20. Summary of Studies of Associations between Human DDT Exposure Metrics and Measures of Post-Birth Offspring Body Weight and Growth[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
		Increased WC	
		All and females	↔(all metrics)
		Males	↔ (DDE) ↑ (DDT) ↑ (*o,p'*-DDT)

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues for each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified.

↑ = positive association; ↓ = inverse association; ↔ = no association; BMI = body mass index; DDE = dichloro-diphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; FLEHS = Flemish Environment and Health Studies; GM = geometric mean; GSD = geometric standard deviation; HUMIS = Norwegian Human Milk Study; IQR = interquartile range; LEM = lactational exposure metric; LOD = limit of detection; NW = normal weight; OW = overweight; PELAGIE = Perturbateurs endocriniens, Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance; Q = quartile or quintile; SD = standard deviation; T = tertile; WC = waist circumference

In a systematic review and meta-analysis, Cano-Sancho et al. (2017) concluded that there was a moderate level of epidemiological evidence for an association between *p,p'*-DDE and BMI in children ages 2.5–20 years, calculating a beta of 0.13 (95% CI 0.01–0.25). Studies in the meta-analysis included those measuring maternal (prenatal) exposure (Agay-Shay et al. 2014; Cupul-Uicab et al. 2010; Delvaux et al. 2014; Hoyer et al. 2014; Warner et al. 2014; see Table 2-20) and childhood exposure (Tang-Peronard et al. 2015a; see Table 2-2 in Section 2.3 Body Weight).

Developmental Toxicity in Laboratory Animals. Numerous adverse developmental outcomes have been reported in the offspring of rodents exposed to DDT/DDE during gestation and/or lactation. Effects include fetotoxicity, alterations in growth, neurodevelopmental toxicity, and impaired development of the reproductive system; these effects are discussed in greater detail below. Some developmental studies also evaluated cardiovascular (La Merrill et al. 2016), renal (La Merrill et al. 2016), and diabetic (La Merrill et al. 2014a, 2014b) outcomes in the offspring of rats perinatally exposed and evaluated as adults; these effects are considered developmental toxicity and are discussed in Sections 2.5, 2.10, and 2.18, respectively.

Fetotoxicity. Fetotoxicity was observed in mice and rats following gestational and early postnatal exposure to technical DDT or *p,p'*-DDE at dose levels >30 mg/kg/day (Clement and Okey 1974; Yamasaki et al. 2009). Exposure of pregnant mice to 34.3 mg technical DDT/kg on GDs 1–21 followed

by cross-fostering of the pups resulted in preweaning death in 39% of the neonates exposed *in utero* and through lactation and 10% of the pups exposed only through lactation (Craig and Ogilvie 1974). All F1 offspring died within 10 days after birth when exposed *in utero* and through lactation when dams were treated with 41.1 mg/kg/day *p,p;*-DDT (Clement and Okey 1974). No deaths occurred in pups exposed *in utero* only (Craig and Ogilvie 1974). Reduced weaning index and decreased number of PND-21 live pups were observed in female Sprague-Dawley rats given gavage doses of 50 mg *p,p'*-DDE/kg/day, but not 15 mg/kg/day, on GD 6 through PND 20 (Yamasaki et al. 2009).

Birth outcomes and subsequent growth patterns. Results from developmental toxicity studies in laboratory animals show no consistent effects of gestational or lactational exposure to DDT and related compounds on birth weight or early growth parameters. The presence of an effect appears to be dependent on the isomeric form, the dose, and the timing of exposure.

Acute-duration exposures during gestation showed small, but significant increases (9–13%) in body weights in adult offspring from pregnant Sprague-Dawley rat dams orally exposed during GDs 15–19 to 28 mg *o,p'*-DDT, *p,p'*-DDT, *o,p'*-DDE/kg/day (Gellert and Heinrichs 1975), but not in Long-Evans or Sprague-Dawley male offspring (at 2 days of age, or as adults) of rat dams exposed during GDs 14–18 of gestation up to 100 mg *p,p'*-DDE/kg/day (Gray et al. 1999; You et al. 1999a, 1998). In a trans-generational study in Sprague-Dawley rats, F0 dams exposed to 100 mg *p,p'*-DDT/kg/day on GDs 8–15 resulted in significant increases (10–19%) in F3 male and female offspring weight at 3 and 8 weeks of age (Song and Yang 2017). Weight effects were only observed in F3 offspring with ancestral exposure via the maternal plus paternal lineages or the paternal lineage; effects were not observed if ancestral exposure was via the maternal lineage only. In CF-1 mice, no clear effects on early life body weights were observed following gavage exposure to doses ranging from 0.02 to 100 mg *o,p'*-DDT/kg/day: small decreases at 20 mg/kg/day and small increases at 100 mg/kg/day were observed on PNDs 2 and 5, but no exposure-related differences from control values were observed on PND 10 (Palanza et al. 2001). In rabbits, acute exposure to doses of 1 mg DDT(NS)/kg/day on GDs 4–7 (Fabro et al. 1984) or to dose levels ≥10 mg *p,p'*-DDT/kg/day by gavage on GDs 7–9 (Hart et al. 1971), resulted in significant reductions in fetal body weights relative to controls (up to 25%). However, treatment late in gestation (GDs 21–23) did not induce such an effect (Hart et al. 1972).

After intermediate-duration exposure studies, a decrease in growth was observed in Wistar rat pups exposed via nursing from dams receiving 16.8 or 42.1 mg *p,p'*-DDT/kg/day or 84 mg *o,p'*-DDT/kg/day, but the effect was reversible once they were switched to a standard diet (Clement and Okey 1974). No

abnormal body weights were reported in rat F1 offspring at birth, or any time point up through sacrifice at 10 weeks of age in Sprague-Dawley rats exposed *in utero* through lactation with dam exposure doses up to 50 mg *p,p'*-DDE /kg/day (Yamasaki et al. 2009). Similarly, no exposure-related birth weight changes or changes in growth were observed in F1 and F2 rat pups from a 2-generation study; F1 offspring were exposed from gestation through weaning from dams fed doses as high as 27.7 mg *p,p'*-DDT/kg/day, and then in their diets through mating, gestation, and lactation (Hojo et al. 2006). In contrast, both CD-1 mouse male and female F1 offspring in a 2-generation study, exposed from gestation through 18 months of age to doses of technical DDT as low as 0.4 mg/kg/day showed significant increases in body weights, relative to controls, beginning from 5–9 months of age (Tomatis et al. 1972).

Neurodevelopmental effects. Acute-duration oral administration of DDT isomers *in utero* or to neonates during sensitive periods in nervous system development has caused behavioral and neurochemical changes in mice. Observations include impaired maze learning and memory functions in surviving 1–2-month-old mice whose dams were exposed to 34.3 mg/kg/day technical-DDT during gestation and lactation (Craig and Ogilvie 1974), and increased spontaneous motor activity (reduced habituation) and decreased cerebral cortex muscarinic receptors in 4–7-month-old mice exposed to 0.5 mg/kg/day technical-grade DDT on 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), and increased urine marking behavior in 70-day-old male mice whose dams were exposed to *o,p'*-DDT doses ≥0.018 mg/kg/day during GDs 11–17; however, because of the lack of statistical analysis or description of the number of males observed, it is unclear at what doses increased urine marking behavior became significant (vom Saal et al. 1995). No statistically significant differences in signs of aggression (latency to attack, number of bites, total attack time, and tail rattling) were observed in 30-day-old male mice from dams exposed from GDs 11–17 to 0.018 or 0.18 mg/kg/day *o,p'*-DDT compared to controls (Palanza et al. 1999); however, the percent of attacking males approached significance, and when subgroups of attacking animals only were evaluated, exposed males showed lower bite frequencies, total attack times, and reduced tail rattling. Exposure during GDs 11–17 to up to 100 mg *o,p'*-DDT/kg/day had no effect on righting reflex or cliff avoidance in pups on PND 2 or 5 (Palanza et al. 2001).

Fetuses (28-day-old) of pregnant rabbits given gavage doses of 1 mg DDT (NS)/kg/day on GDs 4–7 were reported to have decreased brain weight of unspecified magnitude (Fabro et al. 1984); however, male Sprague-Dawley offspring, or the dams, exposed during GD 6 to PND 20 to 5 or 15 mg *p,p'*-DDE/kg/day had no significant changes in relative brain weight (Yamasaki et al. 2009).

Developmental reproductive effects. Findings for effects on developing male reproductive tissues after gestational exposure to *p,p'*-DDT or *p,p'*-DDE include significantly decreased ventral prostate weights in PND-21 male offspring of pregnant Holtzman, Long-Evans, or Sprague-Dawley rats exposed to 50–200 mg *p,p'*-DDE/kg/day on GDs 14–18 (Loeffler and Peterson 1999; Gray et al. 1999); significantly decreased AGD at PND 1 or 2 at ≥100 mg *p,p'*-DDE/kg/day or retained thoracic nipples at PND 13 in male rats gestationally exposed to ≥10 mg *p,p'*-DDE/kg/day (Gray et al. 1999; Kelce et al. 1995; Loeffler and Peterson 1999; You et al. 1998); and decreased number of lipid droplets in Leydig cells, with no changes in testicular testosterone levels, in GD-19.5 male fetuses of Sprague-Dawley rats given 100 mg *p,p'*-DDE/kg/day on GDs 13.5–17.5 (Adamsson et al. 2009). No significant effects on weights of testes, epididymides, seminal vesicles, or ventral prostate were observed in PND 21 male offspring of Sprague-Dawley or Long-Evans rats given gavage doses up to 100 mg *p,p'*-DDE/kg/day on GDs 14–18 (You et al. 1998).

Other reproductive effects associated with gestational exposure to *p,p'*-DDT, DDT(NS), *p,p'*-DDE, or DDE(NS) include decreased fertility index in F1 male and female Sprague-Dawley rats exposed *in utero* to 50 mg *p,p'*-DDE/kg/day on GD 6 to PND 20 (no significant effect on fertility was reported at doses ≤15 mg/kg/day) (Yamasaki et al. 2009); increased resorptions in pregnant New Zealand rabbits exposed to 10 or 50 mg *p,p'*-DDT/kg/day on GDs 7–9, but not when exposure occurred on GDs 21–23 (Hart et al. 1971, 1972); and qualitatively reported histological changes to reproductive organs from adult male Sprague-Dawley rats exposed to gavage doses of 35 mg DDT(NS) or DDE(NS)/kg/day during gestation, lactation, and through PND 90 (Patrick et al. 2016). In a transgenerational study in Sprague-Dawley rats, F0 dams exposed to 100 mg p,p'-DDT/kg/day on GDs 8–15 resulted in a 20–40% decrease in fertility in F1, F2, and F3 generations coupled with decreased motile sperm and area of the seminiferous tubules (Song and Yang 2018). In the F3 generation, these effects were only noted in offspring with DDT exposure via the male germline.

Acute-duration gestational exposure has been associated with delayed vaginal opening and increased ovary weight in female offspring of Sprague-Dawley rat dams given gavage doses of 28 mg/kg/day *o,p'*-DDD or *p,p'*-DDT on GDs 15–19, but these effects were not observed after GD 15–19 exposure to *o,p'*-DDT or *o,p'*-DDE at the same dose level (Gellert and Heinrichs 1975). Earlier vaginal opening was observed in female offspring exposed to 50 mg *p,p'*-DDE/kg/day on GD 6 to PND 20 (Yamasaki et al. 2009).

Decreased fertility was reported in F1 female Wistar rat progeny exposed to 128 mg *o,p'*-DDT/kg/day in food during gestation and lactation and bred to nonexposed males at PND 105, but not in F1 female Wistar rat progeny similarly exposed to up to 26 mg *p,p'*-DDT/kg/day (Clement and Okey 1974).

Three reports from the same group of investigators have specified several reproduction-related effects in adult mice after gestational exposure to very low oral doses of *o,p'*-DDT; significantly decreased testes weight in adult male CD-1 mice exposed to 0.018 mg *o,p'*-DDT/kg/day on GDs 11–17 (~12% decreased compared with control values), but not 0.18 mg/kg/day (Palanza et al. 1999); and significantly increased AGD at birth in female offspring of CF-1 mouse dams exposed to gavage doses ~100 mg *o,p'*-DDT/kg/day on GDs 11–17 (the highest dose tested) and in male offspring at doses of ~0.2 and ~100 mg/kg/day, but not at ~0.02, ~2, or ~20 mg/kg/day (Palanza et al. 2001). These observations in adult mice after gestational exposure to *o,p'*-DDT were not included in Table 2-1 and Figure 2-2 due to the lack of supporting evidence for reproductive or developmental effects in laboratory animals at gestational dose levels <10 mg *o,p'*- isomers/kg/day in studies conducted by other laboratories.

Mechanisms of Developmental Effects of DDT, DDD, or DDE. Effects on growth patterns from prenatal or early-life exposure are not a well-established target of exposure to DDT, DDD, or DDE. Kim et al. (2018) suggested a possible association between increased placental DNA methylation levels of long interspersed element 1 (LINE-1) and decreased birth length in a Korean birth cohort. Additional relevant mechanistic studies were not located, except for those related to associations between obesity, diabetes, and exposure to persistent organochlorine compounds, like DDT, as discussed in Section 2.18.

As discussed in Section 2.15, DDT can disrupt nerve membrane ion fluxes through induced closure of sodium channels, inhibition of potassium transport, and by targeting Na^+/K^+ and Ca^{2+}/Mg^{2+} ATPases, potentiate neurotransmitter release through interference with calcium calmodulin binding, and inhibit the plasma membrane dopamine transporter (DAT) and the vesicular monoamine transporter (VMAT2) (Harada et al. 2016; Hatcher et al. 2008). It is uncertain if these actions may be involved in the increased spontaneous motor activity and decreased cerebral cortex muscarinic receptors observed in 4–7-month-old mice exposed to 0.5 mg/kg/day technical-grade DDT on PND 10 (Eriksson and Nordberg 1986; Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996 supported by Talts et al. 1998).

A series of studies have proposed that epigenetic changes in the male germline may contribute to DDT-associated male developmental reproductive toxicity. Transgenerational inheritance of differentially methylated regions (i.e., epimutations), noncoding RNA, and/or histone retention sites in the sperm

genome of F3 and F4 generation males of DDT-exposed male lineage were observed in rats following DDT exposure in F0 dams only (Ben Maamar et al. 2018, 2019, 2020; King et al. 2019a; Skinner et al. 2018). Similarly, Sadler-Riggelman et al. (2019) reported transgenerational inheritance of epimutations, noncoding RNA, and gene expression changes in pathways associated with abnormal Sertoli cell function and testis pathology in Sertoli cells of F3 male rats. These findings may underly the observed transgenerational decreases in fertility and sperm motility in F3 males following F0 oral exposure to DDT reported by Song and Yang (2018).

Additional mechanistic studies were not located that explained details of male and female reproduction effects observed in laboratory animals following prenatal and early postnatal exposure to DDT and related compounds, with the exception of studies showing that *p,p'*- isomers have anti-androgenic effects and *o,p'*- isomers have estrogenic effects (see Section 2.16).

2.18 OTHER NONCANCER

Epidemiology Studies of Diabetic Outcomes in Humans

Overall summary. Table 2-21 describes results from 43 epidemiological studies that examined possible associations between human DDT exposure biometrics (e.g., serum levels of DDT, DDE, or DDD) and prevalence of DMT2 or biomarkers indicative of DMT2. A clear majority of these studies, along with several meta-analyses, provide evidence for an association between DDT exposure biometrics in groups of humans and increased prevalence of DMT2 (Table 2-21). A majority of studies in adults also provide evidence for an association between DDT exposure biometrics and other indicators of diabetes (e.g., fasting blood glucose, insulin, insulin resistance, impaired glucose tolerance). However, there is inconsistency across the limited number of studies in children evaluating associations with other indicators of diabetes. Table 2-21 also describes a limited number of studies evaluating possible associations between DDT exposure biometrics and gestational diabetes (Vafeiadi et al. 2017; Valvi et al. 2017) and Type 1 diabetes (Rignell-Hydbom et al. 2010).

Table 2-21. Summary of Diabetes Outcomes in Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Type 2 Diabetes (DMT2)			
Airaksinen et al. 2011 Cross-sectional, 1,988 adults including 308 DMT2 cases and 1,680 non-diabetic controls (Finland)	Serum DDE (quartiles, ng/g lipid) Q1: 9.1–170 Q2: 170–470 Q3: 470–1,200 Q4: 1,200–10,000	DMT2 All subjects Q2–Q4 p-trend BMI ≥30 kg/m^3 BMI 25–30 BMI <25	 ↔ ↑ ↔ ↔ ↔
Al-Othman et al. 2015 Case-control; 136 DMT2 cases (60 males, 76 females) and 144 non-diabetic controls (49 males, 95 females) (Saudi Arabia)	Serum DDT metrics (mean±SE, ng/mL) Cases / Controls DDE 6.3±0.84 / 3.9±0.85 *o,p'*-DDE 8.1±0.98 / 3.5±0.55 DDD 4.3±0.73 / 3.2±0.51 DDT 0.22±0.04 / 0.25±0.04 *o,p'*-DDT 0.50±0.08 / 0.38±0.10 ΣDDT 18.3±1.4 / 11.8±1.3 Cases and controls combined for analysis	DMT2 All, male, or female	 ↑ (ΣDDT) ↔ (*o,p'*-DDE, DDE, DDD, *o,p'*-DDT, DDT)
Aminov et al. 2016 Cross-sectional, 601 adults including 111 diabetes cases (self-reported diagnosis and/or FBG >125 mg/dL) and 490 non-diabetic controls (United States, Mohawk Nation Reserve)	Serum DDE (quartiles, ng/g) Q1: 0.08–<0.94 Q2: 0.94–<1.88 Q3: 1.88–<4.02 Q4: 4.02–22.51	Diabetes Q2 versus Q1 Q3–Q4 versus Q1 p-trend	 ↔ ↑ ↑
Arrebola et al. 2013 Cross-sectional, 386 adults including 34 DMT2 cases and 352 non-diabetic controls (Spain)	Adipose DDE (tertiles, ng/g lipid): T1: <45.56 T2: 45.56–154.88 T3: >154.88 Serum DDE (tertiles, ng/g lipid): T1: <127.33 T2: 127.33–266.91 T3: >266.91	DMT2 Adipose T2 versus T1 T3 versus T1 p-trend Serum T2–T3 versus T1 p-trend	 ↔ ↑ ↔ ↔ ↔
Codru et al. 2007 Cross-sectional, 352 adults including 71 diabetes cases (FBG >125 mg/dL or taking diabetes medicine) and 281 non-diabetic controls (Canada-United States, Mohawk Nation Reserve)	Serum DDE (tertiles, ng/g lipid) T1: 246.1 T2: 349.5 T3: 544.6	Diabetes T2 versus T1 T3 versus T1	↔ ↑

Table 2-21. Summary of Diabetes Outcomes in Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Cox et al. 2007 Cross-sectional, 1,303 adults including 89 self-reported diabetes cases and 1,214 non-diabetic controls (United States)	Serum DDT (tertiles, ng/mL) T1: <1 T2: 2.00–3.70 T3: >3.70 Serum DDE (quartiles, ng/mL) Q1: <22.81 Q2: 22.81–39.10 Q3: 39.1–58.60 Q4: >58.60	Diabetes T2 versus T1 T3 versus T1 Q2 versus Q1 Q3 versus Q1 Q4 versus Q1	 ↔ (DDT) ↑ (DDT) ↔ (DDE) ↑ (DDE) ↑ (DDE)
Daniels et al. 2018 Case-control, 192 adults of South Asian descent including 24 cases of DMT2 among and 96 non-diabetic controls (United Kingdom)	Plasma DDE (median (range), ng/g lipid) Cases: NR Controls: 536 (27–25,144) Combined: 710.97 (NR) Plasma DDT (median (range), ng/g lipid) Cases: NR Controls: 17.65 (3.91–316.45) Combined: 17.61 (NR)	DMT2 Odds of exposure metric >median in cases versus controls	 ↑ (DDE) ↔ (DDT)
Eden et al. 2016 Case-control, 114 DMT2 cases and 149 non-diabetic controls (United States, Mississippi, Ohio)	Serum DDE (mean±SD, ng/g lipid) Cases: 448.2±589.4 Controls: 197.9 ±261.4 Combined: 313.1±459.9 Cases and controls combined for analysis	DMT2 Normal BMI ≤45 years ≥55 years High BMI ≤45 years ≥55 years	 ↔ ↑ ↔ ↑
Everett et al. 2007 Cross-sectional, 2,163 diabetic adults including those with diabetes diagnosis (self-report of physician diagnosis) or undiagnosed (HbA1c >6.1%) (United States, NHANES)	Serum DDT (tertile, ng/g lipid) T1: <20.7 T2: 20.8–26.6 T3: >26.6 ng/g	Diabetes Diagnosed, all T2–T3 Undiagnosed T2 versus T1 T3 versus T1	 ↑ ↔ ↑

Table 2-21. Summary of Diabetes Outcomes in Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Everett et al. 2017a Cross-sectional, 1,114 adults including 128 with diabetes (diagnosed or HbA1c ≥6.5%), 124 prediabetic (HbA1c 5–6.4%), and 1,159 with normal HbA1c; groups further defined by presence or absence of nephropathy (United States, NHANES)	Non-fasting serum DDT (ng/g lipid): Low (<MLOD): <14.50 High (>MLOD): ≥14.50 Non-fasting serum DDE (ng/g lipid) <Median: <500.6 Q3: 500.6–1,195.0 Q4: ≥1,195.1	Total diabetes >MLOD Q3 versus Q1 Q4 versus Q1	 ↑ (DDT) ↔ (DDE) ↑ (DDE)
		Diabetes without nephropathy >MLOD Q3–Q4	 ↑ (DDT) ↔ (DDE)
		Diabetes with nephropathy >MLOD Q3–Q4	 ↑ (DDT) ↑ (DDE)
Everett and Matheson 2010 Cross-sectional, 3,049 adults including 334 with diabetes (diagnosed or HbA1c ≥6.5), 462 prediabetic (HbA1c 5.7–6.4%), and 2,253 with normal HbA1c (United States, NHANES)	Non-fasting serum DDT (ng/g lipid): Low (<MLOD): <20.7 High (>MLOD): ≥20.7 Non-fasting serum DDE (ng/g lipid): Low (<MLOD): <168.6 High (>MLOD): ≥168.6	Diabetes >MLOD	 ↑ (DDT) ↑ (DDE)
Everett and Thompson 2015 Cross-sectional, 2,992 adults including 341 diabetes cases (HbA1c ≥6.5), 447 prediabetic cases (HbA1c 5.7–6.4%), and 2,204 controls with HbA1c <5.7%; groups further defined by presence or absence of nephropathy (United States, NHANES)	Non-fasting serum DDT (ng/g): Low (<MLOD): <0.0860 High (>MLOD): ≥0.0860 Non-fasting serum DDE (quartiles, ng/g): Q1: <0.8340 Q2–Q3: 0.8340–3.8410 Q4: ≥3.8410	Diabetes without nephropathy >MLOD Q2–Q4	 ↔ (DDT) ↔ (DDE)
		Diabetes with nephropathy >MLOD Q2–Q4	 ↑ (DDT) ↔ (DDE)
Gasull et al. 2012 Cross-sectional, 886 adults including 143 diabetes cases (FBG ≥126 mg/dL), 202 prediabetic cases (FBG 110–125 mg/dL), and 541 non-diabetic controls (Spain)	Serum DDT (quartiles, ng/mL) Q1: ≤0.086 Q2: 0.087–0.178 Q3: 0.179–0.34 Q4: >0.349 DDE (quartiles, ng/mL) Q1: ≤1.24 Q2: 1.25–2.6 Q3: 2.64–5.5 Q4: >5.56	Diabetes Q2–Q4	 ↔ (DDT) ↔ (DDE)
		Prediabetes Q2–Q4	 ↔ (DDT) ↔ (DDE)

Table 2-21. Summary of Diabetes Outcomes in Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Grandjean et al. 2011 Cross-sectional, 712 elderly adults (70-74 years) including 168 DMT2 cases (91 known and 77 incident), 78 IFG cases, and 466 controls with normal glucose metabolism (Faroe Islands)	Serum DDE (GM (95% CI), ng/g lipid) Known DMT2: 3,200 (2,600–3,900) Incident DMT2: 3,300 (2,600–4,000) IFG: 3,100 (2,500–3,700) Controls: 2,800 (2,600–3,100)	DMT2 IFG	↔ ↔
Han et al. 2020 Case-control, 158 DMT2 cases and 158 non-diabetic controls (China)	Serum DDT metrics (GM±GSD, ng/mL) Cases DDE: 4.184 (0.0029) DDT: 0.097 (0.0021) Controls DDE: 2.300 (0.0036) DDT 0.044 (0.0029) Cases and controls combined for analysis	DMT2	↑ (DDE) ↑ (DDT)
Kim et al. 2014 Cross-sectional, 50 adults including 25 DMT2 cases (FBG ≥126 mg/dL or self-report) and 25 non-diabetic controls (Korea)	Approximate[c] subcutaneous (SAT) or visceral (VAT) adipose tissue levels (IQR, ng/g lipid) SAT / VAT DDD 3–6 / 13–30 DDE 105–310 / 90–160 DDT 16–32 / 2–4 *o,p'*-DDE 0.6–1.8 / 1.5–1.8 *o,p'*-DDT 1.2–3.8 / 0.5–3.4 Tertile levels not reported	DMT2 SAT VAT	 ↑ (∑DDT, T2) ↔ (∑DDT, T3) ↔ (∑DDT, T2) ↑ (∑DDT, T3) ↑ (DDE)
La Merrill et al. 2019 Cross-sectional, 147 Asian Indian adults (United States, California)	Plasma DDT metrics (median (range), ng/g lipid) DDE: 1,850 (85.1–27,900) DDT: 44.8 (8.67–2,880) o,p'-DDE: 1.70 (0.500–8.90) o,p'-DDT: 4.20 (<0.810–209)	Prediabetes Diabetes	↑ (ΣDDT) ↑ (ΣDDT)
Lee et al. 2011a Cohort/cross-sectional, 989 70-year-old adults, including 112 DMT2 cases and 877 non-diabetic controls; follow-up at 75 years of age (n=725, including 36 DMT2 cases and 689 non-diabetic controls) (Sweden)	Fasting serum DDE (quintiles, ng/mL): Q1: 0.01–0.90 Q2: 0.90–1.49 Q3: 1.49–2.30 Q4: 2.30–4.04 Q5: 4.04–23.27	DMT2 Age 70 years (Q2–Q5) Age 75 years (Q2–Q5)	 ↔ ↔

Table 2-21. Summary of Diabetes Outcomes in Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Lee et al. 2010 Cohort/Nested case-control, 90 DMT2 cases (FBG ≥126 mg/dL at 2+ visits over 20-year follow-up) and 90 non-diabetic controls (FBG <100 mg/dL at all 5 follow-ups) (United States)	Fasting DDE serum at study initiation (quartile, ng/mL; based on cohort controls) Q1: ≤2.153 Q2: 2.154–3.312 Q3: 3.313–5.731 Q4: >5.731 DDT quartiles not reported	DMT2	↔ (DDE) ↔ (DDT)
Lee et al. 2006 Cross-sectional, 2,016 adults including 217 diabetes cases (self-reported or FBG ≥126 mg/dL, or non-fasting blood glucose ≥200 mg/dL) and 1,529 nondiabetic controls (United States, NHANES)	Serum DDE (quintiles, ng/g lipid): Q1 (LOD–<25%): 112 Q2 (25–<50): 292 Q3 (50–<75): 717 Q4 (75–<90): 1,560 Q5 (≥90): 3,700	DMT2 Q2 versus Q1 Q3 versus Q1 Q4 versus Q1 Q5 versus Q1 p-trend	 ↔ ↔ ↑ ↑ ↑
Meek et al. 2019 Cross-sectional, 150 adults from the Mississippi Delta region (high exposure) and 150 adults from the Mississippi Hill region (low exposure); included 162 DMT2 cases and 138 non-diabetic controls (United States, Mississippi)	Serum DDE (median (range), ng/g lipid): Delta region: 426.3 (0–21,650) Hill region: 162.7 (0–14,390) DMT2 : 402.3 (0–14,390) Non-diabetic: 225.3 (0–21,650)	DMT2	↔ (All) ↔ (Delta) ↑ (Hill)
Philibert et al. 2009 Cross-sectional, 101 adults including 25 self-reported diabetes cases 76 non-diabetic controls (Canada)	Serum DDE (IQR): Wet weight: 0.92–10.65 ng/mL Lipid-adjusted: 175.38–1,617 ng/g lipid	Self-reported diabetes >75% (ng/mL) >75% (ng/g lipid)	 ↑ ↔
Rignell-Hydbom et al. 2007 Cross-sectional, 542 women including 15 DMT2 cases and 528 non-diabetic controls (Sweden)	Serum DDE (quartile, ng/g lipid): Q1: <91 Q2: 91–144 Q3: >144–240 Q4: >240	DMT2 p-trend (across quartiles) per 100 ng/g lipid increase	 ↑ ↑

Table 2-21. Summary of Diabetes Outcomes in Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Rignell-Hydbom et al. 2009b Cohort/Nested case-control, 371 DMT2 cases and 371 non-diabetic controls; diabetes status based on outcome of glucose tolerance test at baseline examination or up to >7 years after baseline (Sweden)	Serum DDE by year of diabetes status assignment (mean±SD, ng/mL) Case / Control <1 year 3.83±4.12 / 3.77±3.88 >3 years 5.14±5.55 / 3.93±3.16 >7 years 5.68±6.16 / 3.89±3.77 Cases and controls combined for analysis	DMT2 All cases <1 year >3 years >7 years	 ↔ ↔ ↔ ↑
Rylander et al. 2005 Cross-sectional, 196 male and 184 female adults including 22 DMT2 cases and 358 non-diabetic controls (Sweden)	Serum DDE (tertile, ng/g lipid) Men / Women T1 <410 / <180 T2 >410–850 / >180–290 T3 >850 / >290	DMT2 p-trend per 100 ng/g lipid change	 ↑ (male) ↔ (female) ↑ (combined)
Son et al. 2010 Case-control, 40 DMT2 cases and 40 non-diabetic controls (South Korea)	Fasting serum DDT metrics for cases and controls (combined; tertile, ng/g) T1 / T2 / T3 DDE 1.01 / 1.64 / 4.10 DDD 0.017 / 0.027 / 0.048 DDT 0.081 / 0.128 / 0.228 *o,p'*-DDT 0.006 / 0.013 / 0.034 Fasting serum DDT metrics for cases and controls (combined; tertile, ng/g lipid) T1 / T2 / T3 DDE 162.2 / 301.9 / 667.4 DDD 2.7 / 4.7 / 8.4 DDT 12.1 / 22.0 / 36.2 o,p'-DDT 0.9 / 2.3 / 5.4	DMT2 Wet-weight (ng/g) Lipid-adjusted (ng/g lipid)	 ↑ (DDE) ↑ (DDD) ↑ (DDT) ↔ (*o,p'*-DDT) ↑ (DDE) ↔ (DDD) ↑ (DDT) ↑ (*o,p'*-DDT)
Turyk et al. 2009 Cross-sectional, 503 adults including 61 diagnosed DMT2 cases, 14 undiagnosed cases (HbA1c >6.3%), and 428 non-diabetic controls (United States, Great Lakes Region)	Non-fasting serum DDE (quartile, ng/mL) Q1: <LOD–1.2 Q2: 1.3–2.0 Q3: 2.1–4.0 Q4: 4.1–24.0	DMT2 Diagnosed Diagnosed + undiagnosed	 ↑ (Q4) ↑ (Q4)

Table 2-21. Summary of Diabetes Outcomes in Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Ukropec et al. 2010 Cross-sectional, 2,047 adults including 296 diabetes cases (FBG >7.0 mmol/L, 2-hour glucose >11.1mmol/L), 296 prediabetic cases (FBG >5.6 and <7.0 mmol/L and/or impaired glucose tolerance), and 778 non-diabetic controls (Slovakia)	Fasting serum DDT metrics (quintile, ng/g lipid) DDE: Q1: 54–821 Q2: 821–1,410 Q3: 1,410–2,224 Q4: 2,224–3,605 Q5: 3,605–22,328 DDT: Q1: 4–26 Q2: 26–39 Q3: 39–60 Q4: 60–103 Q5: 103–940	Diabetes Q2 versus Q1 Q3 versus Q1 Q4 versus Q1 Q5 versus Q1 Pre-diabetes Q2 versus Q1 Q3–Q5 	 ↔ (DDE) ↔ (DDT) ↑ (DDE) ↑ (DDT) ↔ (DDE) ↑ (DDT) ↑ (DDE) ↑ (DDT) ↔ (DDE) ↔ (DDT) ↑ (DDE) ↑ (DDT)
Wu et al. 2013 Nested case-control within a cohort, Study 1: 24 DMT2 cases and 398 non-diabetic controls, Study 2: 24 DMT2 cases and 649 non-diabetic controls (United States)	Serum DDT metrics (tertiles, ng/g lipid) T1 T2 T3 Study 1: DDE 424.8 989.6 2,099.5 DDT 23.7 43.7 83.3 Study 2: DDE 349.5 773.6 1,535.3 DDT 26.9 53.1 120.9	DMT2 Study 1, Study 2, or pooled	 ↔ (DDE) ↔ (DDT)
Zong et al. 2018 Nested case-control within a cohort, 793 females with DMT2 and 793 age-matched non-diabetic controls (United States)	Plasma DDE (tertiles, ng/g lipid) T1: 126.0 T2: 271.6 T3: 618.1	DMT2 T2 versus T1 T3 versus T1	 ↑ ↑
Zuk et al. 2019 Case-control, 50 males and 95 females with DMT2 and 253 male and 324 female non-diabetic controls (Canada, Cree First Nation Communities)	Plasma DDT (mean±SD, ng/mL) Case Control Males 0.03±1.63 0.03±1.37 Females 0.04±1.81 0.03±1.33 Plasma DDE (mean±SD, ng/mL) Case Control Males 2.99±2.91 1.39±2.87 Females 2.96±3.31 1.04±3.75	DMT2	↑

Table 2-21. Summary of Diabetes Outcomes in Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Diabetes indicators			
Arrebola et al. 2015c Cross-sectional, 109 women with gestational diabetes (Spain) 2-Hour glucose tolerance testing and blood collection after cessation of breastfeeding or at 3 months after delivery, whichever was earlier	Serum DDE (IQR, ng/mL) 1.01–2.75	Fasting outcomes FBG Fasting IRI HbA1C HOMA-IR	 ↔ ↔ ↔ ↔
		2-hour tolerance outcomes 2hIRI 2hBG ISI-gly	 ↑ ↔ ↓
Burns et al. 2014 Cohort, 318 boys (8–9 years) with follow-up at 10–11 years (n=315) and 12–13 years (n=290) (Russia)	Fasting serum DDE at 8–9 years (quintiles, ng/mL) Q1: 0.26–0.52 Q2: 0.832–1.199 Q3: 1.203–1.716 Q4: 1.720–2.659 Q5: 2.7–41.3 Data from both follow-ups combined for analysis	Leptin Q2–Q5 p-trend	 ↓ ↓
		Insulin Q2–Q4 Q5 versus Q1 p-trend	 ↔ ↓ ↓
		HOMA-IR Q2–Q4 Q5 versus Q1 p-trend	 ↔ ↓ ↓
		FBG	↔
		IR	↔
Debost-Legrand et al. 2016a, 2016b Cross-sectional, 268 mother-child pairs including 132 male and 136 female children (France)	Cord blood DDE (quartiles, ng/mL) Q1: ≤0.100 Q2: 0.100–0.180 Q3: 0.180–0.290 Q4: >0.290	Insulin (cord blood)	↔
		Adiponectin (cord blood) Q2–Q4 p-trend	 ↔ ↔ (males) ↓ (females)
Dirinck et al. 2014 Cross-sectional, 195 adults including 151 obese adults without history of DMT2 (BMI >25 kg/m^3) and 44 lean adults (Belgium)	Serum DDE (mean (range), ng/g lipid) Total: 104.5 (8.6–3,373.0) Obese: 120.3 (8.6–3,373) Lean: 99.4 (19–908.6) Adipose DDE measured in 53 obese cases undergoing surgery (levels not reported)	Abnormal glucose tolerance Serum Adipose Total body	 ↑ ↑ ↑

Table 2-21. Summary of Diabetes Outcomes in Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Han et al. 2020 Case-control, 158 DMT2 cases, 158 non-diabetic controls (China)	Serum DDT metrics (GM±GSD, ng/mL) Cases DDE: 4.184 (0.0029) DDT: 0.097 (0.0021) Controls DDE: 2.300 (0.0036) DDT 0.044 (0.0029) Cases and controls combined for analysis	FBG	↔ (DDE) ↔ (DDT)
		HbA1c	↔ (DDE) ↔ (DDT)
Kaur et al. 2020 Cohort, 87 youth (mean 14.2 years at baseline) with type 1 or 2 diabetes, follow-up examination 5 years later (United States)	Serum DDE levels (quartile GM, ng/g lipid): Q1: 22.93 Q2: 39.23 Q3: 65.44 Q4: 127.32	HbA1c	↔
		Insulin sensitivity	↔
Kim et al. 2014 Cross-sectional, 50 adults including 25 DMT2 cases (FBG ≥126 mg/dL or self-report) and 25 non-diabetic controls (Korea)	Approximate[c] subcutaneous (SAT) or visceral (VAT) adipose tissue levels (IQR, ng/g lipid) SAT / VAT DDD 3–6 / 13–30 DDE 105–310 / 90–160 DDT 16–32 / 2–4 *o,p'*-DDE 0.6–1.8 / 1.5–1.8 o,p'-DDT 1.2–3.8 / 0.5–3.4	HOMA-IR SAT VAT	 ↔ (∑DDT) ↑ (∑DDT)
La Merrill et al. 2019 Cross-sectional, 147 Asian Indian adults (United States, California)	Plasma DDT metrics (median (range), ng/g lipid) DDE: 1,850 (85.1–27,900) DDT: 44.8 (8.67–2,880) o,p'-DDE: 1.70 (0.500–8.90) o,p'-DDT: 4.20 (<0.810–209)	Glucose	↔ (∑DDT)
		Insulin	↑ (∑DDT)
		Insulin sensitivity index	↓ (∑DDT)
La Merrill et al. 2018 Cohort, 988 elderly adults 70 years at the time of plasma collection, evaluated at 70, 75, and 80 years (Sweden)	Plasma DDE levels (IQR, ng/g lipid): 170–570	FBG	↑

Table 2-21. Summary of Diabetes Outcomes in Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Langer et al. 2014 Cross-sectional, 2,035 adults including young adults (21–40 years; 248 males, 330 females) and older adults (41–75 years; 568 males, 889 females) (Slovakia)	Serum DDE (IQR, ng/g lipid) Male / Female Young: 592–1,594 / 563–1,194 Older: 1,359–3,881 / 1,307–3,687	FBG Young Older Insulin Young Older	 ↑ (males) ↑ (females) ↑ (males) ↑ (females) ↔ (males) ↔ (females) ↑ (males) ↔ (females)
Lee et al. 2016 Cohort, 214 children, 7–9 years old at baseline; follow-up 1 year later (n=158) (Korea)	Serum DDT metrics at baseline (IQR) ng/mL / ng/g lipid DDE: 0.16–0.41 / 26.74–71.24 DDT: 0.013–0.024 / 2.31–4.04	Glucose	↔
Lee et al. 2007b Cross-sectional, 721 non-diabetic adults including 175 adults with metabolic syndrome cases (United States, NHANES)	Serum DDE (NR)	FBG	↑
Lee et al. 2011b Cohort, 5,115 adults, 18–30 years at initiation (United States)	Serum DDE at initiation (NR)	HOMA-IR at 20-year follow-up Q2–Q4 p-trend	 ↔ (DDT) ↔ (DDE) ↔ (DDT) ↑ (DDE)
Tang-Peronard et al. 2015b Cohort, 520 mother-child pairs including 273 male and 247 female children (Faroe Islands) Insulin and leptin levels measured at 5 years	Maternal serum (n=384) or milk (n=136) DDE (median (75th percentile), ng/g lipid) Males: 570 (1,000) Females: 580 (1,000) 25th percentile not reported	Insulin levels >75th percentile Q2–Q3 Q4 p-trend Leptin levels >75th percentile Q2–Q4, p-trend	 ↔ ↔ (males) ↑ (females) ↔ ↔
Teeyapant et al. 2014 Cross-sectional, 1,137 adults including 484 males and 653 females (Thailand)	Serum DDT metrics (GM (95% CI), ng/g lipid) Males DDE 1,539 (1,242–1,837) DDT 135 (116–164) Females DDE 1,547 (1,293–1,806) DDT 133 (112–147)	FBG	↑ (DDE) ↔ (DDT)

Table 2-21. Summary of Diabetes Outcomes in Humans with DDT Exposure Biometrics[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Type 1 diabetes (DMT1) or gestational diabetes prevalence			
Rignell-Hydbom et al. 2010 Nested case-control, 150 children with DMT1 and 150 non-diabetic controls (Sweden)	Maternal serum DDE (quartile ranges, ng/mL) Q1: <5.8 Q2: 5.8–9.6 Q3: 9.7–16.8 Q4: >16.8	DMT1	↔
Vafeiadi et al. 2017 Cohort, 939 pregnant women including 68 cases of gestational diabetes and 871 controls (Greece)	Serum DDE during first trimester (tertile, ng/mL) T1: 0.15–1.40 T2: >1.40–2.85 T3: >2.85–32.47	Gestational diabetes	↔
Valvi et al. 2017 Cross-sectional, 604 pregnant women including 49 with gestational diabetes and 555 without (Denmark)	Serum DDE levels at gestation week 34 (tertile, µg/g lipid) T1: 0.04–0.37 T2: 0.38–0.73 T3: 0.74–11.4	Gestational diabetes	↔

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDD = *p,p'*-DDD, DDE = *p,p'*-DDE, and DDT = *p,p'*-DDT, unless otherwise specified.
[c]Estimated from graphically presented data.

↑ = increased levels; ↓ = decreased levels; ↔ = no difference; 2hBG = 2-hour blood glucose (in glucose tolerance test); 2hIRI = 2-hour immunoreactive insulin; BMI = body mass index; CI = confidence interval; DDD = dichloro-diphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; DMT1 = type 1 diabetes; DMT2 = diabetes mellitus type 2; FBG = fasting blood glucose; GM = geometric mean; GSD = geometric standard deviation; HbA1c = hemoglobin A1C; HOMA-IR = Homeostasis Model Assessment for Insulin Resistance; IFG = impaired fasting glycemia; IQR = interquartile range; IR = insulin resistance; IRI = immunoreactive insulin; ISI-gly = Insulin Sensitivity Index; MLOD = maximum level of detection; NHANES = National Health and Nutrition Examination Survey; NR = not reported; Q = quartile or quintile; SAT = subcutaneous adipose tissue; SD = standard deviation; SE = standard error; T = tertile; VAT = visceral adipose tissue

Associations with DMT2. Among the 31 studies evaluating associations between DDT exposure biometrics and DMT2 prevalence, 24 found positive associations, 2 found marginal associations, and 5 found no association (see Table 2-21 for citations). The studies reporting positive evidence for a statistically significant association between DDT exposure biometrics and DMT2 include five nationwide studies in the United States (Everett and Matheson 2010; Everett and Thompson 2015; Everett et al. 2007, 2017a; Lee et al. 2006). Associations were reported across a wide range of age groups starting from 18 years of age (Aminov et al. 2016). Four U.S. studies examined whether or not adjustments for other

organochlorine analytes would influence the statistical significance of the association. With adjustments for other analytes in the biological samples, statistical significance was lost in three of these studies (Aminov et al. 2016; Codru et al. 2007; Everett and Matheson 2010) and not influenced in the fourth (Everett et al. 2007). Two studies with marginal associations with DMT2 include a study by Airaksinen et al. (2011) that reports a significant trend for increasing ORs across DDE exposure quartiles, but individual ORs were not elevated for quartiles 2–4, compared with quartile 1. Kim et al. (2014) reported no significant elevation in ORs for DMT2 prevalence for the sum of measured DDT analytes (∑DDT) in subcutaneous or visceral adipose tissues in the two highest exposure tertiles, compared with the first tertile, but found elevated ORs for DDE in visceral adipose tissue in the highest exposure groups. One study suggested that serum DDE levels may have a non-monotonic relationship with DMT2 prevalence, as a positive association was observed in individuals from a "low-exposure" region (Mississippi Hill region), but no association as observed in individuals from a "high-exposure" region (Mississippi Delta region) (Meek et al. 2019).

Several published meta-analyses provide support for the association between DDT exposure biometrics and DMT2 prevalence. From a consideration of 22 ORs (from 18 studies), Tang et al. (2014) calculated a total odds ratio (OR) of 1.33 (95% CI 1.15–1.54) indicative of an association between DDE serum levels and DMT2 prevalence. This analysis also reported significantly elevated ORs for other analytes in these studies: PCB-153 and PCBs (Tang et al. 2014). Evangelou et al. (2016) considered ORs from 14 studies of DMT2 prevalence and calculated a total OR of 1.95 (95% CI 1.44–2.66) for DDE and statistically significant ORs for other analytes included in the evaluated studies (e.g., DDT, dieldrin, heptachlor, hexachlorobenzene). Another analysis of 72 epidemiological studies evaluating associations between persistent organochlorine compounds and DMT2 concluded that heterogeneity of the studies precluded a meta-analysis, but noted that the overall evidence was sufficient to demonstrate an association (but not causality) between several persistent organochlorines (including DDE, PCBs, and dioxins) and DMT2 prevalence (Taylor et al. 2013). Wu et al. (2013) pooled results from their U.S. Nurse's Health study of DMT2 prevalence with data from four other studies (Lee et al. 2010, 2011b; Rignell-Hydbom et al. 2009b; Turyk et al. 2009) and reported a marginally elevated total ORs for DDE (OR 1.25 [95% CI 0.94–1.66]). Fakhri et al. (2017) evaluated ORs from six prospective and seven cross-sectional studies; a total OR of 1.52 (1.26–1.84; $p<0.001$) indicates an association between increasing concentrations of *p,p'*-DDE in serum and adipose tissue with increased risk of DMT2.

Associations with diabetes indicators. Ten studies evaluated diabetes indicators in adult subjects from a wide array of demographics, including young adults, the elderly, and pregnant women. Most of these

studies report associations between DDT exposure metrics and one or more diabetes indicators. Associations with any DDT metric in studies of adults (Table 2-21) were found in:

- 4/6 studies for blood glucose levels (4 associated with increased glucose levels; 2 with no associations);
- 2/2 studies for blood insulin levels (both associated with increased insulin levels);
- 0/1 study for Hb1AC levels (no association);
- 3/3 studies for measures of insulin resistance (all associated with increased insulin resistance and/or decreased insulin sensitivity); and
- 1/1 study for glucose tolerance (associated with decreased tolerance).

Data for children are limited to five studies that evaluated diabetes indicators in children. Definitive conclusions about possible associations with any specific diabetes biomarker cannot be made due to the small number of studies evaluating each indicator, different ages at assessment, and the variety of DDT biomarkers used (e.g., maternal serum, cord blood, child serum). Associations with any DDT metric in studies of children (Table 2-21) were found in:

- 0/2 studies for blood glucose levels (no associations with child serum levels);
- 1/1 study for blood insulin levels (maternal serum levels associated with increased insulin);
- 0/1 study for Hb1AC levels (no association with child serum levels);
- 1/2 studies for measures of insulin resistance (both evaluated child serum levels: 1 associated with decreased insulin resistance; 1 with no association);
- 1/2 studies for serum leptin levels (1 reported child serum levels associated with decreased levels; 1 reported no association with maternal serum levels); and
- 1/1 study for serum adiponectin levels (cord blood levels associated with decreased adiponectin levels).

Associations with gestational or Type-1 diabetes. Maternal levels of DDT biomarkers were not associated with prevalence of gestational diabetes (Vafeiadi et al. 2017; Valvi et al. 2017) or development of Type 1 diabetes in offspring (Rignell-Hydbom et al. 2010). The sparse data for these types of diabetes preclude making definitive conclusions about possible association of gestational diabetes or Type 1 diabetes with levels of DDT exposure biometrics.

Studies of Diabetic Outcomes in Laboratory Animals. There are a limited number of animal studies that directly evaluate associations between exposures to DDT, DDE, or DDD and glucose homeostasis. In an acute exposure study, mice exposed orally to 2.0 mg/kg/day *p,p'*-DDE, but not 0.4 mg/kg/day, for 5 days,

had significant elevations in FBG levels that persisted for up to 21 days (Howell et al. 2014). Glucose tolerance and levels of Akt phosphorylation (an indicator of insulin-induced glucose disposal) in liver and skeletal muscle were comparable to untreated controls. Hyperglycemia was not associated with changes in measured metabolic hormones or adipokines including insulin, glucagon, leptin, resistin, IL-6, TNF-α, or MCP-1 (Howell et al. 2014). Following exposure to 2.0 mg/kg/day *p,p'*-DDE for 14 days, rats showed increases in fasting blood glucose and blood insulin levels, increased insulin resistance (HOMA-IR), and impaired glucose tolerance (Liang et al. 2020). After an additional 7 days of exposure, these rats also showed evidence of metabolic syndrome, including an approximate 65% increase in fat pad weight, an overall 1.5% increase in percent body fat, and an altered plasma lipid profile (Liang et al. 2020).

In an intermediate-exposure duration study, Howell et al. (2015) investigated whether exposure to *p,p'*-DDE would influence the development of obesity and DMT2 using a rodent model of DMT2. Male mice were treated orally with 2.0 mg/kg/day *p,p'*-DDE for 5 days; following 7 days of rest, animals then received 2.0 mg/kg *p,p'*-DDE weekly for 13 weeks, in combination with either a low-fat (LFD) or high-fat diet (HFD) (Howell et al. 2015). Hyperglycemia was observed at 4- and 8-week timepoints in HFD and DDE-HFD animals; by 13 weeks, however, all DDE-HFD exposed animals returned to normoglycemia. This could partially be explained by an observed increase in *Glut4* expression in skeletal muscle of DDE-HFD mice, which facilitates insulin-stimulated glucose uptake, increased insulin sensitivity, and decreased hepatic glucose production (Howell et al. 2015). FBG levels of the DDE-LFD group were comparable to controls at all time points indicating the complexities of diet and weight influences on DDE activity. In contrast to the hypothesis that DDE exposure may enhance the effects of HFDs on diabetic endpoints, prolonged DDE exposure exhibited protective effects. Mice with prolonged exposure to DDE and HFD had values for these endpoints similar to values for LFD-vehicle controls. Only fasting insulin levels and insulin resistance in DDE-HFD mice were slightly, but significantly, elevated, compared to LFD animals; the values were lower than the HDF-vehicle controls. No metabolic effects or other effects relating to DMT2 were observed in DDE-exposed animals on a LFD (Howell et al. 2015). Due to uncertainty of the adversity of the changes observed, and clear understanding of effects that are due to DDE (independent of diet), this study is not included in the LSE table.

In a gestational exposure study, mice exposed perinatally from GD 11.5 to PND 5 to a 1.7 mg/kg/day mixture of *p,p'*-DDT and *o,p'*-DDT had normal glucose tolerance, FBG, insulin, and lipid levels throughout their first 6 months of life (La Merrill et al. 2014a, 2014b). Female mice, but not male mice, however, exhibited signs of compromised thermogenesis including reduced core temperature, oxygen consumption, and energy expenditure, and increased cold intolerance (La Merrill et al. 2014a, 2014b). At

6 months of age, when challenged with a low- or high-fat diet for 12 weeks, DDT gestationally-exposed-only females on HFDs displayed significant glucose intolerance, insulin resistance, and mild dyslipidemia (La Merrill et al. 2014a, 2014b). In a transgenerational study in Sprague-Dawley rats, F0 dam exposure to 100 mg p,p'-DDT/kg/day from GD 8 to 15 resulted in altered glucose homeostasis in F1, F2, and F3 male offspring and F1 female offspring; findings were associated with ultrastructural changes in the pancreas (Song and Yang 2017). Effects were only observed in F3 offspring with ancestral exposure via the maternal plus paternal lineages or the paternal lineage; effects were not observed if ancestral exposure was via the maternal lineage only.

An increased incidence and earlier development of diabetes occurred in pre-diabetic female NOD mice administered via intraperitoneal injection 50 mg/kg p,p′-DDE twice weekly for 16 weeks (Cetkovic-Cvrlje et al. 2016). Elevated blood glucose levels were also observed in these mice. Exposure to a lower dose (25 mg/kg) did not result in significant alterations.

Mechanistic Information on DDT Influence on Diabetic Outcomes. DMT2 is a complex disease of metabolic dysfunction that can take years to develop. The underlying etiologic agents include a multitude of both genetic and environmental factors. Emerging evidence suggests that EDCs, including DDT, are capable of disrupting metabolism and inducing obesity, which then can contribute to the development of obesity-related diseases including DMT2 and cardiovascular disease (Lee et al. 2014; Legler et al. 2015; Tang-Peronard et al. 2011).

