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.

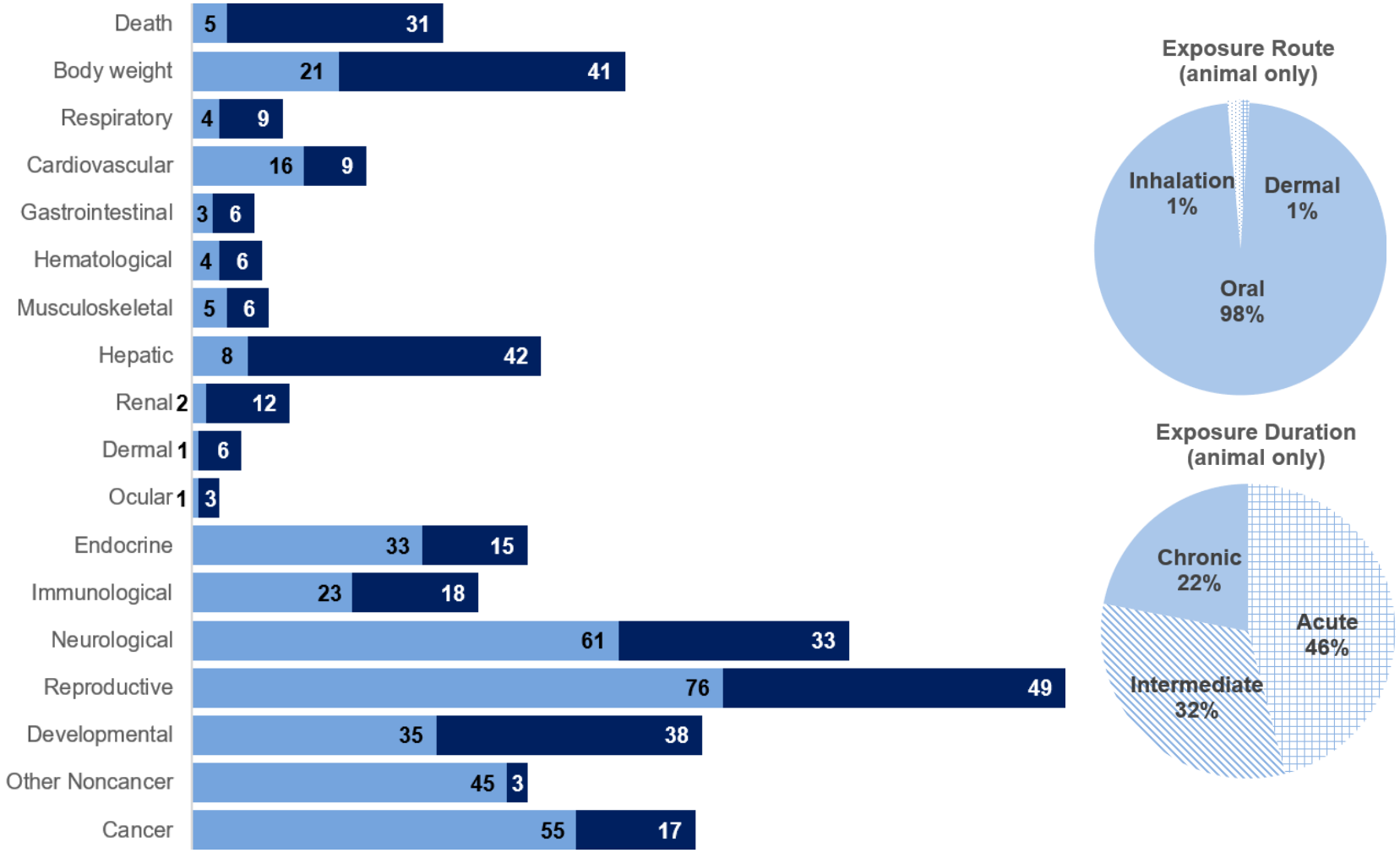
- **Immunological effects:** Suppression or stimulation of various immune system responses have been observed in rats and mice exposed to dietary doses of technical DDT, *p,p'*-DDT, *p,p'*-DDE, *p,p'*-DDD, or *o,p'*-DDD, but evidence is weak for weight changes or histological changes in immune system 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)