There is a vast amount of mechanistic information on organochlorines, including DDT, their hormonal influences, and their ability to disrupt lipid and glucose homeostasis, mitochondrial function, energy expenditure, and insulin signaling (for reviews, see Heindel et al. 2017; Ishikawa et al. 2015; Karami-Mohajeri and Abdollahi 2011; Lee et al. 2014; Mrema et al. 2013). Adipose tissue dysfunction and metabolic changes that contribute to obesity are believed to play a major role in the development of insulin resistance, leading to DMT2. Several studies demonstrate the ability of DDT to disrupt lipid homeostasis. *In vitro* studies with *p,p'*-DDT or *p,p'*-DDE suggest there may be AhR-independent effects causing increased adipogenesis (Kim et al. 2016; Mangum et al. 2015; Moreno-Aliaga and Matsumuru 2002), adipocyte fatty acid uptake (Howell and Mangum 2011), and dipokine (adiponectin, leptin, resistin) levels (Howell and Mangum 2011). In HepG2 cells treated with 1 or 10 ng/mL *p,p'*-DDE, Liu et al. (2017a, 2017b) observed acceleration of lipid accumulation, a reduction in mRNA and protein levels of enzymes involved in hepatic fatty acid β-oxidation (Cpt1α, MCAD, SCAD), and reduced ATP turnover in the mitochondria. Other *in vitro* studies further support the hypothesis that *p,p'*-DDE

exposure is associated with effects on lipid synthesis, accumulation, degradation, and transport or secretion (Ward et al. 2016). Many of these observations translate to *in vivo* studies in mice. Following an 8-week exposure to 1 mg *p,p'*-DDE/kg/day orally, significant increases in protein levels, but not transcripts, of key enzymes involved in fatty acid synthesis (Fas, Acc, Scd1) in the liver were observed, and alterations in metabolomic profiles relevant to fatty acid metabolism and phospholipids were also noted (Liu et al. 2017a, 2017b). Another *in vivo* study in adult female mice perinatally exposed to DDT observed changed gene expression in transcripts involved in lipolysis (*Pnpla*) and thermogenesis (*Ppargc1a*) (La Merrill et al. 2014a, 2014b). Disruptions in gut microbiota has also been hypothesized as a contributing factor to DDT-mediated obesity, altered glucose homeostasis, and altered lipid metabolism (Liang et al. 2020).

A human study, evaluating the metabolomes of 1,016 adults 70 years of age from Uppsala, Sweden with known serum DDE levels found evidence consistent with animal studies linking DDE exposures to altered metabolic effects (Salihovic et al. 2016). DDE was significantly inversely associated with seven metabolites, including several lysophosphatidylcholine congeners, which have been linked to diabetes in other studies; an increase in monoacylglycerol (18:2), which has been associated with insulin secretion and obesity in mice; and increased levels of three fatty acid metabolites that play a role in lipid metabolism (Salihovic et al. 2016). It is unclear, however, whether these changes in metabolite levels translate to functional changes that could trigger, or contribute to, obesity and DMT2.

Timing of exposure may be a crucial factor in the development of DDT-related metabolic pathologies. It has been hypothesized that exposure to obesogens, including DDT, during critical phases of development may lead to metabolic-related consequences later in life (Russ and Howard 2016). This hypothesis is supported by a study in mice (La Merrill et al. 2014a, 2014b), and in a limited number of epidemiological studies relating early exposure to obesity (see Section 2.3) and hyperinsulinemia (Tang-Peronard et al. 2015b). Because of the crucial roles hormones play during early development, it is hypothesized that DDT disruption of hormonal activities, including its estrogenic and anti-androgenic effects, during vulnerable developmental windows, could contribute to the disruption in multiple systems involved in metabolism and adipocyte function that contribute to diseases such as DMT2 later in life. Additional long-term mechanistic studies evaluating early-life exposures that monitor effects later in life will help to further test this hypothesis.

King et al. (2019a, 2019b) proposed that transgenerational inheritance of differentially methylated regions (i.e., epimutations) through the male germline may contribute to DDT-associated obesity. Trans-generational epimutations were observed in F3 rat offspring following intraperitoneal DDT exposure in F0 dams only (King et al. 2019b). Additionally, certain sperm epimutations (differentially methylated region "signatures") were associated with obesity in F3-generation males (King et al. 2019a).

2.19 CANCER

Evidence for Cancer in Humans

Scope of the analysis. Numerous studies have examined possible association 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. Multiple case-control epidemiological studies of this type have been published for the following types of cancer, listed in order of decreasing number of studies: breast cancer in women, NHL, prostate cancer, testicular cancer, liver cancer, pancreatic cancer, and endometrial cancer. In addition, there are single studies that examined associations with risks for acute myeloid leukemia, bladder cancer, colorectal cancer, and thyroid cancer or mortality rates for multiple myeloma or all cancers. The oral route of exposure is the presumed principal route of exposure for the subjects in all of these studied groups, although small contributions from dermal or inhalation exposure cannot be excluded. This section provides overviews of the evidence provided by these specific types of case-control epidemiological studies. The ensuing discussion does not include published studies that examined possible associations between reports of DDT use and cancer risk, because reported-use exposure data are less reliable than internal biometric data. Also not included are studies that compared serum or adipose levels of DDT, DDD, or DDE in cancer cases and controls, but did not examine associations with cancer risk. Studies meeting inclusion criteria are shown in Table 2-22.

Overview of epidemiological results. Consistent evidence from up to 46 case-control studies does not support the hypothesis that serum or adipose tissue levels of DDT, DDE, or DDE in adult women is associated with increased risk of breast cancer (Ingber et al. 2013; Lopez-Cervantes et al. 2004; Park et al. 2014). The lack of an association may be due to the paucity of exposure information during postulated early life periods of breast vulnerability (Cohn 2011; Cohn et al. 2007, 2015). Other case-control studies provide inconsistent evidence for associations with NHL, prostate cancer, or testicular cancer; and no evidence for associations with pancreatic cancer or endometrial cancer (see sections below for references). No evidence for associations was found in single case-control studies for bladder cancer and

colorectal cancer and single studies of mortality rates from multiple myeloma or all cancers. Consistent evidence for associations with liver cancer was found in Chinese populations, but not others.

Table 2-22. Summary of Studies of Associations Between DDT Exposure Biometrics and Cancer[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Breast cancer[c]			
Arrebola et al. 2015a Case-control, 69 breast cancer cases and 54 controls (Tunisia)	Serum DDE (IQR, ng/g lipid) Cases: 106.18–362.86 Controls: 66.02–276.93	Breast cancer risk Individual chemical With β-HCH, hexachlorobenzene, heptachlor, and PCBs as covariates	 ↑ ↔
Bachelet et al. 2019 Case-control, 676 cases and 1,040 controls (France) Analysis stratified by age as a proxy for menopausal status: <50 years (161 cases and 351 controls); and ≥50 years (515 cases and 689 controls)	Plasma DDE (exposure groups, ng/g lipids) "Lower exposure category" <LOD "Upper exposure categories" (tertiles based on controls): All subjects T1: 51.3–131.5 T2: 131.5–212.4 T3: ≥ 212.4 <50 years T1: 53.1–130.6 T2: 130.6–181.1 T3: ≥ 181.1 ≥ 50 years T1: 51.3–132.8 T2: 132.8–222.2 T3: ≥ 222.2	Breast cancer risk All subjects T1 versus <LOD T2 versus <LOD T3 versus <LOD Trend <50 years old T1–T3 versus <LOD Trend ≥50 years old T1 versus <LOD T2 versus <LOD T3 versus <LOD Trend	 ↔ ↓ ↔ ↔ ↔ ↔ ↔ ↔ ↓ ↔ ↔
Boada et al. 2012 Case-control, 121 breast cancer cases and 103 controls (Spanish Canary Islands)	Serum DDT metric (median [5th–95th percentile], ng/g lipid) Controls DDT: 217.0 (0.0–1428.6) DDE: 167.7 (45.0–706.0) DDD: 0.0 (0.0–129.2) Cases DDT: 153.0 (0.0–327.9) DDE: 300.1 (106.1–653.3) DDD: 551.1 (0.0–1108.2	Breast cancer risk	↔ (DDT) ↔ (DDE) ↑ (DDD)

Table 2-22. Summary of Studies of Associations Between DDT Exposure Biometrics and Cancer[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Non-Hodgkin Lymphoma (NHL)			
Bassig et al. 2020 Nested case-control from three cohorts (SWHS, SCS, SCHS); 167 NHL cases and 167 controls (China and Singapore)	Serum DDE (IQR, ng/g lipid) Cases: 2,970–12,000 Controls: 2,850–10,900 Serum DDE for cohorts (cases and controls combined; T1 and T3 tertile cutpoints, ng/g lipid): SWHS: 5,114–7,760 SCS: 9,249–15,910 SCHS: 1,447–2,039	NHL risk SWHS SCS SCHS Pooled cohorts	 ↔ ↔ ↔ ↔
Bertrand et al. 2010 Nested case-control, 205 NHL cases, 409 controls (United States, Massachusetts)	Plasma DDE (quintile median [range], ng/g lipid) Q1: 724 (43–1,045) Q2: 1,369 (>1,045–1,741) Q3: 2,181 (>1,741–2,523) Q4: 2,972 (>2,523–3,595) Q5: 4,830 (>3,595–18,937)	NHL risk Q2–Q5 versus Q1 Trend	 ↔ ↔
Brauner et al. 2012 Nested case-control, 239 NHL cases (126 men, 113 women), 245 controls (126 men, 119 women) (Denmark)	Adipose DDT metrics (IQR, ng/g lipid) DDT: 15–49 DDE: 390–1,700	NHL risk All Men Women	 ↔ (DDE) ↑ (DDT) ↑ (DDT) ↔ (DDT)
Cocco et al. 2008 Case-control, 174 NHL cases, 203 controls (France, Germany, Spain)	Plasma DDE (quartiles, ng/mL) Q1: ≤394.99 Q2: 395.0–791.02 Q3: 791.03–1,431.07 Q4: ≥1,431.08	NHL risk Q2–4 versus 1 Trend	 ↔ ↔
De Roos et al. 2005 Case-control, 100 NHL cases, 100 controls (United States)	Plasma DDT metrics (quartiles, ng/g lipid) DDT / DDE Q1: ≤3.7 / ≤254.5 Q2: >3.7–5.9 / >254.5–450.5 Q3: >5.9–9.9 / >450.5–872.5 Q4: >9.9 / >872.5	NHL risk Q2–Q4 versus Q1 Trend	 ↔ (all metrics) ↔ (all metrics)
Engel et al. 2007 Nested case-control from three cohorts: Janus (190 NHL cases, 190 controls), CLUE I (74 NHL cases, 147 controls), and NHS (102 NHL cases, 102 controls (Norway and United States)	Serum DDE (quartile median, ng/g lipid) Janus / CLUE I / NHS Q1: 2,059.1 / 912.2 / NR Q2: 3,247.2 / 1,616.2 / NR Q3: 4,673.2 / 2,442.8 / NR Q4: 7,513.0 / 4,475.0 / NR	NHL risk Janus cohort CLUE I cohort NHS cohort	 ↔ ↔ ↔

Table 2-22. Summary of Studies of Associations Between DDT Exposure Biometrics and Cancer[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Hardell et al. 2009 Case-control, 99 NHL cases, 99 controls (Sweden)	Plasma DDE (median [range], ng/g lipid) Cases: 307 (5.4–2,786) Controls: 271 (17–1,414)	NHL risk	↔
Hardell et al. 2001 Case-control, 82 NHL cases, 83 controls (Sweden)	Plasma DDE (median [range], ng/g lipid) Cases: 747 (135–4,975) Controls: 668 (51–3,614)	NHL risk	↔
Klil-Drori et al. 2018a, 2018b Case-control, 90 NHL cases (50 Israeli Jews, 40 Palestinian Arabs) and 120 controls (65 Israeli Jews, 55 Palestinian Arabs) (Israel and Palestine)	Serum DDE (IQR, ng/mL) Cases / Controls Jews 0.718–4.304 / 0.900–5.034 Arabs 0.784–4.919 / 0.607–2.362 Serum DDE in all subjects (quartiles, ng/mL) Q1: ≤ 0.772 Q2: 0.773–1.684 Q3: 1.684–3.697 Q4: >3.697	NHL risk All Jews Arabs	 ↔ ↔ ↑
Laden et al. 2010 Nested case-control, 145 female NHL cases, 290 controls (United States)	Plasma DDE (quartile median, ng/g lipid) Q1: 343.6 Q2: 779.6 Q3: 1,327.0 Q4: 2,325.2	NHL risk Q2–4 versus Q1 Trend	 ↔ ↔
Quintana et al. 2004 Nested case-control, 175 NHL cases, 481 controls (United States)	Adipose DDT or DDE (quartiles, ng/g lipid) DDT Q1: <550 Q2: 550–920 Q3: 920–1,560 Q4: >1,560 DDE Q1: <2,400 Q2: 2,400–4,380 Q3: 4,380–7,210 Q4: >7,210	NHL risk Q2,Q3 versus Q1 Q4 versus Q1 Trend With heptachlor epoxide, β-benzene hexachloride, or dieldrin as a covariate	 ↔ (all metrics) ↑ (DDE) ↔ (DDT) ↑ (all metrics) ↔ (all metrics)
Rothman et al. 1997 Nested case-control, 74 NHL cases, 147 controls (Maryland, United States)	Serum DDT (quartiles, ng/g lipid) Q1: 180–1,740 Q2: 1,760–2,660 Q3: 2,690–4,020 Q4: 4,140–20,500	NHL risk Q2–4 versus Q1	 ↔
Spinelli et al. 2007 Case control, 422 NHL cases, 460 controls (Canada)	Plasma DDE (quartiles, ng/g lipid) Q1: ≤134.41 Q2: 134.41–263.91 Q3: 263.91–512.02 Q4: >512.02–18,898	NHL risk Q2–4 versus Q1 Trend	 ↔ ↔

Table 2-22. Summary of Studies of Associations Between DDT Exposure Biometrics and Cancer[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Viel et al. 2011 Case-control, 34 NHL cases, 34 controls (France)	Serum DDT metrics (mean, ng/g lipid) Cases / Controls DDT: 36.83 / 18.87 DDE: 153.1 / 89.49	NHL risk	↑ (DDT) ↔ (DDE)
Prostate cancer			
Aronson et al. 2010 Case-control, 79 prostate cancer cases, 135 controls (Canada)	Plasma DDT metrics (tertiles, ng/g lipid) DDT / DDE T1: <5.3 / <270.0 T2: 5.3–8.4 / 270.0–548.9 T3: >8.4–49.1 / >548.9–2362.3	Prostate cancer risk T2–3 versus T1 Trend	 ↔ (all metrics) ↔ (all metrics)
Emeville et al. 2015 Case-control, 576 prostate cancer cases, 655 controls (French West Indies)	Plasma DDE (quintiles, ng/mL) Q1: <0.79 Q2: 0.79–1.62 Q3: 1.63–2.89 Q4: 2.90–5.18 Q5: ≥5.19	Prostate cancer risk Q2–Q4 versus Q1 Q5 versus Q1 Trend	 ↔ ↑ ↑
Hardell et al. 2006a Case-control, 58 prostate cancer cases, 20 controls (Sweden)	Adipose DDE (median [range], ng/g lipid) Cases: 438 (6.0–3163) Controls: 291 (41–2419)	Prostate cancer risk	↔
Pi et al. 2016a, 2016b Case-control, 60 prostate cancer cases, 60 controls (Singapore)	Serum DDT metrics (geometric mean [95% CI], ng/g lipid) Cases DDT: 616.0 (188.3–2014) DDE: 13,707 (3,575–52,560) DDD: 80.93 (22.88–286.3) Controls DDT: 445.1 (140.4–1411) DDE: 9334.0 (2,572–33,870) DDD: 67.7 (20.43–224.1)	Prostate cancer risk T1–2 versus <LOD T3 versus <LOD Trend	 ↔ (all metrics) ↑ (all metrics) ↑ (all metrics)
Ritchie et al. 2003 Case-control, 58 prostate cancer cases, 99 controls (United States, Iowa)	Serum DDE (tertiles, ng/g lipid) T1: ≤180 T2: 181–340 T3: >340	Prostate cancer risk T2–3 versus T1	 ↔
Sawada et al. 2010 Nested case-control, 201 prostate cancer cases, 402 controls (Japan)	Plasma DDT metrics (quartiles, ng/g lipid) DDT / DDE / *o,p'*–DDT Q1: <24 / <560 / <2.5 Q2: 24–40 / 560–939 / 2.5–4.2 Q3: 41–63 / 940–1,599 / 4.3–7.6 Q4: ≥64 / ≥1,600 / ≥7.7	Prostate cancer risk Q2–Q4 versus Q1 Trend	 ↔ (all metrics) ↔ (all metrics)

Table 2-22. Summary of Studies of Associations Between DDT Exposure Biometrics and Cancer[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Xu et al. 2010 Case-control, 59 prostate cancer cases, 1,841 controls (United States; 1999–2004 NHANES)	Serum DDE (tertile medians, ng/g lipid) T1: 113 T2: 386 T3: 1530	Prostate cancer risk T1–2 versus T3 Trend	 ↔ ↔
Testicular cancer			
Biggs et al. 2008 Case-control, 246 testicular cancer cases, 630 controls (United States)	Serum DDT metrics (ng/g lipid) *o,p*–DDT / DDT / DDE T1: ≤5 / ≤27 / ≤1,101 T2: 5–13 / 27–47 / 1,101–2,473 T3: >13 / >47 / >2,473	Testicular cancer risk T1–2 versus T3 Trend	 ↔ (all metrics) ↔ (all metrics)
Giannandrea et al. 2011 Case-control, 50 testicular cancer cases, 48 controls (Italy)	Serum DDE (LOD, ng/mL) LOD: 0.2	Testicular cancer risk <LOD versus >LOD	 ↔
Hardell et al. 2006b Case-control, 44 testicular cancer cases, 45 controls (Sweden)	Maternal serum DDE (median, ng/g lipid) NR	Testicular cancer risk	↔
McGlynn et al. 2008 Case-control, 739 testicular cancer cases, 915 controls (United States)	Plasma DDT or DDE (quartiles ng/g lipid) DDT / DDE Q1: ≤20.9 / ≤157 Q2: 21.0–259 / 158–250 Q3: 260–397 / 251–390 Q4: >397 / >390	Testicular cancer risk Q2–3 versus Q1 Q4 versus Q1 Trend 	 ↔ (all metrics) ↑ (DDE) ↔ (DDT) ↑ (DDE) ↔ (DDT)
Purdue et al. 2009 Case-control, 49 testicular cancer cases, 51 controls (Norway)	Serum DDT metrics (Median [range], ng/g lipid) *o,p*–DDT Cases: 20.7 (6.0–220.5) Controls: 16.6 (0.3–171.9) DDT Cases: 226.0 (92.2–584.1) Controls: 194.6 (29.3–661.0) DDE Cases: 2,099 (750.0–9,512) Controls: 1,833 (224.9–7,436)	Testicular cancer risk T1–2 versus T3	 ↔ (all metrics)

Table 2-22. Summary of Studies of Associations Between DDT Exposure Biometrics and Cancer[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Liver cancer			
Engel et al. 2019 Nested case-control from two cohorts, 135 cases and 408 controls (MHC cohort, United States) and 84 cases and 252 controls (Janus cohort, Norway)	Serum DDT metrics in the 1960s/1970s (T1–T3, ng/g lipid) MHC (108 cases,324 controls) *o,p'*-DDT: 23.4–96.7 DDT: 650–1,725 DDE: 4,035–11,050 ΣDDT: 4,912–12,883 Janus (55 cases, 165 controls) *o,p'*-DDT: 7.8–30.2 DDT: 123–391 DDE: 971–3,140 ΣDDT: 1,119–3,463 Lower DDT metrics were observed in sera from 1980s, but similar trends were noted	Liver cancer risk MHC cohort Janus cohort	 ↔ (all metrics) ↔ (all metrics)
McGlynn et al. 2006 Nested case-control, 168 liver cancer cases, 385 controls (China)	Serum DDT metrics (quintiles, ng/g lipid) DDT / DDE Q1: <265 / <1,767 Q2: 265–382 / 1,767–2,443 Q3: 383–521 / 2,444–3,478 Q4: 522–787 / 3,479–5,458 Q5: >787 / >5,458	Liver cancer risk Q2–Q4 versus Q1 Q5 versus Q1 Trend	 ↔ (all metrics) ↑ (DDT) ↔ (DDE) ↑ (DDT) ↔ (DDE)
Persson et al. 2012 Nested case-control, 473 liver cancer cases, 492 controls (China)	Serum DDT or DDE (quintiles, ng/g lipid) DDT / DDE Q1: <261 / <10,000 Q2: 262–404 / 10,000–14,746 Q3: 404–545 / 14,746–21,579 Q4: 545–810 / 21,579–32,222 Q5: >810 / >32,222	Liver cancer risk Q2–Q4 versus Q1 Q5 versus Q1 Trend	 ↔ (all metrics) ↑ (DDT) ↔ (DDE) ↑ (DDT) ↔ (DDE)
Zhao et al. 2012 Case-control, 345 liver cancer cases, 961 controls (China)	Serum DDT or DDE (quartiles, ng/mL) DDT / DDE Q1: <16.11 / <2.62 Q2: 16.11–34.63 / 2.62–6.84 Q3: 34.64–43.08 / 6.85–10.55 Q4: ≥43.09 / ≥10.56	Liver cancer risk Q2 versus Q1 Q3 versus Q1 Q4 versus Q1 Trend	 ↔ (all metrics ↑ (DDT) ↔ (DDE) ↑ (all metrics) ↑ (all metrics)

Table 2-22. Summary of Studies of Associations Between DDT Exposure Biometrics and Cancer[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Pancreatic cancer			
Hardell et al. 2007 Case-control, 21 pancreatic cancer cases and 59 controls (Sweden)	Adipose DDE (median [range], ng/g lipid) Cases: 397 (60–2,827) Controls: 261 (41–2,419)	Pancreatic cancer risk	↔
Hoppin et al. 2000 Case-control, 108 cases, 82 controls (United States)	Serum DDE (tertiles, ng/g lipid) T1: <850 T2: 850–1,880 T3: ≥1,880	Pancreatic cancer risk T1–2 versus T3 Trend	 ↔ ↔
Endometrial cancer			
Hardell et al. 2004; Lindstrom et al. 2004 Case-control, 76 endometrial cancer cases, 39 controls (Sweden)	Adipose DDE (Median [range], ng/g lipid) Cases: 418 (4.0–1,767) Controls: 256 (43.4–1,296)	Endometrial cancer risk	↔
Sturgeon et al. 1998 Nested case-control, 90 endometrial cancer cases, 90 controls (United States)	Serum DDT metrics (IQR, ng/g lipid) Cases / Controls *o,p'*–DDT: 0–68 / 0–83 DDT: 0–125 / 0–96 DDE 809–2,169 / 943–2,276	Endometrial cancer risk	↔ (all metrics)
Other cancers			
Bassig et al. 2019 Nested case-control from Janus cohort, 56 acute myeloid leukemia cases, 288 controls (Norway)	Serum DDT metrics (IQR, ng/g lipid) Cases DDT: 209.0–513.8 *o,p'*-DDT: 14.7–37.6 DDE: 1,588.6–4,274.7 ∑DDT: NR Controls DDT: 173.9–402.4 *o,p'*-DDT: 12.8–33.7 DDE: 1,434.3–3,493.2 ∑DDT: NR Cases and controls combined for analysis based on control tertiles (tertile levels NR)	Acute myeloid leukemia risk	↔ (all metrics)

Table 2-22. Summary of Studies of Associations Between DDT Exposure Biometrics and Cancer[a]

Reference, study type, and population	Biomarker[b]	Outcome evaluated	Result
Boada et al. 2016 Case-control, 140 cases of bladder cancer, 206 controls	Serum DDT metrics	Bladder cancer risk	↔ (all metrics)
Howsam et al. 2004 Case-control, 132 colorectal cancer cases, 76 controls (Spain)	Serum DDT metrics (Median [5th–95th percentile], ng/g lipid) Cases DDT: 396 (124–2,077) DDE: 3,936 (600–11,804) Controls: DDT: 609 (137–3,848) DDE: 2,977 (611–13,608)	Colorectal cancer risk	↔ (all metrics)
Lerro et al. 2018 Nested case-control, 108 thyroid cancer cases, 216 controls (Norway)	Serum DDT metrics (median (range), ng/g lipid) Cases DDT: 166.5 (12.5–762) *o,p'*-DDT: 11 (2–75.3) DDE: 1445 (67.6–6,000) ∑DDT: 1630.3 (93–6,793.6) Controls DDT: 198 (10.8–1,450) *o,p'*-DDT: 13.3 (2.1–115) DDE: 1,630 (123–10,800) ∑DDT: 1,845.5 (145–11,511.4) Cases and controls combined for analysis	Thyroid cancer risk	↓ (∑DDT, DDE) ↔ (*o,p'*-DDT, DDT)

[a]Studies in this table were selected because they: (1) measured DDT-related metrics in biological fluids or tissues in each subject, and (2) evaluated associations using linear regression, logistical regression, or correlation techniques, adjusting for possible confounding factors.
[b]DDE = *p,p'*-DDE, unless otherwise specified; DDT = *p,p'*-DDT, unless otherwise specified.
[c]Includes only studies published since recent meta-analyses (Ingber et al. 2013; Lopez-Cervantes et al. 2004; Park et al. 2014)

↑ = positive association; ↓ = inverse association; ↔ = no association; β-HCH = β-hexachlorocyclohexane; CI = confidence interval; CLUE I = Campaign Against Cancer and Stroke; DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; IQR = interquartile range; LOD = limit of detection; MHC = Multiphasic Health Checkup; NHANES = National Health and Nutrition Examination Survey; NHS = Nurse's Health Study; NR= not reported; PCB = polychlorinated biphenyl congeners; Q = quartile or quintile; SCS = Shanghai Cohort Study; SCHS = Singapore Chinese Health Study; SWHS = Shanghai Women's Health Study; T= tertile

Breast cancer. Many epidemiological studies have investigated the association between breast cancer risk in groups of women and levels of DDT or DDE in blood or adipose tissue from the subjects, mostly mature adult women. Wolff et al. (1993) were the first to report a positive association between DDE levels (in serum) and breast cancer prevalence, but many subsequent studies did not find evidence for

associations. Bottom-line conclusions from the three most recent meta-analyses of case-control studies examining associations between DDT or DDE levels in serum or adipose tissue and breast cancer were similar: the available evidence does not support the hypothesized association between DDT/DDE levels and risk of breast cancer (Ingber et al. 2013; Lopez-Cervantes et al. 2004; Park et al. 2014). The meta-analyses were based on 22 (Lopez-Cervantes et al. 2004), 46 (Ingber et al. 2013), and 35 studies (Park et al. 2014).

The literature searches for this document identified three new breast cancer case-control studies not included in the meta-analyses (Arrebola et al. 2015a; Bachelet et al. 2019; Boada et al. 2012), but the results are not expected to affect the overall meta-analytic conclusions. As shown in Table 2-22, clear associations with DDT biometrics were not found in a study of 69 cases and 54 controls from Tunisia (Arrebola et al. 2015a) or a study of 676 cases and 1,040 controls from France (Bachelet et al. 2019). In a study of 121 cases and 103 controls from the Spanish Canary Islands, a very slight (but statistically significant) increase in risk of breast cancer was observed with increasing serum DDD, but not DDT or DDE (Boada et al. 2012).

Each of the meta-analyses noted that exposure metrics in most of the case-control studies were measured in mature adult women and may not reflect exposure during early life periods when the breast may be vulnerable (Ingber et al. 2013; Lopez-Cervantes et al. 2004; Park et al. 2014). Cohn (2011) postulated that the lack of an association might be due to the lack exposure metrics during a critical early period of life. Two studies provide support for this hypothesis (Cohn et al. 2007, 2015). In a study of 129 breast cancer cases and 129 controls who provided blood samples shortly after giving birth in 1959–1967, Cohn et al. (2007) reported that the highest category of serum *p,p'*-DDT levels was associated with increased breast cancer risk in a subgroup of women exposed to DDT before 14 years of age (after 1931 when DDT use became widespread), but no association was found in women born before 1931 who were not expected to have been exposed to DDT in early life periods. In a study of 118 breast cancer cases and 118 controls whose mothers provided perinatal blood samples between 1959 and 1967, Cohn et al. (2015) reported that daughters of mothers in the highest category of serum *o,p'*-DDT had higher risk of breast cancer.

Two studies examined possible associations between DDT or DDE serum levels and increased risk of mortality within 5, 15, or 20 years of breast cancer diagnosis. In a sample of 622 breast cancer cases, Parada et al. (2016) reported that women with DDT levels in the highest tertile of DDT serum levels had an increased risk of dying within the first 5 years of diagnosis from all causes of mortality and breast

cancer mortality; increased risk from all causes of mortality or breast cancer mortality was not observed at 15 years. In a similar study of 748 breast cancer cases, increased risk of mortality (all cause or breast cancer) was not observed within the first 5 years of diagnosis, but increased risk of dying within the first 20 years of diagnosis from all causes of mortality and breast cancer mortality was observed (Parada et al. 2019).

Non-Hodgkin Lymphoma. Inconsistent evidence comes from 14 case-control studies that examined possible associations between risk for NHL and serum or adipose levels of DDT and/or DDE (see Table 2-22). Four of these studies reported statistically significant associations between NHL risk and levels of DDE and/or DDT. Quintana et al. (2004) reported increased risk for NHL with increasing adipose levels of DDT and DDE, but in logistic models that included adipose levels of another organochlorine pesticide (heptachlor epoxide, β-benzene hexachloride, or dieldrin), the significance of the association between DDE levels and increased risk for NHL was not apparent. Two additional studies reported increased risk of NHL with increasing serum or adipose DDT levels, but not DDE levels (Brauner et al. 2012; Viel et al. (2011). When evaluated by sex, Brauner et al. (2012) only observed increased risk in men. In a case-control study in Israel and Palestine, increased risk of NHL associated with serum DDE levels was observed in Palestinian Arabs but not Israeli Jews (Klil-Drori et al. 2018a). Increased risk of NHL was not associated with DDT exposure metrics in the remaining 10 case-control studies (Table 2-22).

In a meta-analysis of 5 DDT and 11 DDE data sets from the references in Table 2-22 (excluding Bassig et al. 2020, Klil-Drori et al. 2018a, and Viel et al. 2011), Luo et al. (2016) reported overall adjusted ORs of 1.02 (95% CI 0.81–1.28) for DDT and 1.38 (1.14–1.66) for DDE.

Prostate cancer. Inconsistent evidence is provided by 7 case-control studies examining possible associations between serum or adipose levels of DDT, DDD, or DDE and increased risk for prostate cancer (see Table 2-22). Two studies reported increased risk of prostate cancer, including increased risk associated with plasma DDE in the French West Indies (Emeville et al. 2015) and increased risk associated with serum DDT, DDE, or DDD in Singapore (Pi et al. 2016a). No associations with increased risk of prostate cancer were found in the remaining five studies from the United States (Ritchie et al. 2003; Xu et al. 2010), Japan (Sawada et al. 2010), Canada (Aronson et al. 2010), or Sweden (Hardell et al. 2006a).

Published meta-analyses suggest that evidence is not strong for an association between DDT, DDD, or DDE concentrations in serum or adipose tissue and risk for prostate cancer. In a meta-analysis of six of

these seven studies (Pi et al. 2016a was not included), plus another report (Kumar et al. 2010) from which the meta-analysis authors calculated an ORs of 2.27 (95% CI 1.21–4.27), Lim et al. (2015) reported an overall OR of 1.41 (95% CI 1.12–1.78). In a separate analysis of data from four studies (Aronson et al. 2010; Ritchie et al. 2003; Sawada et al. 2010; Xu et al. 2010), an overall OR of 1.25 (95% CI 0.86–1.84) was reported for a 10 ng/g lipid increase in DDE serum concentration (Lim et al. 2015). Another meta-analysis reported overall ORs of 1.02 (95% CI 0.69–1.35) for DDE based on data from five studies (Aronson et al. 2010; Emeville et al. 2015; Hardell et al. 2006a; Ritchie et al. 2003; Sawada et al. 2010) and 0.81 (95% CI 0.35–1.26) for DDT based on data from Aronson et al. (2010) and Sawada et al. (2010) (Lewis-Mikhael 2015).

Testicular cancer. Inconsistent evidence is provided by five case-control studies examining possible associations between serum or adipose levels of DDT, DDE, or DDE and increased risk for testicular cancer (Table 2-22). One study reported increased risk of testicular germ cell tumors with increasing plasma DDE, but not DDT, levels in men from the U.S. military (McGlynn et al. 2008). Three additional studies did not find associations between serum DDT metrics and risk of testicular cancer in American, Italian, or Norwegian men (Biggs et al. 2008; Giannandrea et al. 2011; Purdue et al. 2009). Hardell et al. (2006b) did not find an association between maternal serum DDE levels and risk of testicular cancer in adult Swedish men.

Liver cancer. Three case-control studies of Chinese populations provide consistent evidence of associations between serum DDT levels and increased risk of liver cancer (McGlynn et al. 2006; Persson et al. 2012; Zhao et al. 2012) (see Table 2-22). However, no associations were observed between serum DDT metrics and liver cancer in cohorts from the United States or Norway (Engel et al. 2019). In a study that examined associations between DDE levels in 1,968 adipose samples and age-adjusted mortality rates between 1974 and 1994, liver cancer mortality rate increased with adipose DDE levels in U.S. white males and females, but not among African Americans (Cocco et al. 2000).

Pancreatic cancer. No evidence was found in two case-control studies for associations between serum DDE levels and risks for pancreatic cancer (Hardell et al. 2007; Hoppin et al. 2000) (see Table 2-22). However, Hardell et al. (2007) noted shorter mean survival time after diagnosis in cases with serum DDE levels above the median, compared with cases with serum levels below the median (208 versus 427 days). In an occupational study, there was increased risk of death due to pancreatic cancer in workers exposed to DDT (and related materials) for at least 10 years prior to death, compared to controls not exposed within 10 years of death (Garabrant et al. 1992). However, Cocco et al. (2000) found no association between

DDE levels in adipose samples collected in 1968 from subjects in 22 U.S. states and mortality rates from pancreatic cancer between 1974 and 1994.

In a study of 97 pancreatic cancer cases with information about K-ras mutation in tumor tissue (75 with K-ras mutation and 22 with normal K-ras), no association was found between DDE serum levels and risk for K-ras-mutated pancreatic cancer versus cases without the K-ras mutation (Gasull et al. 2010).

Endometrial cancer. No associations were observed between serum or adipose tissue DDT metrics and increased risk of endometrial cancer in the United States (Sturgeon et al. 1998) or Sweden (Hardell et al. 2004, also reported in Lindstrom et al. 2004) (see Table 2-22).

Other cancers. Additional case-control studies did not observe associations between serum DDT metrics and risk of bladder cancer in the Spanish Canary Islands (Boada et al. 2016), colorectal cancer in Spain (Howsam et al. 2004), or thyroid cancer or acute myeloid leukemia in Norway (Bassig et al. 2019; Lerro et al. 2018) (see Table 2-22). Additionally, associations were not observed between DDT metrics and adjusted mortality rates for any cancer between 1975 and 1985 in Charleston, South Carolina (Austin et al. 1989) or mortality rates from multiple myeloma between 1974 and 1994 in several U.S. states (Cocco et al. 2000),

Animal Studies. DDT is one of the most widely studied pesticides in laboratory animals, and data are available from many carcinogenicity studies in several species.

Intermediate-duration exposures, in which animals were exposed to DDT in food, caused cancer increases in mice, but not in rats or hamsters. Mice that were observed for 50–105 weeks after cessation of treatment developed liver hepatomas following dietary exposure to 42.8 mg *p,p'*-DDT/kg/day for 15–30 weeks (Tomatis et al. 1974b). DDT did not produce increases in the tumor incidence in rats exposed to 10–20 mg/kg/day in the food for up to 45 weeks (*p,p'*-DDT: Kimbrough et al. 1964; technical DDT: Laug et al. 1950; DDT(NS): Numoto et al. 1985) or in hamsters fed 50 mg *p,p'*-DDT/kg/day for 30 weeks (Tanaka et al. 1987).

Chronic-duration exposure (>1 year) to technical DDT, *p,p'*-DDT, or DDT(NS) caused cancer in multiple strains of mice and in some rat studies, but not in dogs; most studies in nonhuman primates have also shown no clear evidence of cancer.

Chronic-duration exposure to DDT (technical DDT, *p,p'*-DDT, or DDT(NS)) produced predominantly liver tumors in several mouse strains ([C57BL/6 x C3H/Anf]F_1, [C57BL/6 x AKR]F_1, BALB/c, Swiss inbred, and CF1) fed DDT at dietary doses as low as 0.33 mg/kg/day for a minimum of 78 weeks (*p,p'*-DDT: Innes et al. 1969; Thorpe and Walker 1973; Tomatis et al. 1972, 1974a; technical DDT: Kashyap et al. 1977; Turusov et al. 1973; DDT(NS): Terracini et al. 1973). An increased incidence of pulmonary adenomas was observed in strain A mice (a susceptible strain for lung tumors) after chronic gavage administration of doses ≥1.7 mg technical DDT/kg/day (Shabad et al. 1973). Malignant lymphomas and lung and liver tumors were also observed in Swiss inbred mice fed 16.5 mg technical DDT/kg/day in food for 80 weeks (Kashyap et al. 1977). No significant increases in tumor incidence were observed in ICR mice administered 16.5 technical DDT/kg/day for 55 weeks in several generations (Del Pup et al. 1978), consistent with the hypothesis that DDT-induced tumors develop in later stages of life with continued exposure. No significantly increased incidences of any type of tumors were observed in B6C3F1 mice fed up to 30.2 mg technical DDT/kg/day for 78 weeks (NCI 1978).

Several multigeneration studies have been conducted in mice. In these studies, exposure of the F1 and subsequent generations to DDT was initially perinatal (i.e., *in utero* and through lactation) and was followed postweaning by oral exposure to DDT in the diet. In a study by Tarjan and Kemeny (1969), exposure to 0.4 mg *p,p'*-DDT/kg/day resulted in significant increases in leukemia and pulmonary carcinomas in the F2 generation and occurred with increasing frequency with each subsequent generation of mice. Liver tumors (0.3–0.4 mg/kg/day) (Tomatis et al. 1972; Turusov et al. 1973) and pulmonary tumors (1.7 mg/kg/day) (Shabad et al. 1973) in the F1 generation had a shorter latency period than in the parental generation, but the tumor incidence was comparable and did not increase with consecutive generations.

Liver tumors also have been observed in rats chronically exposed to DDT. Rats maintained on diets containing DDT for >2 years or at doses >25 mg technical DDT/kg/day developed liver tumors, primarily in female rats (Cabral et al. 1982b; Fitzhugh and Nelson 1947; Rossi et al. 1977). Increased incidences of liver tumors also occurred in rats at doses of 12 mg technical DDT/kg/day for 2 years (Cabral et al. 1982b) and in F334 rats receiving doses ≥1.7 mg *p,p'*-DDT/kg/day for 2 years (Harada et al. 2003, 2006). In contrast, no evidence of carcinogenicity was seen in Osborne-Mendel rats receiving up to 45 mg technical DDT/kg/day for 78 weeks in the NCI (1978) bioassay.

Long-term exposure failed to induce significant increases in tumors in monkeys at doses of 3.9–20 mg DDT(NS)/kg/day for up to 5 years (Adamson and Sieber 1979, 1983; Durham et al. 1963) or in dogs at

80 mg technical DDT/kg/day for 49 months (Lehman 1965). A study that involved 11 Rhesus and 13 Cynomolgus monkeys administered approximately 6.4–15.5 *p,p'*-DDT/kg/day in the diet for up to 130 months reported that 2 out of 13 Cynomolgus monkeys (15%) developed malignant tumors: one hepatocellular carcinoma and one adenocarcinoma of the prostate (Takayama et al. 1999). No neoplasms were found in a group of nine Cynomolgus and eight Rhesus untreated control monkeys.

Evidence of carcinogenicity of DDT in hamsters is equivocal. Rossi et al. (1983) reported an increased incidence (14% in controls, 34% in treated hamsters) of adrenal neoplasms in hamsters administered approximately 95 mg technical DDT/kg/day via the diet for 30 months. At lower doses, Cabral et al. (1982a) did not observe a statistically significant increase in adrenal gland tumors; however, the incidence in males was increased compared to controls in animals receiving 71 mg technical DDT/kg/day via the diet for 28 months. Other studies in hamsters did not indicate any carcinogenic effects of DDT; however, early deaths occurred in one study (Agthe et al. 1970) and the duration of exposure was shorter in another (Graillot et al. 1975).

There are several studies of the potential carcinogenicity of DDE and DDD in rats, mice, and hamsters. DDE administered chronically in the diet produced liver tumors in male and female mice at doses of 27–43 mg *p,p'*-DDE/kg/day for 30–78 weeks (NCI 1978; Tomatis et al. 1974a) and in hamsters dosed with approximately 48 mg *p,p'*-DDE/kg/day for 128 weeks (Rossi et al. 1983). DDE did not induce significant increases in tumor incidence in rats at doses ranging from 12 to 42 mg, *p,p'*-DDE/kg/day for 78 weeks (NCI 1978), but doses of approximately 43 mg *p,p'*-DDE/kg/day for 130 weeks significantly increased the incidence of liver tumors in mice (Tomatis et al. 1974a). DDD induced liver tumors and lung adenomas in CF-1 mice at doses of approximately 43 mg *p,p'*-DDD/kg/day (Tomatis et al. 1974a), but it was not tumorigenic in $B6C3F_1$ mice in a 78-week study at doses of approximately 142 mg technical DDD/kg/day (NCI 1978). In rats, the combined incidences of thyroid follicular cell adenoma and follicular cell carcinomas were 1/19, 16/49, and 11/49 in controls, low-dose (116 mg/kg/day), and high-dose (231 mg/kg/day) male rats exposed to technical DDD, respectively (NCI 1978). The difference between the control and low-dose group was significant according to the Fisher Exact test. However, NCI (1978) pointed out that the variation of these tumors in control male rats in the study did not permit a more conclusive interpretation of the lesion.

Dermal exposure (skin painting) of mice to DDT did not result in a significant increase in tumor incidence when applied in a 5% solution in kerosene once weekly for 52 weeks (Bennison and Mostofi

1950) or at 8 mg/kg twice weekly for 80 weeks (Kashyap et al. 1977). No information on dermal exposure of rats or hamsters to DDT or dermal exposure to DDE or DDD was located.

The HHS determined that DDT is "reasonably anticipated to be a human carcinogen", based on sufficient evidence of carcinogenicity in experimental animals (NTP 2016). EPA 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). IARC determined that DDT is "probably carcinogenic to humans", based on limited evidence in humans and sufficient evidence in experimental animals (IARC 2017).

Mechanisms of Carcinogenicity of DDT, DDE, or DDD. Many epidemiological studies have looked for associations between concentrations of DDT, DDE, or DDD in biological fluids and risks for various types of cancer in human populations. Consistent evidence for positive associations has been presented only for liver cancer in humans; consistent evidence for positive associations is not currently available for any other type of cancer. In animals, fairly consistent evidence is also available for increased incidence of liver tumors in rodents exposed chronically to DDT, DDE, or DDD in food. Harada et al. (2016) recently reviewed evidence that DDT and its metabolites may produce liver tumors in rodents via non-genotoxic mechanisms involving mitogenicity in the liver through activation of the *CAR* and induction of eosinophilic foci in liver cells as a result of oxidative DNA damage, in combination with inhibitory effects on GJIC. Evidence presented included concordance between doses producing liver tumors in F344 rats fed *p,p'*-DDT for 2 years and doses producing: (1) early hepatic induction of *CAR*-mediated CYP isozymes (e.g., CYP2B1, CYP3A2); (2) persistently increased hepatic levels of markers of oxidative stress (lipid peroxide and 8-OHdG); (3) transiently enhanced cell proliferation in the liver; and (4) persistently decreased hepatic levels of GJIC protein px32.

2.20 GENOTOXICITY

The genotoxicity of DDT and related compounds has been examined in humans and animals, and in isolated cell systems. Tables 2-23 and 2-24 summarize pertinent results.

Table 2-23. Genotoxicity of DDT, DDE, and DDD *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Epidemiological evidence			
Human (serum; semen)	Chromosomal aberrations (sex-chromosome aneuploidy, total disomy)	+	McAuliffe et al. 2012
Human (serum; semen)	Chromosome aberrations (sperm aneuploidy)	+	Perry et al. 2016
Human (serum; semen)	Chromosomal aberrations (sex ratio changes)	–	Tiido et al. 2005, 2006
Human (serum; semen)	Chromosomal aberrations (sperm chromatin integrity)	–	Rignell-Hydbom et al. 2005b
Human (serum; semen)	Chromosomal aberrations (sperm chromatin integrity)	–	Spanò et al. 2005
Human (serum; semen)	Chromosomal aberrations (sperm chromatin integrity)	(+)	de Jager et al. 2009
Human (lymphocytes)	Chromosome aberrations (sister chromatid exchanges)	+	Nagayama et al. 2003
Human (lymphocytes)	Micronuclei	–	Alvarado-Hernandez et al. 2013
Human (lymphocytes)	Micronuclei	–	Vine et al. 2001
Human (lymphocytes)	DNA damage (comet assay)	–	Alvarado-Hernandez et al. 2013
Human (lymphocytes)	DNA damage (Fpg-modified comet assay)	+	Franken et al. 2017
Human (lymphocytes)	DNA damage (alkaline-modified comet assay)	–	Franken et al. 2017
Human (lymphocytes)	DNA damage (biomarkers in urine, 8-OHdG)	–	Franken et al. 2017
Human (lymphocytes)	DNA damage (comet assay)	+	Jasso-Pineda et al. 2015
Human (lymphocytes)	DNA damage (comet assay)	(+)	Yáñez et al. 2004
Human (lymphocytes)	DNA damage (methylation)	+	Itoh et al. 2014
Human (lymphocytes)	DNA damage (hypomethylation)	(+)	Kim et al. 2010
Human (serum)	DNA damage (methylation)	+	Lind et al. 2018
Human (lymphocytes)	DNA damage (methylation)	(+)	Rusiecki et al. 2008
Human (blood)	DNA damage (methylation)	–	Wu et al. 2020
Human (serum; semen)	DNA damage (sperm DNA methylation)	–	Consales et al. 2016
Human (serum, semen)	DNA damage (comet assay)	–	Hauser et al. 2003
Human (serum, semen)	Sperm DNA fragmentation (TUNEL assay)	–	Stronati et al. 2006
Human (peripheral leukocytes)	DNA damage (telomere length)	–	Guzzardi et al. 2016
Human (peripheral leukocytes)	DNA damage (telomere length)	(+)	Shin et al. 2010
Human (buccal cells)	DNA damage (telomere length)	±	Hou et al. 2013

Table 2-23. Genotoxicity of DDT, DDE, and DDD *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Laboratory animal evidence			
Mouse (spermatocytes)	Chromosomal aberrations	+	Clark 1974
Rat	Chromosomal aberrations	–	Legator et al. 1973
Rabbit (fetus' liver)	Chromosomal aberrations	–	Hart et al. 1972
Mouse (bone marrow)	Chromosomal aberrations	(+)	Larsen and Jalal 1974
Rat (mammary glands)	Chromosomal aberrations	+	Uppala et al. 2005
Rat (mammary glands)	Micronuclei	–	Uppala et al. 2005
Rat (buccal cells)	Micronuclei	+	Canales-Aguirre et al. 2011
Mouse	Dominant lethal	+	Clark 1974
Rat	Dominant lethal	(+)	Palmer et al. 1973
Rat (peripheral blood lymphocytes)	DNA damage	+	Canales-Aguirre et al. 2011
Rat (mammary epithelial cells)	DNA damage	+	Canales-Aguirre et al. 2011
Rat (testicular cells)	DNA damage	+	Marouani et al. 2017
Mouse (inhibition of testicular synthesis)	DNA synthesis	– (DDE)	Seiler 1977
Host-mediated assays			
Serratia marcescens (Mouse hosted-mediated)	Gene mutation	– (DDT, DDE) + (DDD)	Buselmaier et al. 1973
Neurospora crassa	Gene mutation	–	Clark 1974
Invertebrate systems			
Drosophila melanogaster	Dominant lethal	+	Clark 1974

– = negative result; + = positive result; (+) = weakly positive results; ± = equivocal; 8-OHdG = 8-hydroxydeoxyguanosine; DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; DNA = deoxyribonucleic acid

Table 2-24. Genotoxicity of DDT, DDE, and DDD *In Vitro*

		Results		
Species (test system)	Endpoint	With activation	Without activation	Reference
Prokaryotic organisms				
Salmonella typhimurium (TA1535, TA1537, TA98, TA100)	Gene mutation	–	–	McCann et al. 1975
*S. typhimurium (*histidine auxotrophs G46, TA1535, TA1000, C3076, TA1537, D3052, TA1538, TA98*)*	Gene mutation	–	–	Probst et al. 1981

Table 2-24. Genotoxicity of DDT, DDE, and DDD *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Escherichia coli (WP2 and WP2 uvrA$^-$)	Gene mutation	–	–	Probst et al. 1981
E. coli (Pol-A)	Gene mutation	–	–	Fluck et al. 1976
E. coli (Back mutation)	Gene mutation	–	No data	Fahrig 1974
Escherichia marcescens (glucose prototrophy)	Gene mutation	–	No data	Fahrig 1974
Bacillus subtilis (rec-assay)	DNA damage	–	No data	Shirasu et al. 1976
E. coli (col E1 plasmid DNA)	DNA damage	–	No data	Griffin and Hill 1978
E. coli (DNA cell binding assay)	DNA damage	–	No data	Kubinski et al. 1981
Fungal and plant cells				
Neurospora crassa	Recessive lethal	–	No data	Clark 1974
Saccharomyces cerevisiae	Mitotic gene conversion	–	No data	Fahrig 1974
Mammalian cells				
Human (hepatocyte-mediated cell)	Gene mutation	–	–	Tong et al. 1981
Chinese hamster (V79 cells [6-thioguanine resistant mutation])	Gene mutation	–	No data	Tsushimoto et al. 1983
Rat (liver epithelial cell)	Gene mutation	–	No data	Telang et al. 1981
Mouse (L51784 lymphoma cells)	Gene mutation	+	No data	Amacher and Zelljadt 1984
Chinese hamster ovary (CHO) cells	Chromosomal aberrations	+	No data	Amacher and Zelljadt 1984
Chinese hamster V79 cells	Chromosomal aberrations	+ (DDE) – (DDT)	No data No data	Kelly-Garvert and Legator 1973
Chinese hamster (B14F28 cells [chromosomal damage])	Chromosomal aberrations	+	No data	Mahr and Miltenburger 1976
Kangaroo rat (cells)	Chromosomal aberrations	+	No data	Palmer et al. 1972
Cultured human lymphocytes	Micronuclei	No data	+	Ennaceur et al. 2008
Cultured human lymphocytes	Micronuclei	No data	+	Gerić et al. 2012
Cultured human lymphocytes	DNA damage	No data	+	Gerić et al. 2012
Cultured human lymphocytes	DNA damage	No data	+	Yáñez et al. 2004
Rat (hepatocytes-UDS)	DNA damage	–	–	Probst et al. 1981

Table 2-24. Genotoxicity of DDT, DDE, and DDD *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Rat (hepatocytes-UDS)	DNA damage	No data	–	Probst and Hill 1980
Mouse, rat, hamster (hepatocytes-UDS)	DNA damage	No data	–	Maslansky and Williams 1981

+ = positive results; – = negative results; DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; DNA = deoxyribonucleic acid; UDS = unscheduled DNA synthesis

Overview of Genotoxicity Results. For the most part, the evidence for DDT-induced genotoxic effects at the blood levels of DDT (including different isomers and metabolites) currently found in the U.S. population is weak. Genotoxicity has been reported in populations with the highest exposures, usually in foreign countries, and even then, the associations between DDT biomarkers and the outcomes measured have not been strong. Studies in animals *in vivo* have not provided a clear picture, possibly due to differences in the studies' protocols, such as differences in routes of exposure (inhalation, gavage, intraperitoneal injection) or in duration of exposure (single versus repeated doses). Results from *in vitro* studies in mammalian cells were also mixed, whereas *in vitro* studies in prokaryotic organisms were negative for DDT compounds.

Epidemiological Evidence for Effects on Chromosomes and DNA. Studies of humans exposed to DDT have provided information on effects on chromosomes and DNA using a wide variety of tests (Table 2-23). For example, a study by Nagayama et al. (2003) revealed a positive association between the frequency of sister chromatid exchanges (SCEs) in cultured lymphocytes from 10-month-old infants and lactational exposure to DDT (estimated median exposure via maternal milk during the 2nd and 4th months postpartum was 272 mg DDT/kg/day). In another study, an Fpg-modified comet assay in peripheral blood lymphocytes from 606 Belgian adolescents revealed a positive association between increased blood concentrations of DDT (mean in serum was not reported, DDT was detected in only 40% of the blood samples) and DNA damage (Franken et al. 2017). Results from two additional tests, an alkaline-modified comet assay and analysis of 8-OHdG levels in urine (biomarker of DNA damage/repair) produced no associations. In a study of 276 Mexican children living in areas of high risk contamination, high levels of total DDT in blood (1,400–32,000 ng/g lipid) were positively correlated with DNA damage in peripheral lymphocytes (Jasso-Pineda et al. 2015). Yáňez et al. (2004) reported a weak, but statistically significant, correlation between DNA damage in peripheral blood mononuclear cells from 54 healthy women who were residents in malarious communities with previous DDT spraying. Mean serum concentrations of

p,p'-DDT, *p,p'*-DDD, and *p,p'*-DDE were 4.57, 1.15, and 6.21 ng/mL, respectively; the associations remained significant after accounting for confounding factors (smoking habits, nutrition, alcohol consumption). In a study by Alvarado-Hernandez et al. (2013), no significant correlation was found between frequency of micronuclei or DNA damage and plasma levels of *p,p'*-DDT and *p,p'*-DDE in maternal and umbilical cord blood collected from 50 mother-infant pairs (median levels for DDE and DDT in umbilical cord were 192 and 421 ng/g lipid, respectively; median maternal levels of 472 and 204 ng/g lipid, respectively). Similarly, a study of 302 individuals residing near a waste site in North Carolina found that plasma DDE levels (median 2 ng/mL) were not associated with frequency of micronuclei (Vine et al. 2001).

Epidemiological Evidence for Change in Telomere Length. Three studies provide information regarding DDT and telomere length (Table 2-23). The telomere is a region of repetitive nucleotides at the end of linear eukaryotic chromosomes that is essential for maintaining stability and integrity of the genome; it has been shown that loss (shortening) of the telomere can lead to genomic instability. Evaluation of participants in the Agricultural Health Study (AHS) (a prospective cohort study of nearly 90,000 private pesticide applicators [mostly farmers], their spouses, and commercial pesticide applicators in Iowa and North Carolina) showed an association between shortening of relative telomere length (RTL) and lifetime intensity-weighted days of exposure to DDT (as well as other pesticides) in buccal cell DNA from pesticide sprayers. The association, however, was not significant for lifetime days of use of DDT (Hou et al. 2013). No quantitative assessment of exposure was conducted in the AHS. In a cross-sectional study of 84 healthy adult males and females from South Korea, blood levels of *p,p'*-DDE were significantly correlated with a slight increase in telomere length in peripheral blood leukocytes after adjustment for age, sex, BMI, cigarette smoking, and alcohol consumption (Shin et al. 2010). No significant associations were found with *p,p'*-DDD or *p,p'*-DDT. Further analyses categorizing serum *p,p'*-DDE into quintiles showed that telomere length was increased at the lower concentrations of *p,p'*-DDE (<400 ng/g lipid) and decreased at higher concentrations (≥500 ng/g lipid). Shin et al. (2010) had no explanation for the increase in telomere length across low *p,p'*-DDE concentrations, but suggested that *p,p'*-DDE may act as a tumor promoter at low doses. In a study of an elderly population of 1,082 Finish subjects from the Helsinki Birth Cohort Study, there were no significant associations between circulating *p,p'*-DDE (mean concentration of *p,p'*-DDE in serum for all participants was 2.08 ng/mL) and telomere length (Guzzardi et al. 2016).

Epidemiological Evidence for DNA Methylation Effects. Several studies have examined associations between DDT and DNA methylation (Table 2-23). Decreases in global methylation (hypomethylation)

are believed to be a product of chromosomal instability and/or increased mutation events and are associated with an increased risk of cancer. In a cross-sectional study, Itoh et al. (2014) reported significant decreases in mean global methylation levels in leukocyte DNA of 403 Japanese women. Mean blood concentrations of *o,p'*-DDT, *p,p'*-DDT and *p,p'*-DDE were 1.6, 9.9, and 370 ng/g lipid, respectively. Kim et al. (2010) reported weak inverse linear relationships between *p,p'*-DDT and *p,p'*-DDE in serum (medians: 20.2 and 393.0 ng/g lipid, respectively) and global DNA methylation in peripheral blood leukocytes of a population of 86 healthy South Koreans assessed by the *Alu* assay, but not when the LINE-1 (long interspersed nucleotide element) assay was used. No association was found for *p,p'*-DDD in either assay. Inverse linear relationships also were reported between *p,p'*-DDT and *p,p'*-DDE in plasma (means of 44.03 and 1,624.1 ng/g lipid, respectively) and global DNA methylation in peripheral blood leukocytes in a study of 70 Greenlandic Inuit subjects in adjusted models using the *Alu* assay, but not when using the LINE-1 assay (Rusiecki et al. 2008). As in the Kim et al. (2010) study, associations were weak, even though concentrations of *p,p'*-DDT and *p,p'*-DDE were considerably higher. Consales et al. (2016) did not find consistent associations between plasma *p,p'*-DDE and DNA methylation changes in sperm from 607 fertile men from Greenland, Poland, and the Ukraine using four different assays or in separate analyses of the three cohorts (the mean *p,p'*-DDE concentration for the combined cohort was 888.2 ng/g lipid). The most notable finding was an inverse association between *p,p'*-DDE and DNA methylation for the combined cohort in an assay for DNA global methylation, but not in tests that measured methylation at specific repetitive DNA sequences. In a Swedish cohort of 1,000 70-year-old subjects, a positive association between *p,p'*-DDE and calculated "DNA methylation age" (greater than expected degree of regional DNA methylation based on chronological age) was found (Lind et al. 2018). The mean serum *p,p'*-DDE in this group was 308 ng/g lipid.

In a mother-child cohort (n=419), increases in differentially methylated regions in three genes associated with breast cancer (CCDC85A, CYP1A1, and ZFPM2) in middle-aged daughters were associated with increased maternal serum *p,p'*-DDT or *p,p'*-DDE levels (Wu et al. 2020). Due to evidence for no association between breast cancer and DDT exposure from numerous studies and metanalyses, the significance of this finding is unclear. No associations were observed between exposure and differentially methylated regions in genes associated with age at menarche, related to growth and development, or DNA recombination or repair. The mean maternal exposure levels were 12.4 μg/L for *p,p'*-DDT, 47.0 μg/L for *p,p'*-DDE, and 0.51 μg/L for *o,p'*-DDT.

Epidemiological Evidence for Effects on Sperm Genetic Material. Results of studies concerning DDT and alterations in sperm genetic material were mixed (Table 2-23). No associations were found between

p,p'-DDE (geometric mean 254 ng/g lipid) and sperm chromatin integrity of 212 male partners of sub-fertile couples who were previously evaluated for fertility at the Massachusetts General Hospital between January 2000 and April 2002 (Hauser et al. 2003). Similarly, there were no associations between *p,p'*-DDE in serum (mean 233 ng/g lipid) and sperm chromatin integrity in a population of 176 Swedish fishermen with low and high consumption of fatty fish (Rignell-Hydbom et al. 2005a) or in a cross sectional study involving 707 adult males from Greenland, Sweden, Poland, and the Ukraine (serum *p,p'*-DDE means ranged from 340 to 1,300 ng/g lipid) (Spanò et al. 2005). There was a weak association between lipid adjusted *p,p'*-DDT (mean: 109,200 ng/g; median: 83,900 ng/g) and *p,p'*-DDE (mean: 246,200 ng/g; median: 177,800 ng/g) and the incidence of sperm with chromatin defects in a population of 209 men (aged 18–44 years) living in a malaria area in the Limpopo Province, South Africa where DDT is sprayed annually resulting in very high exposure, as evidenced by the measured levels of DDT and DDE in blood (de Jager et al. 2009). A study conducted by Stronati et al. (2006) revealed no correlation between exposure to DDE and sperm DNA fragmentation or apoptotic markers in a group of 652 men (n=200 Inuits from Greenland, 166 from Sweden, 124 from Poland, and 153 from the Ukraine). Similar results were reported when the European populations were taken together and analyzed separately from the Inuit group. McAuliffe et al. (2012) reported associations between serum *p,p'*-DDE and increased rates of XX, XY, and total sex-chromosome disomy, but not YY disomy in sperm nuclei of 192 adult men (aged 20–54 years). Analysis by *p,p'*-DDE quartiles showed that increases in disomy occurred between the 1st and 2nd quartile with no further increases in the 3rd or 4th quartiles. Men were from sub-fertile couples who had previously been evaluated at the Massachusetts General Hospital Fertility Center between January 2000 and May 2003, the geometric mean serum *p,p'*-DDE concentration for the group was 1.11 ng/g serum (McAuliffe et al. 2012). Perry et al. (2016) examined the association between serum *p,p'*-DDE and sperm aneuploidy in a group of 90 adult Faroese men who participated in Faroe Island health studies; cord blood and age-14 serum were also available for a subgroup (n=40). Geometric mean concentrations of *p,p'*-DDE were 280 ng/g lipid, 790 ng/g lipid, and 0.45 ng/mL blood, in adults, adolescents, and cord blood, respectively. Associations were found between *p,p'*-DDE and total disomy in adults and in adolescents, but not for cord blood. Tiido et al. (2006) examined the association between serum *p,p'*-DDE and Y/X chromosome distributions in the same populations studied by Rignell-Hydbom et al. (2005b) and Spanò et al. (2005) (see above). Mean serum concentrations of *p,p'*-DDE ranged from 350 ng/lipid in Swedish fishermen to 1,300 ng/g lipid in men from the Ukraine. Tiido et al. (2006) reported a positive association between Y-chromosome fractions in sperm of Swedish fisherman and *p,p´*-DDE. However, when *p,p'*-DDE was categorized into quintiles, there was no association for the comparison of the highest quintile (>1,500 ng/g lipid) with the lowest (≤250 ng/g lipid). No significant

associations were found between *p,p'*-DDE and Y-chromosome fractions in populations of men from Greenland (n=157), Poland (n=121), or the Ukraine (n=120).

Evidence for Dominant Lethal Mutations in Laboratory Animals. Consistent evidence for dominant lethal mutations comes from studies in rats, mice, and *Drosophila melanogaster* (Table 2-23). In a dominant lethal assay study, treatment of male rats with a single dose of 100 mg *p,p'*-DDT/kg resulted in a statistically significant increase in the proportion of females with one or more dead implantations only in animals mated during the postmeiotic stage of spermatogenesis (Palmer et al. 1973). No such effect was observed in animals given intraperitoneal doses of ≤80 mg/kg for 5 consecutive days. In another dominant lethal assay, DDT was administered orally to male mice at 150 mg/kg/day for 2 days (acute) or 100 mg DDT/kg twice weekly for 10 weeks (intermediate); the final dose was given 24 hours before sequential mating began (Clark 1974). Significant increases occurred in the number of dead implants per female. Acute doses resulted in maximum sensitivity in the induction of dominant lethal effects in week 5 and chronic doses in week 2, with continued increases above control through week 6. Repeated dosing caused significant reductions in testes weight, sperm viability, and a reduction of cell numbers in all stages of spermatogenesis. With acute treatment, the meiotic stage of spermatogenesis appeared to be the most sensitive. Acute treatment produced a significantly increased frequency of chromosome aberrations (breakage, univalents, and stickiness) in spermatocytes. Clark (1974) also investigated dominant lethal effects in *D. melanogaster*. Male Canton-S *D. melanogaster* were treated with a drop containing 1 µg DDT to the surface of a treacle-meal-agar medium and were then mated sequentially with a brood interval of 3 days. There was a significant increase in the proportion of unhatched eggs in broods 3 and 4, which was attributed to dominant lethal mutations. When DDE was administered in a single oral dose to male mice at the rate of 50 mg/kg, it did not inhibit testicular DNA synthesis (Seiler 1977).

Evidence for Effects on Chromosomes and Micronuclei Induction in Laboratory Animals. Studies evaluating chromosomal effects *in vivo* were mixed (Table 2-23). In a study by Uppala et al. (2005), juvenile rats were exposed to *o,p'*-DDT via subcutaneous injection (50 mg/kg) on days 21, 23, 25, 27, 29, 31, 32, and 34 postpartum; selected rats were also gavaged with 40 mg/kg 7,12-dimethylbenz-[a]anthracene (DMBA, a prototype chemical carcinogen) on day 28. Exposure with or without DMBA resulted in significant increases in the frequency of chromosomal aberrations in mammary cells ($p \leq 0.01$), but did not induce significant increases in micronuclei. Cell proliferation (as measured by BrdU) in mammary cells was also significantly increased in rats treated with DDT and DMBA ($p=0.0005$); however, there was no significance with DDT alone. Legator et al. (1973) reported that rats treated orally (by gavage) with *p,p'*-DDT in single doses of 50–100 mg/kg or daily doses of 20–80 mg/kg/day for

5 days did not show a dose-related increase in the percent of chromosomal aberrations over the solvent control. BALB/C mice injected intraperitoneally with 25–250 mg/kg DDT in peanut oil exhibited a significantly higher proportion of deletions in bone marrow cells than controls, but gaps, stickiness, and the mitotic index were not significantly affected (Larsen and Jalal 1974). Administration of up to 50 mg *p,p'*-DDT/kg by gavage to rabbits on GDs 7–9 did not affect chromosomal number distribution or the percentage of aberrations compared with controls (Hart et al. 1972). In addition, the distribution of chromosomes in liver samples from fetuses of DDT-treated rabbits and the percentage of chromosomal aberrations in these fetuses did not differ from controls. In a repeated inhalation exposure study, female rats were exposed to approximately 7 mg/m^3 DDT for 8 hours/day, 6 days/week for 5 months (Canales-Aguirre et al. 2011). Repeated exposure caused statistically significant increases in micronuclei of buccal cells, DNA damage in peripheral lymphocytes and mammary epithelial cells (measured by comet tail length and tail moment), and an increase in lipid peroxidation in mammary tissue (measured by free radical production in tissue). DNA fragmentation was also observed in rat testicular cells following intraperitoneal exposure to DDT for 10 days (Marouani et al. 2017)

Host-mediated Assays. Host-mediated assays have also provided mixed results (Table 2-23). Buselmaier et al. (1973) reported positive results for gene mutation in a mouse host-mediated assay in *Serratia marcescens* following injection of DDD; no mutation was observed after exposures to DDT or DDE (additional details were not provided). Clark (1974) reported negative results in host-mediated assay to detect mutations in *Neurospora crassa*. Mice received an initial oral dose of 150 mg/kg DDT in olive oil 3 hours before injection with conidia of *N. crassa*; a second dose of 150 mg/kg was administered 10 hours after injection of conidia. Results indicated that the host did not potentiate mutagenicity in this assay.

Assays with Prokaryotic Cells. As shown in Table 2-24, DDT and related compounds were non-mutagenic and did not induce DNA damage in prokaryotic organisms under the conditions tested. No evidence of gene mutation was found in *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, G46, C3076, or D3052 or *E. coli* strains *Pol-A, WP2 and WP2 uvrA*$^-$ with or without metabolic activation (Fahrig 1974; Fluck et al. 1976; McCann et al. 1975; Probst et al. 1981). Results were negative in a recessive lethal test in *Neurospora crassa* (Clark 1974) and in a mitotic gene conversion test in *Saccharomyces cerevisiae* (Fahrig 1974) in the absence of metabolic activation. In addition, tests assessing DNA damage in *Bacillus subtilis* (rec assay) and *E. coli* (col E1 plasmid DNA and DNA cell binding) in the absence of metabolic activation yielded negative results (Griffin and Hill 1978; Kubinski et al. 1981; Shirasu et al. 1976).

Mutation Assays in Mammalian Cells. The majority of *in vitro* gene mutation studies with mammalian cells were negative (Table 2-24). DDT did not induce gene mutations in human hepatocyte-mediated cells in the presence or absence of metabolic activation (Tong et al. 1981), in Chinese hamster V79 cells (Tsushimoto et al. 1983), or in rat liver epithelial cells in the absence of activation (Telang et al. 1981). Conversely, a study by Amacher and Zelljadt (1984) reported positive results for gene mutations in mouse L51784 lymphoma cells exposed to *p,p'*-DDE at concentrations between 25 and 35 µg/mL in the absence of metabolic activation. Exposure to 16–24 µg/mL was sufficient to produce a dose-related increase in 6TG-resistant colonies.

Chromosomal Effects in Mammalian Cells. Studies assessing chromosomal aberrations in mammalian cells yielded positive results (Table 2-24). Amacher and Zelljadt (1984) reported a significant increase in chromosome aberrations in Chinese hamster ovary cells exposed to 35–40 µg/mL *p,p'*-DDE for 24 hours. Mahr and Miltenburger (1976) reported chromosomal damage in the B14F28 Chinese hamster cell line after exposure to 44–88 ppm *p,p'*-DDT, DDE, or DDD; no effects were observed for DDA. Palmer et al. (1972) also observed similar results in kangaroo rat cells (*Potorus tridactylis*) after exposure to 20–50 µg/mL *p,p'*- and *o,p'*-DDT, DDE, or DDD; *p,p'*-DDA was toxic at 200 µg/mL. Kelly-Garvert and Legator (1973) reported a significant increase in chromosomal aberrations in Chinese hamster V79 cells after exposure to 33–40 µg/mL DDE; no significant increases in aberrations were observed following exposure to similar concentrations of DDT. Ennaceaur et al. (2008) reported a reduction in cell proliferation and an increase in the frequency of micronuclei in cultured human peripheral blood lymphocytes following exposure to 10–80 mM *p,p'*-DDE; however, effects were only significant at the highest tested concentration (80 mM).

DNA Damage Assays in Mammalian Cells. Results were mixed for DNA damage in mammalian cells (Table 2-24). Gerić et al. (2012) observed significant increases in the number of micronucleated cells and in the frequency of DNA damage (measured in a comet assay) in cultured human peripheral blood lymphocytes following exposure to *p,p'*-DDT (0.1 µg/mL), *p,p'*-DDE (4.1 µg/mL), and *p,p'*-DDD (3.9 µg/mL). Yáñez et al. (2004) also reported significant DNA damage in peripheral blood mononuclear cells (measured in a DNA content assay and a comet assay) from healthy human donors following exposure (24–72 hours) to 40, 80, or 100 µg/mL *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD. Conversely, negative results were obtained in three studies evaluating unscheduled DNA synthesis (UDS) in rodents (Maslansky and Williams 1981; Probst and Hill 1980; Probst et al. 1981). Probst et al. (1981) and Probst and Hill (1980) reported negative results for UDS in rat hepatocytes exposed to DDT at concentrations up to 1,000 nmoles/mL. Similarly, Maslansky and Williams (1984) reported negative results for UDS in

primary cultures of mouse, rat, and hamster hepatocytes exposed to DDT, DDD, and DDE (tested up to 10^{-4} M) for 18 hours.

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

3.1 TOXICOKINETICS

Toxicokinetic data for DDT, DDE, and DDD are summarized below.

- DDT, DDD, and DDE are absorbed following inhalation, oral, or dermal exposure, but humans are predominately exposed via the oral route.
- DDT, DDE, and DDD are readily distributed in the lymph and blood to all body tissues and ultimately stored in proportion to the lipid content of the tissue, regardless of the route of exposure.
- Metabolism of DDT is similar in humans, rats, mice, and hamsters. The stable metabolite, *p,p'*-DDE, is found at higher tissue concentrations than DDT and DDD isomers, and DDA [2,2-bis(4-chlorophenyl)acetic acid] is the major urinary metabolite.
- Excretion of DDT in the form of its metabolites is largely via the urine, but DDT excretion also may occur via feces and breast milk. The excretion of DDT is slow, and DDT and DDE may persist in the human body for decades after exposure.

3.1.1 Absorption

Absorption of DDT by the lung is considered to be a minor route of entry, although evidence of DDT absorption after inhalation exposure was indicated by the appearance of DDA (a DDT metabolite) in the urine (Laws et al. 1967; Ortelee 1958), the presence of DDT in adipose tissue (Laws et al. 1967) and the presence of DDT and/or DDE in plasma or serum (Morgan and Lin 1978; Rabello et al. 1975). However, no studies were located that quantified the rate or extent of absorption of DDT, DDE, or DDD in humans after inhalation exposure. No studies were located regarding the absorption of DDT, DDE, or DDD after inhalation exposure in animals.

Absorption following ingestion of DDT, DDE, or DDD is evident in humans both from measurements of serum and adipose tissue concentrations of these chemicals and from measurements of DDA in the urine (Hayes et al. 1956, 1971; Morgan and Roan 1971, 1974). In subjects chronically exposed to oral doses of DDT up to 20 mg/day (approximately 0.3 mg/kg/day), DDT appeared in the serum and reached peak serum concentrations 3 hours after ingestion (Morgan and Roan 1971). Serum levels remained elevated, but returned to near pre-dose values 24 hours after each dose.

The presence of urinary metabolites in mice, rats, and hamsters (Fawcett et al. 1987; Gold and Brunk 1982, 1983, 1984), and the presence of DDT and its metabolites in bile collections (Jensen et al. 1957), provide evidence of gastrointestinal absorption. In animals, absorption of orally administered DDT was enhanced when it was dissolved in digestible oils (Keller and Yeary 1980). Approximately 70–90% of the administered dose was absorbed by rats after oral exposure to DDT in vegetable oils (Keller and Yeary 1980; Rothe et al. 1957). DDT was absorbed 1.5–10 times more effectively in laboratory animals when given in digestible oils than when dissolved in nonabsorbable solvents (Hayes 1982).

Gastrointestinal absorption by way of the intestinal lymphatic system plays a major role in the uptake of DDT in animals (Jandacek et al. 2009; Noguchi et al. 1985; Palin et al. 1982; Pocock and Vost 1974; Sieber 1976; Turner and Shanks 1980). For example, Sieber (1976) showed that 12–24% of the administered dose was recovered in the 24-hour lymph after intraduodenal administration of ^{14}C-isomers to thoracic duct-cannulated rats, and most of the radioactivity was attributed to parent compounds. Other studies indicate that relatively little DDT is absorbed from the gastrointestinal tract directly into the blood (Jandacek et al. 2009; Palin et al. 1982; Rothe et al. 1957). In studies of rats with cannulated mesenteric lymph ducts and portal veins, radioactivity collected in 4 hours from lymph ducts and portal veins accounted for 29.4 and 4.6%, respectively, of administered radioactivity delivered intraduodenally as ^{14}C-*p,p'*-DDT in olive oil (Jandacek et al. 2009). Similar results were reported after administration of ^{14}C-*p,p'*-DDE (Jandacek et al. 2009).

Dermal absorption of DDT in humans and animals is limited, but can be inferred by observation of toxicity after dermal application of DDT. Acute toxicity studies in several species demonstrate that toxicity, expressed as an LD_{50}, is less when DDT is applied dermally than when given by gavage or by injection, which reflects the difference in the amount of DDT absorbed by the dermal route. The data indicate that DDT is 4 times more toxic when given by intraperitoneal injection than when administered orally and 40 times more potent when given by intraperitoneal injection than when administered by the dermal route (Hayes 1982). Absorption of DDT from soil applied to the abdomen of monkeys, as extrapolated from urinary excretion data, was 3.3% of the applied dose in 24 hours (Wester et al. 1990).

3.1.2 Distribution

The distribution and storage of DDT in humans and animals has been extensively studied. DDT and its metabolites, DDE and DDD, are lipid-soluble compounds. Once absorbed, they are readily distributed

via the lymph and blood to all body tissues and are stored in these tissues generally in proportion to organ tissue lipid content (Morgan and Roan 1971).

Hayes et al. (1971) and Morgan and Roan (1971, 1974) evaluated the distribution of orally administered DDT, DDE, or DDD in volunteers. Morgan and Roan (1971, 1974) and Roan et al. (1971) measured the concentration of DDT, DDE, DDD, and DDA in blood, fat, and urine after oral dosing. The administered doses ranged from 5 to 20 mg DDT/kg/day for up to 6 months; the ratio of concentration of DDT stored in adipose tissue to that present in blood was estimated to be 280:1. DDT uptake into tissues is a function of the blood flow, the lipid content of that tissue, and the partition coefficient for DDT between the blood and lipids in specific organs. The ratio of DDT concentrations in adipose tissue to blood may remain relatively constant; however, the amount of DDT from past exposure cannot be determined from present blood levels only. DDT, DDE, and DDD have been reported to be distributed to, and retained in, the adipose tissue of humans (Morgan and Roan 1971). The affinity for storage in adipose tissue is related to each chemical's lipophilicity and increases in the order *p,p'*-DDD ≤ *o,p,'*-DDT < *p,p'*-DDT < *p,p'*-DDE (Morgan and Roan 1971).

DDT and DDE selectively partition into fatty tissue and into human breast milk, which has a higher fat content than cow's milk. In a 1969–1970 U.S. national human milk study, the *p,p'*- isomers of DDT and DDE were found in 100% of the samples tested, with mean concentrations of 0.19 and 1.9 ppm (lipid-basis), respectively (Takei et al. 1983). Variance in levels of DDT and its metabolites in breast milk may be influenced by such factors as number of parity, children nursed, diet, and cigarette smoking (Bouwman et al. 1990; Bradt and Herrenkohl 1976; Rogan et al. 1986). A steady decrease in the levels of DDT and its metabolites in human milk has been reported as a result of decreased intake of DDT in many regions throughout the world (Needham et al. 2011; Smith 1999; Wickstrom et al. 1983). In recent global surveys of human breast milk samples between 2000 and 2010, ΣDDT concentrations ranged from <100 ng/g lipid in several northern European nations, 100–1,000 ng/g lipid in the United States, Brazil, Chile, Australia, Russia, Spain, and other countries, to >1,000 ng/g lipid in India, Haiti, Mauritius, Mali, the Philippines, Hong Kong, and other countries (van den Berg et al. 2017). A 2012 survey in Northern Tanzania report median ΣDDT breast milk concentrations of 1,350 ng/g lipid (Muller et al. 2019). Consistent with U.S. samples, *p,p'*-DDE was detected in 100% of samples.

DDT and metabolites are known to cross the placenta from their detection in samples of maternal blood levels, umbilical cord blood, placenta, and newborn blood from numerous studies of mother/infant pairs. For example, a study of 90 mother/infant pairs from Mexico found that: (1) all 90 cord blood samples had

detectable levels of *p,p'*-DDE, 9 had detectable levels of *o,p'*-DDT, and 44 had measurable levels of *p,p'*-DDT; (2) concentrations in maternal blood were similar to those in cord blood; and (3) concentrations showed the following order: *p,p'*-DDE > *p,p'*-DDT > *o,p'*-DDT (Waliszewki et al. 2000). In a 2000–2002 study of placentas from 150 mother-infant pairs in Spain, median concentrations in placentas were 2.37 ng/g placenta for *p,p'*-DDE, 1.42 ng/g for *o,p'*-DDD, 1.02 ng/g for *p,p'*-DDT, and 0.60 ng/g for *o,p'*-DDT (Lopez-Espinosa et al. 2007). In a 2014 report on 42 placental specimens collected in three regions of the United States, DDE concentrations ranged from 10 to 1,968 ng/g tissue, with a median of 74 ng/g (Nanes et al. 2014). In 102 Chinese mothers, median ΣDDT levels from 2013 to 2014 were 408, 45, and 260 ng/kg lipid in maternal serum, placental tissue, and cord blood, respectively (Zhang et al. 2018). A 2019 report from Northern Tanzania on 45–47 samples reported median ΣDDT concentrations of 117, 58.7, and 181 ng/g lipid in maternal blood, placenta, and cord blood, respectively (Muller et al. 2019). A recent review of global monitoring studies of DDE placental concentrations indicated a wide range from 58 pg/g lipid to $5x10^6$ pg/g lipid, with a declining trend over time and high variability in recent years (Nanes et al. 2014).

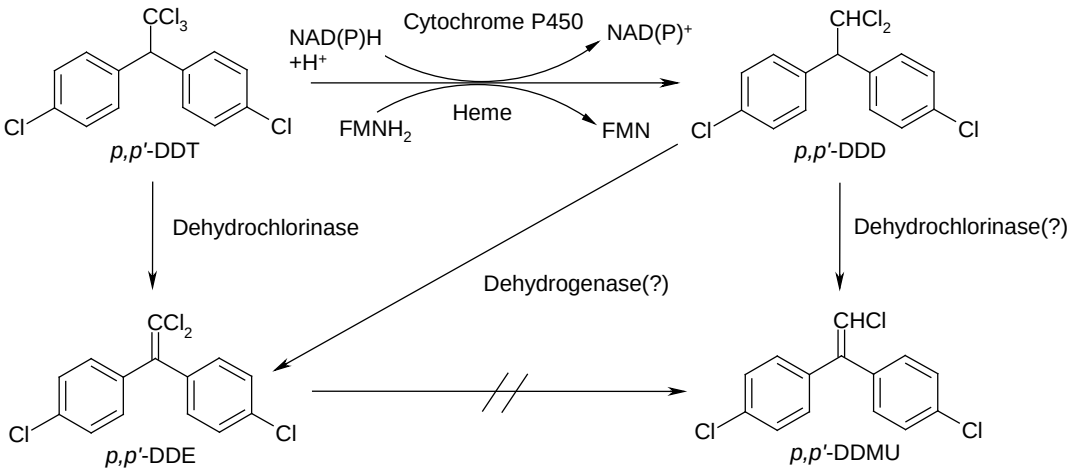
Results from studies of laboratory animals have demonstrated the preferential distribution of DDT and metabolites to fatty tissue, as well as transplacental and lactational transfer. For example, in rats after a single intravenous dose of radiolabeled 5 mg *p,p'*-DDE/kg, peak concentrations of DDE were observed before 1 hour in the liver and muscle, at 3 hours in the skin, and between 1 and 4 days in adipose tissue (Mühlebach et al. 1991). Between 4 and 14 days after exposure, the tissue/blood concentration ratio was about 6 for liver and muscle, 35 for skin, and 400 for adipose tissue (Mühlebach et al. 1991). Similar results were found in a study designed to induce diabetes in high saturated fat-fed mice, administered DDE for 5 days followed by weekly gavage doses of DDE for 13 weeks; the adipose/serum and liver/serum concentration ratios were approximately 950 and 70, respectively (Howell et al. 2015). Another study of rats administered DDE for 5 days showed that serum and liver DDE levels significantly decreased between 7 and 21 days post-exposure; in contrast, adipose levels increased (although the change between days 7 and 21 was not statistically significant) (Howell et al. 2014). Evidence for transplacental and lactational transfer include observations that newborn rats of dams given *p,p'*-DDT in the diet before mating and throughout gestation had detectable levels of *p,p'*-DDT in the brain, liver, kidneys, and stomach, which were lower than levels in offspring sacrificed after suckling (Woolley and Talens 1971). In rats dams given gavage doses of *p,p'*-DDE before mating and during gestation, tissue concentrations in dams after suckling were only about 1/3 of values immediately after exposure, indicating substantial transfer of stored *p,p'*-DDE in rat dam tissue to the milk (You et al. 1999b). Other observation indicate that tissue burdens of rat offspring are influenced more by lactational exposure than

gestational exposure. Rat offspring of dams given gavage doses of *p,p'*-DDE only before mating and during gestation had lower tissue concentrations than tissue concentrations in offspring of dams exposed only during lactation (You et al. 1999b).

3.1.3 Metabolism

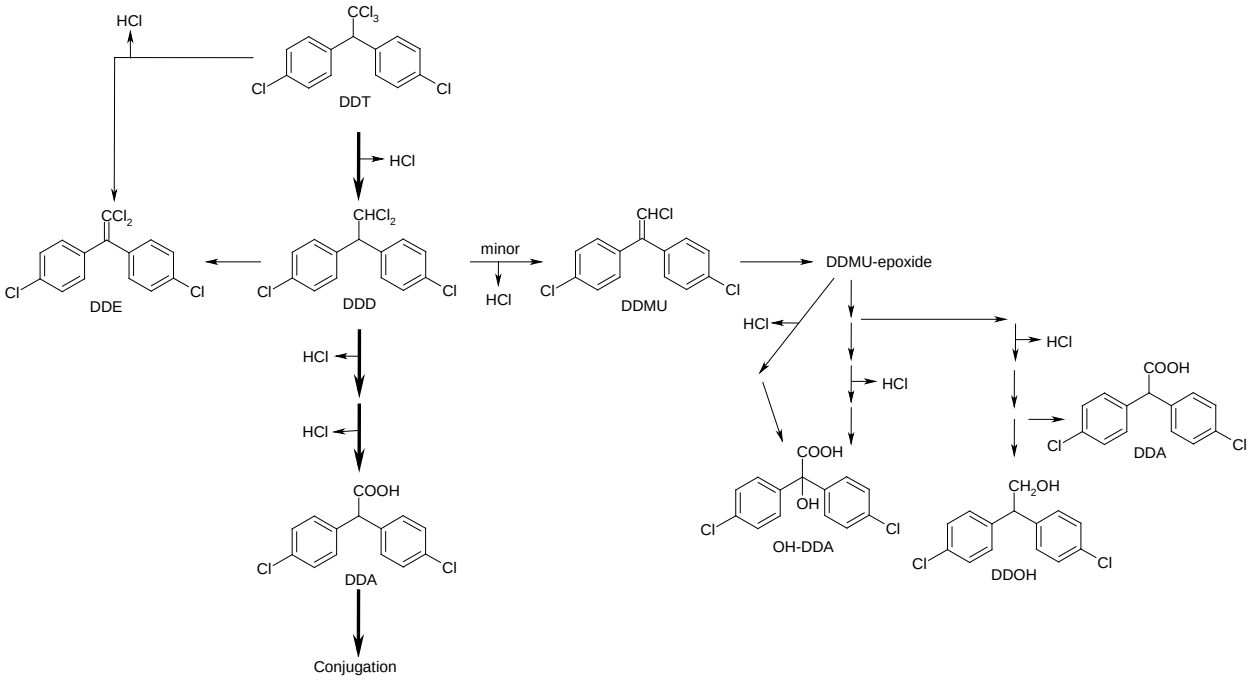
The metabolism of DDT, DDE, and DDD has been studied in humans and a variety of other mammalian species. Observations of higher levels of *p,p'*-DDE in human and animal tissues than levels of *p,p'*-DDT have identified *p,p'*-DDE as a principal stable metabolite (Morgan and Roan 1971; You et al. 1999c). Other studies with liver tissue from laboratory animals established that *p,p'*-DDD is a principal intermediate in the pathway to *p,p'*-DDE involving reductive dechlorination of *p,p'*-DDT to *p,p'*-DDD and a dehydrogenase conversion of *p,p'*-DDD to *p,p'*-DDE (Kitamura et al. 2002). Figure 3-1 describes an initial metabolic pathway that proposes the formation of *p,p'*-DDE directly from *p,p'*-DDT and through *p,p'*-DDD, as well as a dehydrochlorinase step converting *p,p'*-DDD to *p,p'*-DDMU [1-chloro-2,2-bis(4-chlorophenyl)ethylene], another principal metabolite identified in studies with rat liver microsomes (Kitamura et al. 2002). After Phase I metabolism (reactions involving oxidation, reduction, and hydrolysis), many of the DDT metabolites ultimately are excreted in the conjugated form. Conjugates have been reported to include glycine, bile acid conjugates, serine, aspartic acid, and glucuronic acid (Gingell 1975; Pinto et al. 1965; Reif and Sinsheimer 1975). The principal metabolite excreted in urine of animals is *p,p'*-DDA, which has been proposed to be oxidized from *p,p'*-DDT and *p,p'*-DDD in a postulated scheme described in Figure 3-2 (Gold and Brunk 1982).

Figure 3-1. Proposed Metabolic Pathway of *p,p'*-DDT by Rat Liver Microsomes



Source: Kitamura et al. 2002

Figure 3-2. Proposed Metabolic Scheme Converting DDT to DDA, the Principal Metabolite Excreted in Rat Urine



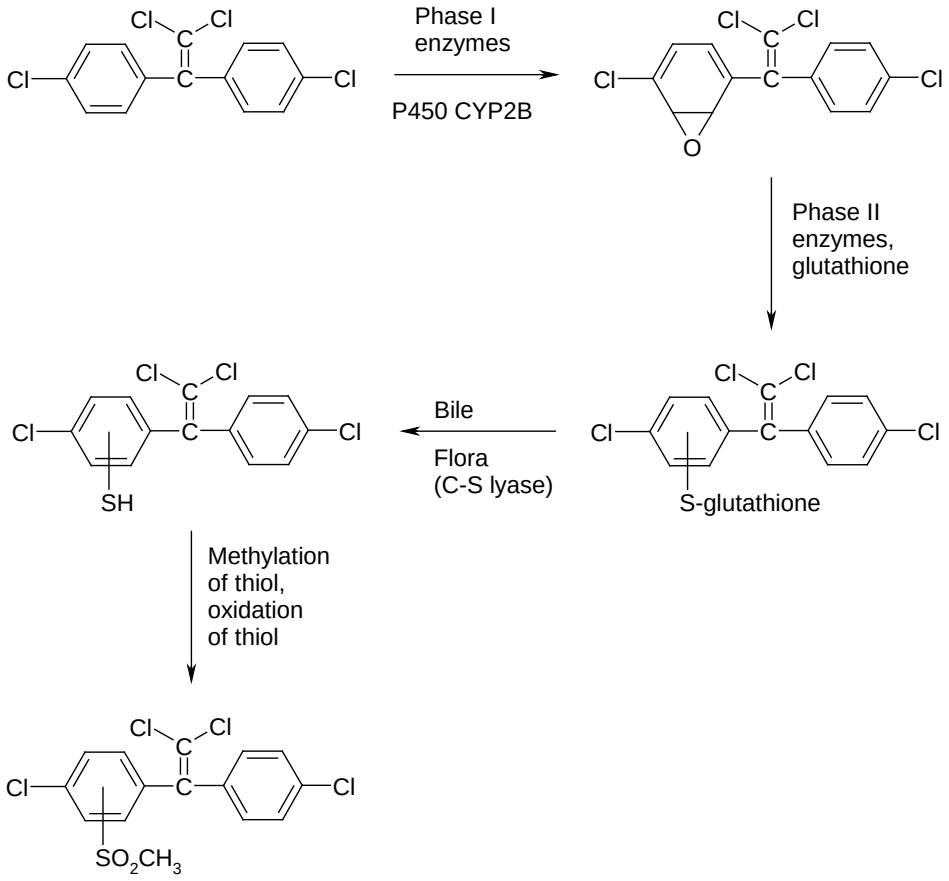
Sources: Gold and Brunk 1982; Kitamura et al. 2002

p,p'-DDT, *p,p'*-DDE, and *p,p'*-DDD are phenobarbital-type cytochrome P-450 (CYP) inducers in rats, causing induction of hepatic CYP2B and CYP3A proteins and CYP1A protein induction to a lesser extent (Nims et al. 1998). Activities for the dechlorinating formation of *p,p'*-DDD from *p,p'*-DDT were much higher with human recombinant CYP3A4 and 2B6 (expressed in human B lymphoblast cells) than with CYP2D6, CYP 2A6, CYP1A1, CYP1A2, and 4A11 (Kitamura et al. 2002). Together, these observations indicate that the metabolic dechlorination of *p,p'*-DDT may be enhanced by previous exposure to DDT and its metabolites (Kitamura et al. 2002; Nims et al. 1998).

The metabolism of DDT can also produce methylsulfonyl metabolites, which are potent toxicants, particularly in the adrenal gland, after metabolic activation. Methylsulfonyl metabolites of DDT (specifically 3- and 2-methylsulfonyl-DDE) were first identified in seal blubber from the Baltic Sea (Jensen and Jansson 1976); they were later found in several species of animals (Bergman et al. 1994) and in humans (Weistrand and Norén 1997). Methylsulfonyl-DDE is formed as follows: products of the reaction between arene oxides, formed in phase I metabolism, and glutathione are degraded and excreted in the bile into the large intestine where they undergo cleavage by a microbial C-S lyase (Bakke et al.

1982; Preston et al. 1984). The thiols formed are methylated and reabsorbed, and the sulfur is further oxidized to the corresponding methylsulfones, which are distributed by the blood (Haraguchi et al. 1989). Figure 3-3 shows a proposed pathway for sulfonyl metabolites.

Figure 3-3. Proposed Metabolic Pathway for the Conversion of *p,p'*-DDE to its Methylsulfone Derivative



Sources: Bergman et al. 1994; Letcher et al. 1998; Weistrand and Norén 1997

3.1.4 Excretion

Excretion of DDT has been studied in humans and a variety of animals. The major route of excretion of absorbed DDT in humans appears to be as DDA conjugates in the urine (Hayes et al. 1956, 1971; Roan et al. 1971), but some excretion also occurs by way of feces (via biliary excretion) (Jensen et al. 1957), sweat (Genuis et al. 2016), and breast milk (Takei et al. 1983). Results of studies with mice, rats, and hamsters indicate that the metabolites of DDT and small amounts of unmetabolized DDT are excreted primarily in the urine and to a lesser degree in feces (Gold and Brunk 1982, 1983, 1984).

The biological half-lives for the elimination of these compounds are ranked as follows: DDE > DDT > DDD. This relationship, and the observation that DDT and DDE can persist for decades in the human body, has been explained to be collectively due to the chemical stability of each compound in the body (i.e., relatively low metabolic efficiencies), the relative efficiencies of excretory mechanisms, and transport in and out of fat depots (Morgan and Roan 1971, 1974). As mentioned in Section 3.1.3, observations of higher levels of *p,p'*-DDE in human and animal tissues than levels of *p,p'*-DDT identify *p,p'*-DDE as a principal stable metabolite (Morgan and Roan 1971; You et al. 1999c).

In volunteers receiving 35 mg DDT/day (approximately 0.5 mg/kg) for up to 18 months, urinary excretion of DDA increased rapidly for the first few days and a steady-state excretion of approximately 13–16% of the daily dose was reached and remained stable for 56 weeks (Hayes et al. 1971). No DDT metabolites were detected in feces. An earlier study by this group (Hayes et al. 1956) reported DDT and DDE levels in the feces of one volunteer receiving approximately 35 mg DDT/day; although DDA was not detected, the investigators did not exclude that it was present in the sample. Another study reported that elevated rates of urinary excretion of DDA occurred within 24 hours of administering single oral doses of DDT (5, 10, or 20 mg), or DDD (5 mg) to volunteers and did not return to pre-exposure rates until >4 months after ingestion (Roan et al. 1971).

Excretion of *p,p'*-DDE via breast milk was monitored during the first 6 months of lactation in 40 healthy Chinese mothers (Song et al. 2018). Zero-order kinetics were observed, with a mean milk levels decreasing from 307.3 to 196 ng/g lipid during the 6-month period. Based on these data, the decline half-time ($t_{dec\ 1/2}$) for *p,p'*-DDE in breast milk is 8 months.

Studies with bile-cannulated laboratory animals have demonstrated that some fecal elimination of DDT metabolites can occur through enterohepatic circulation of conjugated DDA (Gingell 1975; Jensen et al. 1957; Pinto et al. 1965). Other studies with rats given single intravenous doses of radiolabeled DDE indicated a body burden half-life of 120 days with 34 and 1% of the administered dose excreted in feces and urine, respectively, collected for 14 days after dose administration (Mühlebach et al. 1991).

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

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

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

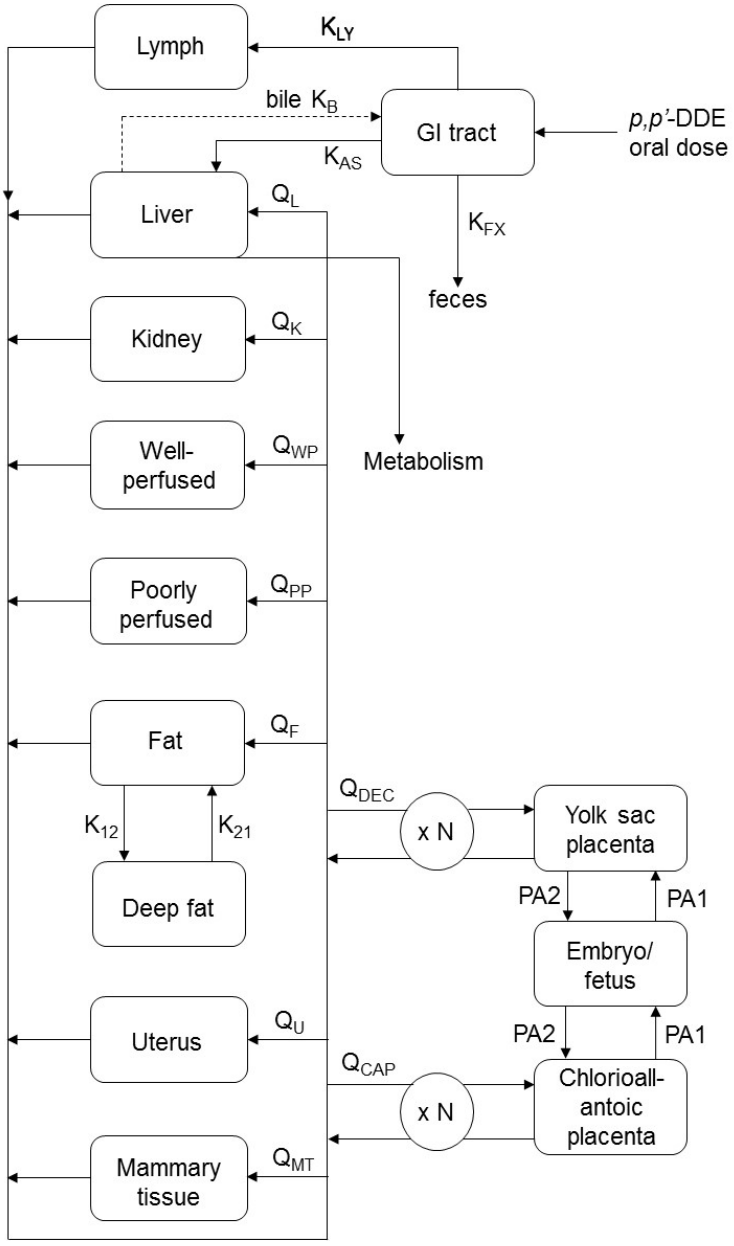
PBPK models of the pharmacokinetics of *p,p'*-DDE, a principal metabolite of DDT, in pregnant and lactating rat dams and nursing pups have been developed by You et al. (1999b). The models were based on experimental studies in which pregnant Sprague-Dawley rats were administered gavage doses of *p,p'*-DDE, and the kinetics of *p,p'*-DDE tissue and blood levels in the dams, fetuses, and pups were measured. The models provide an approach to estimating tissue doses in fetuses and pups associated with maternal oral exposure to *p,p'*-DDE and can be used to explore dose-response relationships for the developmental effects of *p,p'*-DDE in the Sprague-Dawley rat, but are inadequately developed or calibrated to extrapolate to other physiological states, other species (most importantly humans), or other routes of exposure, such as the inhalation or dermal routes.

Figures 3-4 and 3-5 show conceptualized representations of the gestation model and the lactation/nursing models, respectively. Parameters used in the models are shown in Tables 3-1 and 3-2. The gestation model simulates the kinetics of transfer of an oral dose of *p,p'*-DDE from the dam to the developing fetus and the lactation/nursing model simulates the transfer of *p,p'*-DDE from the dam to the nursing pup via mammary milk, followed by exchanges with pup fat, kidney, and other richly- and poorly-perfused tissues.

All exchanges with blood plasma, in both models, were simulated as flow-limited processes, with the exception of the following. Exchanges between maternal fat and a *deep fat* compartment were assumed to be diffusion-limited and were represented with first-order rate constants. Exchanges between the embryo/fetus and placenta were modeled as diffusion-limited processes and were represented with diffusion coefficients (L/day). Parameters used in the model were either taken from the literature, estimated by using the SIMUSOLV simulation program, or optimized by visually inspecting the fit of the collected pharmacokinetic data. Elimination pathways in the maternal model included transfer from mammary tissue to maternal milk (in the lactation model), and fecal excretion, including transfer from the liver via bile to the gastrointestinal tract. A fecal pathway from liver (through bile to the gastrointestinal

tract) was included in the pup model. In models for dams and pups, slow metabolism of *p,p'*-DDE in the liver was assumed to be accounted for by the rate constant for biliary excretion.

Figure 3-4. Diagrammatic Representation of the Physiologically Based Pharmacokinetic Model for Gestation

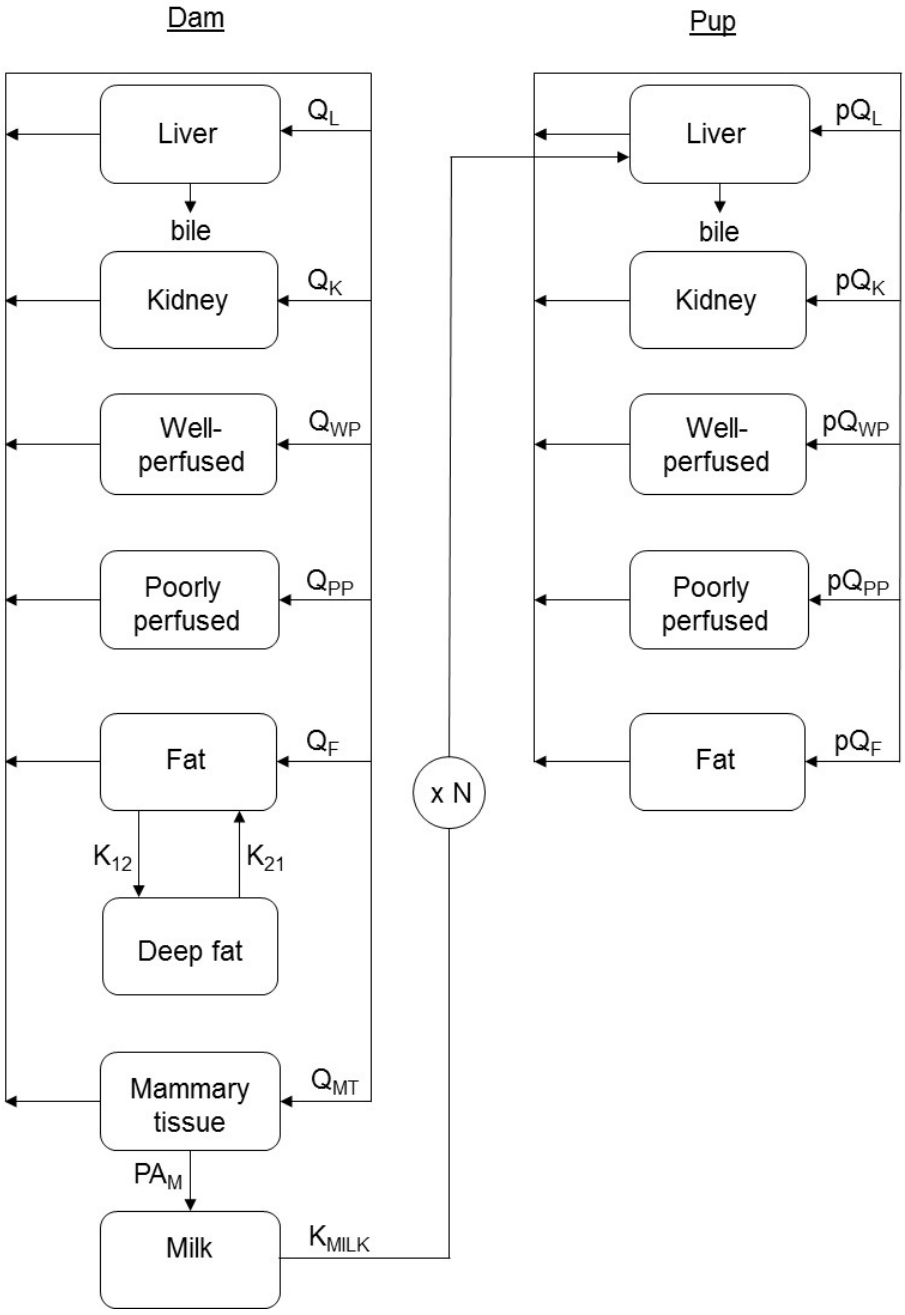


GI = gastrointestinal; N = number of concepti; PBPK = physiologically based pharmacokinetic

Terms are defined in Tables 3-1 and 3-2.

Source: You et al. 1999b

Figure 3-5. Diagrammatic Representation of the Physiologically Based Pharmacokinetic Model for the Lactating Dam and Nursing Pup



N = number of pups; PBPK = physiologically based pharmacokinetic

Portal and lymphatic absorption routes for dams are not shown (see Figure 3-4); terms are defined in Tables 3-1 and 3-2.