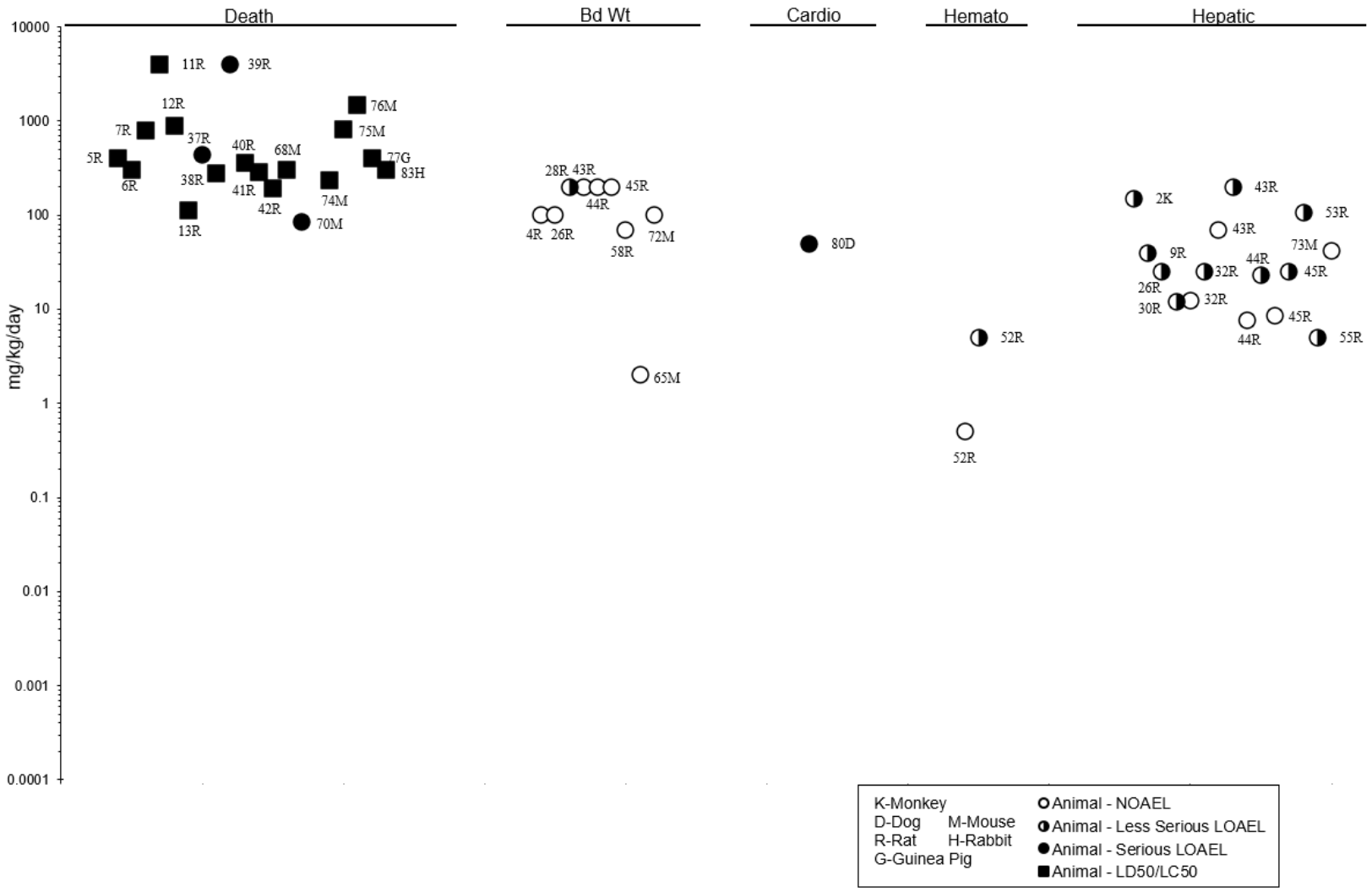


Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Acute (≤14 days)