Source: You et al. 1999b

Table 3-1. Tissue:Blood Partition Coefficients and Pharmacokinetic Constants for Modeling DDE Disposition in the Pregnant Rat

Tissue:blood partition coefficients	
Liver	7
Fat	450
Poorly-perfused tissues	12
Well-perfused tissues	6
Kidney	6
Uterus	6
Placenta	2
Mammary gland	12
Pharmacokinetic constants	
K_{AS} (L/day) Portal absorption rate constant	24
K_{LY} (L/day) Lymphatic absorption rate constant	74
K_{FX} (L/day) Fecal excretion rate constant	230
K_B (L/day) Biliary excretion rate constant	1.2
PA_F (L/day) Fat diffusion coefficient	5
PA1 (L/day) Placenta-to-embryo/fetus diffusion coefficient	1.6
PA2 (L/day) Embryo/fetus-to-placenta diffusion coefficient	1.9
K_{12}/K_{21} Diffusion to deep fat	1.0/0.1
T_{del} (day) Delay in time	0.1

DDE = dichlorodiphenyldichloroethylene

Source: You et al. 1999b

Table 3-2. Physiological Constants Used in the PBPK Model for the Lactating Dam and the Nursing Pup

	Dam	Pup
Body weight (kg) (BW)	0.290–0.340	0.0061–0.58
Tissue volumes (% of body weight)		
Liver, V_L	4	4
Well-perfused tissues, V_{WP}	8	8
Poorly-perfused tissues, V_{PP}	76-V_{MT}	76
Fat, V_F	7	0.0199*pBW+1.664
Mammary tissue, V_{MT}	4.4–9.6	
Milk, V_{milk}	0.002L	

Table 3-2. Physiological Constants Used in the PBPK Model for the Lactating Dam and the Nursing Pup

	Dam	Pup
Cardiac output (L/hour)	$14*pBW^{0.75}$	$18*pBW^{0.74}$
Blood flows (% of cardiac output)		
Liver, Q_L	25	25
Well-perfused tissues, Q_{WP}	41-Q_{MT}	49
Poorly perfused tissues, Q_{PP}	25	25
Fat, Q_F	7	1
Mammary tissue, Q_{MT}	9–15	

DDE = dichlorodiphenyldichloroethylene

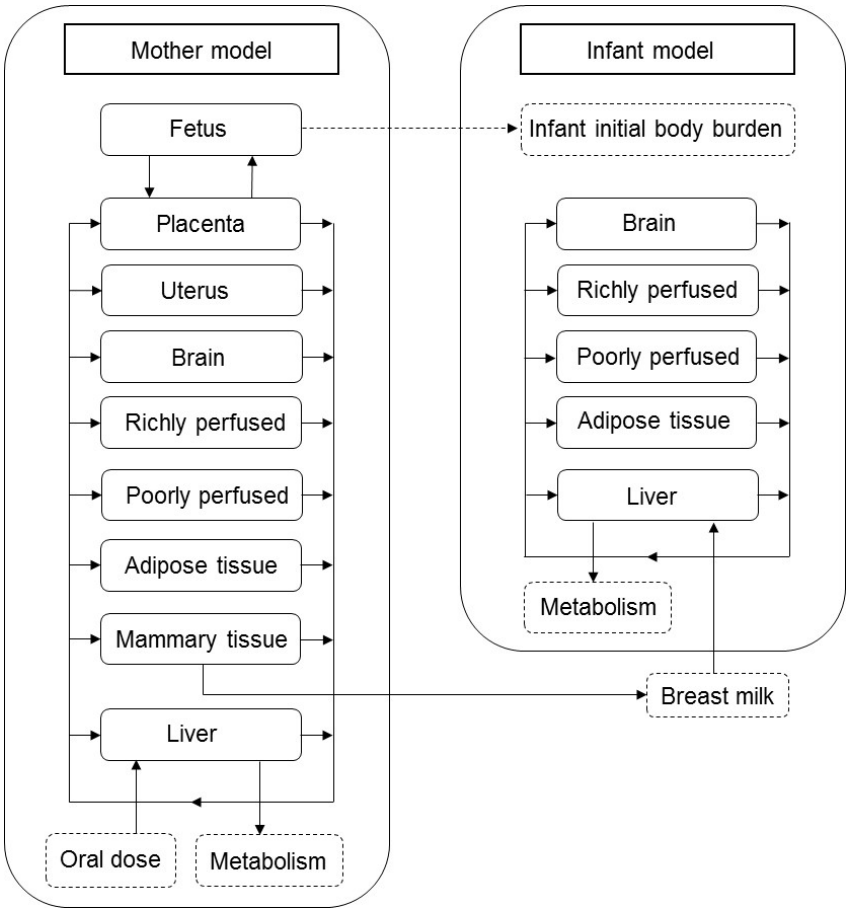
Source: You et al. 1999b

The models were calibrated with data from experimental studies in which pregnant Sprague-Dawley rats were administered gavage doses of 0, 10, or 100 mg *p,p'*-DDE on GDs 14–18 (You et al. 1999b). A subset of the dams was sacrificed 4 hours after each dosing, and tissue levels of *p,p'*-DDE were measured in the dams, placenta, and fetuses. A subset of pups in each dose group was cross-fostered to assess *p,p'*-DDE transfer to tissues from maternal milk. Consistent with the collected data, the models predicted that lactational exposure was more important in determining pup body burden than *in utero* exposure.

Verner et al. (2008, 2009) developed a generic human mother-infant PBPK model to estimate infant exposure to chlorinated persistent organic pollutants (POPs) including *p,p'*-DDT and *p,p'*-DDE via transplacental exposure during gestation and breast milk during 12 months of lactation, based on mothers' exposure during gestation and lactation. Figure 3-6 presents a conceptual representation of the model showing the mother model as a tissue network of nine compartments with ingested POCs assumed to be completely absorbed from contaminated food and directly transferred to the liver. Excretion in milk was modeled as output from the mammary tissue. The infant model consisted of five compartments and was integrated with the mother model via breast milk, which was assumed to be the only source of POC exposure of the infants during the first 12 months of life, and via transplacental transfer from the mother to the developing fetus (see Figure 3-6). The mother and infant models described rates of metabolism in the liver compartment as the product of the hepatic extraction ratio, the liver blood flow and the arterial blood concentration of the pertinent POC; POC-specific hepatic extraction ratios were calculated from hepatic intrinsic clearance values, which were calculated from published half-life values. The POC concentrations in model compartments were modeled with mass balance differential equations that included blood flow, and POC-specific tissue:blood partition coefficients estimated from ratios of lipid

fractions in tissues and blood (Verner et al. 2008, 2009). Predictions from the models for cord blood, breast milk, and infant blood concentrations of *p,p'*-DDE (based on maternal inputs) were significantly correlated (r>0.9) with measured values from a group of Inuit mothers and infants from Northern Quebec, Canada, whereas correlations between predicted and observed values of *p,p'*-DDT concentrations were less strongly correlated (r=0.75–0.78). Verner et al. (2009) proposed that use of the mother-infant model to predict infant exposures from maternal blood levels could reduce sampling efforts in future epidemiological studies of potential effects of POCs on child development (Verner et al. 2009). Verner et al. (2013, 2015) used a similar generic POC human mother-infant PBPK model to predict prenatal exposure to *p,p'*-DDE or *p,p'*-DDT from maternal or children's blood levels collected 9 years after delivery, noting that predictive tools that could back-extrapolate prenatal levels could lead to increased sample sizes in epidemiology studies of associations between POCs and child development endpoints.

Figure 3-6. Conceptual Representation of the Mother-Infant Physiologically Based Pharmacokinetic Model



Source: Verner et al. 2009

Lorber and Toms (2017) developed a single-compartment model of absorption and elimination of ingested DDE and applied the model to predicting infant DDE doses and serum concentrations resulting from breastfeeding and formula feeding. The absorption and elimination model is as follows (see Table 3-3 for parameter values):

$$C_t = \frac{f \cdot D_t + A_t - A_{t-1} \cdot (1 - e^{-kt})}{V}$$

where C_t is the concentration of DDE in body lipid (ng/g lipid) at time *t* (day), *f* is the gastrointestinal absorption fraction, D_t is the oral dose (ng/day) at time *t*, A_t is the *DDE* body burden (ng) at time *t* (day), A_{t+1} is the *DDE* body burden (ng) at time *t+1* (day), *k* is the elimination rate constant (day^{-1}), and V is the lipid volume (g) of the body. The absorption fraction was assigned a value of 0.9 (Lorber and Philips 2002). The assumption that DDE is uniformly distributed in body lipid results in predicted concentrations per gram of serum lipid that are the same as the concentrations in total body lipid. However, alternative assumptions were also explored in which the lipid fraction in infant serum varied with age (see discussion of simulations below). The elimination half-time for DDE was assumed to be zero at birth and to linearly increase to a half-time of 7 years at age 4 years. These values assumed that the half-time for DDE would be similar to PCB 153, as measurements of DDE half-times in humans were not available (Lorber and Toms 2017). The DDE body burden at birth was assigned a value of 200 ng/g lipid, approximately one-third of the maternal body burden, based on levels measured in breast milk (approximately 600 ng/g lipid) (Lorber and Toms 2017). The body lipid volume was estimated based on a lipid fraction of 0.2 (Lorber and Philips 2002) and body weight (EPA 2011). The dose of DDE from formula feeding was assigned a value of 16 ng/kg/day based on a dietary intake rate of 325 ng/day (Schecter et al. 2010) adjusted for infant body weight (EPA 2011). Dietary doses after the end of breastfeeding and formula feeding were assigned a value of 325 ng/day based on a survey of DDE concentrations in foods (Schecter et al. 2001) combined with estimates of food category ingestion rates (EPA 2011).

Table 3-3. Physiological Parameters Used in the PBPK Model to Predict Infant DDE Doses and Serum Concentrations Resulting from Breastfeeding and Formula Feeding

Parameter	Description	Value	Source
BM	Breast milk DDE concentration (ng/g lipid)	600 at start of breastfeeding with linear decrease to 150 ng/g during first 12 months of breastfeeding	Lorber and Philips 2002

Table 3-3. Physiological Parameters Used in the PBPK Model to Predict Infant DDE Doses and Serum Concentrations Resulting from Breastfeeding and Formula Feeding

Parameter	Description	Value	Source
D diet	DDE dose from diet (ng/kg/day) after cessation of breastfeeding and formula feeding	325 ng/day divided by body weight	EPA 2011; Schecter et al. 2010
D formula	DDE dose from formula (ng/kg/day)	16 based on 325 ng/day and 20 kg body weight	EPA 2011; Schecter et al. 2010
f	Gastrointestinal absorption fraction	0.9	Lorber and Philips 2002
fl	Breast milk lipid fraction	0.0325	EPA 2011; Lorber and Toms 2017
I	Breast milk ingestion rate (kg/day)	0.5 for age 0–1 month 0.7 for ages ≥1 month	EPA 2011; Lorber and Toms 2017
k	Elimination rate constant (day^{-1}); ln(2)/half-time	Half-time is zero at birth with linear increase to 7 years at age 4 years	Lorber and Toms 2017
V	Lipid volume of body (g); lipid fraction × body weight	Lipid fraction is 0.2 (see text for alternative variable fractions)	EPA 2011; Lorber and Philips 2002

DDE = dichlorodiphenyldichloroethylene; PBPK = physiologically based pharmacokinetic

The model for DDE dose from breast milk is as follows (see Table 3-3 for parameter values):

$$\mathrm{DBM_t} = \frac{\mathrm{BM_{t\text{-}1}} + BM_{t-1}}{2} \cdot I_t \cdot fl$$

where *DBM* is the breast milk DDE dose (ng/day), *BM* is the breast milk concentration (ng/g lipid), *I* is the rate in ingestion of breast milk (g/day), and *fl* is the lipid fraction of breast milk. Breast milk DDE concentrations were estimated based on measurements made in samples collected from 10 women (Lorber and Toms 2017). The concentration of DDE in breast milk was assigned a value of 600 ng/g lipid at the start of breastfeeding. Transfer of DDE to the nursing infant was assumed to result in a linear decrease to 150 ng/g during 12 months of breastfeeding. The lipid fraction of breast milk was assigned a value of 0.0325 (Lorber and Toms 2017) (based on EPA 2011). Breast milk ingestion rates were assigned values of 0.5 kg/day at birth to age 1 month and 0.7 kg/day for ages >1 month (EPA 2011; Lorber and Toms 2017).

Lorber and Toms (2017) compared simulated serum lipid DDE concentrations in infants to observations obtained from serum collected as part of routine pathology testing of infants (pooled serum from approximately 30 infants per 6-month age intervals, out to age 4 years). Mean serum DDE concentrations

ranged from 146 ng/g lipid (birth to 0.5 years) to 277 ng/g lipid (2–2.5 years). Information on actual feeding patterns of these infants was not available. In the absence of information on feeding patterns, a series of simulations were run representing a range of plausible durations of breastfeeding followed by formula feeding out to an age of 7 months, and dietary intakes thereafter out to age 4 years. The selected patterns were based on a longitudinal study of infants (AIHW 2009). Average serum DDE concentrations based on these simulations were presented graphically with overlays of observed serum lipid DDE levels. Based on the graphical presentations, the model appeared to predict observed serum DDE concentrations for ages 1–4 years (variance in observations were not reported), the period following breastfeeding and formula feeding; however, the model overpredicted serum concentrations observed during the first age year. A peak in predicted serum concentrations at approximately 6 months was not evident in the observations. Predicted serum concentrations at age 6 months were approximately 3-fold higher than the observed mean concentration. Improved agreement with observations was achieved by adjusting the serum lipid fraction during the first year from 0.01 at birth to 0.2 at age >1 year.

Using a generalized human PBPK model for persistent chlorinated organic chemicals developed by Cahill et al. (2003), Sonne et al. (2014) found that model-predicted blood levels of DDE (and other chemicals studied like hexachlorobenzene) based on estimated intakes from dietary sources were within a 2–3-fold factor of measured blood levels in members of Greenland Inuit communities with a traditional diet high in fish, whale, polar bear, reindeer, and musk oxen.

3.1.6 Animal-to-Human Extrapolations

The metabolism of DDT, DDE, or DDD in animals is similar to that in humans, but observed interspecies metabolic differences suggest that interspecies differences in susceptibility to the neurotoxicity or hepatotoxicity of these chemicals may exist. Comparisons of elimination rates of DDT from fat showed that the process is faster in rats, followed by dogs and monkeys, and is slowest in humans (Morgan and Roan 1974). Rats eliminated DDT 10–100 times faster than humans. Morgan and Roan (1974) suggested that the differences in elimination rates could be due to differences in liver metabolism, gut bacterial metabolism, enterohepatic recirculation, or factors related to the accessibility of plasma-transported pesticide to the excretory cells of the liver.

Development of a human PBPK model similar to the rat dam-infant model developed by You et al. (1999b) may be useful to improve extrapolation from rats to humans in the development of risk assessment values (e.g., MRLs) for DDT, DDE, and DDD. The development of such a model or a model

for nonpregnant humans, however, is limited by the lack of suitable kinetics data for adult humans, human mother-fetuses pairs, or human mother-infant pairs to calibrate the model.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

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

Available epidemiological studies provide some evidence for the potential susceptibility of developing fetuses, infants, or children to toxic actions of DDT, DDE, or DDD, depending on the endpoint. Seven case-control studies provided consistent evidence for associations between very high maternal serum levels of DDT, DDE, or DDD with abortion or preterm births (see Section 2.16), and five case-control studies provided consistent evidence for associations between maternal levels of DDE during pregnancy and prevalence of wheeze in infant or child offspring (see Section 2.14). However, inconsistent evidence has been provided by studies looking for associations between maternal levels of DDT, DDE, or DDD in biological fluids or tissues and other immune conditions in infant or child offspring, such as prevalence of asthma or infections (Section 2.14); adverse early neurodevelopmental effects in offspring (see Section 2.15); and changes in birth weight or early growth patterns in offspring (see Section 2.17). Six case-control studies provided consistent evidence for no significant associations between levels of DDT, DDE, or DDD in maternal fluids or tissues and risk for the male birth defects of cryptorchidism and hypospadias (see Section 2.16).

Other case-control studies suggest that chronic exposure of older adults to DDT, DDE, or DDD may be associated with increased risks for elevated body mass index (BMI) or development of DMT2. Consistent evidence for significant positive associations between serum DDE levels and BMI was found in most studies examining this endpoint in adults ≥50 years of age (see Section 2.3). A clear majority of studies, including several meta-analysis, provided evidence for an association between serum levels of DDT, DDE, or DDD in adults and increased prevalence of DMT2 (see Section 2.18).

Results from a few animal studies suggest that young and older animals exhibit different susceptibility to DDT toxicity, at least regarding neurotoxicity in response to relatively high doses of DDT. For example, the LD_{50} values for DDT in newborn, pre-weanling, weanling, and adult rats were ≥4,000, 438, 355, and 195 mg/kg, respectively (Lu et al. 1965). However, when one-quarter of the daily LD_{50} dose was administered daily for 4 days to pre-weanling and adult rats, both groups had similar 4-day LD_{50} values. Lu et al. (1965) suggested that the elimination mechanisms in the preweaning rats is less developed than in the adult rats, thus making them more susceptible to repeated small doses. In another study, 10-day-old rats were more resistant to the acute lethal toxicity of purified *p,p'*-DDT than 60-day-old rats (Henderson and Woolley 1970). In both groups, respiratory failure was the cause of death; however, the time course of DDT poisoning in the young rats was prolonged considerably as compared to the adults. Furthermore, the immature rats did not exhibit seizures nor the hyperthermia that preceded death in the older animals. The decreased sensitivity of the younger rats was attributed to an incomplete development of the neural pathways involved in seizure activity and in thermoregulation. The relevance of these findings to human health is unknown.

In animals, DDT can cause abnormal development of sex organs, embryotoxicity, and fetotoxicity in the absence of maternal toxicity (Clement and Okey 1974; Fabro et al. 1984; Hart et al. 1971, 1972). Developmental effects, including pre-weanling mortality and premature puberty, have been reported in animals in multigeneration studies (Del Pup et al. 1978; Green 1969; Ottoboni 1969; Ottoboni et al. 1977; Tomatis et al. 1972; Turusov et al. 1973). DDT has shown estrogenic properties in animals administered the pesticide orally or parenterally (Bitman and Cecil 1970; Clement and Okey 1972; Fabro et al. 1984; Gellert et al. 1972, 1974; Singhal et al. 1970). In female neonates injected subcutaneously with *o,p'*-DDT or *o,p'*-DDD, there were significant alterations in the estrous cycle, decreases in ovary weight, and decreases in corpora lutea when the animals were evaluated as adults (Gellert et al. 1972, 1974). In general, the estrogenic potency of DDT is orders of magnitude lower than that of estradiol.

p,p'-DDE, a persistent metabolite of DDT, was an androgen receptor antagonist in male rats exposed *in utero*, and also as juveniles (Gray et al. 1999; Kelce et al. 1995, 1997; Krause et al. 1975; Loeffler and Peterson 1999; You et al. 1998, 1999a). Rat pups from dams exposed during GDs 14–18 to 100 mg *p,p'*-DDE/kg/day and then exposed indirectly to maternally stored *p,p'*-DDE via breast milk had significantly reduced AGD at birth and retained thoracic nipples on PND 13 (Kelce et al. 1995, 1997). Treatment of weanling male rats until day 57 of age with 100 mg *p,p'*-DDE/kg/day resulted in a statistically significant delayed onset of puberty by 5 days (Kelce et al. 1995, 1997). Gray et al. (1999) and You et al. (1998) reported that AGD was not affected in male Sprague-Dawley rats on PND 2 after treating the dams with up to 100 mg *p,p'*-DDE/kg on GDs 14–18, but was significantly reduced in similarly exposed Long-Evans pups. A 10 mg/kg dose to the dams was without effect in the Long-Evans pups. AGD was not affected in female pups from either strain. Treatment of the dams with 10 mg *p,p'*-DDE/kg resulted in retention of thoracic nipples in Sprague-Dawley pups, but only the higher dose (100 mg/kg) had this effect in Long-Evans pups. An additional study from the same group showed that prenatal exposure to *p,p'*-DDE was associated with expression of TRPM-2, an androgen-repressed gene (You et al. 1999a). A similar study in Holtzman rats exposed during GDs 14–18 to doses between 1 and 200 mg *p,p'*-DDE/kg (offspring were exposed to *p,p'*-DDE *in utero* and via breast milk) found reduced AGD in males on PND 1 and reduced relative ventral prostate weight on PND 21 at 50 mg *p,p'*-DDE/kg, but not at 10 mg *p,p'*-DDE/kg (Loeffler and Peterson 1999). Doses up to 100 mg/kg/day to the dams had no effect on onset of puberty, but 200 mg/kg/day did significantly delay puberty in males by <2 days. Androgen receptor staining in the ventral prostate was also reduced on PND 21. Serum levels of testosterone or 3α-diol androgens were not significantly altered at any time. This study also reported that at the 100 mg/kg dose level, cauda epididymal sperm number was reduced by 17% on PND 63 relative to controls.

Alterations in learning processes and in other behavioral patterns have also been described in adult mice exposed to DDT perinatally (Craig and Ogilvie 1974; Palanza et al. 1999; vom Saal et al. 1995) or as neonates (Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996); this endpoint is the basis of an acute-duration oral MRL, which is discussed in detail in Section 1.3 and Appendix A. These studies suggest that exposure of the developing fetus or newborn to DDT during critical stages in nervous system development can cause developmental toxicity manifested later in life. Eriksson et al. (1990a, 1990b) pointed out that the dose levels that caused behavioral alterations in mice are comparable to those levels to which human neonates might be exposed in areas where DDT is still being used. Behavioral neurotoxicity has been described in rats treated with DDT as adults (Sobotka 1971), but only at doses at least 50 times those that produced learning deficits in neonates.

Studies in animals have demonstrated placental transfer of DDT and DDE to fetuses and also to newborns via mother's milk (Fang et al. 1977; Seiler et al. 1994; Woolley and Talens 1971; You et al. 1999b). The results of these studies indicate that the amounts of chemical transferred via mother's milk are much greater than the amounts that reach the fetus through the placenta.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to DDT, DDE, and DDD are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for DDT, DDE, and DDD from this report are discussed in Section 5.6, General Population Exposure.

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

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the

biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Levels of DDT, DDE, or DDD in serum, blood, or breast milk (expressed on a lipid basis, ng/g lipid) are the most widely used biomarkers of exposure in biomonitoring and epidemiological studies (e.g., Axmon and Rignell-Hydbom 2006; Berg et al. 2018; Bonde et al. 2016; Chen et al. 2005; Everett and Matheson 2010; Jaga and Dharmani 2003; Kim et al. 2015a; Parajuli et al. 2018; Patterson et al. 2009; Roberts and Karr 2012; Sexton et al. 2006; Thomas et al. 2017; van den Berg et al. 2017). Hair analysis has also been shown to produce reliable biomarker data for DDT and its metabolites in epidemiology studies (Barmpas et al. 2020). In rats exposed orally to a pesticide mixture for 90 days, concentrations of DDT, DDD, and DDE exhibited similar kinetics in both plasma and hair (Appenzeller et al. 2017). It has been suggested that determination of concentrations of pesticides, including DDT and metabolites, in multiple sources (e.g., blood, hair, placenta) may increase rates of exposure detection, compared with single source determinations (Ostrea et al. 2008).

For biomonitoring of DDT, DDE, and DDD, as well as other persistent halogenated organic chemicals, levels in breast milk are popular biomarkers of exposure, because breast milk is easily obtained through non-invasive techniques, extraction from the medium is not difficult due to the high lipid content, and levels are thought to be reflective of whole body burdens (Song et al. 2018; van den Berg et al. 2017). The excretion kinetics of DDE in breast milk during the first 6 months after birth are described in the Section 3.1.4. Recent global surveys of concentrations of DDT, DDE, and DDD (ΣDDT) in human breast milk samples for numerous countries collected from 2000 to 2010 indicate levels ranging from about 20 ng/g lipid in Finland to about 1,400 ng/g lipid in India, with tropical countries (where DDT is still used for malaria control) representing the majority of the upper half of the distribution of concentrations (van den Berg et al. 2017).

There are no quantitative data available that allow correlation of DDT/DDD/DDE levels in human tissue or fluids and exposure to specific levels of environmental contamination. Studies of pesticide production workers reported that blood levels of these compounds are generally higher in persons exposed in the workplace. Since the biological half-lives for elimination of these compounds are ranked as follows: DDE > DDT > DDD, detection of higher ratios of DDD or DDT to DDE has been proposed to indicate more recent exposure, while lower ratios are believed to correlate with long-term exposure and storage

capacity (Morgan and Roan 1971). There is a direct correlation between DDT and DDE levels in blood and adipose tissue when concentrations are expressed on a lipid basis (Hayes et al. 1971; Morgan and Roan 1971; Mussalo-Rauhamaa 1991). On a wet tissue basis, concentrations of DDT in adipose tissue are approximately 280 times higher than those of blood (Anderson 1985). However, because DDT and DDE are extensively stored in fatty tissue and slowly released from storage sites, there is no correlation between levels in tissues and the time course of exposure in short time spans.

3.3.2 Biomarkers of Effect

The primary target organs for DDT, DDE, and DDD toxicity include the nervous system, the reproductive system, and the liver. No biomarkers of effect specific for DDT, DDE, or DDD exposure alone were identified in the literature. Tremors and convulsions have been observed in both humans and laboratory animals after DDT exposure (Hsieh 1954; Hwang and Van Woert 1978; Matin et al. 1981). Exposure to DDT has been shown to induce hepatic microsomal enzymes in both humans and laboratory animals (Kolmodin et al. 1969; Morgan and Lin 1978; Pasha 1981; Street and Chadwick 1967). However, these biomarkers of effect are not specific for DDT, DDE, or DDD exposure, and not all the body compartments in which these changes occur are accessible for sampling in living humans.

3.4 INTERACTIONS WITH OTHER CHEMICALS

DDT may have broad effects by changing the metabolism of other chemicals, both xenobiotics and endogenous macromolecules. As discussed in Section 3.1.3, *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD are phenobarbital-type cytochrome P-450 (CYP) inducers in rats, causing induction of hepatic CYP2B and CYP3A proteins and CYP1A protein induction to a lesser extent (Nims et al. 1998). For some chemicals, this enhancement of biotransformation produces less toxic metabolites and may inhibit toxic effects, whereas, for other chemicals with toxic metabolites, the metabolic enhancement could lead to enhancement of toxic effects.

One interaction of concern is the enhanced conversion of other chemicals to active, carcinogenic forms mediated by microsomal enzymes induced by DDT. Several investigations indicate that DDT administered to animals along with a known carcinogen may result in either an increase or a decrease in tumor production relative to the carcinogen tested without DDT. A study by Walker et al. (1972) suggested that the liver enlargement was greater and the time to palpability of liver masses was earlier in mice fed dieldrin and DDT than those fed either pesticide separately. A potentiation of carcinogenic activity of dieldrin was suggested but not conclusively shown. It is possible that DDT could also promote

the formation of hepatic tumors initiated by other carcinogens. DDT has been reported to promote the tumorigenic effects of several known carcinogens, such as 3-methyl-(4-dimethylamine)-azobenzene (Kitagawa et al. 1984), 2-acetylaminofluorene (2-AAF) (Peraino et al. 1975), diethyl-nitrosamine (DEN) (Diwan et al. 1994; Nishizumi 1979), and carbon tetrachloride (CCl_4) (Preat et al. 1986) when given after the putative carcinogen. The promoting effect of DDT in rats was reported to act in a dose-dependent fashion, with DDT decreasing the latency period of tumor development and increasing the incidence and yield of hepatic tumors, mainly hepatocellular carcinomas.

Pretreatment of animals with DDT was also reported to decrease the tumorigenic effects of some previously determined carcinogens. For example, pretreatment of rats with DDT significantly lowered the incidence of mammary tumors per rat after treatment with 7,12-dimethylbenz[a]anthracene (DMBA), versus DMBA-treated controls (Silinskas and Okey 1975). The authors suggested that DDT may inhibit DMBA-induced mammary tumors by stimulating hepatic metabolism and accelerating the excretion of DMBA, so that less carcinogen is available to peripheral tissues. Other studies also have reported the DDT induction of hepatic microsomal enzymes, which reduced the carcinogenicity of azo dyes and similar carcinogens (Williams and Weisburger 1991).

Similarly, the hepatocarcinogenicity of aflatoxin B_1 in mice was inhibited by pretreatment with DDT and by co-treatment with DDT when given throughout aflatoxin B_1 dosing (Rojanapo et al. 1988, 1993). However, DDT acted as a hepatocarcinogenic promoter to aflatoxin B_1 initiation when a 14-week DDT administration followed an 8-week aflatoxin B_1 treatment, or when the DDT administration began halfway through aflatoxin B_1 treatment (Rojanapo et al. 1988, 1993). Also, in groups receiving both aflatoxin B_1 and DDT, in any order, absolute and relative liver weights were significantly increased over both the vehicle control and the group receiving just aflatoxin B_1; treatment with aflatoxin B_1 alone increased liver weights, while treatment with DDT alone did not (Rojanapo et al. 1993).

The effects of DDT on the nervous system can be altered when DDT is given in combination with certain neurologically-active pharmacological agents. Some pharmacological agents (hydantoin, phenobarbital), prevent some or all of the neurological effects seen in animals treated with DDT (see Section 2.15), while other agents (trihexyphenidyl, haloperidol, propranolol) enhance DDT-induced neurotoxicity (Herr et al. 1985; Hong et al. 1986; Matin et al. 1981). One of the effects of DDT is to hold sodium channels open, which probably contributes to DDT-induced neurological effects (tremors and hyperexcitability). Studies by Rubin et al. (1993) have shown that DDT analogues and metabolites, as well as several pyrethroids, modify radioligand binding of batrachotoxinin A to sodium channels in mouse brain synaptosomes. DDT

and pyrethroids do not, by themselves, stimulate Na^+ uptake, but they enhance activator-dependent uptake. DDT is more efficacious than the pyrethroids tested. Eriksson et al. (1993) have shown that the pyrethroid bioallethrin and DDT can interact *in vivo* in rats.

In an immature rat uterotrophic assay, mixtures of six synthetic chemicals with demonstrated estrogenic activities (*o,p'*-DDT and five other chemicals) were shown, at low concentrations, to not alter responses induced by a mixture of phytoestrogens and to act in an additive manner when exposed in the absence of external phytoestrogens (Charles et al. 2007).

A series of studies examined the effects of oral exposure to binary mixtures of 1,4-dichlorobenzene and *p,p'*-DDE (Makita 2005, 2008a) or tributyl tin and *p,p'*-DDE (Makita 2008b; Makita et al. 2003b) on reproductive capabilities of immature male and female rats, but the designs of the studies were inadequate to conclude whether or not the components of these mixtures displayed joint actions that were additive, less-than-additive, or greater-than-additive.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

When we refer to DDT, we are generally referring to *p,p'*-DDT, which was produced and used for its insecticidal properties. However, technical-grade DDT, the grade that was generally used as an insecticide, was composed of up to 14 chemical compounds, of which only 65–80% was the active ingredient, *p,p'*-DDT. The other components included 15–21% of the nearly inactive *o,p'*-DDT, up to 4% of *p,p'*-DDD, and up to 1.5% of 1-(*p*-chlorophenyl)-2,2,2-trichloroethanol (Metcalf 1995).

The chemical formulas, structures, and identification numbers for *p,p'*-DDT, *p,p'*-DDE, *p,p'*-DDD, *o,p'*-DDT, *o,p'*-DDE, and *o,p'*-DDD are listed in Table 4-1. The latter five compounds are either impurities or metabolites of technical DDT.

Table 4-1. Chemical Identity of *p,p'*- and *o,p'*-DDT, DDE, and DDD[a]

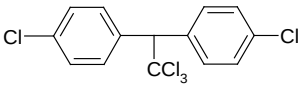
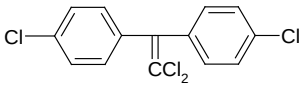
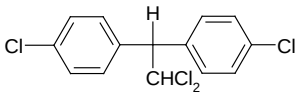
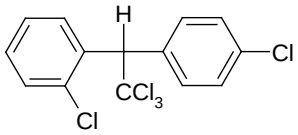
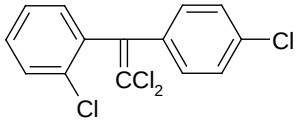
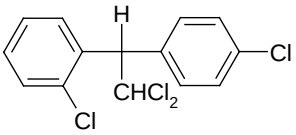
Characteristic	Information		
Chemical name	*p,p'*-DDT	*p,p'*-DDE	*p,p'*-DDD
Synonym(s) and registered trade names	4,4'-DDT; 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl) ethane; dichlorodiphenyl trichloroethane; DDT; 1,1'-(2,2,2-trichloro-ethylidene) bis(4-chloro-benzene); α-α-bis(*p*-chloro-phenyl)-β,β,β-trichloro-ethane; Genitox; Anofex; Detoxan; Neocid; Gesarol; Pentachlorin; Dicophane; Chlorophenothane[b]	4,4'-DDE; dichlorodiphenyl-dichloroethane; 1,1-dichloro-2,2-bis (p-chlorophenyl) ethylene; 1,1'-(2,2-dichloro-ethylidene) bis(4-chloro-benzene); DDE	4,4'-DDD; dichlorodiphenyl-dichloroethane; DDD; 1,1-dichloro-2,2-bis(p-chlorophenyl) ethane; 1,1-bis(4-chloro-phenyl)-2,2-dichloro-ethane; TDE; tetrachloro-diphenylethane; DDD; Rothane; Dilene; TDE
Chemical formula	$C_{14}H_9Cl_5$	$C_{14}H_8Cl_4$	$C_{14}H_{10}Cl_4$
Chemical structure			
CAS Registry Number	50-29-3	72-55-9	72-54-8

Table 4-1. Chemical Identity of *p,p'*- and *o,p'*-DDT, DDE, and DDD[a]

Characteristic	Information		
Chemical name	*o,p'*-DDT	*o,p'*-DDE	*o,p'*-DDD
Synonym(s) and registered trade names	2,4'-DDT; 1,1,1-trichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane; *o,p'*-dichlorodiphenyltrichloroethane	2,4'-DDE; 1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl) ethylene; 1-chloro-2-(2,2-dichloro-1-(4-chlorophenyl)ethenylbenzene	2,4'-DDD; Mitotane; *o,p'*-DDD; 1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane; *o,p'*-TDE; Choditane; 2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl; Lysodren
Chemical formula	$C_{14}H_9Cl_5$	$C_{14}H_8Cl_4$	$C_{14}H_{10}Cl_4$
Chemical structure			
CAS Registry Number	789-02-6	3424-82-6	53-19-0

[a]Howard and Neal (1992) except where noted.
[b]Klassen et al. 1991.

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Technical DDT is a white amorphous powder that melts over the range of 80–94°C (Metcalf 1995). Physical and chemical properties of *p,p'*-DDT, *p,p'*-DDE, *p,p'*-DDD, *o,p'*-DDT, *o,p'*-DDE, and *o,p'*-DDD are listed in Table 4-2.

Table 4-2. Physical and Chemical Properties of *p,p'*- and *o,p'*-DDT, DDE, and DDD[a]

Property	*p,p'*-DDT	*p,p'*-DDE	*p,p'*-DDD
Molecular weight	354.5	318.03[b]	320.05[b]
Color	Colorless crystals	White	Colorless crystals, white powder
Physical state	Solid	Crystalline solid	Solid
Melting point	108.5–109°C	89°C[b]	109–110°C[b]
Boiling point	Decomposes; 185–187 at 0.05 mmHg	336°C[b]	350°C[b]
Density at 20°C	1.56 g/cm^3	No data	1.385 g/cm^3
Odor	Odorless or weak aromatic odor[c]	No data	Odorless
Odor threshold:			
Water	0.35 mg/kg[d]	No data	No data
Air	No data	No data	No data
Solubility:			
Water	0.025 mg/L at 25°C[b]	0.12 mg/L at 25°C[b]	0.05 mg/L at 25°C
Organic solvents	1,000 g/L in cyclohexane and dioxane; 850 g/L in dichloromethane; 770 g/L in benzene; 600 g/L in xylene; 50 g/L in acetone; 470 g/L in carbon tetrachloride; 310 g/L in chloroform; 270 g/L in diethyl ether; 60g/L in ethanol; 40 g/L in methanol	Lipids and most organic solvents	No data
Partition coefficients:			
Log K_{ow}	6.91[b]	6.51[b]	6.02[b]
Log K_{oc}	5.18[e]	4.70[f]	5.18[g]
Vapor pressure at 20°C	1.60x10^{-7}, torr[b]	6.0x10^{-6} at 25°C, torr[b]	1.35x10^{-6} at 25°C, torr[b]
Henry's law constant at 25°C	8.3x10^{-6} atm-m^3/mol[b]	2.1x10^{-5} atm-m^3/mol[b]	4.0x10-6 atm-m^3/mol[b]
Autoignition temperature	No data	No data	No data
Flashpoint	72.2–77.2 °C	No data	No data
Flammability limits	No data	No data	No data
Conversion factors			
Ppm (v/v) to mg/m^3 in air at 20°C	Not applicable[h]	Not applicable[h]	Not applicable[h]
mg/m^3 to ppm (v/v) in air at 20°C	Not applicable	Not applicable	Not applicable
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of *p,p'*- and *o,p'*-DDT, DDE, and DDD[a]

Property	*o,p'*-DDT	*o,p'*-DDE	*o,p'*-DDD
Molecular weight	354.49[b]	318.03[b]	320.05[b]
Color	White crystalline powder[d]	No data	No data
Physical state	Solid	No data	Solid
Melting point	74.2°C[c]	No data	76–78°C
Boiling point	No data	No data	No data
Density at 20°C	0.98–0.99 g/cm^3	No data	No data
Odor	Odorless or weak aromatic odor[c]	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	0.085 mg/L at 25°C[b]	0.14 mg/L at 25°C	0.1 mg/L at 25°C[b]
Organic solvents	No data[j]	No data[j]	Soluble in ethanol, isooctane, carbon tetrachloride[h]
Partition coefficients:			
Log K_{ow}	6.79[e]	6.00[b]	5.87[b]
Log K_{oc}	5.35[g]	5.19[g]	5.19[g]
Vapor pressure at 20°C	1.1x10^{-7}, torr[b]	6.2x10^{-6} at 25°C, torr[b]	1.94x10^{-6} at 30°C, torr[b]
Henry's law constant at 25°C	5.9x10^{-7} atm-m^3/mol[b]	1.8x10^{-5} atm-m^3/mol[b]	8.17x10^{-6} atm-m^3/mol[b]
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors			
ppm (v/v) to mg/m^3 in air at 20°C	Not applicable[h]	Not applicable[h]	Not applicable[h]
mg/m^3 to ppm (v/v) in air at 20°C	Not applicable	Not applicable	Not applicable
Explosive limits	No data	No data	No data

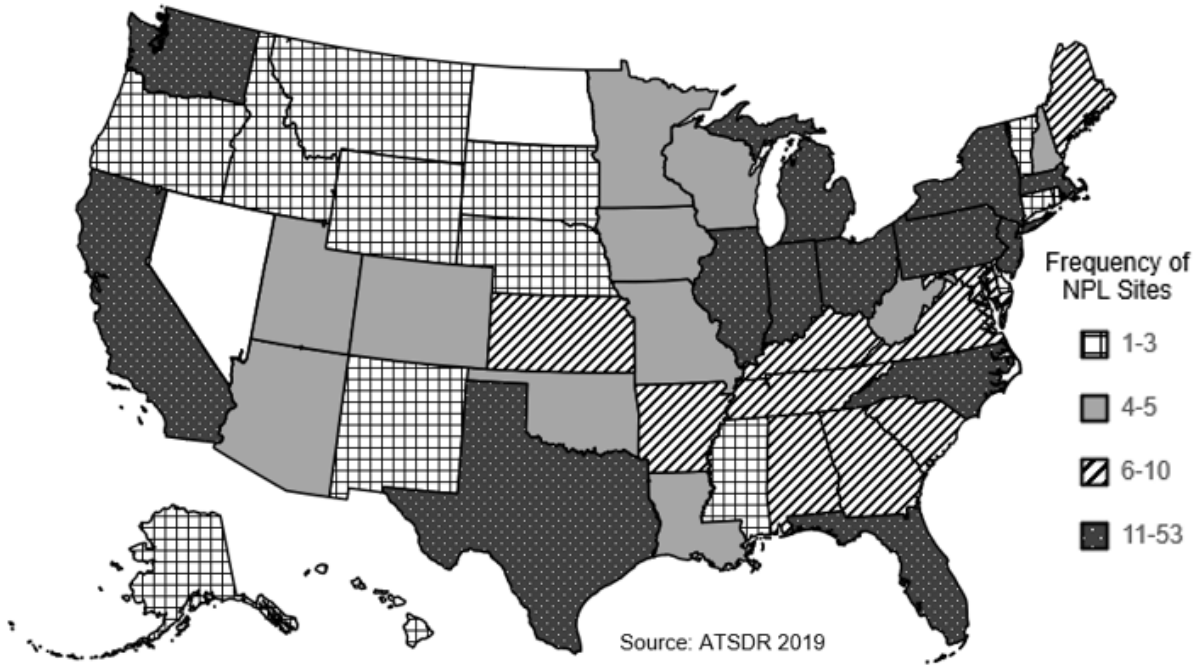
[a]Macbean 2011, unless otherwise noted.
[b]Howard and Meylan 1997.
[c]Sax 1979.
[d]Verschueren 1983.
[e]Swann et al. 1981.
[f]Sabljic 1984.
[g]Meylan et al. 1992 (values estimated from a fragment constant method).
[h]Exists partially in particulate form in air. Conversion factors are only applicable for compounds that are entirely in the vapor phase.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

DDT, DDE, and DDD have been identified in at least 375, 322, and 260, respectively, of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which DDT, DDE, and DDD have been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 455 are located within the United States, 1 is located in the Virgin Islands, and 1 is located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with DDT, DDE, and DDD Contamination



- Food intake, especially meat, fish, and dairy products, continues to be the primary source of DDT exposure for the general population; however, DDT and DDE intakes have decreased over time.

- Inhalation of ambient air and ingestion of drinking water are not considered major exposure pathways to the general population.

While this document is specifically focused on the primary forms or isomers of DDT, DDE, and DDD (namely *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD), other isomers of these compounds will be discussed when appropriate. It should be noted that DDT, DDE, and DDD are also synonyms for *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD, respectively, and it is usually understood that when DDT, for example, is mentioned

p,p'-DDT is being referred to and not both *o,p'*- and *p,p'*-DDT. Technical-grade DDT, the grade that was generally used as an insecticide was composed of up to 14 chemical compounds, of which only 65–80% was the active ingredient, *p,p'*-DDT. The other components included 15–21% of the nearly inactive *o,p'*-DDT, up to 4% of *p,p'*-DDD, and up to 1.5% of 1-(*p*-chlorophenyl)-2,2,2-trichloroethanol (Metcalf 1995). In some cases, the term DDT will be used to refer to the collective forms of DDT, DDE, and DDD. Should this not be clear from the context, the term ΣDDT (Σ is used to mean sum of) will be used.

DDT and its primary metabolites, DDE and DDD, are manufactured chemicals and are not known to occur naturally in the environment (WHO 1979). Historically, DDT was released to the environment during its production, formulation, and extensive use as a pesticide in agriculture and vector control applications. DDD was also used as a pesticide, but to a far lesser extent than was DDT. Although it was banned for use in the United States after 1972, DDT is still being used in some areas of the world. DDT and its metabolites are very persistent and bioaccumulate in the environment.

DDT gets into the atmosphere as a result of spraying operations in areas of the world where it is still used. DDT and its metabolites also enter the atmosphere through the volatilization of residues in soil and surface water, much of it a result of past use. These chemicals will be deposited on land and in surface water as a result of dry and wet deposition. The process of volatilization and deposition may be repeated many times, and results in what has been referred to as a 'global distillation' from warm source areas to cold polar regions. As a result, DDT and its metabolites are transported to the Arctic and Antarctic regions, where they are found in the air, sediment, and snow and accumulate in biota.

When in the atmosphere, about 50% of DDT will be found adsorbed to particulate matter and 50% will exist in the vapor phase (Bidleman 1988). A smaller proportion of DDE and DDD are adsorbed to particulate matter than DDT. Vapor-phase DDT, DDE, and DDD react with photochemically-produced hydroxyl radicals in the atmosphere; their estimated half-lives are 37, 17, and 30 hours, respectively. However, based on the ability of DDT, DDE, and DDD to undergo long-range global transport, these estimated half-lives do not adequately reflect the actual lifetimes of these chemicals in the atmosphere.

The dominant fate processes in the aquatic environment are volatilization and adsorption to biota, suspended particulate matter, and sediments. Transformation includes biotransformation and photolysis in surface waters. The fate of DDT in the aquatic environment is illustrated by a microcosm study in which DDT was applied to a pond, and a material balance was performed after 30–40 days. At this time, DDT concentrations in the water column had declined to below the detectable limit (EPA 1979). It was

found that 90% of the initial DDT was not present in the water, sediment, algae, invertebrates, or fish, and was presumed to have volatilized. ΣDDT was present in water mainly as DDT during the first 30 days, as DDT and DDD during the next 30 days, and as DDD in the last 30 days. ΣDDT levels rapidly rose in invertebrates, reaching equilibrium in 5 days and then declining as the ΣDDT content of the water declined. Degradation of DDT is altered by invertebrates, with the conversion of DDT to DDMU. ΣDDT levels in fish rose rapidly and reached a high equilibrium level. In a study of a freshwater lake, DDT was found to accumulate to higher concentrations in fattier fish occupying higher trophic levels than in leaner species occupying lower trophic levels (Kidd et al. 2001). Also, accumulation of DDT was significantly higher in the pelagic food web than in the benthic food web.

When deposited on soil, DDT, DDE, and DDD are strongly adsorbed. However, they may also re-volatilize into the air, which is more likely to occur from moist soils than dry soils. They may photodegrade on the soil surface and biodegrade. DDT biodegrades primarily to DDE under unflooded conditions (e.g., aerobic) and to DDD under flooded (e.g., anaerobic) conditions. As a result of their strong binding to soil, DDT, DDE, and DDD mostly remain on the surface layers of soil; there is little leaching into the lower soil layers and groundwater. DDT may be taken up by plants that are eaten by animals and accumulate to high levels, primarily in adipose tissue and milk of the animals.

In discussing DDT and other pesticides in soil, agricultural chemists generally speak of persistence and degradation, but it is not always clear what mechanisms are responsible for the loss or dissipation of the chemical. This issue is further complicated in the case of DDT because what is often reported is the disappearance of ΣDDT residues rather than just *p,p'*-DDT. Many studies use first-order kinetics to model the dissipation of DDT in soils because a half-life for the chemical can be defined. The half-life represents the calculated time for loss of the first 50% of the substance, but the time required for the loss of half of that which remains may be substantially longer, and the rate of disappearance may decline further as time progresses. The rate and extent of disappearance may result from transport processes as well as degradation or transformation processes. Initially, much of the disappearance of DDT is a result of volatilization losses, after which biodegradation becomes more important. When more than one process is responsible for loss, the decrease in the amount of substance remaining will be nonlinear. Assessments of long-term monitoring studies have indicated that even DDT biodegradation does not follow first-order kinetics (Alexander 1995, 1997). The reason is that over long periods of time, DDT may become sequestered in soil particles and become less available to microorganisms. The term half-life in this document is used to indicate the estimated time for the initial disappearance of 50% of the compound, and does not necessarily imply that first-order kinetics were observed throughout the

experiment unless otherwise noted. The persistence of DDT in soil is highly variable. Dissipation is much greater in tropical regions than in temperate regions. In tropical and subtropical regions, most of the DDT is lost within a year; the half-life of ΣDDT in 13 countries ranged from 22 to 327 days. The half-life of DDE, the primary degradation product of DDT, ranged from 151 to 271 days. In another country where the soil was extremely acidic, the half-life was >672 days. Comparable half-lives in temperate regions have been reported to range from 837 to 6,087 days. One investigator concluded that the mean lifetime of DDT in temperate U.S. soils was about 5.3 years. In a study of sprayed forest soils in Maine, the half-time for the disappearance of DDT residues was noted to be 20–30 years (Dimond and Owen 1996). Highest residues are found in muck soils and in deeply plowed, unflooded fields (Aigner et al. 1998; Spencer et al. 1996). Significant concentrations of DDT have been found in the atmosphere over agricultural plots. Irrigating the soil dramatically increased the volatilization flux of DDT, which is probably related to the amount of DDT in the soil solution. Volatilization, air transport, and redeposition were found to be the main avenues of contaminating forage eaten by cows.

When deposited in water, DDT will adsorb strongly to particulate matter in the water column and primarily partition into the sediment. Some of the DDT may revolatilize. DDT bioconcentrates in aquatic organisms and bioaccumulates in the food chain. Marine mammals in the Arctic often contain very high levels of DDT and DDE (Hargrave et al. 1992; Welfinger-Smith et al. 2011).

Concentrations of DDT in all media have been declining since DDT was banned in the United States and most of the world (Arthur et al. 1977; Boul et al. 1994; Van Metre and Callender 1997; Van Metre et al. 1997; Ware et al. 1978). For example, the concentration of DDT in lake sediments decreased by 93% from 1965 to 1994 and declined by 70% in silt loam between 1960 and 1980 (Boul et al. 1994; Van Metre and Callender 1997; Van Metre et al. 1997). ΣDDT levels in sea lions decreased by 2 orders of magnitude between 1970 and 1992 (Lieberg-Clark et al. 1995). The Market Basket Surveys have shown an 86% decline in DDT levels measured in all classes of food from 1965 to 1975 (EPA 1980). However, because of the extensive past use of DDT worldwide and the persistence of DDT and its metabolites, these chemicals are virtually ubiquitous and are continually being transformed and redistributed in the environment.

Human exposure to DDT is primarily through the diet. Exposure via inhalation at the ambient levels in air (Whitmore et al. 1994) is thought to be insignificant compared with dietary intake. The main source of DDT in food is meat, fish, poultry, and dairy products. DDT residues in food have declined since it was banned. Residues are more likely to occur in food imported from countries where DDT is still used.

People eating fish from the Great Lakes were found to consume greater amounts of DDT in their diets (Hanrahan et al. 1999; Laden et al. 1999), but as DDT levels in Great Lakes fish continue to decline, exposure from consuming fish should also decline (Anderson et al. 1998; Hanrahan et al. 1999; Hovinga et al. 1993). The populations having the greatest exposure to DDT are indigenous people in the Arctic who eat traditional foods (e.g., seals, caribou, narwhal whales, etc.) (Kuhnlein et al. 1995).

Releases of DDT, DDE, or DDD are not required to be reported in the Toxics Release Inventory (TRI) database (EPA 2005).

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Figures relating to the production, import/export, use, and disposal of a pesticide generally refer to those of the active ingredient. In the case of DDT, the active ingredient is *p,p'*-DDT. Most DDT production can be assumed to have been technical-grade material that included 15–21% of the nearly inactive *o,p'*-DDT, up to 4% of *p,p'*-DDD, and up to 1.5% of 1-(*p*-chlorophenyl)-2,2,2-trichloroethanol (Metcalf 1995).

5.2.1 Production

Technical DDT is made by condensing chloral hydrate with chlorobenzene in concentrated sulfuric acid (Metcalf 1995). It was first synthesized in 1874, but it was not until 1939 that Müller and his coworkers discovered its insecticidal properties (Metcalf 1995). Production of DDT in 1971 in the United States was estimated to be 2 million kg. This represented a sharp decline from the 82 million kg produced in 1962, and from the 56 million kg produced in 1960. At the peak of its popularity in 1962, DDT was registered for use on 334 agricultural commodities and about 85,000 tons were produced (Metcalf 1995). Production then declined and by 1971, shortly before it was banned in the United States, production had dipped to about 2,000 tons. The cumulative world production of DDT has been estimated as about 2.8 million metric tons, with roughly half of that production attributed to the United States (UNEP 2015). As of January 1, 1973, all uses of DDT in the United States were canceled except emergency public health uses and a few other uses permitted on a case-by-case basis (Meister and Sine 1999). Currently, no companies in the United States manufacture DDT (Meister and Sine 1999). DDT is still being produced by India and possibly the Democratic People's Republic of Korea (North Korea). China discontinued production in 2007 (UNEP 2015). The average annual production in China from 2000 to 2004 was reported to be 4,500 metric tons; however, most of that production was used to manufacture the acaricide, dicofol (van den Berg 2009). An average annual production of 160 metric tons of DDT was reported for

North Korea. The total DDT production for India in 2009, 2010, and 2011 was reported to be 3,315, 3,610, and 3,192 metric tons, respectively (UNEP 2015).

Analytical studies have shown that DDT compounds, including *p,p'*-DDT and *p,p'*-DDE, may be contaminants in technical grades of the insecticide, dicofol (Risebrough et al. 1986). In addition, another DDT-related impurity in dicofol, 1,1,1,2-tetrachloro-2,2-bis(*p*-chlorophenyl)ethane, has been shown to degrade to *p,p'*-DDE.

No information is available in the TRI database on facilities that manufacture or process DDT, DDE, and DDD because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005).

5.2.2 Import/Export

DDT was last imported into the United States in 1972, when imports amounted to 200 tons. Although the use of DDT was banned in the United States after 1972, it was still manufactured for export. Presently, there are no producers of DDT in the United States, and therefore, there are no exports of DDT. Currently, India is the only exporter of DDT in the world. In 2012/2013, India exported 286 metric tons of 98–99% active ingredient and in 2013/2014, India exported 77 metric tons of 98–99% active ingredient, primarily to the nations of Botswana, Mynmar, Namibia, South Africa, and Zimbabwe (UNEP 2015).

5.2.3 Use

DDT is a broad-spectrum insecticide that was very popular due its effectiveness, long residual persistence, low acute mammalian toxicity, and low cost (Metcalf 1989). DDT was first used as an insecticide starting in 1939 and was widely used until about 1970 (Van Metre et al. 1997). Its usage peaked in the United States in the early 1960s. During World War II, it was extensively employed for the control of malaria, typhus, and other insect-transmitted diseases. DDT has been widely used in agriculture to control insects, such as the pink boll worm on cotton, codling moth on deciduous fruit, Colorado potato beetle, and European corn borer. In 1972, 67–90% of the total U.S. consumption of DDT was on cotton; the remainder was primarily used on peanuts and soybeans. DDT has been used extensively to eradicate forest pests, such as the gypsy moth and spruce budworm. It was used in the home as a mothproofing agent and to control lice. The amount of DDT used in U.S. agriculture was

27 million pounds in 1966 and 14 million pounds in 1971 (Gianessi and Puffer 1992). Since 1973, use of DDT in the United States has been limited to the control of emergency public health problems. In some regions of the world where malaria is endemic, such as South Africa, Swaziland, and Madagascar, DDT is sprayed onto the interior surfaces of homes to decrease the incidence and spread of the disease by controlling mosquitoes (Attaran et al. 2000; Roberts et al. 1997). Not only is DDT a contact toxin for mosquitoes, it is also a contact irritant and repellent. As such, DDT has been shown to be effective in controlling malaria by not only limiting the survival of the mosquito, but also decreasing the odds of an individual being bitten within the sprayed homes. *p,p'*-DDD was also used as an insecticide. *o,p'*-DDD (Mitotane) is used medically in the treatment of cancer of the adrenal gland (PDR 1999). DDE has no commercial use.

As per the Stockholm Convention, DDT can still be used for vector control. According to the United Nations, 4,953, 5,219, and 3,950 metric tons were used in 2003, 2005, and 2007, respectively, with the majority used for malaria and leishmaniasis control (UNEP 2015). In 2009, 2010, and 2011, 6,987, 6,779, and 6,553 metric tons of DDT were used, with consumption by India accounting for >90% each year (UNEP 2015).

5.2.4 Disposal

Under current federal guidelines, DDT and DDD are potential candidates for incineration in a rotary kiln at 820–1,600°C. Disposal of DDT formulated in 5% oil solution or other solutions is mainly by using liquid injection incineration at 878–1,260°C, with a residence time of 0.16–1.30 seconds and 26–70% excess air. Destruction efficiency with this method is reported to be >99.99%. Multiple-chamber incineration is also used for 10% DDT dust and 90% inert ingredients at a temperature range of 930–1,210°C, a residence time of 1.2–2.5 seconds, and 58–164% excess air. DDT powder may be disposed of by molten salt combustion at 900°C (no residence time or excess air conditions specified). A low temperature destruction method involving milling DDT with Mg, Ca, or CaO is under development on a laboratory scale (Rowlands et al. 1994). Landfill disposal methods are rarely used at the present time.

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011,

1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5.3.1 Air

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

During the period when DDT was extensively used, a large source of DDT release to air occurred during agricultural or vector control applications. Emissions could also have resulted during production, transport, and disposal. Because use of DDT was banned in the United States after 1972, release of DDT in recent years should be negligible in this country.

Nevertheless, DDT residues in bogs or peat lands across the midlatitudes of North America indicate that DDT was still released, even after it was banned for use in the United States (Rapaport et al. 1985). These areas are unique in that they receive all of their pollutant input from the atmosphere, and therefore, peat cores are important indicators of the atmospheric deposition of a substance and also of its atmospheric levels in the present and the past. An analysis of peat cores, as well as rain and snow samples, indicated that DDT was still present in the atmosphere, although levels were lower compared to those in the 1960s. The implication is that DDT is still being released to the atmosphere either from its current production and use in other countries and transport to the United States or from the volatilization of residues resulting from previous use. The estimated release of DDT into the atmosphere from the Great Lakes in 1994, excluding Lake Huron, was 14.3 kg (Hoff et al. 1996).

5.3.2 Water

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

Historically, DDT was released to surface water when it was used for vector control in the vicinity of open waters. This source of release may still be occurring in countries that rely on DDT in insect pest control near open waters. DDT also enters surface water as a result of dry and wet deposition from the atmosphere and direct gas transfer. Atmospheric DDT deposited into tributaries will contribute to the loading in rivers, lakes, and oceans. In 1994, the estimated loading of ΣDDT into the Great Lakes as a result of dry and wet deposition was estimated as 148 kg, down from 278 kg in 1988 (Hoff et al. 1996). Fluvial sources and erosion also contribute to the DDT burden, and they were the predominant source of DDT in many areas in the past. This was clearly shown in a U.S. Geological Survey (USGS) study of sediment in reservoirs and lakes in Georgia and Texas compared with DDT levels in nearby peat bogs (Van Metre et al. 1997).

Contaminated sediment near an outfall can act as a source of contamination in distant parts of a body of water. This was clearly illustrated in a Norwegian lake that received insecticidal wastes. Nineteen years after closing the outfall, DDT concentrations in pike and perch were 5–10 times those in uncontaminated lakes (Brevik et al. 1996). DDT was disposed to the Joint Water Pollution Control Plant, Los Angeles County by Montrose Chemical Company from about 1950 to 1970, and eventually to the Palos Verdes Shelf via sewer pipes. The distribution of DDT with respect to the outfall diffusers and the fact that the DDT concentration in the overlying water column exponentially decreased with increasing distance from the sea floor indicated that the main source of DDT in the water column was contaminated sediments (Zeng et al. 1999).

5.3.3 Soil

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

In the United States, large amounts of DDT were released to the soil during spraying operations or from direct or indirect releases during manufacturing, formulation, storage, or disposal. Since almost all of the DDT produced was used to control insects damaging crops and trees or responsible for insect-transmitted diseases, it can be assumed that a large fraction of the DDT produced was released to soil during spraying operations. The largest amounts of DDT released to soil were those used in agriculture which amounted to 27 million pounds in 1966 and 14 million pounds in 1971, shortly before it was banned (EPA 1992).

5.4 ENVIRONMENTAL FATE

A large proportion of the environmental fate studies on pesticides such as *p,p'*-DDT are performed in laboratory or field studies by agricultural chemists interested in the persistence of the active ingredient of the pesticide in the tilled layer of soil. Therefore, studies may not reveal whether the loss of active ingredient is a result of volatilization, leaching, or microbial degradation. Field studies may also report the occurrence of obvious metabolites remaining in surface soil months or years after a pesticide was applied. Clearly, it is not possible to separate these studies into 'Transport and Partitioning' (Section 5.4.1) and 'Transformation and Degradation' (Section 5.4.2). These studies are discussed in Section 5.4.2 with the understanding that 'degradation' may only account for part of the reported loss.

5.4.1 Transport and Partitioning

Air. There is abundant evidence that DDT gets into the atmosphere as a result of volatilization from water or soil surfaces. Because DDT is so slow to degrade in the environment, the process of volatilization from soil and water may be repeated many times and, consequently, DDT may be transported long distances in the atmosphere by what has been referred to as a 'global distillation' from warm source areas to cold polar regions (Bard 1999; Bidleman et al. 1992; Goldberg 1975; Ottar 1981; Wania and MacKay 1993). As a result, DDT and its metabolites are found in arctic air, sediment, and snow with substantial accumulations in animals, marine mammals, and humans residing in these regions (Anthony et al. 1999; Harner 1997). An analysis of sediment cores from eight remote lakes in Canada indicated that ΣDDT concentrations in surface sediments (0–1.3 cm depth) declined significantly with latitude (Muir et al. 1995). The maximum ΣDDT concentrations in core slices in midcontinent lakes date from the late 1970s to 1980s, which is about 5–10 years later than the maximum for Lake Ontario.

Transport of DDT in the atmosphere of central and eastern North America is facilitated by a circulation pattern that brings moisture from the Gulf of Mexico into the Midwest and the airflow patterns across the eastern seaboard (Rapaport et al. 1985). DDT is removed from the atmosphere by wet and dry deposition and diffusion into bodies of water. The largest amount of DDT is believed to be removed from the atmosphere in precipitation (Woodwell et al. 1971).

Water. Volatilization of DDT, DDE, and DDD is known to account for considerable losses of these compounds from soil surfaces and water. Their tendency to volatilize from water can be predicted by their respective Henry's law constants, which for the respective *p,p'*- and *o,p'*- isomers are 8.3×10^{-6}, 2.1×10^{-5}, 4.0×10^{-6}, 5.9×10^{-7}, 1.8×10^{-5}, and 8.2×10^{-6} atm-m^3/mol (Howard and Meylan 1997). The

predicted volatilization half-lives from a model river 1 m deep, flowing at 1 m/second, with a wind of 3 m/second are 8.2, 3.3, 10.5, 6.3, 3.7, and 8.2 days, respectively. Laboratory studies of the air/water partition coefficient of DDE indicate that it will volatilize from seawater 10–20 times faster than from freshwater (Atlas et al. 1982). The authors suggest that this process may be related to interaction at the bubble-water surface.

Sediment and Soil. Organic carbon partition coefficients (K_{oc}) of $1.5x10^5$ (Swann et al. 1981), $5.0x10^4$ (Sabljic 1984), and $1.5x10^5$ (Meylan et al. 1992) reported for *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD, respectively, suggest that these compounds adsorb strongly to soil. These chemicals are only slightly soluble in water, with solubilities of 0.025, 0.12, and 0.090 mg/L for *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD, respectively (Howard and Meylan 1997). Therefore, loss of these compounds in runoff is primarily due to transport of particulate matter to which these compounds are bound. For example, DDT and its metabolites have been found to fractionate and concentrate on the organic material that is transported with the clay fraction of the washload in runoff (Masters and Inman 2000). The amount of DDT transported into streams as runoff is dependent on the methods of irrigation used (USGS 1999). In the western United States, DDT concentrations in streambed sediment increased as the percentage of furrow irrigation, as opposed to sprinkler or drip irrigation, increased. In the San Joaquin River Basin, more DDT was transported during winter runoff than during the irrigation season (Kratzer 1999). Since the compounds are bound strongly to soil, DDT would remain in the surface layers of soil and not leach into groundwater. However, DDT can adsorb to free-moving dissolved organic carbon, a soluble humic material that may occur in the soil solution. This material behaves as a carrier and facilitates transport of DDT into subsurface soil (Ding and Wu 1997). DDT released into water adsorbs to particulate matter in the water column and sediment. Sediment is the sink for DDT released into water. There, it is available for ingestion by organisms, such as bottom feeders. Reich et al. (1986) reported that DDT, DDE, and DDD were still bioavailable to aquatic biota in a northern Alabama river 14 years after 432,000–8,000,000 kg of DDT was discharged into the river. DDT in the water column above the Los Angeles County's Joint Water Pollution Control Plant's outfall was present both in the dissolved phase and the particulate phase (defined as particles size >0.7 μm) (Zeng et al. 1999). It is interesting to note that more of the DDT was present in the dissolved phase than in the particulate phase, despite its high hydrophobicity.

Volatilization from moist soil surfaces can be estimated from the Henry's law constant divided by the absorptivity to soil (Dow Method) (Thomas 1990). The predicted half-life for DDT volatilizing from soil with a K_{oc} of 240,000 is 23 days, compared to an experimental half-life of 42 days. Sleicher and Hopcraft

(1984) estimated a volatilization half-life of 110 days for DDT from soil in Kenya based on mass transfer through the boundary layers, and claimed that volatilization of DDT was sufficient to account for its rapid disappearance from soil. However, laboratory experiments in which ^{14}C-*p,p'*-DDT was incubated in an acidic (pH 4.5–4.8), sandy loam soil maintained at 45°C for 6 hours/day for 6 weeks resulted in neither volatilization of DDT or its metabolites nor mineralization (Andrea et al. 1994). Other studies conducted in Indonesia using a latosol soil (pH 5.7) found that 5.9% of the radioactivity was lost through volatilization during a 6-week incubation at 45°C (Sjoeib et al. 1994). The volatilization rate of DDT from soil is significantly enhanced by temperature, sunlight, and flooding of the soil (Samuel and Pillai 1989).

Other Media. DDT, DDE, and DDD are highly lipid soluble, as reflected by their log octanol-water partition coefficients (log K_{ow}) of 6.91, 6.51, and 6.02, respectively for the *p,p'*- isomers and 6.79, 6.00, and 5.87, respectively, for the *o,p'*- isomers (Howard and Meylan 1997). This lipophilic property, combined with an extremely long half-life is responsible for its high bioconcentration in aquatic organisms (i.e., levels in organisms exceed those levels occurring in the surrounding water). Organisms also feed on other animals at lower trophic levels. The result is a progressive biomagnification of DDT in organisms at the top of the food chain. Biomagnification is the cumulative increase in the concentration of a persistent contaminant in successively higher trophic levels of the food chain (i.e., from algae to zooplankton to fish to birds). Ford and Hill (1991) reported increased biomagnification of DDT, DDE, and DDD from soil sediment to mosquito fish, a secondary consumer. No distinct pattern of biomagnification was evident in other secondary consumers such as carp and small mouth buffalo fish. The biomagnification of DDT is exemplified by the increase in DDT concentration in organisms representing four trophic levels sampled from a Long Island estuary. The concentrations in plankton, invertebrates, fish, and fish-eating birds were 0.04, 0.3, 4.1, and 24 mg/kg, whole-body basis (Leblanc 1995). Evans et al. (1991) reported that DDE biomagnified 28.7 times in average concentrations from plankton to fish and 21 times from sediment to amphipods in Lake Michigan. In some cases, humans may be the ultimate consumer of these contaminated organisms.

The bioconcentration factor (BCF) is defined as the ratio of the equilibrium concentration of contaminant in tissue compared to the concentration in ambient water, soil, or sediment to which the organism is exposed. There are numerous measurements and estimates of BCF values for DDT in fish. Oliver and Niimi (1985) estimated the steady-state BCF in rainbow trout as 12,000. Other BCF values that have been reported include 51,000–100,000 in fish, 4,550–690,000 in mussels, and 36,000 in snails (Davies and Dobbs 1984; Geyer et al. 1982; Metcalf et al. 1973; Reish et al. 1978; Veith et al. 1979). DDT

bioconcentration studies in aquatic environments with representatives of various trophic levels demonstrate that bioconcentration increases with increasing trophic level (LeBlanc 1995). Trophic level differences in bioconcentration are largely due to increased lipid content and decreased elimination efficiency among higher level organisms. However, biomagnification also contributes to the increased concentration of DDT in higher trophic organisms (LeBlanc 1995).

The BCF values of *p,p'*-DDT in brine shrimp (*Artemia nauplii*) exposed to a mixture containing 0.5 or 1.0 ng/mL of four DDT analogues for 24 hours were significantly higher than for the three other chemicals. The BCF values were 41, 54, 128, and 248 for *p,p'*-DDE, *p,p'*-DDD, *o,p'*-DDT, and *p,p'*-DDT, respectively (Wang and Simpson 1996). The differences in BCF values are due to the different lipid solubility and selectivity of the compounds partitioned in the zooplanktonic organisms. *p,p'*-DDT, which has the greatest polarity of the four tested analogues, may have been adsorbed to a greater extent to the surface of the shrimp. In addition to absorbing DDT directly from the water, fish obtain DDT from their diet (Miller 1994; Wang and Simpson 1996). Wang and Simpson (1996) fed brook trout contaminated *A. nauplii* for 24 days followed by depuration for another 24 days during which the trout were fed uncontaminated *A. nauplii*. Although the concentration of *p,p'*-DDE was the lowest of the four analogues in the contaminated brine shrimp, the concentration of this compound in the trout at day 24 was 42.5 ng/g, which was roughly 5 times more than the other analogues. The levels of the *p,p'*- isomers initially ranged from 1.0 to 2.7 ng/g, while *o,p'*-DDT was absent. The abnormal accumulation of *p,p'*-DDE in the fish suggests that mixed-function oxidases may have induced the dechlorination of *p,p'*-DDT to *p,p'*-DDE. This may account for the fact that about 70% of ΣDDT in fish is *p,p'*-DDE (Schmitt et al. 1990). After the fish were fed uncontaminated food, *p,p'*-DDE had the lowest percentage depuration. After feeding the trout for 24 days with the more highly contaminated brine shrimp, 14, 62, 17, and 32% depuration were observed for *p,p'*-DDE, *p,p'*-DDD, *o,p'*-DDT, and *p,p'*-DDT, respectively.

Fish move from the Great Lakes or other bodies of water with elevated DDT levels to rivers that feed into these lakes. In doing so, they transport DDT, which may represent a risk to wildlife along the tributaries (Giesy et al. 1994).

Despite being strongly bound to soil, at least a portion of DDT, DDE, and DDD is bioavailable to plants and soil invertebrates. Nash and Beall (1970) studied the DDT residues in soybean plants resulting from the application of [^{14}C]DDT to the surface or subsurface soil. They found that the major source of DDT contamination was due to sorption of volatilized residues from surface-treated soil. This was 6.8 times

greater than that obtained through root uptake and translocation after subsurface treatment. In other experiments with oats and peas, root uptake of DDT was low and there was little or no evidence of translocation of the insecticide (Fuhremann and Lichtenstein 1980). Verma and Pillai (1991a) reported that grain, maize, and rice plants accumulate DDT adsorbed to soil. Most of the residues were found in the roots of the plant, and the lowest concentration of DDT residues was found in the shoots, indicating low translocation of DDT. Earthworms are capable of aiding the mobilization of soil-bound DDT residues to readily bioavailable forms (Verma and Pillai 1991b). DDT may collect on the leafy part of plants from the deposition of DDT-containing dust.

5.4.2 Transformation and Degradation

Air. In the atmosphere, about 50% of DDT is adsorbed to particulate matter and 50% exists in the vapor phase (Bidleman 1988). In the vapor phase, DDT reacts with photochemically produced hydroxyl radicals with an estimated rate constant of 3.44×10^{-12} cm^3/molecule-second determined from a fragment constant estimation method (Meylan and Howard 1993). Assuming an average hydroxyl radical concentration of 1.5×10^6 per cm^3, its half-life is estimated to be 37 hours. Both DDE and DDD have higher vapor pressures than DDT, and a smaller fraction of these compounds will be adsorbed to particulate matter. The estimated half-lives of vapor-phase DDE and DDD are 17 and 30 hours, respectively. Direct photolysis may also occur in the atmosphere.

It should be noted that the estimated half-lives for vapor-phase DDT, DDE, and DDD do not necessarily reflect the lifetimes of these compounds in air. DDT, DDE, and DDD can be adsorbed on particulate matter, where they are not expected to undergo rapid photooxidation, and therefore, may be subject to long-range transport. Indeed, long-range transport through the atmosphere has been demonstrated for DDT and several of its metabolites (Bard 1999; Bidleman et al. 1992; Goldberg 1975; Ottar 1981; Wania and MacKay 1993). The work of Bidleman (1988) suggests that 50% of DDT in the atmosphere is adsorbed to particulate matter. Further, when atmospheric sampling of pesticides was performed at nine localities in the United States during a time of high DDT usage, DDT was mostly present in the particulate phase (Stanley et al. 1971).

Water. DDT, DDE, and DDD present in water may be transformed by both photodegradation and biodegradation. Since the shorter wave radiation does not penetrate far into a body of water, photolysis primarily occurs in surface water and is dependent on the clarity of the water. Direct photolysis of DDT and DDD are very slow in aquatic systems, with estimated half-lives of >150 years (EPA 1979). Direct

photolysis of DDE will vary as a function of photoperiod and brightness, resulting in different half-lives depending on the season and latitude. Over the United States, the direct photolysis of DDE results in a half-life of about 1 day in summer and 6 days in winter. DDE also undergoes photoisomerization when exposed to sunlight. Photolysis of DDE photoisomers is slower by at least one order of magnitude compared to DDE. Studies with DDT at shorter wavelengths suggest that the initial reaction results in the dissociation of the Cl_2C–Cl bond. Some information exists on the indirect photolysis of DDT; no information on the indirect photolysis of DDE or DDD was located (Coulston 1985; EPA 1979; Zepp et al. 1977).

Photo-induced 1,2 addition of DDT to a model lipid, methyl oleate, indicates that light-induced additions of DDT to unsaturated fatty acids of plant waxes and cutins may occur on a large scale (Schwack 1988).

DDT undergoes hydrolysis by a base-catalyzed reaction resulting in a half-life of 81 days at pH 9. The product formed in the hydrolysis is DDE. Hydrolysis of DDE and DDD is not a significant fate process (EPA 1979).

Biodegradation of DDT in water is reported to be a minor mechanism of transformation (Johnsen 1976). Biodegradation of DDE and DDD in the aquatic environment is slower than that of DDT (EPA 1979).

Sediment and Soil. Four mechanisms have been suggested to account for most losses of DDT residues from soils: volatilization, removal by harvest (e.g., plants that have absorbed the residue), water runoff, and chemical transformation (Fishbein 1973). Three of these are transport processes, and the fourth, chemical transformation, may occur by abiotic and biotic processes. Photooxidation of DDT and DDE is known to occur on soil surfaces or when adsorbed to sediment (Baker and Applegate 1970; Lichtenstein and Schulz 1959; Miller and Zepp 1979). The conversion of DDT to DDE in soil was enhanced by exposure to sunlight in a 90-day experiment with 91% of the initial concentration of DDT remaining in the soil for an unexposed dark control and 65% remaining for the sample exposed to light (Racke et al. 1997). However, UV-irradiation of ^{14}C-*p,p'*-DDT on soil for 10 hours mineralized <0.1% of the initial amount (Vollner and Klotz 1994). (Mineralization is the complete degradation of a chemical, generally to carbon dioxide and water for an organic chemical containing carbon, hydrogen, and oxygen.) The amount of DDT that may have been converted to DDE was not reported. Biodegradation may occur under both aerobic and anaerobic conditions due to soil microorganisms including bacteria, fungi, and algae (Arisoy 1998; EPA 1979; Lichtenstein and Schulz 1959; Menzie 1980; Stewart and Chisholm 1971; Verma and Pillai 1991b). Since biodegradation studies generally focus on the loss of the parent

compound rather than complete degradation or mineralization, and since DDT initially biodegrades to DDD or DDE, there still may be dangerous compounds remaining after almost all of the DDT that was originally present has biodegraded.

During biodegradation of DDT, both DDE and DDD are formed in soils. Both metabolites may undergo further transformation, but the extent and rate are dependent on soil conditions and, possibly, microbial populations present in soil. The degradation pathways of DDT under aerobic and anaerobic conditions have been reviewed by Zook and Feng (1999) and Aislabie et al. (1997). Ligninolytic or lignin-degrading fungi have been shown to possess the biodegradative capabilities for metabolizing a large variety of persistent compounds, including DDT. Mineralization of DDT and DDE was even observed in laboratory experiments using a member of this group of fungi, *Phanerochaete chrysosporium* (a white rot fungus) (Aislabie et al. 1997; Singh et al. 1999). Other soil microorganisms, such as *Aerobacter aerogenes*, *Pseudomonas fluorescens*, *E. coli*, and *Klebsiella pneumoniae*, have also been shown to have the capability to degrade DDT under both aerobic and anaerobic conditions, forming 4-chlorobenzoic acid and DDE, respectively (Singh et al. 1999). Biodegradation of DDT and its metabolites involves co-metabolism, a process in which the microbes derive nutrients for growth and energy from sources other than the compound of concern. DDE, the dominant DDT metabolite found, is often resistant to biodegradation under aerobic and anaerobic conditions (Strompl and Thiele 1997). In laboratory experiments with marine sediments, DDT has been shown to degrade to DDE and DDD under anaerobic conditions (Kale et al. 1999). In these same experiments, it was shown that extensive degradation of DDT occurred in clams, converting DDT to DDMU. Laboratory experiments in marine sediment showed that DDE is dechlorinated to DDMU (1-chloro-2,2-bis[*p*-chlorophenyl]ethylene) under methanogenic or sulfidogenic conditions (Quensen et al. 2001). The rate of DDE dechlorination to DDMU was found to be dependent on the presence of sulfate and temperature (Quensen et al. 2001). DDD is also converted to DDMU, but at a much slower rate. DDMU degrades further under anaerobic conditions to 2,2-bis(chloro-phenyl)acetonitrile (DDNU) and other subsequent degradation species, such as 2,2-bis(chlorophenyl) ethanol (DDOH) and 2,2-bis(chlorophenyl)acetic acid (DDA), through chemical action (Heberer and Dünnbier 1999; Ware et al. 1980). No evidence was found that methylsulfonyl metabolites of DDT are formed as a result of microbial metabolism. The rate at which DDT is converted to DDD in flooded soils is dependent on the organic content of the soil (Racke et al. 1997). In a laboratory study, Hitch and Day (1992) found that soils with a low metal content (e.g., Al, Ba, Cd, Co, Cr, Fe, and K were the major metals examined) degrade DDT to DDE much more slowly than soils with high metal content.

As mentioned earlier, the half-life represents the estimated time for the initial disappearance of 50% of the compound in question and does not necessarily imply that first-order kinetics were observed throughout the experiment unless otherwise noted. In the case of DDT, the disappearance rate slows considerably so that after the initial concentration is reduced by half, the time required for the loss of half of that which remains is substantially longer. This is largely because much of the initial loss of compound is due to volatilization, rather than biodegradation. However, the biodegradation rate also slows in time. This is because DDT migrates into micropores in soil particles where it becomes sequestered and unavailable to soil microorganisms (Alexander 1995, 1997). In addition, the disappearance of DDT is often reported as the disappearance of ΣDDT residues, and therefore, the reported rate of loss is a summation of the component DDT-related chemicals. DDT breaks down into DDE and DDD in soil, and the parent-to-metabolite ratio (DDT to DDE or DDD) decreases with time. However, this ratio may vary considerably with soil type. In a 1995–1996 study of agricultural soils in the corn belt of the central United States, the ratio of *p,p'*-DDT/*p,p'*-DDE varied from 0.5 to 6.6 with three-quarters of the soils having ratios above 1 (Aigner et al. 1998). In a study of forest soils in Maine, the half-life for the disappearance of DDT residues was noted to be 20–30 years (Dimond and Owen 1996). DDT was much more persistent in muck soils than in dry forest soils. A study of DDT in agricultural soils in British Colombia, Canada reported that over a 19-year period, there was a 70% reduction of DDT in muck soils and a virtual disappearance of DDT from loamy sand soils (Aigner et al. 1998).

Land management practices also affect the persistence of DDT. In 1971, an experiment was conducted in a field containing high amounts of DDT to evaluate the effect of various management tools in the disappearance of the insecticide (Spencer et al. 1996). The site was revisited in 1994 to determine the residual concentrations of DDT and its metabolites and to measure volatilization fluxes. Concentrations of DDT were reduced in all plots and the major residue was *p,p'*-DDE. The highest concentrations of residues were found in deep plowed and unflooded plots. Deep plowing places the DDT deeper into the soil profile, possibly reducing volatilization. As was noted in Section 5.4.1, the volatilization rate of DDT is enhanced by flooding the soil (Samuel and Pillai 1989). Under flooded, reducing conditions, DDD was a more common degradation product of DDT than DDE. Significant concentrations of both *o,p'*- and *p,p'*-DDE and *p,p'*-DDT were detected in the atmosphere over the plots. Irrigating the soil dramatically increased the volatilization flux of all DDT analogues, especially *p,p'*-DDE. This is probably related to the amount of DDT in the soil solution. Volatilization, air transport, and redeposition were found to be the main avenues of contaminating forage eaten by cows. In microcosm experiments, Boul (1996) found that increasing soil water content enhanced DDT loss from generally aerobic soil. His results suggested

that increased biodegradation contributed to these effects. Boul et al. (1994) analyzed DDT residues in pasture soil as they were affected by long-term irrigation and superphosphate fertilizer application. They found that ΣDDT residues in irrigated soil were about 40% that of unirrigated soil. The predominant residue was *p,p'*-DDE, and these residues were much higher in unirrigated than in irrigated soil. *p,p'*-DDE is lost at a lower rate than *p,p'*-DDT. *p,p'*-DDD residues were very low in both irrigated and unirrigated soil, indicating that loss of *p,p'*-DDD must occur at a rate at least as great as it is generated from *p,p'*-DDT. Superphosphate treatment, which is known to increase microbial biomass, also resulted in lower levels of *p,p'*-DDT and ΣDDT than in unfertilized controls. The distribution of ΣDDT with depth suggests that irrigation did not cause increased leaching of the insecticide.

A set of experiments was conducted during 1982–1987 and 1989–1993 in 14 countries under the auspices of the International Atomic Energy Agency (IAEA) on the dissipation of ^{14}C-DDT from soil under field conditions in tropical and subtropical areas (Racke et al. 1997). After 12 months, the quantity of DDT and metabolites remaining in soil at tropical sites ranged from 5% of applied in Tanzania to 15% in Indonesia. The half-life of ΣDDT ranged from 22 days in Sudan to 365 days in China. One exception was in an extremely acidic soil (pH 4.5) in Brazil in which the half-life was >672 days. The conclusion of the study was that DDT dissipated much more rapidly under tropical conditions than under temperate conditions. The major mechanisms of dissipation under tropical conditions were volatilization, biological and chemical degradation, and to a lesser extent, adsorption. Comparable half-lives in temperate regions that have been reported range from 837 to 6,087 days (Lichtenstein and Schulz 1959; Racke et al. 1997; Stewart and Chisholm 1971). One investigator concluded that the mean lifetime of DDT in temperate U.S. soils was about 5.3 years (Racke et al. 1997). The primary metabolite detected in tropical soil was DDE. With the exception of highly acidic soil from Brazil, the half-lives for DDE ranged from 151 to 271 days, much less than the >20 years reported for DDE in temperate areas. The increased dissipation of DDT in the tropics compared with that in temperate zones is believed to be largely due to increased volatility under tropical conditions (Racke et al. 1997).

5.5 LEVELS IN THE ENVIRONMENT

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

DDD levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

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

Table 5-1. Lowest Limit of Detection of DDT, DDE, and DDD Based on Standards[a]

Media	Detection limit	Reference
Air	0.16 ng/m^3	Bidleman et al. 1978
Drinking water	0.012 µg/L	EPA 2017a
Surface water and groundwater	0.012 µg/L	EPA 2017a
Soil	0.0036 µg/kg	EPA 1998
Sediment	0.0036 µg/kg	EPA 1998
Serum	1.4 ng/g (lipid)	CDC 2018
Human milk	~0.5 ng/g (lipid)	van den Berg et al. 2017

[a]Detection list based on using appropriate preparation and analytics; National Health and Nutrition Examination Survey (NHANES) data.

DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane

Table 5-2. Summary of Environmental Levels of DDT, DDE, and DDD

Media	Low	High	Reference
Outdoor air (µg/m^3)	0.001	8.5	WHO 2004
Surface water (µg /L)	0.01	0.84	WHO 2004
Drinking water (µg//L)	–	3	EPA 2008

DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane

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

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

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
p,p'-DDT					
Water (ppm)	$4.80x10^{-4}$	$7.76x10^{-4}$	34.4	42	31
Soil (ppm)	11	11.3	79.7	208	120
Air (mg/m^3)	$1.95x10^{-5}$	$9.59x10^{-5}$	46.5	13	7
o,p'-DDT					
Water (ppm)			No data		
Soil (ppm)	15.0	35.9	5.97	3	2
Air (mg/m^3)			No data		
p,p'-DDE					
Water (ppm)	$1.95x10^{-4}$	$2.84x10^{-4}$	11.7	30	22
Soil (ppm)	1.17	1.67	51.7	127	82
Air (mg/m^3)	$1.50x10^{-6}$	$1.21x10^{-5}$	38.3	7	5
o,p'-DDE					
Water (ppm)	0.365	0.295	2.60	2	1
Soil (ppm)	30.0	27.9	1.72	2	1
Air (mg/m^3)			No data		
p,p'-DDD					
Water (ppm)	$3.09x10^{-4}$	$4.38x10^{-4}$	23.2	34	25
Soil (ppm)	3.30	3.22	81.4	102	67
Air (mg/m^3)	$3.50x10^{-5}$	$8.49x10^{-5}$	52.0	5	4
o,p'-DDD					
Water (ppm)	2.80	2.36	2.33	2	1
Soil (ppm)	136	61.3	25.0	4	3
Air (mg/m^3)			No data		

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

DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane

5.5.1 Air

DDT is transported long distances from source areas to the Arctic and Antarctic. Mean ΣDDT levels in air over a period of 17 weeks at Signy Island, Antarctica in 1992 and over the ocean separating New Zealand and Ross Island, Antarctica between January and March 1990 were 0.07–0.40 and 0.81 pg/m^3,

respectively (Bidleman et al. 1993; Kallenborn et al. 1998). The concentration declined with increasing latitudes.

Ten samples taken over the Gulf of Mexico in 1977 contained an average of 34 pg/m^3 of DDT, with a range of 10–78 pg/m^3 (Bidleman et al. 1981). Iwata et al. (1993) collected and analyzed 71 samples of air over several oceans (18 sampling locations) from April 1989 to August 1990. The range of mean and maximum concentrations of DDTs were (substance, range of means, maximum concentration): *p,p'*-DDE, 0.3–180 pg/m^3, 180 pg/m^3; *o,p'*-DDT, 0.3–180 pg/m^3, 420 pg/m^3; *p,p'*-DDT, 1.2–220 pg/m^3, 590 pg/m^3; and ΣDDT, 2.4–580 pg/m^3, 1,000 pg/m^3. The highest concentrations of DDT were found at locations near areas where DDT is still used, such as the Arabian Sea off the west coast of India. Other locations with high air concentrations of DDT were the Strait of Malacca, South China Sea, and the Gulf of Mexico. *p,p'*-DDT concentrations obtained from monthly air samples collected from Saginaw Bay, Sault Ste. Marie, and Traverse City, Michigan between November 1990 and October 1991 were below the detection limit during most of the winter months at Saginaw and Traverse City, and were above the detection limit at Sault Ste. Marie only in March, May, July, and August (Monosmith and Hermanson 1996). The highest monthly *p,p'*-DDT concentrations were 35 pg/m^3 in Saginaw (August), 31 pg/m^3 in Sault Ste. Marie (May), and 21 pg/m^3 in Traverse City (July). The corresponding highs for *p,p'*-DDE were 63 pg/m^3 (August), 119 pg/m^3 (May), and 92 pg/m^3 (July). An analysis of the results suggests that higher DDT and DDE levels correlated with air mass movement from the south, perhaps from areas where DDT is still used (i.e., Central America or Mexico). The fact that the ratio of DDT to DDE was <1 in each instance suggests that there is no new DDT use in Michigan. DDT and DDE levels over Green Bay, Wisconsin in 1989 were 8.7 and 15 pg/m^3, and those over the four lower Great Lakes obtained during a cruise were 38 and 59 pg/m^3 (McConnell et al. 1998). An analysis of air masses indicated that the atmospheric sources were not long-range transport, but rather local or regional volatilization.

Stanley et al. (1971) measured atmospheric levels of pesticides in the United States during a time of high DDT usage. Nine localities were sampled representing both urban and agricultural areas. Of 12 pesticides evaluated, only DDT was detected at all localities. Maximum levels of *p,p'*-DDT ranged from 2.7 ng/m^3 in Iowa City, Iowa to 1,560 ng/m^3 in Orlando Florida. Maximum levels of *o,p'*-DDT and *p,p'*-DDE ranged from 2.4 to 131 ng/m^3. The highest levels were found in the agricultural areas of the South. The pesticides were predominantly detected in the particulate phase. Some agricultural areas in which DDT was extensively used have been monitored periodically since usage was halted. Atmospheric conditions in the Mississippi Delta were monitored intermittently from 1972 to 1975 (Arthur et al. 1977). Air samples taken in 1975 from an area with extensive cotton acreage had a mean ΣDDT concentration of

7.5 ng/m^3, compared to 11.9 ng/m^3 in 1974. This represents a 36% decline in ΣDDT levels in 1 year. Between 1972 and 1974, the first 2 years after the use of DDT was banned, the atmospheric ΣDDT levels had declined by 88%. In 3 years, the decrease in ΣDDT air levels was 92%, representing a much more rapid decline than had been expected. In a comparison of the results from a 1995 study of the occurrence and temporal distribution of pesticides in Mississippi with the results obtained in 1967, a decline in the concentration of *p,p'*-DDE in air over agricultural lands was also noted (Coupe et al. 2000). Concentrations of *p,p'*-DDE in air were lower in the 1995 measurements, ranging from 0.13 to 1.1 ng/m^3, as compared to a range of 2.6–7.1 ng/m^3 obtained in 1967. However, these results also attest to the persistence of *p,p'*-DDT degradation products after >2 decades since the ban on DDT use in the United States (Coupe et al. 2000).

p,p'-DDT, *p,p'*-DDE, and *p,p'*-DDD have all been detected in the dissolved and particulate phases of fogwater and air and in rainwater (Millet et al. 1997). Fogwater samples were 1.5–30 times higher in DDT, DDE, and DDD concentration than rainwater samples, and the distribution between dissolved and particulate phase appeared to be governed by the solubility of the chemical. The site of the measurements was a rural area in France between 1991 and 1993. DDT had not been used in the area since the 1970s. Ligocki et al. (1985) conducted concurrent rain and air sampling for rain events in Portland, Oregon, in 1984. In rain samples, no *p,p'*-DDT, *p,p'*-DDE, or *p,p'*-DDD were detected. However, in the gas phase associated with this rainfall, *p,p'*-DDE was detected in five of seven samples. Levels detected in the samples ranged from nondetected to 420 pg/m^3. In another study, Poissant et al. (1997) reported the mean concentration of *p,p'*-DDT in precipitation over a rural site near the St. Lawrence river was 500 pg/L with a 75% frequency of detection. Rapaport et al. (1985) measured DDT residues in rain and snow samples in Minnesota. Samples of snow taken in 1981–1982, 1982–1983, and 1983–1984 contained an average of 0.32, 0.60, and 0.18 ng/L of *p,p'*-DDT, respectively. Two rain samples taken in 1983 contained 0.2 and 0.3 ng/L of *p,p'*-DDT. In rainwater samples taken from a forested region in northeast Bavaria in 1999, *p,p'*-DDT and *p,p'*-DDE were detected in three of six and four of six rainwater samples, respectively, ranging in concentration from not detected to 12.9 ng/L and not detected to 13.3 ng/L, respectively. In the vapour phase, *p,p'*-DDT and *p,p'*-DDE were detected in two of five and three of five air samples, respectively, ranging in concentration from not detected to 0.03 ng/m^3 and from not detected to 0.055 ng/m^3, respectively (Streck and Herrmann 2000).

5.5.2 Water

ΣDDT levels were measure in surface water of the Lauritzen Channel on the east side of San Francisco Bay in Richmond, California (EPA 2014). As a result of activities of the former United Heckathorn facility where organochlorine pesticides had previously been produced and shipped, this waterway was affected by releases from this plant. Waterway traffic continuously re-suspends DDT from the sediment column to the surface water in this area. Sampling conducted in 2012–2013 showed porewater levels ranging from about 10 to >1,000 ng/L and surface water levels in the range of approximately 0.1–10 ng/L (EPA 2014).

Although there are numerous reports in the literature of DDT levels in specific bodies of water throughout the United States, there is little information providing evidence of trends in the DDT levels over time. EPA operates STORET (STOrage and RETrieval), a computerized water quality database. Staples et al. (1985) reported limited data on priority pollutants from STORET. Information from data collected from 1980 to 1983 indicated that 3,500–5,700 ambient water samples were analyzed for DDT, DDE, and DDD with approximately 45% of the samples containing one of these compounds. The median level reported for both DDT and DDE was 0.001 μg/L, while the median level reported for DDD was 0.000 μg/L. Approximately 50 samples of industrial effluents were sampled and showed median levels of 0.010 μg/L for all three compounds. DDT, DDE, and DDD were infrequently detected in 1,092 water samples collected from January 1, 2015 to January 1, 2017 in STORET (WQP 2017). Maximum levels of 0.005 μg/L were reported for DDT in samples collected in California. DDT was monitored in surface water and sediment as part of the National Surface Water Monitoring Program in 1976–1980. The percent occurrence and maximum concentrations of the reported DDT-related compounds in surface water were: *p,p'*-DDT, 0.5%, 0.70 μg/L (ppb); *o,p'*-DDT, 0.1%, 0.42 μg/L; *p,p'*-DDE, 0.7%, 0.55 μg/L; and *o,p'*-DDE, 0.3%, 0.54 μg/L (Carey and Kutz 1985). The USGS and EPA cooperatively monitored levels of pesticides in water and sediment at Pesticide Monitoring Network stations between 1975 and 1980 (Gilliom 1984). Of the 177 stations (approximately 2,700 samples) monitored, 2.8, 0.6, and 4.0% contained detectible levels of DDT, DDE, and DDD in water, respectively. Fewer than 0.4% of the samples contained detectable DDT-related residues. The levels detected in water were not reported, but the limit of detection was 0.05 μg/L for DDT and DDD, and 0.3 μg/L for DDE. The percentage of sites having detectable levels of DDT-related residues in sediment was much higher (see Section 5.5.3).

Johnson et al. (1988) reported DDT and metabolite levels in the Yakima River basin in Washington State. Use of DDT was halted in this area when the 1972 ban was initiated; however, considerable residues are

present in the river and sediments. Whole unfiltered water samples, collected mainly from the tributaries between May and October 1985, were reported to contain between not detectable to 0.06 μg/L of DDT-related compounds. Concentrations of *p,p'*-DDT in water equaled or exceeded those of *p,p'*-DDE; an unexpected finding in light of what is believed concerning biological half-lives of DDT and its normal environmental degradation (Singh et al. 1999; Wolfe and Seiber 1993). The authors have suggested an unusually long half-life for DDT in Yakima basin soils, which would enter the river through runoff to explain the higher than expected *p,p'*-DDT/*p,p'*-DDE ratios.

In the Malheur watershed, DDT was found to be persistent in the watershed, with estimated concentrations for ΣDDT ranging from 0.13–0.34 ng/L in rural regions of the watershed to 3.0–4.7 ng/L in urbanized areas of the Malheur River near Ontario, Oregon (Anderson and Johnson 2001). Unlike the relative concentrations of DDT and DDE in the Yakima River, the concentrations of DDE in water samples were higher than those measured for DDT (ranges of 0.03–0.25 and 0.07–0.14 ng/L for DDE and DDT, respectively, in rural areas and 1.9–4.3 and 0.25–0.61 ng/L near Ontario, respectively), indicating that although DDT was still persistent in this watershed, it was undergoing the expected environmental degradation.

A summary of pesticide levels in surface waters of the United States during 1967 and 1968 was reported by Lichtenberg et al. (1970). During these 2 years (which were prior to the ban of DDT use), a total of 224 samples (unfiltered) were analyzed from various sites in all regions of the country. DDT was found in 27 samples at levels ranging from 0.005 to 0.316 μg/L; DDE was found in 3 samples at levels of 0.02–0.05 μg/L; and DDD was found in 6 samples at levels of 0.015–0.840 μg/L.

According to the USGS National Water Quality Assessment Plan initiated in 1991, that focuses on the water quality in >50 major river basins and aquifer systems, the frequency of detection of DDT and its metabolites in streams and groundwater was very low (USGS 1999). The top 15 pesticides found in water were those with high current use.

Only a few studies report levels of DDT in drinking water. Drinking water in Oahu, Hawaii, was found to contain *p,p'*-DDT at an average level of 0.001 μg/L in 1971 (Bevenue et al. 1972). In a study of Maryland drinking water during the September 1995, *p,p'*-DDE was detected in 22 out of 394 (5.6%) water samples, ranging in concentration from 0.039 to 0.133 μg/L (MacIntosh et al. 1999). Concentrations of *p,p'*-DDT and *p,p'*-DDD could not be measured above their limits of detection of 0.021 and 0.028 ppb, respectively. Keith et al. (1979) reported that DDE was found in 2-month

equivalent (the amount of water a person would theoretically consume over a 2-month period) samples collected over 2 days from two of three drinking water plants in New Orleans in 1974; the DDE concentration was 0.05 μg/L in both samples.

p,p'-DDE was monitored for in drinking water as part of EPA's first Unregulated Contaminant Monitoring Rule (UCMR 1) program. DDE was only detected one time at or above the MRL of 0.8 μg/L, in 33,797 drinking water samples collected from 3,874 public drinking water systems across the United States (EPA 2008). *p,p'*-DDE was measured at 3 μg/L at a large groundwater based system; however, there were no detections of DDE at any small public water systems (serving <10,000 people).

Iwata et al. (1993) collected and analyzed 68 samples of surface water from several oceans (18 sampling locations) mainly affected by atmospheric deposition from April 1989 to August 1990. The range of mean and maximum concentrations of DDTs were (substance, range of means, maximum concentration): *p,p'*-DDE, 0.2–3.0 pg/L, 7.9 pg/L; *o,p'*-DDT, <0.1–5.8 pg/L, 14 pg/L; *p,p'*-DDT, 0.1–7.5 pg/L, 19 pg/L; and ΣDDT, 0.3–16 pg/L, 41 pg/L. The highest concentrations of DDT-related compounds were in the East China Sea. Other seas with high concentrations of DDT were the Bay of Bengal, Arabian Sea, and South China Sea.

Canter and Sabatini (1994) reviewed Records of Decision at 450 Superfund Sites and found 49 cases in which contaminated groundwater threatened local public water supply wells. However, chlorinated organic pesticides were not found to be a major class of contaminants in these cases. In only one of the six sites in which the findings were presented in any detail was a DDT analogue found at detectable levels. *p,p'*-DDD was found in monitoring wells from the upper aquifer at Pristine, Inc., an industrial site in Reading, Ohio at 0–0.14 μg/L but not in the lower aquifer or in water supply samples that were taken from the lower aquifer. No *p,p'*-DDT, or *p,p'*-DDE was detected in groundwater samples. Surface water samples contained levels of *p,p'*-DDE, *p,p'*-DDD, and *p,p'*-DDE at ranges of 0–0.86, 0–0.78, and 0–1.82 μg/L, respectively. Even at sites where the surficial soil concentrations of *p,p'*-DDT are extremely high (29–959 mg/kg), the concentration of *p,p'*-DDT and its metabolites, *p,p'*-DDE and *p,p'*-DDD, in groundwater were close to their detection limits (≤0.05 μg/L) (Vine et al. 2000). *p,p'*-DDE was detected in monitoring wells (depth range of 20–110 feet) set up around orchards and row crop fields in the Columbia Basin Irrigation Project, but was not detected in shallow domestic wells (depth range of 80–250 feet) that were within 100 feet of these agricultural sites (Jones and Roberts 1999).

5.5.3 Sediment and Soil

ΣDDT levels were measure in sediment of the Lauritzen Channel on the east side of San Francisco Bay in Richmond, California (EPA 2014). This area is nearby the United Heckathorn Superfund Site where organochlorine pesticides had previously been produced and shipped. Average concentrations of ΣDDT ranged from 969 µg/kg on the eastern side of the channel to 32,401 µg/kg near the former plant location (EPA 2014).

Gilliom (1984) presented results of pesticide monitoring in sediment at USGS/EPA Pesticide Monitoring Network stations between 1975 and 1980. Of the 171 stations (approximately 900 samples) monitored, 26, 42, and 31 contained detectible levels of DDT, DDE, and DDD, respectively. Fewer than 17% of the samples contained detectable DDT-related residues (limit of detection was 0.5 µg/kg for DDT and DDD, and 3 µg/kg for DDE). The percentage of sites with detectable levels of DDT-related residues in sediment was much higher than in water, reflecting the preferential partitioning of DDT to sediment. From 1980 to 1983, approximately 1,100 samples of sediments in EPA's STORET database were analyzed for DDT, DDE, and DDD (Staples et al. 1985). The median levels for DDT, DDE, and DDD were 0.1, 0.1, and 0.2 µg/kg dry weight, respectively. In order to investigate circumstances contributing to the high level of DDT in fish and wildlife, soil and sediment samples (n=28) were collected in 1987 from the Upper Steele Bayou Watershed in west-central Mississippi at two depths (2.54–7.62 cm and 25.40–30.48 cm) (Ford and Hill 1991). The results are provided below in Table 5-4.

Table 5-4. DDD, DDE, and DDT Levels in Sediment Obtained from the Upper Steele Bayou Watershed

Compound	Depth (cm)	Percent detection	Mean (µg/kg)	Range (µg/kg)
p,p'-DDD	2.54–7.62	86	40	ND–410
p,p'-DDD	25.40–30.38	64	20	ND–390
p,p'-DDE	2.54–7.62	93	100	ND–660
p,p'-DDE	25.40–30.38	79	40	ND–560
p,p'-DDT	2.54–7.62	79	30	ND–600
p,p'-DDT	25.40–30.38	64	20	ND–860

DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; ND = not detected

River bed sediment samples collected in 1985 from the Yakima River basin in Washington contained 0.1–234 µg/kg (dry weight) of ΣDDT and its metabolites (Johnson et al. 1988). Use of DDT was halted in this area in 1972 when the ban was initiated.

The concentrations of DDE, DDD, DDT, and ΣDDT in bed sediment from the San Joaquin River and its tributaries in California (7 sites) in 1992 were 1.4–115, 0.7–14, 0.4–39, and 2.2–170 ng/L, respectively (Pereira et al. 1996). One of the seven sites, Orestimba Creek, had DDT levels far higher than the other sites. Land use along this creek was dominated by orchards and a variety of row crops. Runoff that occurs during winter storms and the irrigation season contributes significant amounts of DDT-ladened sediment into the San Joaquin River and its tributaries (Kratzer 1999). For example, during the 1994 irrigation season, it was estimated that approximately 136 g/day of ΣDDT entered the river and its tributaries from runoff, totaling around 5,190–8,920 g of ΣDDT for the season. Additionally, winter storm runoff can input large amounts of DDT within sediments into these surface waters in short periods of time. For example, a winter storm in January 1995 sent sediment-ladened runoff into the river and its tributaries, carrying upwards of 4,500 g/day of ΣDDT into these surface waters for a total contribution of 1,750–2,620 g of ΣDDT from this one storm alone.

Total DDT in surface sediment collected in eight remote lakes in Canada along a midcontinental transect from 49°N to 82°N declined significantly with latitude from 9.7 μg/kg (dry weight) to 0.10 μg/kg (Muir et al. 1995). The pattern of DDT deposition in lake sediment in the continental United States is exemplified by that in White Rock Lake in Dallas. Total DDT concentrations in the lake sediment increased from the mid-1940s to a maximum of 27 μg/kg in about 1965 when DDT usage peaked in the United States and have decreased by 93% to 2 μg/kg in the samples collected in 1994 (Van Metre and Callender 1997; Van Metre et al. 1997). On the average, DDE accounted for 58% of the total DDT in the lake. DDD levels were about half those of DDE. The mean concentration of ΣDDT in sediment in the Newark Bay Estuary, New Jersey collected between February 1990 and March 1993 ranged from about 100 to 300 μg/kg except for the Arthur Kill, where the mean concentrations exceeded 700 μg/kg (Gillis et al. 1995). These levels may pose a potential threat to aquatic organisms. The maximum concentrations of *p,p'*-DDD, *p,p'*-DDE, and *p,p'*-DDT in sediment from 168 sites sampled along the southeastern coast of the United States as part of the Environmental Monitoring and Trends Program (EMAP) in 1994–1995 were 150.9, 34.2, and 35.0 μg/kg, respectively (Hyland et al. 1998). The median concentrations of these compounds were below the detection limit. DDT was monitored in surface water and sediment as part of the National Surface Water Monitoring Program in 1976–1980. The percent occurrence and maximum concentrations of the reported DDT analogues in sediments were: *p,p'*-DDT, 13.2%, 110.6 μg/kg; *o,p'*-DDT, 2.9%, 7.2 μg/kg; *p,p'*-DDE, 22.7%, 163.0 μg/kg; and *o,p'*-DDE, 0.5%, 1.3 μg/kg (Carey and Kutz 1985). Results were not presented for DDD. In 1983–1984, quarterly samples of bottom sediment were taken from six sites on tributaries of the Tennessee River near Huntsville, Alabama, and were

analyzed for ΣDDT (Webber et al. 1989). From 1947 to 1970, DDT was manufactured along the tributary, and DDT-contaminated waste water was discharged into the river. The concentration of ΣDDT in sediment above the discharge point averaged less than 1 mg/kg dry weight. Remaining stations showed a decreasing gradient of ΣDDT with annual means ranging from 2,730 mg/kg at the closed site to the point of discharge to 12 mg/kg where the tributary empties into the Tennessee River 18 km away.

According to the USGS National Water Quality Assessment Plan initiated in 1991, which focuses on the water quality in >50 major river basins and aquifer systems, the frequency of detection of DDT and its metabolites in bed sediment in the 1990s remains high (USGS 1999). The metabolite with the highest frequency of detection was *p,p'*-DDE which was approximately 60% in urban areas, 48% in agricultural areas, and 46% in mixed land use areas followed by *p,p'*-DDD, *p,p'*-DDT, *o,p'*-DDD, *o,p'*-DDT, and *o,p'*-DDE. The frequency of detection of *o,p'*-DDT and *o,p'*-DDE was <5%. Sediments can act as repositories for DDT and its metabolites, serving as sources for these compounds for long periods of time, given the long half-lives of these compounds and their resistance to biodegradation (Sanger et al. 1999). Because DDT and its metabolites will fractionate and concentrate in organic material, the sediments of some waterways, such as salt marshes, that receive a large amount of organic content in wash-loads discharged from sources of water originating from urban and agricultural areas can act as potential DDT repositories (Masters and Inman 2000). Also, the concentrations of DDT and its metabolites are high enough in some sediments to exceed the threshold effects level (TEL), probable effects level (PEL), and the effects range low and median (ER-L, ER-M) for specific biota in marine and estuarine environments (Carr et al. 2000; Long et al. 1995).

The mean ΣDDT level in five U.S. cities ranged from 120 to 560 μg/kg in 1971 (Carey et al. 1979a). Urban areas generally had higher pesticide levels than did nearby agricultural areas except in some southern cities near which the agricultural use of pesticides was traditionally heavy.

DDT was heavily used in the corn belt in the mid-central United States. In a 1995–1996 sampling of 38 soils in this region, ΣDDT varied from below quantitation to 11,846 μg/kg, with a geometric mean value of 9.63 μg/kg (Aigner et al. 1998). The geometric mean concentrations for *p,p'*-DDE, *p,p'*-DDT, *p,p'*-DDD, and *o,p'*-DDT were 3.75, 4.67, 1.20, and 1.79 μg/kg, respectively. At least one DDT analogue was found in 33 of the soils. Nine of the samples contained ΣDDT above 200 μg/kg, while the concentrations in the rest of the samples were below 40 μg/kg. Two garden soils had ΣDDT levels of 30 and 1.07 μg/kg. The soil with the high ΣDDT level was a muck soil with a concentration that was 10 times higher than the sample next highest in concentration and 1,000 times higher than most sample

concentrations. *o,p'*-DDD was not found in any of the samples. The DDT/DDE ratio was determined in 21 of the samples and ranged from 0.5 to 6.6. It is interesting to note that the geometric mean *o,p'*-DDT concentration is 38% of the *p,p'*-DDT concentration. Since *o,p'*-DDT comprises between 15 and 21% of technical-grade DDT and 5.5% is comprised of other compounds, it would appear that *o,p'*-DDT degrades more slowly than *p,p'*-DDT. It was shown that the residue level of *p,p'*-DDT decreased about 70% in a silt loam in New Zealand over a 30-year period (1960–1989), while the *o,p'*-DDT level only decreased by about 50% in the same time frame (Boul et al. 1994). Most of the degradation occurred during the time frame of 1960–1980, with very little loss occurring from 1980–1989. Forest soils in Maine that had been subject to aerial spraying with DDT had ΣDDT levels ranging from 270 to 1,898 µg/kg compared with a maximum concentration of 11 µg/kg in unsprayed locations. A study of DDT in agricultural soils in British Colombia, Canada report that ΣDDT levels ranged from 194 to 763 µg/kg in silt loam soils and from 2,984 to 7,162 µg/kg in muck soils (Aigner et al. 1998). The difference in residue levels reflects DDT's longer persistence in muck soil.

Hitch and Day (1992) reported that three soil samples taken near Dell City, Texas in 1980 contained an average of 4.94 and 0.46 mg/kg (dry weight) of DDT and DDE, respectively. It was suspected that the higher DDT concentrations indicated the possible illegal use of DDT. However, further analysis indicated that the "suspect" soil degraded DDT much slower than most soils and the high levels originally detected in soil were attributed to DDT persistence for many years. DDD was not measured in this study. DDT was extensively used in Arizona for 18 years, after which agricultural residues were closely monitored following a statewide moratorium on DDT use in January 1969. Levels of DDT plus metabolites in green alfalfa fell steadily from an average level of 0.22 mg/kg at the time of the ban to a level of 0.057 mg/kg 18 months later, and a level of 0.027 mg/kg after almost 7 years (Ware et al. 1978). After 3 years, residues in agricultural soils had decreased 23%. Furthermore, the ratio of DDE to DDT was increasing, indicating a transformation of DDT to DDE. Buck et al. (1983) reported similar results from monitoring these same sites over 12 years following the ban on DDT use. After 12 years, residues in green alfalfa averaged 0.020 mg/kg. At the end of the same period, combined DDT and DDE residues in agricultural soils had fallen from 1.2 to 0.39 mg/kg, while those in surrounding desert soil had fallen from 0.40 to 0.09 mg/kg.

In 1985, DDT, DDE, and DDD levels were measured at the Baird and McGuire Superfund Site in Holbrook, Massachusetts. Contamination was due to 60 years of mixing and batching of insecticides. In the highly contaminated areas, the average concentrations of DDT, DDE, and DDD were 61, 10, and 70 mg/kg, respectively. DDT, DDE, and DDD levels in leaf litter and leaf litter invertebrates ranged from

0.2 to 8.4, from non-detected to 60, and from 0.4 to 25 mg/kg, respectively (Menzie et al. 1992). The high levels of DDT relative to DDE probably indicate that the Superfund Site is largely anaerobic, and that DDT is largely degrading to DDD. In the Palos Verdes Shelf off of Los Angeles where waste from a large DDT manufacturer was discharged via a sewer outfall, sediments contain high levels of DDT isomers and metabolites. The levels of these compounds in surface sediment (0–2 cm) at five sites in the area were (chemical, concentration range): *o,p'*-DDE, 6–45 mg/kg; *p,p'*-DDE, 10–327 mg/kg; *p,p'*-DDD, 1–13 mg/kg; *p,p'*-DDD, 9–25 mg/kg; *o,p'*-DDT, not detectible–2 mg/kg; and *p,p'*-DDT, not detectible–6 mg/kg (Venkatesan et al. 1996).

In summary, DDT, DDE, and DDD have been detected in many soil and sediment surfaces throughout the world. Concentrations are highest in areas with a history of extensive DDT use and are often detected at concentrations close to 1 mg/kg (ppm) or more. Even though concentrations of DDT, DDE, and DDD in soils are declining due to the discontinued production and use of DDT in most countries, detectable levels will probably exist for decades to come because of the long persistence time of these compounds.

5.5.4 Other Media

According to the USGS National Water Quality Assessment Plan initiated in 1991, which focuses on the water quality in >50 major river basins and aquifer systems, DDT and its metabolites were detected in 94% of whole fish samples analyzed in the 1990s even though the total DDT concentration in fish continues to decline (USGS 1999). This is attributed to the presence of DDT in stream beds and continued inputs of DDT to streams as contaminated soils erode. The metabolite with the highest frequency of detection was *p,p'*-DDE followed by *p,p'*-DDD, *p,p'*-DDT, *o,p'*-DDD, *o,p'*-DDE, and *o,p'*-DDT. The frequency of detection of the *o,p'*- isomers was <15%.

ΣDDT concentrations in fish (8 species, 23 samples) collected in August and September 1990 from 3 rivers in Michigan ranged from 4.71 to 976.92 μmol/kg, wet weight with a median of 82.1 μmol/kg (Giesy et al. 1994). The range of concentrations of DDT and metabolites were (chemical, range in μg/kg wet weight): *p,p'*-DDE, 3.54–627.13; *o,p'*-DDE, 0.15–37.95; *p,p'*-DDD, 0.43–58.82; *o,p'*-DDD, 0.13–81.70; and *p,p'*-DDT, <0.42–89.58. The mean ΣDDT concentrations in samples taken below dams that separated the rivers from the Great Lakes, 0.5–1.6 μmol/kg, were higher than those taken above, 0.05–0.35 μmol/kg. The relative contribution of DDE to ΣDDT was fairly constant in all three rivers both above and below the dams. The ratio of DDE:DDT ranged from 5 to 758, which suggests that the accumulation of DDE resulted from direct exposure to DDE in the diet rather than from recent exposure

to parent DDT. The fact that DDT is still observed in the fish was ascribed to long-range transport and deposition.

From 1986 to 1988, elements of the arctic marine food web near the Canadian Ice Island in the Arctic Ocean were sampled for DDT, DDE, and DDD (Hargrave et al. 1992). The average concentration of ΣDDT in plankton was 11.8 ng/g dry weight (43.5 μg/kg lipid), and the level increased with decreasing size of the plankton. Amphipods collected under pack ice in the open sea, over the Canadian continental shelf (190–315 m depth), and near the bottom of the Alpha Ridge (2,075 m depth), had mean ΣDDT concentrations of <57, 299, and 3,769 μg/kg dry weight (<347, 1,594, and 12,511 μg/kg lipid), respectively. Pelagic fish contained a mean ΣDDT of 200 μg/kg lipid, while abyssal fish (2,075 m) contained 819 μg/kg dry weight (1,465 μg/kg lipid). Similar comparisons have also been conducted on surface and deep-sea fish caught in the North and South Atlantic oceans and northwest Pacific ocean off California, showing higher concentrations of ΣDDT in deep-sea fish (Atlantic 175–1,090 μg/kg lipid; Pacific 2,380–2,420 μg/kg lipid) in comparison to surface fish (Atlantic 59–125 μg/kg lipid; Pacific 1,260–1,875 μg/kg lipid) (Looser et al. 2000). The DDT levels in Arctic plankton are generally lower than those reported elsewhere. It is not clear why the DDT levels are higher in organisms living at greater depths since DDT appears to be evenly distributed in the water column. Since DDT adsorbs to particulate matter that sinks into the sediment, as with detritus from aquatic organisms, fish and other organisms living at the bottom of the sea may accumulate higher levels of DDT than organisms living at the surface because their food chain is associated with benthic feeders. Regional differences in DDT levels in biota may be associated with the productivity of the ocean and greater sedimentation of detritus from aquatic organisms. Arctic mammals feeding on DDT-contaminated fish bioaccumulate the chemical in their fat (Bard 1999). The ringed neck seal (n=19) and polar bear (n=10) had mean ΣDDT concentrations of 1,482 and 266 μg/kg (lipid basis) (Muir et al. 1988). Beluga whales, ringed neck seals, and walruses near Baffin Island in the eastern Arctic had mean ΣDDT levels (wet weight) of 3.16, 0.33, and 1.42 μg/g, respectively (Kuhnlein et al. 1995).

A comparison of ΣDDT concentrations between farmed-raised salmon (from eight regions in Europe, North America, and South America) and wild Pacific salmon found significantly higher levels of total DDT in farm-raised salmon versus wild salmon (Huang et al. 2006). A comparison of total DDT levels across regions demonstrated significantly higher levels in Europe compared to North America and in North America when compared to South America.

Exposure to DDT could occur to populations that consume fish from DDT-contaminated marine environments. DDT in white croaker and Dover sole of the Southern California Bight, especially the Palos Verdes shelf area, are the highest in the United States. This is due to the fact that this area received 1,000,000 kg of DDT discharged into the Bight from the Montrose Chemical Company and also receives a large amount of sewage outfall from the southern California region (Zeng et al. 1999). Historically, DDT levels in these fish exceeded the FDA action level of 5 mg/kg wet weight of fish tissue, and fish intended for human consumption were confiscated to prevent human exposure to DDT (NOAA 1988).

Levels of ΣDDT have declined markedly since the early 1970s in fish, shellfish, and aquatic mammals (Addison and Stobo 2001; Bard 1999; Lauenstein 1995; Lieberg-Clark et al. 1995; Odsjo et al. 1997; Schmitt et al. 1990). Levels of DDT in fish were determined at 112 locations across the United States by the National Contaminant Biomonitoring Program in 1976 and 1984 (Schmitt et al. 1990). The mean concentrations of *p,p'*-DDT, *p,p'*-DDE, *p,p'*-DDD, and ΣDDT decreased from 50, 260, 80, and 370 μg/kg, respectively, in 1976 to 30, 190, 60, and 260 μg/kg, respectively, in 1984. A follow-up study of DDT in California sea lions reported a decrease in ΣDDT and DDE of over 2 orders of magnitude between 1970 and 1992 (Lieberg-Clark et al. 1995). ΣDDT concentrations in maternal grey seals decreased from 12 μg/g lipid in 1974 to 0.5 μg/g lipid in 1994; ΣDDT concentrations in seal pups were lower (60% of maternal concentrations) and decreased at similar rates over the same 20-year period (Addison and Stobo 2001). ΣDDT for mussels and oysters analyzed as part of the National Oceanic and Atmospheric Administration's National Status and Trends Mussel Watch Project in 1992 reported a geometric mean ΣDDT concentration for mussels and oysters at 51 sites of 20 μg/kg dry weight, down from a high of 53 μg/kg in 1977 (Lauenstein 1995). Over 90% of the ΣDDT present was as metabolites rather than the parent compounds (*p,p'*- and *o,p'*-DDT).

Among the metabolites of DDT are two methylsulfonyl metabolites of DDE, 2-methylsulfonyl-DDE (2-$MeSO_2$-DDE) and 3-methylsulfonyl-DDE (3-$MeSO_2$-DDE). These DDE metabolites are known to be persistent and have been measured in several species of mammals, including humans (Bergman et al. 1994). The methylsulfonyl derivatives of DDE are formed through the action of phase I and II enzymes in the liver and the mercapturic acid pathway (Letcher et al. 1998; Weistrand and Norén 1997). DDE is converted to an arene oxide through the action of the phase I cytochrome (CYP) P450 2B-type enzymes, followed by the conjugation of the arene oxide with glutathione as part of the phase II reactions. As part of the mercapturic acid pathway, the glutathione function is converted to a cysteine residue, which is then cleaved by C-S lyase to form the thiol-substituted intermediates, 2-SH-DDE or 3-SH-DDE. These thiolated DDE derivatives are methylated by adenosyl-methionine and then oxidized to the methylsufonyl

derivatives of DDE. The ratio of 2-$MeSO_2$-DDE to 3-$MeSO_2$-DDE varies between species and tissue site (Bergman et al. 1994).

The two sulfonyl DDE metabolites have been measured in fat and various tissues of arctic mammals and in humans (Bergman et al. 1994; Haraguchi et al. 1989; Letcher et al. 1998; Norén et al. 1996; Weinstrand and Norén 1997). In pooled adipose tissue of polar bears from 12 Arctic regions, the concentration of 3-$MeSO_2$-DDE ranged from 0.60 to 11 μg/kg lipids, and the ratio of methylsulfone to DDE ranged from 0.009 to 0.056 with a mean of 0.033 (Letcher et al. 1995). These ratios may be the result of both biotransformation of DDE to methylsulfonyl-DDE in the animal and bioaccumulation (Letcher et al. 1998). In the polar bear food chain, lipid adjusted concentrations of 3-$MeSO_2$-DDE in arctic cod (<0.01 ng/g, in whole body pools), ringed seal (0.4 ng/g, in blubber), and polar bear (2.0 ng/g, in fat tissue) were measured, showing an increase in the concentration of 3-$MeSO_2$-DDE as a function of the trophic level (Letcher et al. 1998). In humans, methylsulfonyl-DDE has been measured in liver, lung, and adipose tissue at respective concentrations of 1.1, 0.3, and 6.8 ppb, wet weight (Haraguchi et al. 1989). In plasma, the concentration of 3-$MeSO_2$-DDE (0.1–2 ng/g lipid) was 2–3 orders of magnitude lower than the concentration of DDE (0.11–0.88 μg/g lipid) (Norén et al.1999). In a comparison of the concentrations of the two methylsulfonyl-DDE isomers in paired human liver and adipose tissues, 3-$MeSO_2$-DDE is the most abundant of the two isomers in these tissues (Weistrand and Norén 1997). In human breast milk, the concentration of 3-$MeSO_2$-DDE has been found to range between 0.4 and 5 ng/g lipid (Norén et al. 1996).

From 1979 to 1983, a study was conducted on the presence of DDT and metabolites in wildlife, predominantly birds, in orchards in central Washington State (Blus et al. 1987). Technical DDT was applied at very high rates to orchards in Washington between 1946 and 1970 with some areas probably receiving more than 1,000 kg/ha over this period. High levels of DDE, DDT, and DDD were found in the wildlife. Ninety-six percent of the wildlife samples (n=552) contained >0.01 μg/g of DDE, and 70% contained levels >0.1 μg/g. In addition, many samples contained unusually low (≤10:1) DDE:DDT ratios. The study attempted to identify whether the residues resulted from past legal use of DDT, ongoing illegal use, use of dicofol and related compounds, or foreign sources. While this matter wasn't completely resolved, it was suspected that residues were from several sources. However, residues in certain samples, particularly resident wildlife, apparently originated from past legal use of the insecticide. High concentrations have been noted in animals from areas of historically high DDT use. Mean ΣDDT concentrations were 1,188 μg/kg in spring peeper frogs living in southern Ontario, Canada (Russell et al. 1995). These concentrations exceed the suggested maximum concentration of 1,000 μg/kg proposed by

the Great Lakes Water Quality Agreement of 1978. DDT was also applied at very high rates in the Delta region of Mississippi. The geometric mean concentration of *p,p'*-DDE residues in resident wood ducks decreased from 0.75 mg/kg in 1984 to 0.21 mg/kg in 1988 (Ford and Hill 1990). This decrease also corresponded with the reduction of residue levels in wood duck eggshells. Studies reporting concentrations of DDT and its metabolites in various biota is shown in Table 5-5.

Even with the reduction in the levels of DDT in the environment, there are still areas of concern where heavy applications of DDT during past legal uses of the pesticide have resulted in high concentrations of residual DDT and its metabolites that can, in turn, have potentially adverse effects on wildlife. For example, the transfer of DDT, DDE, and DDD from fruit orchard soils to American robins had been investigated in Okanagan, British Columbia, and Ontario, Canada, showing increasing concentrations of these compounds in soil→earthworm→robin eggs (Harris et al. 2000). In Okanagan, high average concentrations (mg/kg, dry weight) of DDE and DDT in soil (5.5 and 9.2), earthworms (52 and 21), and robin eggs (484 and 73) were consistent with the recorded contamination of this area. These concentrations are comparable to those where mortality or reproductive effects have been observed to occur in field studies. These results also illustrate one way in which DDT and its metabolites in soil can be mobilized and bioaccumulated by soil organisms which, in turn, are further accumulated in higher trophic levels.

Market Basket Surveys indicated that there were decreases in the overall residue levels on a lipid basis of DDT and DDE in all classes of food tested from 1965 to 1975 (EPA 1980). The Market Basket Survey samples a broad variety of commodities commonly consumed in the United States, typically about 280 foods and beverages purchased from different geographic regions. These commodities are then tested for the presence of toxic and nutritional elements, pesticides, industrial chemicals, and radionuclides. Between 1970 and 1973, DDE residues decreased only 27% compared to decreases of 86 and 89% for DDT and DDD, respectively (EPA 1980). A study by Duggan et al. (1983) reported the following average residues of *p,p'*-DDT and *o,p'*-DDT in grocery items from 1969 to 1976: domestic cheese, 3 ppb; ready-to-eat meat, fish, and poultry, 5 ppb; eggs, 4 ppb; domestic fruits, 13 ppb; domestic leaf and stem vegetables, 24 ppb; domestic grains, 7 ppb; corn and corn products, 0.7 ppb; and peanuts and peanut products, 11 ppb.

Table 5-5. Concentrations of DDT and Metabolites in Biota

Species	Location	Year	Concentration	Type	Reference
Marine mammals					
Pilot whale (n=7)	North Atlantic	Since 1987	3,847 (942–7,118) ng/g (f.w.) [DDE] 7,748 (1,708–13,035) ng/g (f.w.) [ΣDDT]	Mean (range)	Becker et al. 1997[a]
Harbor Porpoise (n=5)	North Atlantic	Since 1987	3,260 (1,880–4,900) ng/g (f.w.) [DDE] 7,280 (4,690–11,200) ng/g (f.w.) [ΣDDT]	Mean (range)	Becker et al. 1997[a]
Beluga whale (n=12)	Arctic	Since 1987	1,415 (142–2,230) ng/g (f.w.) [DDE] 2,492 (332–3,820) ng/g (f.w.) [ΣDDT]	Mean (range)	Becker et al. 1997[a]
Beluga whale (n=12)	Cook Inlet	Since 1987	624 (65.9–1,630) ng/g (f.w.) [DDE] 1,050 (133–2,350) ng/g (f.w.) [ΣDDT]	Mean (range)	Becker et al. 1997[a]
Northern fur seal (n=2)	North Pacific	Since 1987	1,190 (1,050–1,330) ng/g (f.w.) [DDE] 1,280 (1,090–1,480) ng/g (f.w.) [ΣDDT]	Mean (range)	Becker et al. 1997[a]
Ringed seal (n=4)	Arctic	Since 1987	198 (27–350) ng/g (f.w.) [DDE] 543 (35–1,430) ng/g (f.w.) [ΣDDT]	Mean (range)	Becker et al. 1997[a]
Harbour seals (n=18)	Northern Sea	1987	3,161 (355–6,598) µg/kg (f.w.) [ΣDDT]	Mean (range)	Vetter et al. 1996
Harbour seals (n=32)	Northern Sea	1988	3,903 (1,501–11,475) µg/kg (f.w.) [ΣDDT]	Mean (range)	Vetter et al. 1996
Beluga whale	Canadian Arctic	1988	3.16 µg/g (w.w.) [ΣDDT]	Mean	Kuhnlein et al. 1995
Narwhal whale (n=unspecified)	Canadian Arctic	1988	2.73 µg/g (w.w.) [ΣDDT]	Mean	Kuhnlein et al. 1995
Walrus (n=unspecified)	Canadian Arctic	1988	1.42 µg/g (w.w.) [ΣDDT]	Mean	Kuhnlein et al. 1995
Ringed seal (n=unspecified)	Canadian Arctic	1988	0.33 µg/g (w.w.) [ΣDDT]	Mean	Kuhnlein et al. 1995
Beluga whale (neonate) (n=1)	St. Lawrence estuary near Quebec	1991	702 ng/g (brain); 2,332 ng/g (kidney); 3,467 ng/g (liver); 2,230 ng/g (fat) [ΣDDT] 689 ng/g (brain); 2,289 ng/g (kidney); 3,370 ng/g (liver); 2,106 ng/g (fat) [DDE] ND (brain); ND (kidney); 15 ng/g (liver); 17 ng/g (fat) [DDD]		Gauthier et al. 1998

Table 5-5. Concentrations of DDT and Metabolites in Biota

Species	Location	Year	Concentration	Type	Reference
Terrestrial mammals					
Polar bear (n=320)	Arctic (16 regions)	1989–1993	219 µg/kg (f.w.) [DDE] 52–560 µg/kg (f.w.) [DDE]	Median range of geomeans	Norstrom et al. 1998
Arctic ground squirrel (n=13)	Elusive Lake	1991–1993	6.13 (0.34–34.08) µg/kg (w.w.) (liver) [ΣDDT] 1.51 (0.33–5.57) µg/kg (w.w.) (liver) [DDE]	Mean (range)	Allen-Gil et al. 1997
Arctic ground squirrel (n=6)	Feniak Lake	1991–1992	1.43 (0.19–5.16) µg/kg (w.w.) (liver) [ΣDDT] 0.86 (0.19–3.10) µg/kg (w.w.) (liver) [DDE]	Mean (range)	Allen-Gil et al. 1997
Arctic ground squirrel (n=17)	Schrader Lake	1992–1993	12.25 (0.12–39.76) µg/kg (w.w.) (liver) [ΣDDT] 4.47 (0.12–13.63) µg/kg (w.w.) (liver) [DDE]	Mean (range)	Allen-Gil et al. 1997
Birds					
Bald eagle chicks (n=51)	Great Lakes region	1990–1996	ND–0.0171 mg/kg (plasma) [DDT] 0.0036–0.1484 mg/kg (plasma) [DDE]	Range	Donaldson et al. 1999
Bald eagle eggs (n=6)	Lake Erie	1974–1980	24.4 (13.8–35.8) mg/kg [DDE]	Mean (range)	Donaldson et al. 1999
Bald eagle eggs (n=6)	Lake Erie	1989–1994	10.8 (2.7–22.2) mg/kg [DDE]	Mean (range)	Donaldson et al. 1999
Bald eagle eggs (n=7)	Lake of the Woods, Canada	1993–1996	3.3 (0.9–12.6) mg/kg [DDE]	Mean (range)	Donaldson et al. 1999
Blue heron eggs (n=10)	Southern Lake Michigan	1993	0.02 (ND–0.12) (µg/g) (w.w.) [DDT] 1.58 (0.23–13.00) (µg/g) (w.w.) [DDE] 0.03 (ND–0.12) (µg/g) (w.w.) [DDD]	Mean (range)	Custer et al. 1998
Fish and shellfish					
Mussels and oysters	United States (51 sites)	1992	0.51–1,400 ng/g (d.w.) [ΣDDT] 20 ng/g (d.w.) [ΣDDT]	Range of sites geomean	Lauenstein 1995
Clams	San Joaquin River (Orestimba Creek)	1992	4,350 ng/g (w.w.) [ΣDDT] 3,300 ng/g (w.w.) [DDE] 390 ng/g (w.w.) [DDD]	Mean	Pereira et al. 1996
Clams	San Joaquin River (Dry Creek)	1992	29 ng/g (w.w.) [ΣDDT] 25 ng/g (w.w.) [DDE] 0.5 ng/g (w.w.) [DDD]	Mean	Pereira et al. 1996

Table 5-5. Concentrations of DDT and Metabolites in Biota

Species	Location	Year	Concentration	Type	Reference
Clams	San Joaquin River (Mokelumne River)	1992	15 ng/g (w.w.) [ΣDDT] 13 ng/g (w.w.) [DDE] 0.5 ng/g (w.w.) [DDD]	Mean	Pereira et al. 1996
Clams	San Joaquin River (Stanislaus River)	1992	24 ng/g (w.w.) [ΣDDT] 22 ng/g (w.w.) [DDE] <0.5 ng/g (w.w.) [DDD]	Mean	Pereira et al. 1996
Mountain whitefish (10 composites from 7 sites)	Yakima River Basin, Washington	1989–1991	0.10–1.7 mg/kg (w.w.) (whole fish) [ΣDDT]	Range of composites	Marien and Laflamme 1995
Largescale sucker (18 composites from 13 sites)	Yakima River Basin, Washington	1989–1991	0.05–4.37 mg/kg (w.w.) (whole fish) [ΣDDT]	Range of composites	Marien and Laflamme 1995
Perch (n=5)	Lake Ørsjøen, Norway Mid-lake	1994	1.15 ng/g (w.w.), 1,643 ng/g (f.w.) [ΣDDT] 0.53 ng/g (w.w.), 757 ng/g (f.w.) [DDE] 0.26 ng/g (w.w.), 371 ng/g (f.w.) [DDD] 0.28 ng/g (w.w.), 400 ng/g (f.w.) [DDT]	Mean	Brevik et al. 1996
Perch (n=5)	Lake Ørsjøen, Norway	1994	5.59 ng/g (w.w.), 11,180 ng/g (f.w.) [ΣDDT] 2.56 ng/g (w.w.), 5,120 ng/g (f.w.) [DDE] 1.48 ng/g (w.w.), 2,960 ng/g (f.w.) [DDD] 1.15 ng/g (w.w.), 2,300 ng/g (f.w.) [DDT]	Mean	Brevik et al. 1996
Perch (n=5)	Lake Ørsjøen, Norway Mid-lake	1994	7.3 ng/g (w.w.), 8,111 ng/g (f.w.) [ΣDDT] 3.5 ng/g (w.w.), 3,888 ng/g (f.w.) [DDE] 1.5 ng/g (w.w.), 1,667 ng/g (f.w.) [DDD] 1.8 ng/g (w.w.), 2,000 ng/g (f.w.) [DDT]	Mean	Brevik et al. 1996
Lake trout (n=59)	Lake Ontario	1992	1.159 µg/g (w.w.) [DDE]	Mean	Kiriluk et al. 1995
Rainbow smelt (n=8)	Lake Ontario	1992	0.256 µg/g (w.w.) [DDE]	Mean	Kiriluk et al. 1995

[a]U.S. National Biomonitoring Specimen Bank.

DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; d.w. = dry weight; f.w. = fat weight basis; n = number; ND = not detected; geomean = geometric mean; w.w.= wet weight

Mean DDT residues by food group have been reported by Gartrell et al. (1985, 1986a, 1986b) as part of the FDA Total Diet Studies for October 1979–September 1980 and October 1980–March 1982. The average DDE and DDT residues for 12 food groups and the daily intake for each of these groups obtained from the Total Diet Studies are shown in Table 5-6. The highest intake of DDE is shown to come from meat, fish, and poultry. Other Total Diet Studies have only reported the number of occurrences of a pesticide and not the concentration levels. In the survey for 1984–1986, there were 433 findings of DDE out of 1,872 samples analyzed (Gunderson 1995b). In the Total Diet Study for 1993–1994, *p,p'*-DDE was found in 115 out of 783 (15%) items analyzed (FDA 1995). In the 1999 FDA Total Diet Study, DDT was found in 255 out of 1,040 (22%) items analyzed (FDA 1999). In an FDA study, the mean concentrations of *p,p'*-DDT and *o,p'*-DDT ranged from 0.0002 to 0.005 ppm. The mean concentrations of *p,p'*-DDE ranged from 0.0001 to 0.0257 ppm, with the highest values found in dairy, fish and vegetable products (FDA 2001). Analyses of samples from 10 states taken during fiscal years (FY) 1988 (n=13,980) and 1989 (n=13,085) resulted in a frequency of detection of 0.028 and 0.12%, respectively, for *p,p'*-DDT. DDE (any isomer) was detected in 1.5 and 0.99% of samples and *p,p'*-DDE in 0.18 and 0.25% of samples in 1988 and 1989, respectively (Minyard and Roberts 1991). Overall, these surveys indicate that DDT and DDE levels are very low in food commodities.

Table 5-6. Average Residues in Food Groups and Average Daily Intake from U.S. Food and Drug Administration (FDA) Total Diet Studies

	October 1979–September 1980[a]				October 1980–March 1982[b]			
	DDE		DDT		DDE		DDT	
Food group	Residue (ppb)	Intake (µg/day)	Residue (ppb)	Intake (µg/day)	Residue (ppb)	Intake (µg/day)	Residue (ppb)	Intake (µg/day)
Dairy products	0.9	0.626	0	0	1.5	1.05	0	0
Meat, fish, and poultry	4.8	1.28	0.8	0.219	3.0	0.777	0	0
Grains and cereal	0	0	0	0	0	0	0	0
Potatoes	0.5	0.0847	<0.1	0.0079	0.5	0.0864	0	0
Leafy vegetables	1.7	0.0954	0.2	0.0137	2.4	0.132	0	0.0195
Legumes	0	0	0	0	<0.1	0.0014	0.4	0
Root vegetables	1.0	0.0309	0	0	4.6	0.146	0	0.0192
Garden vegetables	0.2	0.0185	0	0	0.1	0.0095	0.6	0
Fruits	0	0	0	0	<0.1	0.0081	0	0
Oils and fats	<0.1	0.0028	0	0	<0.1	0.0018	0	0

Table 5-6. Average Residues in Food Groups and Average Daily Intake from U.S. Food and Drug Administration (FDA) Total Diet Studies

	October 1979–September 1980[a]				October 1980–March 1982[b]			
	DDE		DDT		DDE		DDT	
Food group	Residue (ppb)	Intake (µg/day)	Residue (ppb)	Intake (µg/day)	Residue (ppb)	Intake (µg/day)	Residue (ppb)	Intake (µg/day)
Sugar	<0.1	0.0042	0	0	<0.1	0.0018	0	0
Beverages	0	0	0	0	0	0	0	0

DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane

[a]Gartrell et al. 1985
[b]Gartrell et al. 1986b

The results of the FDA Total Diet Study Market Basket Surveys from food items collected between October 2003 and August 2005 for DDT and related compounds are provided in Table 5-7.

Table 5-7. Results of the FDA Market Basket Surveys from 2004 to 2005 for DDT, DDE, and DDD

Description	Number of analyses	Number ≥LOQ[a]	Number of traces[b]	Level in ppm (mean[c])	Level in ppm (minimum[d])	Level in ppm (maximum)
p,p'-DDE						
Milk, whole	8	0	6	0.00028	0.0001	0.0010
Milk, 2%	8	0	4	0.00024	0.0002	0.0009
Milk, chocolate, lowfat	8	0	2	0.00010	0.0004	0.0004
Milk, skim	8	0	1	0.00001	0.0001	0.0001
Milk shake, chocolate	8	0	4	0.00018	0.0001	0.0006
Cheese, American	8	7	1	0.00488	0.0010	0.0100
Cheese, cheddar	8	2	5	0.00180	0.0003	0.0060
Beef, ground	8	2	6	0.00171	0.0003	0.0090
Beef roast, chuck	8	0	5	0.00018	0.0001	0.0004
Pork chop	8	0	1	0.00001	0.0001	0.0001
Pork sausage	8	0	6	0.00020	0.0001	0.0004
Pork bacon	8	0	4	0.00011	0.0002	0.0003
Pork roast, loin	8	0	1	0.00005	0.0004	0.0004
Lamb chop	8	2	6	0.00151	0.0002	0.0060
Turkey breast	8	0	2	0.00003	0.0001	0.0001
Liver	8	0	3	0.00009	0.0001	0.0004
Frankfurter	8	0	7	0.00056	0.0003	0.0010
Bologna	8	0	4	0.00015	0.0002	0.0005

Table 5-7. Results of the FDA Market Basket Surveys from 2004 to 2005 for DDT, DDE, and DDD

Description	Number of analyses	Number ≥LOQ[a]	Number of traces[b]	Level in ppm (mean[c])	Level in ppm (minimum[d])	Level in ppm (maximum)
Salami, luncheon	8	0	8	0.00020	0.0001	0.0004
Fish, sticks/patty	8	0	1	0.00005	0.0004	0.0004
Eggs, scrambled	8	0	3	0.00020	0.0002	0.0010
Eggs, boiled	8	0	2	0.00012	0.0001	0.0009
Lima beans, immature	8	0	1	0.00001	0.0001	0.0001
Peanut butter, smooth	8	0	7	0.00095	0.0005	0.0020
Peanuts, dry roasted, salted	8	0	5	0.00046	0.0004	0.0010
Cornbread	8	0	3	0.00013	0.0001	0.0006
Raisin bran cereal	8	0	1	0.00001	0.0001	0.0001
Grapes (red/green)	8	0	2	0.00004	0.0001	0.0002
Raisins	8	0	7	0.00035	0.0002	0.0006
Spinach, fresh/frozen	8	5	2	0.00328	0.0004	0.0080
Collards, fresh/frozen	8	4	2	0.00299	0.0003	0.0140
Broccoli, fresh/frozen	8	0	5	0.00013	0.0001	0.0003
Celery	8	1	6	0.00054	0.0002	0.0020
Asparagus, fresh/frozen	8	0	2	0.00005	0.0001	0.0003
Tomato sauce, plain	8	0	6	0.00014	0.0001	0.0004
Green beans, fresh/frozen	8	0	3	0.00009	0.0002	0.0003
Green beans, canned	8	0	1	0.00003	0.0002	0.0002
Summer squash, fresh/frozen	8	0	6	0.00045	0.0003	0.0010
Pepper, sweet, green	8	0	2	0.00003	0.0001	0.0001
Potato, boiled	8	0	3	0.00005	0.0001	0.0002
Potato, baked	8	3	4	0.00199	0.0002	0.0090
Potato chips	8	0	4	0.00024	0.0002	0.0010
Spaghetti with meat sauce	8	0	7	0.00029	0.0001	0.0010
Chili con carne with beans	8	0	8	0.00035	0.0001	0.0008
Macaroni and cheese	8	0	6	0.00039	0.0001	0.0010
Quarter-pound hamburger	8	1	7	0.00096	0.0002	0.0040
Meatloaf	8	2	5	0.00157	0.0001	0.0090
Butter	8	7	0	0.01600	0.0060	0.0340
Mayonnaise	8	0	1	0.00013	0.0010	0.0010
Cream, half & half	8	1	7	0.00056	0.0001	0.0020
Tomato catsup	8	0	6	0.00024	0.0001	0.0010
Ice cream, light, vanilla	8	0	4	0.00013	0.0001	0.0005
Sweet roll/Danish pastry	8	0	1	0.00001	0.0001	0.0001
Chocolate chip cookies	8	0	1	0.00006	0.0005	0.0005
Pie, apple, fresh/frozen	8	0	1	0.00003	0.0002	0.0002

Table 5-7. Results of the FDA Market Basket Surveys from 2004 to 2005 for DDT, DDE, and DDD

Description	Number of analyses	Number ≥LOQ[a]	Number of traces[b]	Level in ppm (mean[c])	Level in ppm (minimum[d])	Level in ppm (maximum)
Pie, pumpkin, fresh/frozen	8	0	2	0.00014	0.0004	0.0007
Candy bar, milk chocolate	8	0	7	0.00035	0.0002	0.0008
Baby food, beef and broth/gravy	8	1	7	0.00069	0.0002	0.0020
Baby food, chicken and broth/gravy	8	0	2	0.00004	0.0001	0.0002
Baby food, vegetables and beef	8	0	5	0.00019	0.0002	0.0004
Baby food, vegetables and chicken	8	0	3	0.00005	0.0001	0.0002
Baby food, vegetables and ham	7	0	3	0.00007	0.0001	0.0003
Baby food, chicken noodle dinner	8	0	5	0.00009	0.0001	0.0002
Baby food, macaroni, tomato and beef	8	0	3	0.00006	0.0001	0.0003
Baby food, turkey and rice	8	0	1	0.00001	0.0001	0.0001
Baby food, green beans	8	0	2	0.00004	0.0001	0.0002
Yogurt, lowfat, fruit-flavored	8	0	1	0.00001	0.0001	0.0001
Cheese, Swiss, natural	8	2	5	0.00090	0.0003	0.0020
Cream cheese	8	7	1	0.00510	0.0008	0.0110
Shrimp	8	0	3	0.00008	0.0002	0.0002
Graham, crackers	8	0	1	0.00001	0.0001	0.0001
French-fries	8	0	1	0.00011	0.0009	0.0009
Carrot, fresh	8	0	3	0.00009	0.0001	0.0005
Brussels sprouts, fresh/frozen	8	0	3	0.00010	0.0001	0.0005
Turnip, fresh/frozen	8	1	2	0.00036	0.0004	0.0020
Beef stroganoff with noodles	8	1	2	0.00034	0.0002	0.0020
Tuna noodle casserole	8	0	7	0.00055	0.0002	0.0010
Quarter-pound cheeseburger	8	4	3	0.00153	0.0004	0.0030
Fish sandwich	8	0	6	0.00025	0.0002	0.0007
Egg, cheese, and ham on English muffin	8	0	6	0.00059	0.0004	0.0010
Taco/tostada with beef and cheese	8	2	5	0.00096	0.0003	0.0020
Pizza, cheese and pepperoni	8	1	6	0.00076	0.0002	0.0020
Clam chowder, New England	8	0	5	0.00023	0.0001	0.0010
Ice cream, vanilla	8	3	4	0.00213	0.0003	0.0070
Sherbet, fruit-flavored	8	0	2	0.00009	0.0001	0.0006
Black olives	8	0	4	0.00008	0.0001	0.0002
Sour cream	8	1	7	0.00244	0.0003	0.0150

Table 5-7. Results of the FDA Market Basket Surveys from 2004 to 2005 for DDT, DDE, and DDD

Description	Number of analyses	Number ≥LOQ[a]	Number of traces[b]	Level in ppm (mean[c])	Level in ppm (minimum[d])	Level in ppm (maximum)
Baby food, teething biscuits	8	0	1	0.00006	0.0005	0.0005
Salmon	8	6	2	0.00650	0.0010	0.0340
Baby food, squash	8	0	1	0.00009	0.0007	0.0007
Baby food, veal with gravy	8	1	3	0.00046	0.0001	0.0030
Baby food, lamb with gravy	8	6	2	0.00283	0.0006	0.0090
Baby food, turkey with gravy	8	0	1	0.00001	0.0001	0.0001
Cottage cheese, 2% fat	8	1	1	0.00028	0.0002	0.0020
Sour cream dip	8	1	5	0.00053	0.0003	0.0020
Beef steak	8	1	6	0.00065	0.0002	0.0020
Lunch meat (chicken/turkey)	8	0	1	0.00003	0.0002	0.0002
Chicken thigh, oven	8	0	1	0.00003	0.0002	0.0002
Chicken leg, fried	8	0	1	0.00003	0.0002	0.0002
Catfish	8	8	0	0.01850	0.0060	0.0500
Tuna	8	0	3	0.00020	0.0002	0.0010
Macaroni salad	8	0	3	0.00006	0.0001	0.0002
Potato salad	8	0	4	0.00015	0.0001	0.0008
Potatoes, mashed	8	2	6	0.00118	0.0004	0.0020
Coleslaw	8	0	1	0.00001	0.0001	0.0001
Carrot, baby, raw	8	0	2	0.00008	0.0003	0.0003
Lettuce, leaf, raw	8	0	7	0.00061	0.0002	0.0010
Tomato salsa, bottled	8	0	5	0.00010	0.0001	0.0002
Stew, beef and vegetable	8	0	5	0.00013	0.0001	0.0003
Lasagna	8	0	7	0.00060	0.0003	0.0010
Beef with vegetables, Chinese	8	0	2	0.00008	0.0003	0.0003
Chicken with vegetables, Chinese	8	0	2	0.00005	0.0001	0.0003
Burrito with beef, beans, cheese	8	0	7	0.00046	0.0002	0.0009
Cake, white with icing	8	0	2	0.00009	0.0002	0.0005
Candy, chocolate w/nuts	8	0	5	0.00048	0.0005	0.0010
Sweet and sour sauce	8	0	1	0.00001	0.0001	0.0001
Brown gravy	8	0	2	0.00005	0.0002	0.0002
Ranch dressing, low-calorie	8	0	1	0.00001	0.0001	0.0001
Olive oil	8	0	6	0.00038	0.0003	0.0007
Baby food, zwieback toast	8	0	1	0.00001	0.0001	0.0001
Baby food, chicken with rice	8	0	1	0.00005	0.0004	0.0004
Baby food, beef and noodles	8	0	6	0.00031	0.0001	0.0010

Table 5-7. Results of the FDA Market Basket Surveys from 2004 to 2005 for DDT, DDE, and DDD

Description	Number of analyses	Number ≥LOQ[a]	Number of traces[b]	Level in ppm (mean[c])	Level in ppm (minimum[d])	Level in ppm (maximum)
Baby food, macaroni and cheese	8	0	5	0.00023	0.0001	0.0008
o,p'-DDT						
Spinach, fresh/frozen	8	0	3	0.00009	0.0001	0.0003
Collards, fresh/frozen	8	0	1	0.00006	0.0005	0.0005
Potato, baked	8	0	2	0.00004	0.0001	0.0002
Turnip, fresh/frozen	8	0	1	0.00001	0.0001	0.0001
Potato salad	8	0	1	0.00001	0.0001	0.0001
Lettuce, leaf, raw	8	0	2	0.00015	0.0002	0.0010
p,p'-DDT						
Milk, whole	8	0	1	0.00003	0.0002	0.0002
Beef, ground	8	0	1	0.00004	0.0003	0.0003
Spinach, fresh/frozen	8	0	4	0.00030	0.0004	0.0010
Collards, fresh/frozen	8	0	4	0.00015	0.0001	0.0004
Celery	8	0	2	0.00010	0.0001	0.0007
Summer squash, fresh/frozen	8	0	2	0.00005	0.0001	0.0003
Potato, baked	8	1	4	0.00080	0.0002	0.0050
Potato chips	8	0	2	0.00008	0.0002	0.0004
Chocolate chip cookies	8	0	1	0.00004	0.0003	0.0003
Cream cheese	8	0	1	0.00004	0.0003	0.0003
Turnip, fresh/frozen	8	0	1	0.00003	0.0002	0.0002
Clam chowder, New England	8	0	1	0.00003	0.0002	0.0002
Mustard	8	0	1	0.00001	0.0001	0.0001
Salmon	8	0	1	0.00004	0.0003	0.0003
Sour cream dip	8	0	1	0.00003	0.0002	0.0002
Catfish	8	0	1	0.00011	0.0009	0.0009
Potato salad	8	0	1	0.00004	0.0003	0.0003
Lettuce, leaf, raw	8	1	3	0.00050	0.0001	0.0030

[a]Number ≥LOQ is the number of results for the residue that were greater than or equal to the method's limit of quantitation (LOQ).
[b]Number of traces is the number of results for the residue that were equal to or greater than the method's limit of detection (LOD), but less than the method's LOQ.
[c]The mean values were calculated using a value of 0 for results below the LOD. This may result in a mean value that is lower than the minimum detected value in samples for which the residue is ≥LOQ.
[d]The minimum level detected in samples with results ≥LOQ.

DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane

Source: FDA 2006

The USDA Pesticide Data Program tested 10,619 samples of foods produced domestically and imported into the United States in 2014 (USDA 2016). Fresh and processed fruit and vegetables accounted for >80% of the total 10,619 samples collected, infant formula accounted for 9.9%, salmon accounted for 3.3%, and oats and rice, accounted for 3.0% each. The results pertaining to DDT, DDD, and DDE are summarized in Table 5-8.

Table 5-8. DDD, DDE, and DDT Residues in Food Items Sampled in 2014

Food item	Number of samples	Detections	Concentration (ppm)
o,p'-DDD			
Apples	177	0	Not applicable
Blueberries, cultivated, fresh	354	0	Not applicable
Blueberries, frozen	5	0	Not applicable
Celery	708	0	Not applicable
Salmon	354	0	Not applicable
Grape juice	531	0	Not applicable
Green beans canned	378	0	Not applicable
Green beans frozen	378	0	Not applicable
Infant formula, dairy based	528	0	Not detected
Infant formula, soy based	527	0	Not detected
Oats	314	0	Not detected
Rice	314	0	Not detected
Strawberries	176	0	Not detected
Summer squash	270	1	0.003
Sweet corn fresh	78	0	Not detected
Sweet corn frozen	12	0	Not detected
Tomatoes	177	0	Not detected
Watermelon	390	0	Not detected
p,p'-DDD			
Apples	177	0	Not detected
Bananas	179	0	Not detected
Blueberries, cultivated, fresh	688	0	Not detected
Blueberries, frozen	19	0	Not detected
Broccoli	712	0	Not detected
Celery	708	0	Not detected
Cherries fresh	228	0	Not detected
Cherries frozen	282	0	Not detected
Salmon	354	0	Not detected
Grape juice	531	0	Not detected
Green beans fresh	757	0	Not detected

Table 5-8. DDD, DDE, and DDT Residues in Food Items Sampled in 2014

Food item	Number of samples	Detections	Concentration (ppm)
Green beans canned	378	0	Not detected
Green beans frozen	378	0	Not detected
Infant formula, dairy based	528	0	Not detected
Infant formula, soy based	527	0	Not detected
Oats	314	0	Not detected
Peaches	707	0	Not detected
Rice	314	0	Not detected
Strawberries	176	0	Not detected
Summer squash	531	1	0.003
Sweet corn fresh	134	0	Not detected
Sweet corn frozen	41	0	Not detected
Tomatoes	177	0	Not detected
Watermelon	390	0	Not detected
o,p'-DDE			
Apples	177	0	Not detected
Blueberries, cultivated, fresh	354	0	Not detected
Blueberries, frozen	5	0	Not detected
Carrots	708	1	0.003
Celery	348	0	Not detected
Salmon	354	0	Not detected
Grape juice	531	0	Not detected
Infant formula, soy based	527	0	Not detected
Nectarines	681	0	Not detected
Oats	314	0	Not detected
Rice	314	0	Not detected
Strawberries	176	0	Not detected
Summer squash	270	0	Not detected
Sweet corn fresh	78	0	Not detected
Sweet corn frozen	12	0	Not detected
Watermelon	390	0	Not detected
p,p'-DDE			
Apples	177	0	Not detected
Bananas	179	0	Not detected
Blueberries, cultivated, fresh	688	0	Not detected
Blueberries, frozen	19	0	Not detected
Broccoli	712	0	Not detected
Carrots	708	175	0.003–0.066
Celery	708	75	0.002–0.006
Cherries fresh	228	0	Not detected
Cherries frozen	282	0	Not detected

Table 5-8. DDD, DDE, and DDT Residues in Food Items Sampled in 2014

Food item	Number of samples	Detections	Concentration (ppm)
Salmon	354	0	Not detected
Grape juice	531	0	Not detected
Green beans fresh	757	1	0.009
Green beans canned	378	0	Not detected
Green beans frozen	378	4	0.002
Infant formula, dairy based	528	0	Not detected
Infant formula, soy based	527	0	Not detected
Oats	314	0	Not detected
Peaches	707	0	Not detected
Rice	314	0	Not detected
Strawberries	176	0	Not detected
Summer squash	531	16	0.003–0.011
Sweet corn fresh	134	0	Not detected
Sweet corn frozen	41	0	Not detected
Tomatoes	157	0	Not detected
Watermelon	390	0	Not detected
o,p'-DDT			
Blueberries, cultivated, fresh	325	0	Not detected
Blueberries, frozen	4	0	Not detected
Carrots	708	30	0.002–0.004
Celery	650	0	Not detected
Green beans canned	378	0	Not detected
Green beans frozen	378	0	Not detected
Infant formula, dairy based	528	0	Not detected
Infant formula, soy based	527	0	Not detected
Nectarines	681	0	Not detected
Oats	314	0	Not detected
Rice	314	0	Not detected
Strawberries	176	0	Not detected
Summer squash	240	5	0.003–0.012
Sweet corn fresh	78	0	Not detected
Sweet corn frozen	12	0	Not detected
Tomatoes	177	0	Not detected
p,p'-DDT			
Apples	177	0	Not detected
Bananas	179	0	Not detected
Blueberries, cultivated, fresh	659	0	Not detected
Blueberries, frozen	18	0	Not detected
Broccoli	712	0	Not detected
Carrots	708	67	0.002–0.007

Table 5-8. DDD, DDE, and DDT Residues in Food Items Sampled in 2014

Food item	Number of samples	Detections	Concentration (ppm)
Celery	679	2	0.001–0.003
Cherries fresh	228	0	Not detected
Cherries frozen	282	0	Not detected
Salmon	354	7	0.001–0.003
Grape juice	531	0	Not detected
Green beans canned	378	0	Not detected
Green beans frozen	378	0	Not detected
Infant formula, dairy based	528	0	Not detected
Infant formula, soy based	527	0	Not detected
Oats	314	0	Not detected
Nectarines	681	0	Not detected
Peaches	707	0	Not detected
Rice	314	0	Not detected
Strawberries	176	0	Not detected
Summer squash	270	13	0.003–0.011
Sweet corn fresh	78	0	Not detected
Sweet corn frozen	12	0	Not detected
Tomatoes	177	0	Not detected
Watermelon	390	0	Not detected

DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane

Source: USDA 2016

Baking, frying, broiling, smoking, and microwaving all effectively reduce the total DDT concentration in fish and meat tissue (Bayarri et al. 1994; Khanna et al. 1997; Wilson et al. 1998). The average reduction in fish ranged from 16 to 82% and in lamb from 37 to 56% depending on cooking method. It is not clear whether residues are lost as a result of volatilization or decomposition or carried away in fat runoff. *p,p'*-DDT (but not *p,p'*-DDE or *p,p'*-DDD) decomposes on heating (see Table 4-2). Concentrations of *p,p'*-DDT in tomatoes could be reduced by between 11.5 and 33.7% by washing the fruit with acetic acid and sodium chloride solutions; the concentrations of *p,p'*-DDT, *o,p'*-DDE, *p,p'*-DDD, and *o,p'*-DDD residues in tomatoes could be reduced by up to approximately 80% by simply removing the peel (Abou-Arab 1999). Production of tomato paste through home-canning methods reduced *p,p'*-DDT concentrations by 30.7%.

Djordjevic et al. (1995) assessed the chlorinated pesticide residues in U.S. and foreign cigarettes manufactured from the 1960s to the 1990s. Since 1970, the concentration of DDT analogues decreased by >98%. Concentration ranges of DDT-related compounds in samples of cigarettes manufactured between 1961 and 1979 and between 1983 and 1994 were (chemical, 1961–1979 levels, 1983–1994 levels): *p,p'*-DDD, 1,540–30,100 ng/g, 12.6–99.7 ng/g; *o,p'*-DDD, 396–7,150 ng/g, ND-19.0 ng/g; *p,p'*-DDT, 720–13,390 ng/g, 19.7–145 ng/g; *o,p'*-DDT, 105–1,940 ng/g; ND-88 ng/g; *p,p'*-DDE, 58–959 ng/g, 6.6–15.8 ng/g; and *p,p'*-DDMU (1-chloro-2,2-bis(*p*-chlorophenyl)ethylene), 92.7–2,110 ng/g, ND–27.5 ng/g. The transfer rate from tobacco into mainstream smoke amounts to 22% for DDD, 19% for DDT, and 27% for DDE.

Monitoring in older homes revealed that carpeting in these homes may have high levels of DDT, DDE, and DDD (Lewis et al. 1994). In one house built in 1930, the carpeting, which was believed to be at least 25 years old, contained up to 10.8 μg/m^2 or 5.7 μg/g of ΣDDT (*p,p'*-DDT, DDD, and DDE).

Organochlorine pesticides have been detected and quantified in composting feedstocks and finished compost (Büyüksönmez et al. 2000). Although banned for several decades, DDT and its metabolites have been detected in lawn trimmings and municipal waste compost in 1990–1996, with concentrations of DDT, DDE, and DDD at 0.01–0.21, 0.01–0.11, and 0.007–0.13 ppm, respectively. The concentrations of the DDT, DDE, and DDD have been found to typically decrease as composting feedstocks are converted to finished compost. For example, DDT and DDE concentrations in lawn trimmings were found to decrease from 0.0466 and 0.0143 ppm to 0.0159 and 0.0108 ppm, respectively, after 90 days of composting. However, under some compositing conditions, DDE concentrations have been observed to increase in the finished compost (mean concentration of 0.0807 ppm, maximum value of 0.483 ppm) compared to the initial feedstock (mean concentration of 0.0516 ppm, maximum value of 0.201 ppm) (Strom 2000).

5.6 GENERAL POPULATION EXPOSURE

The general population is currently exposed to DDT and its metabolites primarily in food, with smaller amounts coming from inhalation exposure. As indicated in the previous section, although residue levels in food continue to slowly decline, there are measurable quantities in many commodities. A 1989 pesticide screening program of produce delivered to supermarkets in Texas, for example, found *p,p'*-DDE residues in 41 of the 6,970 produce samples tested (Schattenberg and Hsu 1992). An FDA study of residues in infant foods and adult food eaten by infants and children in which over 10,000 samples of

domestic and imported foods were analyzed during 1985–1991 was published (Yess et al. 1993). ΣDDT was detected in 2 of 2,464 apples at a maximum concentration of 0.08 ppm; 312 of 2,464 plain milk samples at a maximum concentration of 0.92 ppm; 8 of 180 vitamin D fortified milk samples at a maximum concentration of 0.10 ppm; and 1 of 735 imported apple juice samples at 0.18 ppm (Yess et al. 1993). A similar 1992–1994 Canadian survey found DDE or DDT residues in 1 of 380 domestic heads of lettuce; 1 of 769 domestic potatoes; 36 of 612 imported carrots; 4 of 721 imported cucumbers; 1 of 702 imported heads of lettuce; 14 of 121 imported green onions; 7 of 17 imported parsnips; 1 of 933 imported peppers; 5 of 264 imported spinach; 1 of 155 imported tomato pastes; and 1 of 1,153 imported tomatoes (Neidert and Saschenbrecker 1996). In a U.S. Market Basket study of ready to eat foods, *o,p'*-DDE was detected 8 times in 4 different food items at an average concentration of 0.0025 μg/g; *p,p'*-DDE was detected 1,700 times in 142 different food items at an average concentration of 0.0026 μg/g; *o,p'*-DDT was detected 5 times in 4 different food items at an average concentration of 0.0053 μg/g; *p,p'*-DDT was detected 98 times in 31 different food items at an average concentration of 0.0045 μg/g (KAN-DO Office and Pesticide Team 1995).

Because of the extreme persistence of DDT and DDE, it is anticipated that low levels of residues will be present in commodities for decades. In fact, depending on use and export patterns in other countries, levels in the diet may even increase (Coulston 1985). Even in domestic commodities, the potential for low levels of dietary exposure of consumers may result from residues bioaccumulated in some food items, including fish.

The estimated dietary intake of DDT and metabolites in the United States was 62 μg/person/day in 1965, 240 μg/person/day in 1970, and 8 μg/person/day in 1974 (Coulston 1985). The FDA Adult Total Diet Study for FY 1980 (October 1979–September 1980) found that the intakes of ΣDDT, DDE, DDT, and DDD were 0.034, 0.003, 0.031, and <0.001 μg/kg body weight/day, respectively, down from highs of 0.093, 0.004, 0.087, and 0.002, respectively, in FY 1979 (Gartrell et al. 1986a). The adult intake was assumed to be the diet of a 16–19-year-old male. Analogous studies for infants and toddlers for FY 1980 reported daily intakes of the respective DDTs as 0.034, 0.034, ND (not determined), and ND μg/kg body weight/day for infants and 0.049, 0.045, 0.002, and 0.002 μg/kg body weight/day for toddlers (Gartrell et al. 1986b). Estimated dietary intakes of DDT determined from the FDA Total Diet Studies for June 1984–April 1986 and July 1986–April 1991 for eight population groups appear in Table 5-9 (Gunderson 1995a, 1995b). To facilitate comparisons of DDT intakes from Gunderson (1995a, 1995b) with those of earlier estimates (Coulston 1985), the daily intake of ΣDDT for a 70 kg 16-year-old male as reported by Gunderson (1995a, 1995b) would have been 6.51, 2.38, 1.49, and 0.97 μg/day for 1978–1979, 1979–

Table 5-9. Mean Daily Intake of DDT Per Unit Body Weight (µg/kg body weight/day) for Various Age Groups in the United States

Analyte	6–11 months	2 years	14–16 years, female	14–16 years, male	25–30 years, female	25–30 years, male	60–65 years, female	60–65 years, male
1984–1986								
ΣDDT	0.0485	0.0499	0.0154	0.0213	0.0128	0.0155	0.0111	0.0124
o,p'-DDE	0.0002	0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001
p,p'-DDE	0.0468	0.0484	0.0149	0.0207	0.0123	0.0150	0.0105	0.0119
p,p'-DDT	0.0004	0.0010	0.0003	0.0004	0.0003	0.0003	0.0003	0.0003
p,p'-DDD	0.0011	0.0004	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
1986–1991								
ΣDDT[a]	0.0448	0.0438	0.0138	0.0139	0.0106	0.0127	0.0090	0.0104
o,p'-DDE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
p,p'-DDE	0.0441	0.0420	0.0130	0.0151	0.0099	0.0119	0.0082	0.0096
o,p'-DDT	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
p,p'-DDT	0.0004	0.0011	0.0005	0.0005	0.0005	0.0005	0.0006	0.0006
p,p'-DDD	0.0003	0.0007	0.0003	0.0003	0.0002	0.0003	0.0002	0.0002

[a]The average daily ΣDDT intake of 0.8 µg/day for an adult was derived from the average intakes for 25–30-year-old males and females assuming a body weight of 70 kg. The data presented in the table were derived from the June 1984 through April 1991 FDA Total Diet Studies.

DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane

Source: Gunderson 1995a, 1995b

1980, 1984–1986, and 1986–1991, respectively. The acceptable daily intake of DDT established by WHO/FAO is 10 μg/kg/day (WHO 2000).

Exposure to DDT, DDE, and DDD in imported foods is minimized due to FDA enforcement programs. FDA randomly collects and analyzes a wide variety of imported commodities (e.g., coffee, tropical fruits) to determine if pesticide residues are above EPA tolerances. Pesticide tolerances established by EPA apply equally to domestic and imported food (Wessel and Yess 1991).

Arctic indigenous people ingest high levels of DDT from traditional foods. A study covering three age groups in communities in the eastern and western Canadian Arctic found the average daily ΣDDT intake of 24.2–27.8 μg/day for the eastern Arctic community and 0.51 to 1.0 μg/day for the western Arctic communities (Kuhnlein et al. 1995). The foods with the highest ΣDDT concentrations were raw Beluga whale blubber (316 μg/g wet weight) and aged Narwhal whale blubber (273 μg/g wet weight) in the eastern Arctic, and baked Loch (species of fish) liver (1.85 μg/g wet weight) and smoked Canada goose meat (1.47 μg/g wet weight) in the western Arctic.

DDT and its metabolites are ubiquitous in the atmosphere, but are typically present in low concentrations. In 1986–1988, EPA collected data at two sites, Jacksonville, Florida and Springfield/Chicopee, Massachusetts, to assess the nonoccupational exposure to pesticides (NOPES) for residents of these cities (Whitmore et al. 1994). Indoor *p,p'*-DDE and *p,p'*-DDT levels in air were higher than outdoor levels in these communities, and the highest number of indoor air samples with detectable DDT was observed in the spring season in Jacksonville (14%) and in the winter season in Springfield/Chicopee (20%), with estimated mean air DDE and DDT concentrations of ≤1.0 ng/m^3. Mean ΣDDT air exposures were estimated as 22 ng/day in Jacksonville and 94 ng/day in Springfield/Chicopee. For comparison, dietary exposures in these two communities for 1982–1984 were estimated to be around 1,900 ng/day. Nine of 11 carpets tested in Jacksonville contained ΣDDT with median and mean levels of 0.7 and 1.2 μg/g, respectively. Although the contribution of inhaled DDT to the overall body burden is expected to be small, this has not been adequately investigated.

Until 1970, tobacco smoke contributed significantly to the intake of DDT by humans, but since then, the amount of DDT in tobacco has dropped markedly and today, cigarette smoke is a minor source of human exposure (Djordjevic et al. 1995).

Because of the extremely low solubility of DDT and DDE in water and the efficiency of standard water treatment methods in eliminating DDT-type chemical residues, intake of these compounds via drinking water is believed to be negligible. The criterion cited in the EPA Ambient Water Quality Criteria document is 0.059 ng/L, based on ingestion of 2 L of drinking water/day plus 6.5 g of fish and shellfish per person (EPA 1999). This criterion corresponds to an estimated increased cancer risk level of $1x10^{-7}$ or 1 in 10 million.

Data indicate that, even with relatively high doses, there is minimal absorption of DDT through skin (Gaines 1969; Wester et al. 1990; Wolfe and Armstrong 1971). Therefore, exposure via dermal absorption was considered to be negligible. However, in reviewing the literature and using a dermal absorption factor of 15% measured in their laboratory, Moody and Chu (1995) calculated that in the worst-case scenario where a swimmer was in contact with 1 ppm of DDT from a water slick or sediment for 1 hour, a swimmer would absorb 200 μg of DDT, equivalent to a dose from a meal of contaminated fish.

DDT and DDE elimination from the body is not an efficient process; therefore, tissue levels will increase with repeated exposure if the absorbed dose is high enough. For this reason, body burdens of DDT and DDE tend to correspond with exposure levels, as indicated in long-term studies. From July 1969 to 1975, residues of DDT and its metabolites were measured in human adipose tissue collected through an annual, national survey—the National Human Monitoring Program for Pesticides (Kutz et al. 1977). During that time, levels of DDT and DDE in tissue samples declined. However, the frequency of occurrence in lipid samples did not decline, indicating both a long biological half-life and the ubiquitous occurrence of these compounds in the population. For FYs 1970–1974, all samples were positive for DDT and metabolites (a total of 1,412 samples). Using all age groups sampled, the geometric mean lipid DDT and metabolite (combined) levels reported for each year from 1970–1974 were 7.88, 7.95, 6.88, 5.89, and 5.02 ppm, respectively. Notable trends reported in Kutz et al. (1977) included increasing body burden with increasing age as well as a significant increase in residues in blacks when compared to whites. Results published for 1975 showed little change compared to 1974 (Kutz et al. 1979). Exposure to DDT in nonoccupationally exposed individuals, as manifested by their plasma DDE concentrations, was most reliably predicted by age and serum cholesterol concentration (Laden et al. 1999). Kutz et al. (1991) contains a listing of studies on DDT, DDE, and DDD levels in human adipose tissue in the general population of various countries from the 1950s to the mid-1980s.

The Second National Health and Nutrition Examination Survey (NHANES II) has served as a continuation of the National Human Monitoring Program. Murphy and Harvey (1985) published selected results from the NHANES II survey for 1976–1980 based on data from the Northeast, Midwest, and South. These results are based, not on adipose samples, but on serum samples. For the years covered, 3,300 serum specimens were analyzed for DDT and DDE. In 31% of those samples *p,p'*-DDT was detected, with a median quantifiable level of 3.3 ppb whole weight (0.0033 ppm). However, *p,p'*-DDE was detected in 99% of samples tested, with a median quantifiable level of 11.8 ppb (0.0118 ppm). The limits of detectability were 2 ppb for *p,p'*-DDT and 1 ppb for *p,p'*-DDE. These results offered further proof of the extensive biological half-life of DDE as compared to DDT. Again, for both compounds, serum levels increased with increasing age. Another report on NHANES II for the period of 1976–1980 confirmed the above results on serum samples from 5,994 persons. *p,p'*-DDE was detected in the serum of 99.5% of persons with a median level of 12.6 ppb (range: 0–379 ppb) whereas *p,p'*-DDT was quantifiable (>2 ppb) in only 10% of serum samples (Stehr-Green 1989). Levels of *p,p'*-DDE increased with age and were higher in farm residents and in the South and West.

Wattigney et al. (2015) studied the regional variation of *p,p'*-DDE levels in adults ≥20 years old from the NHANES 1999–2004 data. They observed that levels were consistently greater in U.S. residents of western states as compared to residents of the midwest, south, and northeast. The geometric means in ng/g lipid (ppb lipid) were 247, 232, 311, and 476 for residents of the northeast, midwest, south, and west, respectively. The authors noted that there has been approximately a 5-fold decrease in DDE serum levels in the U.S. population when comparing data on a lipid or whole weight basis from NHANES years 1976–1980 to 1999–2004. Using data from NHANES 2003–2004, Patterson et al. (2009) observed that *p,p'*-DDT levels increased with increasing age and were statistically significantly higher in Mexican Americans as compared to the non-Hispanic white population. The lipid adjusted and unadjusted serum levels from NHANES 1999–2004 for *p,p'*-DDT are presented in Tables 5-10 and 5-11 and for *p,p'*-DDE in Tables 5-12 and 5-13 (CDC 2018). The levels of *o,p'*-DDT were below the level of detection for the U.S. population.

Results of EPA's 1986 National Human Adipose Tissue Survey (NHATS) in which 671 adipose tissue specimens were pooled into composite samples according to age, census region, sex, and race showed significant differences in *p,p'*-DDT and *p,p'*-DDE levels depending on age and census region (Lordo et al. 1996). The concentration of both compounds increased with age group, and while levels of *p,p'*-DDT were highest in the Northeast and lowest in the South, those of *p,p'*-DDE were highest in the West and lowest in the North Central region. Levels of both compounds had significantly increased from the 1984

Table 5-10. Geometric Mean and Selected Percentiles of Serum *p,p'*-DDT (Lipid Adjusted in ng/g of Lipid or ppb on a Lipid-Weight Basis) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% confidence interval)				Sample size
			50th	75th	90th	95th	
Total	1999–2000	*	<LOD	<LOD	<LOD	28.0 (21.9–34.0)	1,679
	2001–2002	*	<LOD	<LOD	<LOD	26.6 (22.5–36.0)	2,305
	2003–2004	*	<LOD	<LOD	11.9 (10.0–15.1)	19.5 (15.1–27.5)	1,965
Age group							
12–19 years	1999–2000	*	<LOD	<LOD	<LOD	<LOD	677
	2001–2002	*	<LOD	<LOD	<LOD	<LOD	756
	2003–2004	*	<LOD	<LOD	<LOD	9.10 (<LOD–12.2)	595
≥20 years	1999–2000	*	<LOD	<LOD	<LOD	30.5 (23.0–37.3)	1,002
	2001–2002	*	<LOD	<LOD	<LOD	28.1 (23.8–39.0)	1,549
	2003–2004	*	<LOD	<LOD	12.9 (10.3–16.5)	20.7 (15.9–28.7)	1,370
Gender							
Males	1999–2000	*	<LOD	<LOD	<LOD	25.1 (<LOD–39.3)	799
	2001–2002	*	<LOD	<LOD	<LOD	21.6 (<LOD–25.8)	1,073
	2003–2004	*	<LOD	<LOD	10.6 (9.10–13.7)	15.2 (11.8–26.9)	959
Females	1999–2000	*	<LOD	<LOD	<LOD	29.4 (23.0–35.8)	880
	2001–2002	*	<LOD	<LOD	18.3 (<LOD–21.9)	36.6 (25.5–54.3)	1,232
	2003–2004	*	<LOD	<LOD	14.0 (10.8–17.5)	21.0 (18.0–27.8)	1,006
Race/ethnicity							
Mexican Americans	1999–2000	*	<LOD	<LOD	61.3 (27.0–155)	155 (59.3–590)	635
	2001–2002	*	<LOD	<LOD	83.1 (33.3–236)	293 (104–541)	566
	2003–2004	*	<LOD	8.90 (<LOD–12.9)	24.0 (18.6–33.3)	48.6 (31.1–71.1)	461
Non-Hispanic blacks	1999–2000	*	<LOD	<LOD	22.3 (<LOD–31.5)	31.5 (23.2–65.0)	356
	2001–2002	*	<LOD	<LOD	23.2 (<LOD–40.9)	40.9 (21.2–95.8)	514
	2003–2004	*	<LOD	9.00 (<LOD–10.4)	17.5 (14.8–23.2)	30.7 (19.0–53.4)	490

Table 5-10. Geometric Mean and Selected Percentiles of Serum *p,p'*-DDT (Lipid Adjusted in ng/g of Lipid or ppb on a Lipid-Weight Basis) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% confidence interval) 50th	75th	90th	95th	Sample size
Non-Hispanic whites	1999–2000	*	<LOD	<LOD	<LOD	<LOD	564
	2001–2002	*	<LOD	<LOD	<LOD	17.9 (<LOD–20.7)	1,061
	2003–2004	*	<LOD	<LOD	9.70 (8.50–11.2)	12.9 (10.7–16.6)	890

Source: CDC 2018

[a]The LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 20.7. 17.4, and 7.8 ng/g, respectively.

* = not calculated; the proportion of results below the limit of detection was too high to provide a valid result; CI = confidence interval; DDT = dichlorodiphenyl-trichloroethane; LOD = limit of detection

Table 5-11. Geometric Mean and Selected Percentiles of Serum *p,p'*-DDT (Whole Weight Lipid in ng/g of Serum or ppb) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% confidence interval) 50th	75th	90th	95th	Sample size
Total	1999–2000	*	<LOD	<LOD	<LOD	0.170 (0.130–0.180)	1,679
	2001–2002	*	<LOD	<LOD	<LOD	0.180 (0.160–0.220)	2,305
	2003–2004	*	<LOD	<LOD	0.078 (0.065–0.097)	0.128 (0.096–0.167)	1,965
Age group							
12–19 years	1999–2000	*	<LOD	<LOD	<LOD	<LOD	677
	2001–2002	*	<LOD	<LOD	<LOD	<LOD	756
	2003–2004	*	<LOD	<LOD	<LOD	0.048 (<LOD–0.069)	595
≥20 years	1999–2000	*	<LOD	<LOD	<LOD	0.190 (0.150–0.230)	1,002
	2001–2002	*	<LOD	<LOD	<LOD	0.200 (0.170–0.260)	1,549
	2003–2004	*	<LOD	<LOD	0.084 (0.068–0.106)	0.142 (0.105–0.189)	1,370

Table 5-11. Geometric Mean and Selected Percentiles of Serum *p,p'*-DDT (Whole Weight Lipid in ng/g of Serum or ppb) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% confidence interval)				Sample size
			50th	75th	90th	95th	
Gender							
Males	1999–2000	*	<LOD	<LOD	<LOD	0.150 (<LOD–0.240)	799
	2001–2002	*	<LOD	<LOD	<LOD	0.150 (<LOD–0.180)	1,073
	2003–2004	*	<LOD	<LOD	0.071 (0.059–0.095)	0.108 (0.078–.0180)	959
Females	1999–2000	*	<LOD	<LOD	<LOD	0.190 (0.150–0.230)	880
	2001–2002	*	<LOD	<LOD	0.130 (<LOD–0.150)	0.240 (0.180–0.400)	1,232
	2003–2004	*	<LOD	<LOD	0.087 (0.071–0.106)	0.146 (0.106–0.207)	1,006
Race/ethnicity							
Mexican Americans	1999–2000	*	<LOD	<LOD	0.400 (0.190–1.00)	1.00 (0.330–4.26)	635
	2001–2002	*	<LOD	<LOD	0.530 (0.250–1.34)	1.62 (0.570–4.01)	566
	2003–2004	*	<LOD	0.063 (<LOD–0.079)	0.146 (0.114–0.203)	0.313 (0.189–0.627)	461
Non-Hispanic blacks	1999–2000	*	<LOD	<LOD	0.120 (<LOD–0.170)	0.180 (0.140–0.420)	356
	2001–2002	*	<LOD	<LOD	0.130 (<LOD–0.290)	0.250 (0.120–0.530)	514
	2003–2004	*	<LOD	0.051 (<LOD–0.061)	0.112 (0.080-0.143)	0.201 (0.132–0.343)	490
Non-Hispanic whites	1999–2000	*	<LOD	<LOD	<LOD	<LOD	564
	2001–2002	*	<LOD	<LOD	<LOD	0.130 (<LOD–0.140)	1,061
	2003–2004	*	<LOD	<LOD	0.64 (0.054–0.075)	0.086 (0.074–0.107)	890

Source: CDC 2018

[a]The LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 20.7. 17.4, and 7.8 ng/g, respectively.

* = not calculated; the proportion of results below the limit of detection was too high to provide a valid result; CI = confidence interval; DDT = dichlorodiphenyl-trichloroethane; LOD = limit of detection

Table 5-12. Geometric Mean and Selected Percentiles of *p,p'*-DDE (Lipid Adjusted in ng/g of Lipid or ppb on a Lipid-Weight Basis) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% confidence interval)				Sample size
			50th	75th	90th	95th	
Total	1999–2000	260 (226–298)	226 (184–278)	537 (476–631)	1,150 (976–1,350)	1,830 (1,410–2,300)	1,964
	2001–2002	295 (267–327)	251 (228–278)	598 (521–699)	1,410 (1,210–1,500)	2,320 (1,830–2,780)	2,298
	2003–2004	238 (195–292)	203 (163–275)	509 (376–655)	1,170 (836–1,570)	1,860 (1,400–2,380)	1,956
Age group							
12–19 years	1999–2000	118 (102–135)	108 (97.7–119)	185 (141–237)	339 (243–479)	528 (339–812)	686
	2001–2002	124 (106–146)	113 (100–140)	213 (172–253)	319 (282–389)	456 (343–722)	758
	2003–2004	105 (84.7–129)	93.6 (81.0–114)	167 (123–240)	341 (211–586)	522 (313–1,430)	588
≥20 years	1999–2000	297 (256–344)	269 (213–323)	608 (530–693)	1,260 (1,030–1,550)	2,020 (1,520–2,730)	1,278
	2001–2002	338 (303–376)	285 (249–337)	695 (595–798)	1,480 (1,310–1,700)	2,550 (1,980–3,080)	1,540
	2003–2004	268 (217–332)	233 (175–314)	557 (420–734)	1,270 (877–1,800)	1,990 (1,500–2,470)	1,368
Gender							
Males	1999–2000	249 (220–283)	223 (182–262)	494 (380–578)	1,010 (789–1,130)	1,430 (1,080–2,160)	937
	2001–2002	285 (252–323)	248 (222–285)	520 (441–627)	1,160 (937–1,360)	1,900 (1,580–2,490)	1,069
	2003–2004	235 (193–288)	200 (164–262)	466 (331–653)	1,000 (763–1,400)	1,610 (1,210–2,320)	955
Females	1999–2000	270 (226–322)	234 (184–302)	601 (492–711)	1,350 (1,040–1,720)	2,210 (1,570–2,810)	1,027
	2001–2002	305 (273–341)	256 (219–297)	708 (567–844)	1,480 (1,410–1,710)	2,670 (1,940–3,300)	1,229
	2003–2004	241 (193–301)	207 (161–281)	539 (386–735)	1,250 (813–1,900)	2,010 (1,500–2,450)	1,001
Race/ethnicity							
Mexican Americans	1999–2000	674 (574–792)	624 (545–701)	1,350 (1,090–1,660)	3,090 (2,040–4,950)	4,950 (3,070–9,350)	657
	2001–2002	652 (569–747)	561 (455–690)	1,400 (1,050–1,950)	4,110 (2,520–6,550)	7,080 (3,080–15,600)	566
	2003–2004	444 (362–545)	373 (283–522)	875 (608–1,170)	2,150 (1,520–2,470)	3,290 (2,380–9,240)	457
Non–Hispanic blacks	1999–2000	295 (241–362)	251 (199–313)	668 (492–874)	1,850 (1,040–2,220)	2,300 (1,560–5,680)	416
	2001–2002	324 (262–400)	248 (223–296)	762 (583–999)	1,620 (1,180–2,980)	3,260 (1,270–6,900)	515
	2003–2004	262 (233–295)	216 (173–267)	589 (453–747)	1,620 (1,130–2,310)	2,860 (1,880–3,440)	487

Table 5-12. Geometric Mean and Selected Percentiles of *p,p'*-DDE (Lipid Adjusted in ng/g of Lipid or ppb on a Lipid-Weight Basis) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% confidence interval)				Sample size
			50th	75th	90th	95th	
Non–Hispanic whites	1999–2000	217 (189–249)	194 (162–238)	438 (355–507)	825 (647–1,010)	1,160 (1,010–1,350)	732
	2001–2002	253 (226–284)	225 (203–254)	463 (402–558)	1,150 (878–1,340)	1,640 (1,410–1,940)	1,053
	2003–2004	208 (165–263)	177 (148–238)	417 (302–564)	907 (574–1,480)	1,490 (909–2,300)	888

Source: CDC 2018

[a]The LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 18.6, 8.3, and 7.8 ng/g, respectively.

CI = confidence interval; DDE = dichlorodiphenyldichloroethylene; LOD = limit of detection

Table 5-13. Geometric Mean and Selected Percentiles of *p,p'*-DDE (Whole Weight in ng/g of Serum or ppb) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% confidence interval)				Sample size
			50th	75th	90th	95th	
Total	1999–2000	1.54 (1.33–1.79)	1.31 (1.09–1.66)	3.50 (2.97–4.27)	7.49 (6.14–9.25)	11.6 (9.25–14.8)	1,964
	2001–2002	1.81 (1.64–2.01)	1.57 (1.37–1.72)	3.97 (3.43–4.59)	8.81 (7.85–10.1)	15.4 (12.9–17.6)	2,298
	2003–2004	1.45 (1.18–1.79)	1.28 (1.00-1.58)	3.16 (2.40–4.21)	7.07 (5.55–9.80)	12.1 (8.37–16.0)	1,956
Age group							
12–19 years	1999–2000	.561 (.488–.646)	0.520 (0.430–0.600)	0.870 (0.680–1.18)	1.52 (1.13–2.25)	2.32 (1.76–3.56)	686
	2001–2002	.623 (.534–.716)	0.590 (0.500–0.730)	1.00 (0.820–1.22)	1.65 (1.39–2.07)	2.30 (1.91–3.14)	758
	2003–2004	.516 (.419–.635)	0.456 (0.385–0.557)	0.796 (0.611–1.19)	1.69 (0.994–2.69)	2.51 (1.56–6.71)	588
≥20 years	1999–2000	1.83 (1.56–2.14)	1.61 (1.26–2.07)	4.17 (3.48–4.66)	8.12 (6.37–10.6)	12.3 (9.87–16.7)	1,278
	2001–2002	2.14 (1.91–2.39)	1.77 (1.61–2.05)	4.59 (4.10–5.26)	9.75 (8.34–11.5)	16.8 (13.7–19.1)	1,540
	2003–2004	1.69 (1.36–2.10)	1.46 (1.12–1.96)	3.68 (2.66–4.96)	7.91 (6.01–11.0)	12.8 (9.25–16.8)	1,368

Table 5-13. Geometric Mean and Selected Percentiles of *p,p'*-DDE (Whole Weight in ng/g of Serum or ppb) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2004

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% confidence interval)				Sample size
			50th	75th	90th	95th	
Gender							
Males	1999–2000	1.49 (1.30–1.70)	1.25 (1.10–1.44)	3.02 (2.57–3.80)	6.43 (5.40–8.00)	9.63 (6.63–15.6)	937
	2001–2002	1.77 (1.57–2.01)	1.59 (1.36–1.76)	3.40 (3.03–4.10)	7.48 (6.43–8.75)	13.1 (9.66–17.6)	1,069
	2003–2004	1.46 (1.18–1.80)	1.30 (1.04–1.58)	2.80 (2.18–4.13)	6.71 (5.51–8.54)	9.93 (7.51–15.4)	955
Females	1999–2000	1.59 (1.32–1.92)	1.38 (1.03–1.99)	4.05 (3.15–4.79)	8.18 (6.36–11.5)	13.2 (9.81–18.5)	1,027
	2001–2002	1.85 (1.66–2.06)	1.49 (1.32–1.75)	4.57 (3.81–5.47)	10.2 (9.01–11.9)	16.8 (13.4–19.7)	1,229
	2003–2004	1.45 (1.16–1.82)	1.25 (0.965–1.66)	3.55 (2.43–4.59)	7.87 (5.41–12.6)	13.7 (8.50–17.3)	1,001
Race/ethnicity							
Mexican Americans	1999–2000	3.92 (3.40–4.51)	3.52 (3.17–3.91)	8.22 (7.26–10.4)	22.0 (12.2–32.2)	32.2 (19.7–48.1)	657
	2001–2002	3.92 3.37–4.57)	3.53 (2.68–4.34)	9.34 (7.31–12.5)	26.6 (17.9–38.3)	40.9 (26.8–90.5)	566
	2003–2004	2.69 (2.18–3.32)	2.24 (1.70–3.24)	5.78 (4.54–7.21)	13.0 (9.53–15.6)	22.9 (15.3–43.4)	457
Non–Hispanic blacks	1999–2000	1.63 (1.31–2.02)	1.37 (1.11–1.66)	3.84 (3.01–5.69)	11.2 (6.57–13.3)	14.6 (8.88–35.2)	416
	2001–2002	1.82 (1.46–2.28)	1.38 (1.22–1.72)	4.39 (3.52–6.06)	10.6 (7.24–17.6)	19.4 (8.51–49.3)	515
	2003–2004	1.47 (1.30-1.65)	1.20 (0.963–1.51)	3.76 (2.85–4.75)	9.23 (7.19–14.9)	16.8 (14.7–20.6)	487
Non–Hispanic whites	1999–2000	1.32 (1.14–1.53)	1.13 (1.01–1.35)	2.88 (2.34–3.36)	5.75 (4.62–6.53)	8.04 (6.32–9.81)	732
	2001–2002	1.57 (1.39–1.76)	1.41 (1.27–1.58)	3.11 2.56–3.68)	7.00 (6.02–8.34)	11.3 (8.60–13.7)	1,053
	2003–2004	1.29 (1.01–1.64)	1.12 (0.890–1.49)	2.63 (1.84–3.90)	6.36 (3.90–8.71)	9.71 (6.01–15.0)	888

Source: CDC 2018

[a]The LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 18.6, 8.3, and 7.8 ng/g, respectively.

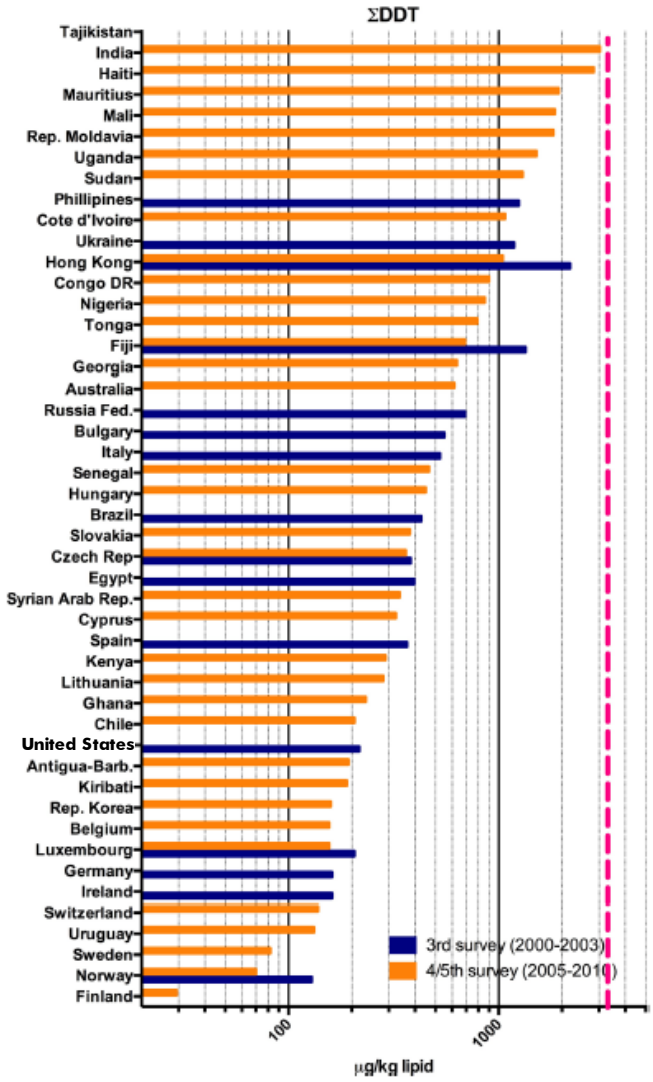
CI = confidence interval; DDE = dichlorodiphenyldichloroethylene; LOD = limit of detection

NHATS. The estimated national mean with relative standard error (%) *p,p'*-DDT concentrations for the 1982, 1984, and 1986 NHATS were 189 (31%), 123 (11%), and 177 (20%) ng/g, respectively. Those for *p,p'*-DDE were 1,840 (350%), 1,150 (90%), and 2,340 (270%) ng/g, respectively. A 1985 survey of 108 Canadian autopsy samples resulted in respective mean and maximum levels of *p,p'*-DDE at 811 and 6,070 ng/g and *p,p'*-DDT at 48 and 250 ng/g (Mes et al. 1990). Adeshina and Todd (1990) analyzed DDT isomer and metabolite levels in 35 human adipose tissue samples of North Texas residents who were not occupationally exposed to DDT. The samples were obtained during autopsy in 1987 and 1988. The geometric mean concentrations were (substance, ng/g lipid): *o,p'*-DDE, 8 ng/g; *p,p'*-DDE, 679 ng/g; *o,p'*-DDT, 14 ng/g; *p,p'*-DDT, 294 ng/g; and ΣDDT, 1,031 ng/g. The ΣDDT levels can be compared with those from the human adipose tissue survey which were 7,950 ng/g lipid in 1970, 5,150 ng/g lipid in 1974, and 1,670 ng/g lipid in 1983 (Adeshina and Todd 1990).

The results of a World Health Organization Survey for years 2000–2003 and 2005–2010 examined levels of ΣDDT in pooled human milk from 52 nations around the world (van den Berg et al. 2017). The highest levels of ΣDDT were measured in Asian countries, particularly Tajikistan, which had levels nearly 3 times greater than those in India (see Figure 5-2). Tropical countries that still use DDT for the prevention of malaria tended to have elevated levels in human milk, while levels in the United States and Europe tended to be lower.

Levels of DDE and DDT in human milk, blood, and tissue appear in Table 5-14. Correlations in the concentrations of DDT and its metabolites in human milk, adipose tissue, and blood serum have been observed. The lipid adjusted mean concentrations of *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD in human milk (0.65, 4.00, and 0.01 mg/kg, respectively) have been shown to correlate well (r^2=0.95, 0.89, and 0.75, respectively) with concentrations in adipose tissue (1.22, 4.36, and 0.02 mg/kg, respectively) (Waliszewski et al. 2001). The lipid adjusted serum concentrations of *p,p'*-DDE were observed to correlate with concentrations of this compound in breast adipose tissue (Dorea et al. 2001). The concentrations of *p,p'*-DDT and *p,p'*-DDE in blood serum taken from mothers in Veracruz, Mexico (1.848 and 4.378 mg/kg fat, respectively) have also been observed to correlate (r^2=0.854 and 0.779, respectively) with concentrations in umbilical cord blood (2.800 and 4.676 mg/kg fat, respectively) (Waliszewski et al. 2000).

Figure 5-2. Sum of DDT-like Compounds in µg/kg Lipid in Pooled Human Samples from Different Countries



The dotted red line represents the calculated safe level of these compounds for the breastfed infant based on the WHO provisional tolerable daily intake, EPA reference dose, and ATSDR ZMRL values.

Source: van den Berg et al. 2017 (used under http://creativecommons.org/licenses/by/4.0/; modified USA to United States)

Table 5-14. Levels of DDT Compounds in Human Milk, Blood, and Tissues

DDT compound	Population	Tissue	Mean[a] concentration	Units as reported	Reference
Milk					
p,p'-DDT	Maternity patients in Mexico City, Cuernavaca and rural Morelos	Milk fat	0.71, 1.69, 4.84[b]	mg/kg	Elvia et al. 2000
p,p'-DDT	Mothers in Sweden	Milk fat	14	µg/g	Norén and Meironyté 2000
p,p'-DDT	Maternity patients in Mexico City	Milk fat	0.162	mg/kg	Torres-Arreola et al. 1999
p,p'-DDT	Women in Germany	Milk fat	0.7 (estimated from graph)	mg/kg	Scheele et al. 1995
o,p'-DDT	Maternity patients in Mexico City	Milk fat	0.138	mg/kg	Torres-Arreola et al. 1999
p,p'-DDE	Maternity patients in Mexico City, Cuernavaca and rural Morelos	Milk fat	3.85, 6.51, 16.52[b]	mg/kg	Elvia et al. 2000
p,p'-DDE	Mothers in Sweden	Milk fat	129	µg/g	Norén and Meironyté 2000
p,p'-DDE	Inuit women in Canada	Milk fat	962	µg/g	Dewailly et al. 2000
p,p'-DDE	Quebec women between 1989 and 1990 (n=536)	Milk fat	0.34	mg/kg	Dewailly et al. 1996
p,p'-DDE	Maternity patients in Mexico City	Milk fat	0.594	mg/kg	Torres-Arreola et al. 1999
p,p'-DDE	Maternity patients in Veracruz, Mexico	Milk fat	5.302	mg/kg	Pardio et al. 1998
p,p'-DDE	Mothers of hospitalized children in Zagreb, Croatia	Milk fat	0.318	mg/kg	Krauthacker et al. 1998
ΣDDT	Canadian women, 1986 (n=412)	Milk fat	0.385	mg/kg	Smith 1999
ΣDDT	Arkansas women, 1986 (n=536)	Milk fat	0.99	mg/kg	Smith 1999

Table 5-14. Levels of DDT Compounds in Human Milk, Blood, and Tissues

DDT compound	Population	Tissue	Mean[a] concentration	Units as reported	Reference
Blood					
p,p'-DDT	Workers in Sao Paulo, Brazil	Serum	13.5 (DDT appliers) 1.5 (unexposed)	µg/L	Minelli and Ribeiro 1996
o,p'-DDT	Workers in Sao Paulo, Brazil	Serum	<0.7–4.7 (range; DDT appliers)	µg/L	Minelli and Ribeiro 1996
p,p'-DDE	Workers in Sao Paulo, Brazil	Serum	64.3 (DDT appliers) 14.3 (unexposed)	µg/L	Minelli and Ribeiro 1996
p,p'-DDT	Men in southeast Sweden	Blood plasma	0.11 (lipid adjusted)	ng/g	Asplund et al. 1994
p,p'-DDE	Female hospital patients in New Haven, Connecticut	Serum (lipid-adjusted)	967 (median), <1.0–2261.5 (range) (n=36)	ng/g	Archibeque-Engle et al. 1997
p,p'-DDE	Iowa and North Carolina farmers and spouses	Serum	0.39–6.51 (range)	µg/L	Brock et al. 1998
o,p'-DDE	Iowa and North Carolina farmers and spouses	Serum	0.71–2.31 (range)	µg/L	Brock et al. 1998
p,p'-DDE	Women without breast cancer in Long Island	Serum	4.7	µg/L	Stellman et al. 1998
p,p'-DDE	New York University Women's Health Study (1985–1991)	Serum	11.0±9.1 in cancer patients (n=58) 7.7±6.8 controls (n=171)	µg/L	Wolff et al. 1993
p,p'-DDE	Female hospital patients in New York City	Plasma	6.93–7.29 (range of mean values)	µg/L	Gammon et al. 1997
p,p'-DDE	Female hospital patients in New York City	Plasma (lipid-adjusted)	0.963–0.997 (range of mean values)	µg/mL	Gammon et al. 1997
p,p'-DDE	191 Children from California Childhood Leukemia Study (1999–2007)	Whole blood	690 (median), 1,400 (75th percentile), 4,100 (90th percentile), 110,000 (maximum)	pg/mL	Whitehead et al. 2015
p,p'-DDE	Mothers in Veracruz, Mexico	Serum	14.5	ng/mL	Waliszewski et al. 2001
p,p'-DDE	Men in southeast Sweden	Plasma	2.4–14 (range of mean values among groups of men with different levels of fish consumption)	ng/g	Asplund et al. 1994

Table 5-14. Levels of DDT Compounds in Human Milk, Blood, and Tissues

DDT compound	Population	Tissue	Mean[a] concentration	Units as reported	Reference
p,p'-DDE	Men in southeast Sweden	Plasma (lipid-adjusted)	750–4,500 (range of mean values among groups of men with different levels of fish consumption)	ng/g	Asplund et al. 1994
DDE	Controls in a case-control study nested within the Nurses Health Study (n=240)	Plasma	7.09	ppb[c]	Laden et al. 1999
p,p'-DDE	Four groups of refugees from Asia, 'USSR,' Africa, 'Yugoslavia' (n=103); controls from Germany (n=34)	Plasma	2.30–16.90 (range of median values) 12.20–93.00 (range of maximum values) (refugees) 1.14 (median), 4.97 (maximum) (controls)	µg/L	Schmid et al. 1997
p,p'-DDT	Residents of Nainital, India	Serum	4.46 (mean), range (0.78–14.29)	mg/L	Dua et al. 2001
p,p'-DDE	Residents of Nainital, India	Serum	1.55 (mean), range (0.14–4.10)	mg/L	Dua et al. 2001
p,p'-DDD	Residents of Nainital, India	Serum	0.91 (mean), range (ND–2.82)	mg/L	Dua et al. 2001
p,p'-DDE	New Bedford area infants	Cord blood	0.493	ng/g serum	Korrick et al. 2000
p,p'-DDE	Maternity patients in Veracruz, Mexico	Cord blood	6.0	ng/mL	Waliszewski et al. 2001
p,p'-DDE	Maternity patients in Nicaragua	Venous blood (lipid-adjusted)	7.12 (mean), range (0–35.23) (n=52)	ng/g	Dorea et al. 2001
p,p'-DDE	Maternity patients in Nicaragua	Cord blood (lipid-adjusted)	6.39 (mean), range (0–9.35) (n=52)	ng/g	Dorea et al. 2001
p,p'-DDT	Great Lakes fishermen (n=30); controls (n=180)	Serum	0.3 (median), 0.05–0.8 (range) ND (controls)	ppb[c]	Anderson et al. 1998
o,p'-DDT	Great Lakes fishermen (n=30); controls (n=180)	Serum	0.06 (median), 0.03–0.3 (range) ND (controls)	ppb[c]	Anderson et al. 1998
p,p'-DDE	Great Lakes fishermen (n=30); controls (n=180)	Serum	5.2 (median), 0.6–23.9 (range) 2.8 (median), ND–38.5 (range) (controls)	ppb[c]	Anderson et al. 1998
DDE	Frequent GLSCF (Lake Michigan) males (n=98); females (n=83); male controls (n=23); female controls (n=22)	Serum	6.9 (males), 2.9 (females), 2.6 (controls, males), 1.4 (controls, females) (geometric means)	ppb[c]	Hanrahan et al. 1999

Table 5-14. Levels of DDT Compounds in Human Milk, Blood, and Tissues

DDT compound	Population	Tissue	Mean[a] concentration	Units as reported	Reference
DDE	Frequent GLSCF (Lake Huron) males (n=65); females (n=37); male controls (n=3); female controls (n=3)	Serum	3.5 (males), 2.3 (females), 2.6 (controls, males), 0.6 (controls, females) (geometric means)	ppb[c]	Hanrahan et al. 1999
DDE	Frequent GLSCF (Lake Erie) males (n=89); females (n=67); male controls (n=31); female controls (n=17)	Serum	3.8 (males), 2.0 (females), 2.0 (controls, males), 1.7 (controls, females) (geometric means)	ppb[c]	Hanrahan et al. 1999
ΣDDT	1982 Great Lakes fish eaters (n=572); controls (n=419)	Serum	28.8 10.6 (controls)	ppb[c]	Hovinga et al. 1992
ΣDDT	1982 Southern Great Lakes fish eaters (n=115); controls (n=95)	Serum	25.8 9.6 (controls)	ppb[c]	Hovinga et al. 1992
ΣDDT	1989 Southern Great Lakes fish eaters[d] (n=115); controls (n=95)	Serum	15.6 6.8 (controls)	ppb[c]	Hovinga et al. 1992
Adipose and other tissue					
p,p'-DDT	Children in Germany	Adipose	0.6 (estimated from graph)	mg/kg	Scheele et al. 1995
p,p'-DDT	Children in Germany	Bone marrow (lipid-adjusted)	1.75 (estimated from graph)	mg/kg	Scheele et al. 1995
p,p'-DDT	Female hospital patients in New Haven, Connecticut	Adipose, breast (lipid-adjusted)	132.2 (median), 54.0–418.2 (range) (n=36)	ng/g	Archibeque-Engle et al. 1997
p,p'-DDT	Maternity patients in Veracruz, Mexico	Adipose, abdominal (lipid-adjusted)	1.22 (mean), 0.01–9.03 (range) (n=60)	mg/kg	Waliszewski et al. 2001
p,p'-DDE	Maternity patients in Veracruz, Mexico	Adipose, abdominal (lipid-adjusted)	4.36 (mean), 0.31–16.04 (range) (n=60)	mg/kg	Waliszewski et al. 2001
p,p'-DDD	Maternity patients in Veracruz, Mexico	Adipose, abdominal (lipid-adjusted)	0.02 (mean), ND–0.25 (range) (n=60)	mg/kg	Waliszewski et al. 2001
p,p'-DDE	Female hospital patients in New Haven, Connecticut	Adipose, breast (lipid-adjusted)	970 (median), 240.0–2,644.1 (range) (n=36)	ng/g	Archibeque-Engle et al. 1997
p,p'-DDT	Adults in Germany	Bone marrow (dry lipid-adjusted)	0.364	ppm[c]	Scheele 1998
p,p'-DDE	Adults in Germany	Bone marrow (dry lipid-adjusted)	1.689	ppm[c]	Scheele 1998

Table 5-14. Levels of DDT Compounds in Human Milk, Blood, and Tissues

DDT compound	Population	Tissue	Mean[a] concentration	Units as reported	Reference
p,p'-DDE	Women without breast cancer in Long Island	Adipose	546.7	ng/g	Stellman et al. 1998
p,p'-DDE	Adults in Sweden who suffered sudden death	Liver (lipid-adjusted)	836	ng/g	Weistrand and Norén 1998
p,p'-DDE	Adults in Sweden who suffered sudden death	Adipose, abdominal	788	ng/g	Weistrand and Norén 1998
p,p'-DDE	FY 1986 National Adipose Tissue Survey Composite samples (n=50, from 671 specimens)	Adipose	2,340 (SE 12) (nation) 1,710 (SE 22%) (0–14 years) 2,150 (SE 17%) (15–44 years) 3,080 (SE 13%) (45+ years)	ng/g	Lordo et al. 1996
p,p'-DDT	FY 1986 National Adipose Tissue Survey Composite samples (n=50, from 671 specimens)	Adipose	177 (SE 11%) (nation) 73.0 (SE 36%) (0–14 years) 177 (SE 16%) (15–44 years) 252 (SE 13%) (45+ years)	ng/g	Lordo et al. 1996
p,p'-DDE	Women patients at Hartford Hospital, Hartford, Connecticut	Adipose, breast (lipid basis)	2,200±1,470 cancer patients (n=20) 1,487±842 controls (n=20)	ng/g	Falck et al. 1992
p,p'-DDT	Women patients at Hartford Hospital, Hartford, Connecticut	Adipose, breast (lipid-adjusted)	216±174 cancer patients (n=20) 148±75 controls (n=20)	ng/g	Falck et al. 1992
p,p'-DDE	Rochester, New York; Milwaukee, Wisconsin; Sacramento, California	Placenta	205 (n=169)	pg/g	Nanes et al. 2014

[a]Arithmetic mean concentrations are reported unless otherwise specified.
[b]Geometric mean concentrations.
[c]ppm=µg/g; ppb=ng/g.
[d]Same Southern Great Lakes fish eaters who participated in the 1982 study.

DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; FY = fiscal year; GLSCF = Great Lakes sport caught fish; ND = not detected; SE = standard error

Comparison of the concentrations of DDT and its metabolites in breast tissues and serum have been conducted in women with breast cancer in comparison to control subjects. The mean concentrations (unadjusted for age) of *p,p'*-DDT and *p,p'*-DDD in breast tissues of U.S. women with breast cancer (261.6 and 9.8 ng/g lipid, respectively) did not statistically differ (p=0.23 and 0.79) from those measured in control subjects (267.3 and 24.0 ng/g lipid); however, the concentration of *p,p'*-DDE was statistically higher (p=0.006) in breast cancer patients (800.0 ng/g lipid) than in control subjects (709.1 ng/g lipid) (Bagga et al. 2000). When the mean concentrations for *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD were adjusted for age, there was no statistical difference ($p \leq 0.001$) between cases and controls for all three compounds. Statistically higher concentrations ($p < 0.05$) of *p,p'*-DDE in serum were observed in both premenopausal (2.40 μg/g lipid) and postmenopausal (5.10 μg/g lipid) breast cancer patients from Mexico City, Mexico, in comparison to controls (1.93 and 3.12 μg/g lipid, respectively) (Romieu et al. 2000). The increased concentrations of *p,p'*-DDE in breast tissues of cancer patients has been attributed to increased exposures of these women to *p,p'*-DDE rather than to differences in the metabolism of *p,p'*-DDE by cancer cells (Romieu et al. 2000). However, in a study of breast cancer patients and control subjects in the New York University Women's Health Study, there was no statistical difference between the geometric means of the *p,p'*-DDE concentrations in serum (1,097 ng/g lipid in patients versus 977 ng/g lipid in controls) obtained from these two groups of women (Wolff et al. 2000b). A number of other studies have also found no statistical differences in the mean concentrations of DDT and/or its metabolites in serum or adipose tissue between cancer cases and controls (Demers et al. 2000; Dorgan et al. 1999; Helzlsouer et al. 1999; Krieger et al. 1994; Laden et al. 2001a; Liljegren et al. 1998; Lopez-Carrillo et al. 1997; Mendonca et al. 1999; Moysich et al. 1998; Schecter et al. 1997; Unger et al. 1984; van't Veer et al. 1997; Ward et al. 2000; Wolff et al. 2000a; Zheng et al. 1999, 2000).

Methyl sulfonyl metabolites of *p,p'*-DDE, primarily the 3-methylsulfone isomer, have been found in seven surveys of human milk in Sweden between 1972 and 1992 (Norén et al. 1996). In that time, levels declined from 5.05 to 0.46 ng/g lipids and the ratio of the 3-methylsulfone metabolite to *p,p'*-DDE remained constant at 0.002.

Fish from areas like the Great Lakes and Baltic Sea appear to be an important source of exposure to DDT and DDE, and human blood levels of these compounds have been found to correlate with the consumption of fish containing high levels of DDT and DDE (Anderson et al. 1998; Asplund et al. 1994; Hovinga et al. 1992). A Swedish study found that the mean plasma lipid concentrations of *p,p'*-DDE were 750, 1,200, and 4,500 ng/g in groups of men eating no fish, moderate quantities of fish, and large quantities of fish, respectively, from the Baltic Sea (Asplund et al. 1994). The respective lipid plasma

concentrations of *p,p'*-DDT in these groups of men were 20, 45, and 130 ng/g. The mean serum DDT level in individuals eating more than 20 pounds of sport-caught Great Lakes fish dropped from 25.8 to 15.6 ppb (65% decrease) during the period from 1982 to 1989. Mean serum DDT levels in the controls dropped from 9.6 to 6.8 ppb (41% decrease). It was concluded that the decrease in serum DDT concentrations was due to lower levels of DDT in the fish and in the environment, rather than to a decrease in fish consumption (Hovinga et al. 1992).

A study of residents in Triana, Alabama, living downstream from a former DDT manufacturing facility revealed mean serum levels of total DDT of 76.2 ppb (Kreiss et al. 1981). This was several times higher than other reported levels. Kreiss et al. (1981) also found that serum DDT levels increased with increasing age. Residents living near a pesticide dump site in Aberdeen, North Carolina, known to contain high concentrations of DDT, have been shown to have age-adjusted mean levels of DDE in their blood of 4.05 ppb, which is higher than the mean value of 2.95 ppb obtained from residents of neighboring communities (Vine et al. 2000).

Mean levels of total equivalent of DDT, DDE, and DDD in maternal blood in pregnant women in India (20 samples) were found to be 25.3 ppb compared to levels in placental tissue of 22.2 ppb (Saxena et al. 1987). Similar levels (30.8 ppb) were seen in maternal blood in Brazilian women (Procianoy and Schvartsman 1981). Saxena et al. (1981, 1983) presented data on a limited number of samples of blood and placental tissues of women that aborted or delivered prematurely, which suggested that *p,p'*-DDE concentrations were elevated compared to control groups. *p,p'*-DDE was detected in 100% of 169 placental specimens collected in Rochester, New York; Milwaukee, Wisconsin; and Sacramento, California (Nanes et al. 2014). The mean concentration was 205 pg/g (0.205 ppb) and the median level was 81 pg/g (0.081 ppb). The authors noted that higher concentrations were observed from the samples collected in Sacramento as compared to Rochester (p=0.03).

Adipose tissue from a subgroup of 40 workers engaged in spraying DDT for malaria control in Mexico contained the following median and maximum levels of DDT metabolites (μg/g): ΣDDT, 114.60, 665.56; *p,p'*-DDT, 46.96, 344.98; *o,p'*-DDT, 2.96, 29.74; *p,p'*-DDE, 64.96, 298.42; and *p,p'*-DDD, 0.62, 3.51 (Rivero-Rodriguez et al. 1997). Based on these measurements and a survey of the work habits of other workers, a geometric mean *p,p'*-DDE concentration of 67.41 μg/g was predicted for the population of 331 workers, 80% of whom were employed in the sanitation campaign for 20 years. Mean ΣDDT serum level in a group of 26 malaria control sprayers in Brazil was 76.9 μg/L and ranged from 7.5 to 473.5 μg/L, whereas 16 unexposed workers had mean serum levels of 16.1 μg/L (range: 5.1–32.9 μg/L)

(Minelli and Ribeiro 1996). The ranges of *p,p'*-DDT and *p,p'*-DDE serum levels in the exposed workers were 1.6–62.9 and 5.9–405.9 μg/L, respectively.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Children are exposed to DDT through their diet. Since the greatest dietary intake of DDT is from meat, fish, poultry, and dairy products, infants and young children for whom a substantial part of their food is milk may be exposed to DDT. According to the FDA study of 1986–1991, the mean daily intake of DDT and its metabolites is 0.0448, and 0.0438 μg/kg body weight/day for a 6–11-month-old infant and 2-year-old child, respectively (Gunderson 1995b). This is roughly 4 times the intake per unit body weight for an adult (see Table 5-3).

DDT and DDE selectively partition into fatty tissue and into human breast milk, which has a higher fat content than cow's milk. The concentration of DDT, or other hydrophobic pollutants, in milk is often expressed on a lipid basis (i.e., μg/g lipid rather than μg/mL milk) as it is a more accurate measure of DDT content due to the fluctuating fat content of the milk. Generally, these compounds are found in human breast milk in concentrations higher than in cow's milk or other infant foods. As a result, breastfed infants may receive higher dietary exposure than those who are not breastfed. If a woman has been exposed to high levels of DDT in the past, her milk may contain high levels of DDT, which would be transferred to her child. Women exposed to high levels of DDT would include Eskimos and Indian women in Arctic regions who eat traditional foods as well as women who eat large quantities of fish from lakes and rivers known to have high concentrations of DDT, such as the Great Lakes and the Yakima River, Washington (Bard 1999; Kuhnlein et al. 1995; Marien and Laflamme 1995). Methods have been proposed for estimating breast milk lipid concentrations of DDT from a mother's daily intake (Marien and Laflamme 1995). Mean levels of *p,p'*-DDT in human breast milk in pooled milk from the Mothers' Milk Center in Stockholm steadily declined from 0.71 μg/g lipid in 1972 to 0.36, 0.18, and 0.061 μg/g lipid in 1976, 1980, and 1984–1985, respectively (Norén 1988). Mean levels of *p,p'*-DDE for these years were 2.42, 1.53, 0.99, and 0.50 μg/g lipid, respectively. Between 1967 and 1985, the levels of *p,p'*-DDE and *p,p'*-DDT in human milk in Sweden declined by 75 and 95% (Norén 1993). In another study conducted between 1972 and 1992, this same group of investigators noted a similar decline in *p,p'*-DDE and *p,p'*-DDT concentrations in human milk in Sweden; the rates at which the concentration of these two compounds have been declining has also been progressively decreasing with time during this same period (Norén et al. 1996). The use of DDT was banned in Sweden in 1970. Mean (maximum) *p,p'*-DDT concentrations in 54 samples of mothers' milk from Hawaii (1979–1980) were 0.16 (0.52) μg/g lipid

compared with 0.19 (1.7) µg/g lipid in 102 samples from the U.S. mainland (Takei et al. 1983). Mean (maximum) *p,p'*-DDE levels in Hawaiian and mainland samples were 2.0 (5.7) and 1.9 (11.0) µg/g lipid. A 1982 Canadian survey that included 210 samples of breast milk from across the country resulted in mean levels of *p,p'*-DDE, *p,p'*-DDT, *p,p'*-DDD, and *o,p'*-DDT in ng/g milk (ng/g milkfat) of 34 (911), 3 (80), 1 (27), and trace (12), respectively, down from 103, 33, 4, and 5 ng/g milk, respectively, obtained in a 1967 survey (Mes et al. 1986). The maximum *p,p'*-DDE, *p,p'*-DDT, *p,p'*-DDD, and *o,p'*-DDT levels in the 1982 survey were 5,500, 450, 113, and 58 ng/g milkfat. Levels of DDT in breast milk have shown a downward trend starting in about 1970. In 28 studies from the United States and Canada, average DDT levels in breast milk were about 4,000–5,000 ng/g lipid in the early 1970s, and then steadily declined by 1975. For 13 studies from 1975 on, there was an 11–21% reduction in mean ΣDDT levels per year. Another way of viewing this is that the mean breast milk level in the population is being reduced by one-half in 4.2–5.6 years. Similar reductions have been observed in Western European countries. While eating fish from the Great Lakes has been a source of concern for human exposure, a study by Mes and Malcolm (1992) revealed that levels of DDE and DDT in breast milk were lower in women in the Great Lakes Basin than in women in the rest of Canada. Levels of DDE in cow's milk have similarly declined. The mean level of DDE in milk supplies in Southern Ontario, Canada declined from 96 ng/g lipid in 1970–1971 to 16 ng/g lipid in 1985–1986, indicating that the levels are being reduced by one-half in 5.8 years (Frank and Braun 1989). Since levels of DDT in food have been declining, exposure of children to DDT through their diet is anticipated to be much less than in the past.

Children may be exposed to DDT by ingesting contaminated soil or dust, from dermal contact with the soil, or by inhaling dust and then swallowing it after mucociliary transport up out of the lungs. DDT is extremely persistent in soil and there are soils that still contain high levels of the insecticide. No reports have been found, however, concerning childhood exposures to DDT by ingesting dirt. DDT is strongly adsorbed to soil, especially when the organic content of the soil is high. No studies were found as to how bioavailable DDT-adsorbed soil is when ingested. In addition, no information was found on the absorption of ingested DDT in any form in children. Children may also be exposed to DDT improperly stored at waste sites. One study indicated that old carpeting may contain high levels of DDT (Lewis et al. 1994). The DDT may have contaminated the carpet material or may have been tracked in from outside. Children may be exposed to this DDT while crawling around or playing on contaminated carpeting.

Since DDT partitions into lipids and is not readily metabolized, levels of DDT in adipose tissue increase with age. Levels of DDT and DDE in children aged 0–14 as reported in EPA's FY 1986 National Adipose Tissue Survey appear in Table 5-14 (Lordo et al. 1996).

Because of the ban on DDT use after 1972, fewer persons in the United States are anticipated to be exposed to high levels of these compounds today than in the past. Only fish and marine mammal consumption in the Arctic appear to be significant dietary contributors to human exposure to DDT in the general population (Laden et al. 1999). A 1982 study by the Michigan Department of Public Health found that people eating large quantities of Great Lakes fish had significantly higher serum DDT levels compared to non-fish-eating control populations. A follow-up study in 1989 found that serum DDT levels were primarily a reflection of historic exposures and previously established body burden rather than recent exposure (Hovinga et al. 1993). Other studies confirm these findings (Anderson et al. 1998; Hanrahan et al. 1999). The best predictors of serum DDE levels in frequent Great Lakes sport fish consumers were found to be age, years of eating sport caught fish, male gender, and BMI, which respectively accounted for 20, 10, 9, and 9% of the variance (Hanrahan et al. 1999). In general, DDT-contaminated fish are caught by sport or subsistence fisherman and not purchased at the market (Laden et al. 1999). As the levels of DDT in Great Lakes fish decline, fish consumption is less likely to be a source of potentially high exposure. Because of the partitioning of DDT and DDE into fatty tissue and fluids, breastfed infants are likely to receive doses in excess of those occurring from ingestion of cow's milk or other infant foods. Monitoring exposure of infants via breast milk has been extensive and provides evidence of the persistence of DDT and DDE in fatty tissues. The finding that old carpeting may contain high levels of DDT indicates that this may be an important, but unevaluated source of exposure, especially in small children crawling on the carpeting (Lewis et al. 1994).

A study of Mexican Americans, born in Mexico, found elevated serum levels of *p,p'*-DDT that declined with increasing years in the United States and increased with age (Everett et al. 2017b). Significantly higher serum levels were found in Mexican Americans living in the United States for <5 years, as compared to those living in the United States for >30 years. The percentage of individuals with serum *p,p'*-DDT levels >0.086 ng/g were 10.1, 55.8, 29.5, and 4.6% for 12–19, 20–39, 40–64, and ≥65 years of age, respectively. The study also found a decline in serum *p,p'*-DDT serum levels 3–4 years after Mexico banned the use of DDT in 2000.

Workers involved with formulation, packaging, and application of DDT in the past would be expected to have been exposed to levels higher levels than those encountered in the general environment. Persons who live near NPL sites containing DDT, DDE, or DDD might be exposed to higher levels than the general population.

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of DDT, DDE, and DDD is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of DDT, DDE, and DDD.

Data needs are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 INFORMATION ON HEALTH EFFECTS

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

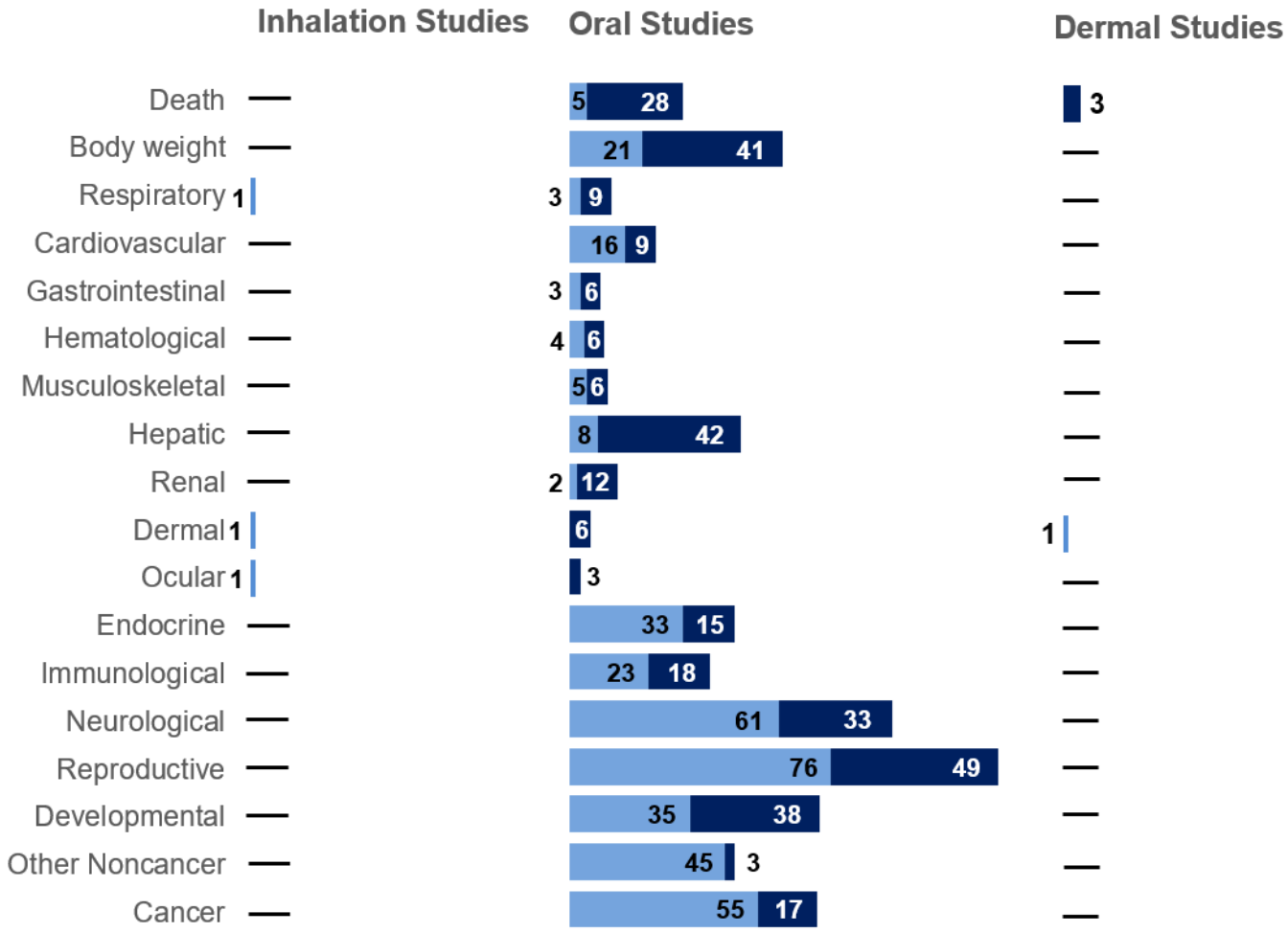
As illustrated in Figure 6-1, most of the data on the toxicity of DDT, DDE, and DDD come from epidemiology studies with a presumed oral route of exposure and from oral exposure studies in laboratory animals. A small number of studies have examined toxicity following inhalation or dermal exposure. Most of the oral exposure studies examined reproductive, neurological, cancer, and developmental endpoints.

6.2 IDENTIFICATION OF DATA NEEDS

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

Figure 6-1. Summary of Existing Health Effects Studies on DDT, DDE, and DDD By Route and Endpoint*

Most health effects research on DDT, DDE, and DDD focused on oral exposure
The most studied endpoints (in **humans** & **animals**) were reproductive, neurological and developmental effects and cancer



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

Acute-Duration MRLs. Information on health effects following acute-duration inhalation of DDT, DDE, or DDD in humans (Neal et al. 1944) was limited. Because of the lack of adequate inhalation data in humans or animals, an acute-duration inhalation MRL for DDT, DDE, and DDD was not derived. Additional inhalation data are needed to identify critical targets of toxicity and evaluate concentration-response relationships.

With acute-duration oral exposure to high doses, the nervous system appears to be the major target in both humans and animals. Acute-duration oral exposure has been associated with tremors or convulsions in humans (e.g., Hsieh 1954; Velbinger 1947a, 1947b) and animals (e.g., Hong et al. 1986; Matin et al. 1981). An acute-duration oral MRL for DDT, DDE, and DDD was based on neurobehavioral effects observed in adult mice following acute-duration perinatal exposure to technical DDT (Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996; Talts et al. 1998). Further acute-duration oral exposure studies during critical windows of embryonic, fetal, or neonatal development in different species may provide confirmatory evidence. Also of interest would be comparison of the neurodevelopmental toxicity of different isomers of DDT, DDD, and DDE. Of most interest would be studies on the isomer, *p,p'*-DDE, detected at the highest concentrations in environmental media, human tissues and fluids, and foods.

Intermediate-Duration MRLs. A single study of volunteers repeatedly exposed to oral doses up to 0.5 mg technical DDT/kg/day reported no effects on body weight, cardiovascular performance (e.g., blood pressure, heart rate), liver function tests, or self-reported neurological symptoms (Hayes et al. 1956). 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 most sensitive outcomes were hepatic, reproductive, developmental, immunological, and neurological effects. An intermediate-duration oral MRL was derived based on hepatic toxicity (hepatocellular hypertrophy) in rats fed *p,p'*-DDT for 26 weeks (Harada et al. 2003, 2006).

Additional inhalation data are needed to identify critical targets of toxicity and evaluate concentration-response relationships.

Chronic-Duration MRLs. Human data suitable for deriving chronic-duration MRLs are not available. At least 35 animal studies have evaluated the oral toxicity of DDT, DDE, or DDD and their related isomers following chronic-duration exposure. These studies examined a wide range of potentially

sensitive targets and provide data suitable for deriving a chronic-duration oral MRL. The most sensitive effects appear to be hepatic, body weight, developmental, hematological, and neurological outcomes. Liver effects were selected as the critical effect, because the lowest LOAEL was for liver effects and extensive supporting data support it as the most sensitive effect. A chronic-duration oral MRL was derived based on hepatocellular hypertrophy in rats fed *p,p'*-DDT for 2 years (Harada et al. 2003, 2006).

No chronic-duration inhalation toxicity studies in animals that could be used to establish concentration-response relationships were located; these data are needed for derivation of a chronic-duration inhalation MRL.

The derivation of acute, intermediate, or chronic-duration oral MRLs based on human epidemiological data might be possible with additional research to develop and validate a human PBPK model that could reliably estimate oral intake levels from levels of DDT, DDE, or DDD in biological fluids or tissues. To date, limited but consistent epidemiological evidence has been provided for associations with risks for a few noncancer health outcomes (abortion or preterm births, wheeze in infant or child offspring, and DMT2 in adults).

Health Effects. Toxicity studies of laboratory animals exposed by the inhalation or dermal routes are very small in number. Air monitoring data suggest that DDT and its metabolites are still present decades after its use was banned. Health effect studies are needed to evaluate possible health effects associated with long-term exposure to low concentrations of DDT in air.

Numerous epidemiological studies have examined possible associations between levels of DDT, DDE, or DDD in samples of biological fluids or tissues and a wide array of health outcomes. To date, consistent epidemiological evidence for positive associations (across studies) was provided for only a few health outcomes (abortion or preterm births, wheeze in infant or child offspring, DMT2 in adults, and liver cancer).

In contrast, numerous studies of laboratory animals orally exposed to DDT, DDE, or DDD for acute, intermediate, and chronic durations and a few controlled-exposure studies of volunteers have identified several sensitive toxicity targets. For each of these toxicity targets, additional research comparing the potency of the various isomers and pertinent mixtures in various short-term *in vivo* or *in vitro* test systems may lead to refinements of the current MRLs, which are assumed to be applicable to exposure to any of the isomers or their mixtures.

Hepatic. Recent mechanistic studies in rats indicate that p,p'-DDT initially induces (presumably through activation of the *CAR*) liver microsomal xenobiotic metabolizing enzymes and transient bursts in DNA synthesis and cell proliferation that lead to increased liver weight, hypertrophy, eosinophilic abnormal hepatic foci, and eventually liver tumors (Harada et al. 2003, 2006, 2016). Additional similar research with other isomers and other species may provide useful information to evaluate the relevance of DDT-induced liver effects in rodents to humans. Studies with micro-dissected liver tissues or liver tissue culture systems may be particularly useful, especially for cross-species extrapolation issues.

Neurological and Neurodevelopmental. Neurological symptoms such as tremors from relatively high oral doses of DDT and DDE isomers or mixtures like technical DDT have been observed following acute-duration exposures in human adults and laboratory animals after acute, intermediate, or chronic-duration oral exposure, but limited evidence indicates that this response does not occur in laboratory animals exposed to DDD (NCI 1978). Brain chemistry changes have been associated with these high-dose symptoms in adult laboratory animals (Hong et al. 1986; Hrdina et al. 1973; Hudson et al. 1985; Hwang and Van Woert 1978; Tilson et al. 1986), but brain neurochemical changes and behavioral changes have been observed after acute-duration exposure to a very low dose of technical DDT (0.5 mg/kg/day) on 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). As discussed for the acute-duration MRL data needs, additional acute-duration oral exposure studies during critical windows of embryonic, fetal, or neonatal neurodevelopment using different isomers (e.g., *p,p'*-DDE) or mixtures or species may be informative.

Reproductive and Developmental Reproductive. Epidemiological studies examining possible associations between levels of DDT, DDE, or DDD in biological fluids or tissues and a wide array of reproductive health outcomes have provided inconsistent evidence for associations or no evidence for association, except for studies providing consistent evidence of increased risk for abortions or preterm births in women with elevated levels of biomarkers (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). Further case-control studies in regions where DDT continues to be used for insect control may be useful to better determine if increased risk for abortions or preterm birth is a human health outcome associated with DDT exposure. Studies of mature and developing laboratory animals orally exposed to DDT, DDE or DDD have reported effects on reproductive

endpoints at dose levels ≥~5 mg/kg/day. Additional reproductive toxicity animal studies are not needed, because reproductive effects in laboratory animals appear to be less sensitive to DDT, DDE, or DDD exposure than liver and neurodevelopmental effects.

Immunological. Epidemiological studies provided consistent evidence for 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), but inconsistent evidence for associations with 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) and associations between serum levels of *p,p'*-DDE or *p,p'*-DDT and immune function biomarkers or immune-related conditions (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). Suppression or stimulation of various immune responses have been observed in mature laboratory animals exposed for intermediate durations to dietary doses of technical DDT, *p,p'*-DDT, *p,p'*-DDE, *p,p'*-DDD, or *o,p'*-DDD ranging from about 2 to 20 mg/kg/day (Banerjee 1987a, 1987b; Banerjee et al. 1986, 1995, 1996, 1997a, 1997b; Hamid et al. 1974; Gabliks et al. 1975; Koner et al. 1998; Rehana and Rao 1992; Street and Sharma 1975). Additional studies of immune endpoints in laboratory animal offspring following gestational or early postnatal exposure may be useful to determine the relative sensitivity of developmental immune system effects, compared with liver and neurodevelopmental effects.

Metabolic/DMT2 (Other Noncancer). Numerous epidemiological studies provided consistent evidence for associations between serum levels of DDT, DDE, or DDD and DMT2 in human adults (e.g., Evangelou et al. 2016; Fakhri et al. 2017; Lee et al. 2010, 2011b; Rignell-Hydbom et al. 2009b; Tang et al. 2014; Taylor et al. 2013; Turyk et al. 2009; Wu et al. 2013). Results from a few mechanistic laboratory animal studies provided limited evidence for perturbations of energy metabolism and homeostasis from exposure to *p,p'*-DDE (Howell et al. 2014, 2015) or gestational and early life exposure to a mixture of *p,p'*-DDT and *o,p'*-DDT and chronic-duration exposure to a high-fat diet (La Merrill et al. 2014a, 2014b). Additional research to better characterize DDT-, DDE-, or DDD-induced perturbations of energy-metabolism homeostasis (e.g., dependence on dose levels, duration of exposure, or critical windows of development) may be useful to better determine: (1) if exposure to DDT, DDE, or DDD is an

important risk factor in the development of DMT2 and (2) the relative sensitivity of DDT-induced energy-metabolism perturbations, compared with liver and neurodevelopmental effects.

Cancer. Numerous epidemiological provide inconsistent evidence for associations, or consistent evidence for no association, between DDT, DDE, or DDD levels in biological fluids or tissue and increased risk for many types of cancer. In contrast, several epidemiological studies provide consistent evidence for association with increased risk of liver cancer, particularly in groups with relatively high levels of DDT, DDE, or DDD biomarkers (Cocco et al. 2000; McGlynn et al. 2006; Persson et al. 2012; Zhao et al. 2012). Chronic-duration oral exposure of laboratory rats and mice to DDT, DDE or DDD has produced increased incidence of liver tumors in multiple studies; a few studies also show an increased incidence of lung tumors. Mechanistic studies in rats indicate that *p,p'*-DDT initially induces (presumably through activation of the *CAR*) liver microsomal xenobiotic metabolizing enzymes and transient bursts in DNA synthesis and cell proliferation that lead to increased liver weight, hypertrophy, eosinophilic abnormal hepatic foci, and eventually liver tumors (Harada et al. 2003, 2006, 2016). Additional mechanistic research with other isomers and liver tissues from other species (including human tissue) may help to better determine the relevance of the observed rat liver tumors to humans.

Epidemiology and Human Dosimetry Studies. Considerable epidemiological research has been conducted within the past 15–20 years to examine possible associations between levels of DDT, DDE, or DDD (and other persistent halogenated chemicals) in samples of biological fluids or tissues and a wide array of health outcomes. To date, consistent epidemiological evidence for positive associations (across studies) was provided for only a few health outcomes (abortion or preterm births, wheeze in infant or child offspring, DMT2 in adults, and liver cancer). Further epidemiological studies in geographical regions where DDT continues to be used for insect control may be useful to better determine if increased risk for these adverse health outcomes are associated with biomarkers of DDT exposure.

Biomarkers of Exposure and Effect. Levels of DDT, DDE, and DDD in biological fluids and tissues are widely used as biomarkers of exposure. Additional research is needed to develop and validate a human PBPK model that could reliably estimate oral intake levels from internal levels of DDT, DDE, or DDD in biological fluids or tissues.

Absorption, Distribution, Metabolism, and Excretion. The ADME and toxicokinetic properties of DDT, DDE, and DDD are well characterized. However, there are limited data to evaluate potential

toxicokinetic differences associated with obesity or diabetes. These data would be useful given the associations between DDT/DDE exposure and obesity and DMT2. Development, calibration, and application of animal and human PBPK models to extrapolate human intake levels from animal intake levels could decrease toxicokinetic uncertainties in the current MRLs, which are based on laboratory animal points of departure (PODs). A calibrated PBPK model for pregnant rats and fetuses has been developed by You et al. (1999c). The development of a similar model for pregnant mothers or nonpregnant humans is limited by the lack of suitable kinetics data for adult humans, human mother-fetus pairs or human mother-infant pairs to calibrate the model. As discussed earlier, the development of a human PBPK to predict intake levels from internal DDT, DDE, or DDD metrics also could aid in exploring the use of dose-response data from epidemiological studies to derive MRLs.

Comparative Toxicokinetics. The metabolism of DDT, DDE, or DDD in animals is similar to that in humans, but observed interspecies metabolic differences suggest that interspecies differences in susceptibility to the neurotoxicity or hepatotoxicity of these chemicals may exist. Comparisons of elimination rates of DDT from fat showed that the process is faster in rats followed by dogs and monkeys and slowest in humans (Morgan and Roan 1974). Rats eliminated DDT 10–100 times faster than humans. Morgan and Roan (1974) suggested that the differences in elimination rates could be due to differences in liver metabolism, gut bacterial metabolism, enterohepatic recirculation, or factors related to the accessibility of plasma-transported pesticide to the excretory cells of the liver. Some of this information could be useful to the development of a human PBPK model for DDT, DDE, or DDD.

Children's Susceptibility. There is little evidence about whether children or young animals differ from adults in their susceptibility to the toxicity of DDT, DDE, or DDD. Some animal studies found that young rats are less susceptible than older ones to the acute neurotoxic effects produced by a single dose of DDT, but the relevance of these findings to humans is unknown (Lu et al. 1965). Studies in animals have shown that DDT and related compounds can alter the development and maturation of the male and female reproductive system, but these effects have generally been observed at higher exposure levels than liver or neurodevelopmental effects (Bitman and Cecil 1970; Clement and Okey 1972; Duby et al. 1971; Gellert et al. 1972; Gray et al. 1999; Kelce et al. 1995, 1997; Loeffler and Peterson 1999; Singhal et al. 1970; You et al. 1998, 1999a). There is evidence that acute perinatal exposure of mice to technical DDT at a critical developmental window (PND 10) results in altered behavioral responses measured in adulthood (Eriksson et al. 1992, 1993; Johansson et al. 1995, 1996; Talts et al. 1998). Additional acute oral exposure studies during critical windows of embryonic, fetal, or neonatal neurodevelopment using

different isomers (e.g., *p,p'*-DDE) or mixtures or species are needed to better understand the effects of DDT, DDE, and DDD on early life neurodevelopment.

There are no adequate data to evaluate whether pharmacokinetics of DDT in children are different from adults. DDT and analogues can cross the placenta and are transferred to offspring via breast milk. It is unknown whether the efficiency of gastrointestinal absorption of DDT and analogues in nursing neonates differs from adults and what influence the fat content of human milk might have. Further information on the kinetics of DDT, DDE, or DDD during pregnancy and lactation would be useful. Important information was published on estimates of body burden of DDE that result from nursing by using a model that incorporates a wide array of variables (LaKind et al. 2000). The only calibrated PBPK model for DDT is that of You et al. (1999b), which focuses on pregnant and lactating Sprague-Dawley rats. There is no information to evaluate whether metabolism of DDT is different in children than in adults since the specific phase I and II enzymes involved in DDT metabolism have not been identified.

Physical and Chemical Properties. The physical and chemical properties of *p,p'*-DDT, DDE, and DDD are well described in the literature although there are some gaps in data for the *o,p'*- isomers (see Table 4-2). The *p,p'*- isomers are those of primary environmental concerns and the data available are sufficient to allow estimation of the environmental fate of DDT, DDE, and DDD.

Production, Import/Export, Use, Release, and Disposal. Since the banning of DDT in the early 1970s in the United States, there has been little information published on the production of DDT. DDT is no longer produced in the United States or in most countries in the world. The most recent information indicates that it is produced in at least two countries, and is used in some underdeveloped countries for vector control. However, data would be useful on the production and use of DDT worldwide. This type of information is important for estimating the potential for environmental releases from various uses, as well as estimating the potential environmental burden. In turn, this would provide a basis for estimating potential exposure and public health risk.

Disposal information is equally important for determining environmental burden and areas where environmental exposure may be high. Although disposal methods for DDT and its metabolites are reported to a limited extent, no current information on disposal sites and quantity disposed was located. Information on how the current users (e.g., hazardous waste clean-up crews) wash DDT equipment and dispose of the remaining waste would be helpful for estimating potential environmental and human exposure.

Environmental Fate. DDT, DDE, and DDD released to the environment may be transported from one medium to another by the processes of solubilization, adsorption, bioaccumulation, or volatilization. The transport of DDT, DDE, and DDD between environmental compartments has been predicted mostly from their physical and chemical properties. Volatilization and adsorption account for loss of DDT and its metabolites from surface water and soil. Monitoring studies indicate that DDT and its isomers and metabolites are extremely persistent in soil (EPA 1986a) and substantiate their predicted environmental fate. DDT, DDE, and DDD are highly lipid soluble. This, combined with their extremely long persistence, contributes to bioaccumulation of DDT and its metabolites in freshwater and marine life. Limited data were located on the soil degradation rates of DDT and its metabolites. Data are available for disappearance rates including losses due to transport processes. While adequate data are available on the time for the disappearance of 50% of the DDT initially applied to a variety of soils, there is abundant evidence that subsequent declines in DDT in soil occur at a much slower rate largely due to an aging process. More data on the biodegradation rates of DDT and its metabolites as well as how soil properties and aging affect these rates would be useful. Experimental information characterizing the environmental fate of DDT, DDE, and DDD, particularly on those properties that govern transport to air, would be helpful to further confirm their predicted environmental behavior and potential human exposure.

Bioavailability from Environmental Media. Limited information was located regarding the bioavailability of DDT, DDE, and DDD from environmental media. It has been shown that the bioavailability of DDT in soil declines with time (Alexander 1995, 1997; Robertson and Alexander 1998) and soil properties that influence the bioavailability of DDT and its toxicity to certain organisms have been studied (Peterson et al. 1971). More information regarding the aging process of DDT in soil and its effect on bioavailability would be helpful in identifying potential routes of human exposure. It is known that fish and some plants bioaccumulate these compounds and that those who consume these fish and plants will incur some exposure to these compounds. However, because of universal body burdens of these compounds, the relative contribution of any particular medium, especially soil and sediment, is not clearly understood. Even if DDT, DDE, and DDD concentrations in various media are known, the difference between the exposure level and the absorbed dose is still unknown.

Food Chain Bioaccumulation. Information was located regarding food chain biomagnification of total DDT in the arctic marine food web (Hargrave et al. 1992). Extensive monitoring of fish populations has been performed and a bioconcentration factor in fish is available. The steady-state BCF in rainbow trout was reported as 12,000, suggesting that bioconcentration in aquatic organisms is very high (Oliver

and Niimi 1985). Although DDT has been detected in plants and vegetables, root uptake of DDT is considered low (Fuhremann and Lichtenstein 1980). A clearer understanding of the potential for bioaccumulation would aid in determining how levels in the environment affect the food chain and potentially influence human exposure levels. This type of information could be obtained by studying accumulation of these compounds in organisms from several trophic levels.

Exposure Levels in Environmental Media. Information on environmental levels of DDT, DDE, and DDD are abundant for the 1970s and 1980s (Blus et al. 1987; Carey et al. 1979b; Crockett et al. 1974; Ford and Hill 1990; Hargrave et al. 1992; Lichtenberg et al. 1970; Stanley et al. 1971). Subsequent monitoring data have been more limited in scope (Aigner et al. 1998; McConnell et al. 1998; Monosmith and Hermanson 1996). Continuation of data collection on environmental levels would contribute to the understanding of current worldwide concentrations and trends, especially in regions where DDT is currently used in vector control for malaria and as an agricultural pesticide.

Reliable monitoring data for the levels of DDT, DDE, and DDD in contaminated media at hazardous waste sites are needed. This information on levels of DDT, DDE, and DDD in the environment can be used in combination with the known body burden of DDT, DDE, and DDD to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Estimates of human intake have been limited to dietary intakes based on current market basket surveys (EPA 1980; Gartrell et al. 1985, 1986a, 1986b; Gunderson 1995a). Additional information is needed relating to the levels in environmental media to which the general population is exposed, particularly at or near hazardous waste sites, and data on the subsequent development of any adverse health effects.

Exposure Levels in Humans. Data are available on levels of DDT and its metabolites in adipose tissue, blood, and milk (CDC 2018; Hovinga et al. 1992; Lordo et al. 1996; Smith 1999). Continued biomonitoring data are needed to determine the temporal trends of DDT exposure to the U.S. population and for integrating these data into existing health information systems.

Exposures of Children. More data are needed on the concentrations of DDT in breast milk of exposed women and on the DDT intake of breastfed infants. In addition, the oral availability of DDT from soil and dust is lacking. Such data would allow for the estimation of the exposure of children to DDT from ingestion of soil and dust.

6.3 ONGOING STUDIES

A number of ongoing studies were identified in the National Institutes of Health (NIH) RePORTER (2021); these studies are summarized in Table 6-1.

Table 6-1. Ongoing Studies on DDT, DDE, and DDD

Investigator	Affiliation	Research description	Sponsor
Human Studies			
Anand, Shuchi	Stanford University	Chronic kidney disease of unknown etiology: applying a multidisciplinary approach to investigate the world's most common tubulointerstitial kidney disease	NIDDK
Brown, Alan Stewart	New York State Psychiatric Institute	A national birth cohort study of prenatal factors and neurodevelopmental psychiatric disorders	NIEHS
Chatzi, Vaia Lida	University of Southern California	Effects of DDE exposure on adipose tissue function, weight loss, and metabolic improvement after bariatric surgery: a new paradigm for study of lipophilic chemicals	NIEHS
Chatzi, Vaia Lida	University of Southern California	Environmental chemical exposures and longitudinal changes of glucose metabolism, insulin sensitivity and B cell function in youth	NIEHS
Chen, Aimin	University of Pennsylvania	Impact of pre- and postnatal chemical mixture exposures on child neurobehavior and neuroimaging	NIEHS
Chevreir, Johnathan	McGill University	Exposure to insecticides and child growth and pubertal development in a South African population exposed through indoor residual spraying	NIEHS
Juul, Anders	Region Hovedstaden	Prenatal exposure to endocrine Disrupting Chemicals and Risk of Testicular Cancer (DISRUPT)	NCI
Turyk, Mary Ellen	University of Illinois at Chicago	Endocrine disruption by perfluoroalkyl substances and mercury	NIEHS
Animal Studies			
De Assis, Sonia	Georgetown University	Paternal DDT exposure and programming of metabolic dysfunction and cancer in offspring: understanding the role of sperm miRNAs and placenta development	NIEHS
Howell, George E	Mississippi State University	Organochlorine compound-induced alterations in adipocyte/macrophage crosstalk and effects on wound healing	NIEHS
La Merrill, Michele A	University of California at Davis	Perinatal DDT causes insulin resistance in mice through impaired thermogenesis	NIEHS
Richardson, Jason R	Florida International University	Mechanism of gene environment interactions in Alzheimer's disease	NIEHS

Table 6-1. Ongoing Studies on DDT, DDE, and DDD

Investigator	Affiliation	Research description	Sponsor
Reviews			
Conis, Elena Christine	University of California Berkeley	The DDT myths: history, science, and stories of health and environment	NLM

DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; NCI = National Cancer Institute; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; NIEHS = National Institute of Environmental Health Sciences; NLM = National Library of Medicine

Source: RePORTER 2021

CHAPTER 7. REGULATIONS AND GUIDELINES

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

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

Table 7-1. Regulations and Guidelines Applicable to DDT, DDE, and DDD

Agency	Description	Information	Reference
	Air		
EPA	RfC	No data	IRIS 2002a, 2002b, 2003
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories	Not listed	EPA 2018a
	National primary drinking water regulations	Not listed	EPA 2009
	RfD		IRIS 2002a
	p,p'-DDT	$5x10^{-4}$ mg/kg/day	
	Provisional peer reviewed toxicity value		
	p,p'-DDE		EPA 2017c
	Provisional subchronic RfD	$3x10^{-4}$ mg/kg/day	
	p,p'-DDD		EPA 2017b
	Screening provisional subchronic RfD	$3x10^{-5}$ mg/kg/day	
	Screening provisional chronic RfD	$3x10^{-5}$ mg/kg/day	
WHO	Drinking water quality guidelines for DDT and metabolites		WHO 2017
	Guideline value	0.001 mg/L (1 µg/L)	
	Provisional tolerable daily intake	0.01 mg/kg-body weight	
FDA	Substances added to food[a]	Not listed	FDA 2021

Table 7-1. Regulations and Guidelines Applicable to DDT, DDE, and DDD

Agency	Description	Information	Reference
	Cancer		
HHS	Carcinogenicity classification		NTP 2016
	DDT	Reasonably anticipated to be a human carcinogen	
EPA	Carcinogenicity classification		IRIS 2002a, 2002b, 2003
	p,p'-DDT, *p,p'*-DDE, *p,p'*-DDD	Group B2[b]	
	Oral slope factor		
	p,p'-DDT	$3.4x10^{-1}$ per mg/kg/day	IRIS 2002a
	p,p'-DDE	$3.4x10^{-1}$ per mg/kg/day	IRIS 2003
	p,p'-DDD	$2.4x10^{-1}$ per mg/kg/day	IRIS 2002b
	Inhalation unit risk		
	p,p'-DDT	$9.7x10^{-5}$ per µg/m^3 [c]	IRIS 2002a
IARC	Carcinogenicity classification		IARC 2018
	DDT	Group 2A[d]	
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction		OSHA 2020a, 2020b, 2020c
	DDT	1 mg/m^3 [e]	
NIOSH	REL (up to 10-hour TWA)		NIOSH 2016
	DDT	0.5 mg/m^3 [f]	
	IDLH		NIOSH 2014
	DDT	500 mg/m^3 [f]	
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2018a
DOE	PACs-air		DOE 2018b
	DDT		
	PAC-1[g]	3 mg/m^3	
	PAC-2[g]	34 mg/m^3	
	PAC-3[g]	210 mg/m^3	
	DDE		
	PAC-1[g]	6.5 mg/m^3	
	PAC-2[g]	72 mg/m^3	
	PAC-3[g]	170 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to DDT, DDE, and DDD

Agency	Description	Information	Reference
	DDD		
	PAC-1[g]	2.4 mg/m^3	
	PAC-2[g]	26 mg/m^3	
	PAC-3[g]	160 mg/m^3	

[a]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited from use in food, delisted color additives, and some substances "no longer FEMA GRAS."
[b]Group B2: probable human carcinogen.
[c]The unit risk should not be used if the air concentration exceeds 1x10^2 µg/m^3, since above this concentration the unit risk may not be appropriate.
[d]Group 2A: probably carcinogenic to humans.
[e]Skin designation.
[f]Potential occupational carcinogen.
[g]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018a).

AEGL = acute exposure guideline levels; DDD = dichlorodiphenyldichloroethane; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 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.

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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: 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.

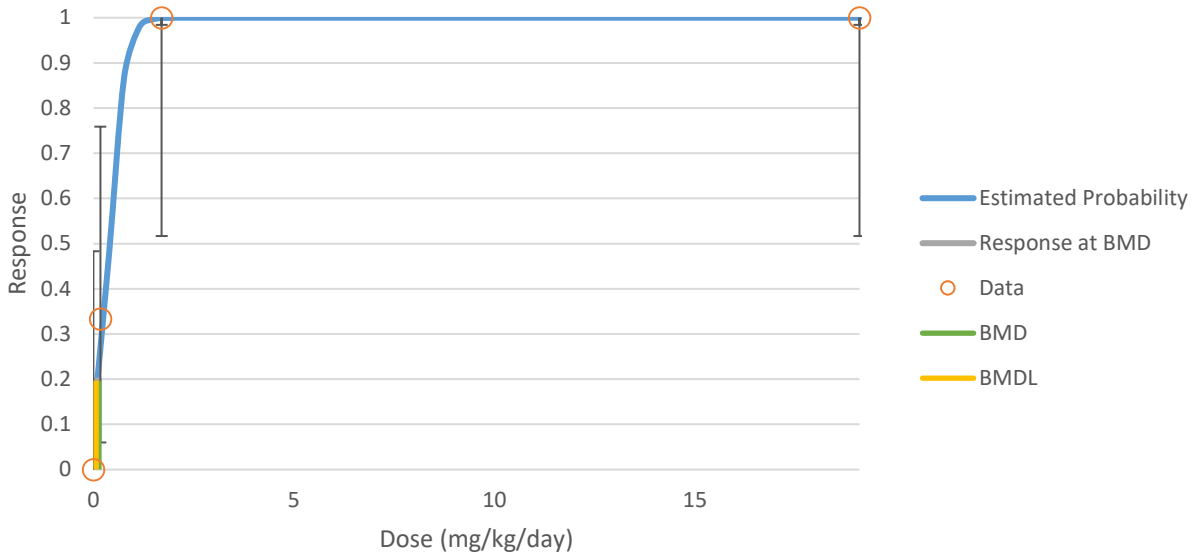
Table A-5. Model Predictions for Hepatocyte Hypertrophy in Male F344/DuCrj Rats Administered *p,p'*-DDT in Their Diet For 26 Weeks (Harada et al. 2003, 2006)

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

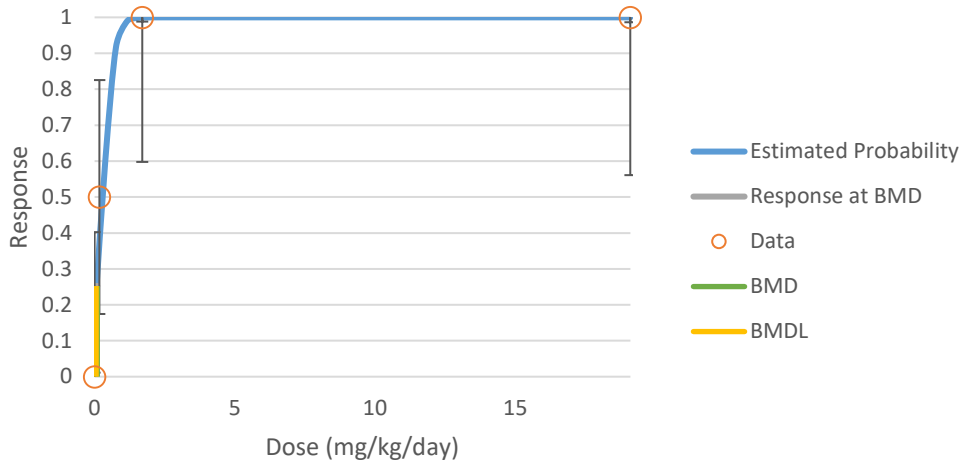
Table A-8. Model Predictions for Hepatocyte Hypertrophy in Male F344/DuCrj Rats Administered *p,p'*-DDT in Their Diet For 78 Weeks (Harada et al. 2003, 2006)

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.

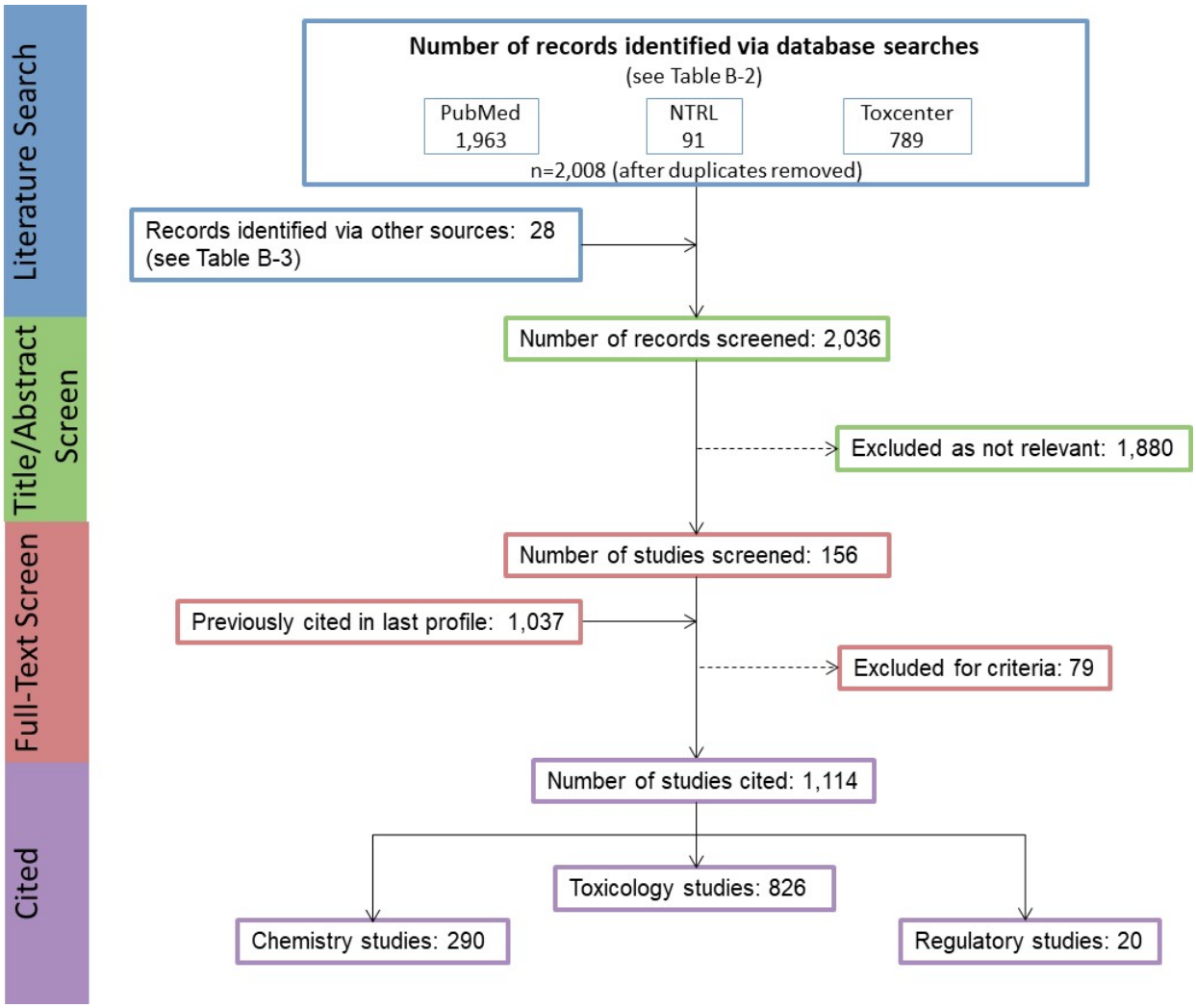
- Number of titles and abstracts screened: 2,036
- Number of studies considered relevant and moved to the next step: 156

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									

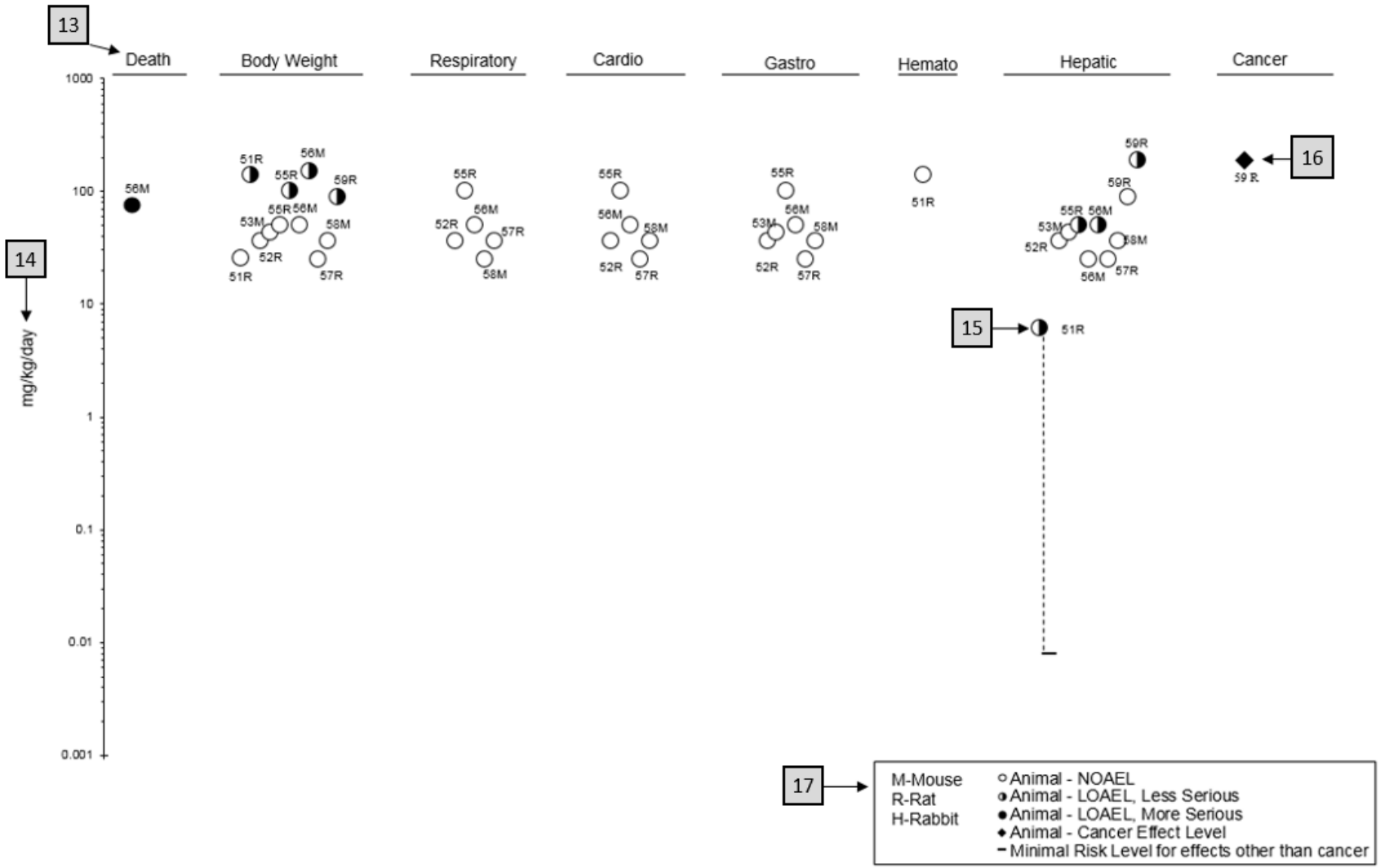
(11)

[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

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