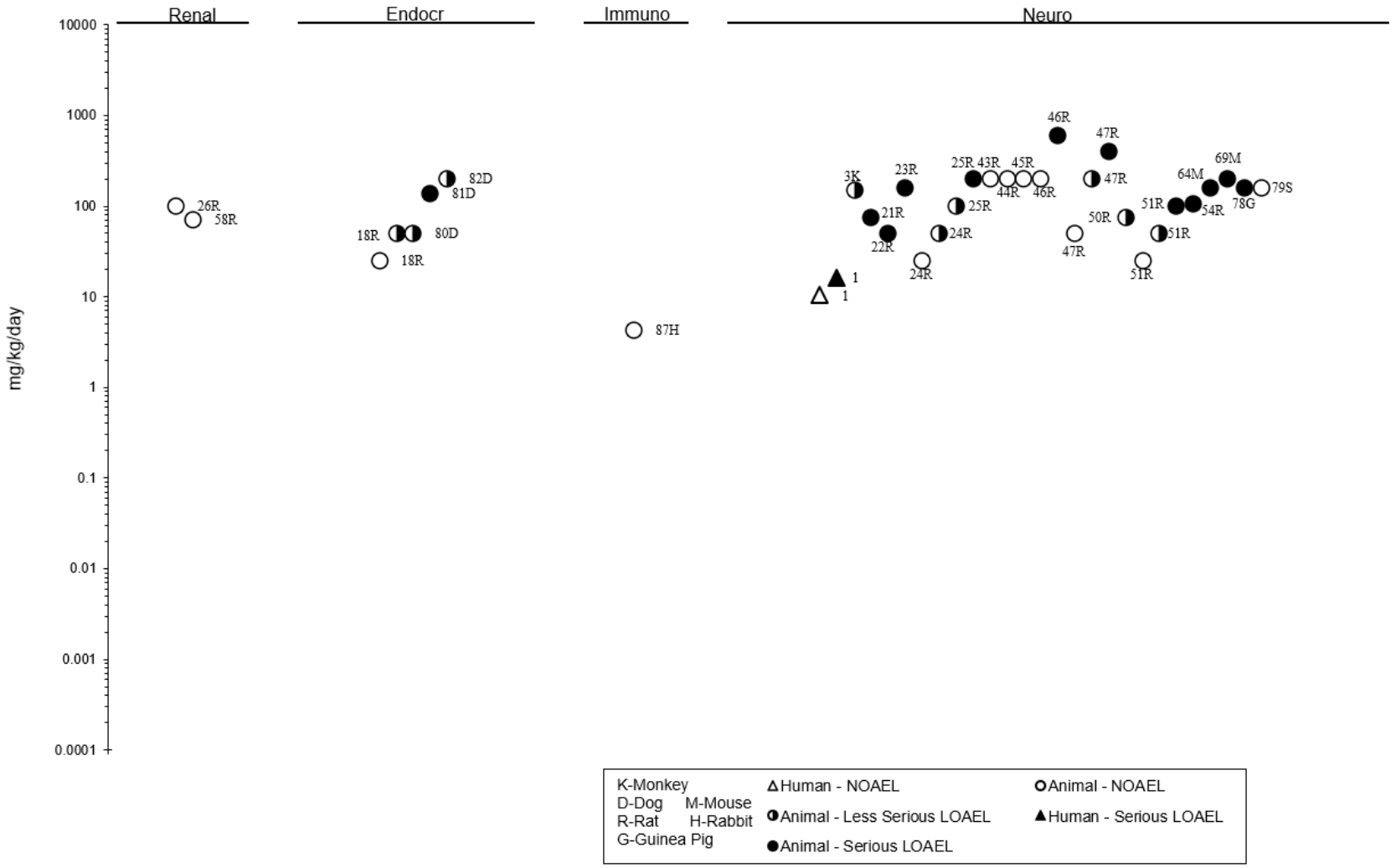


Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Acute (≤14 days)

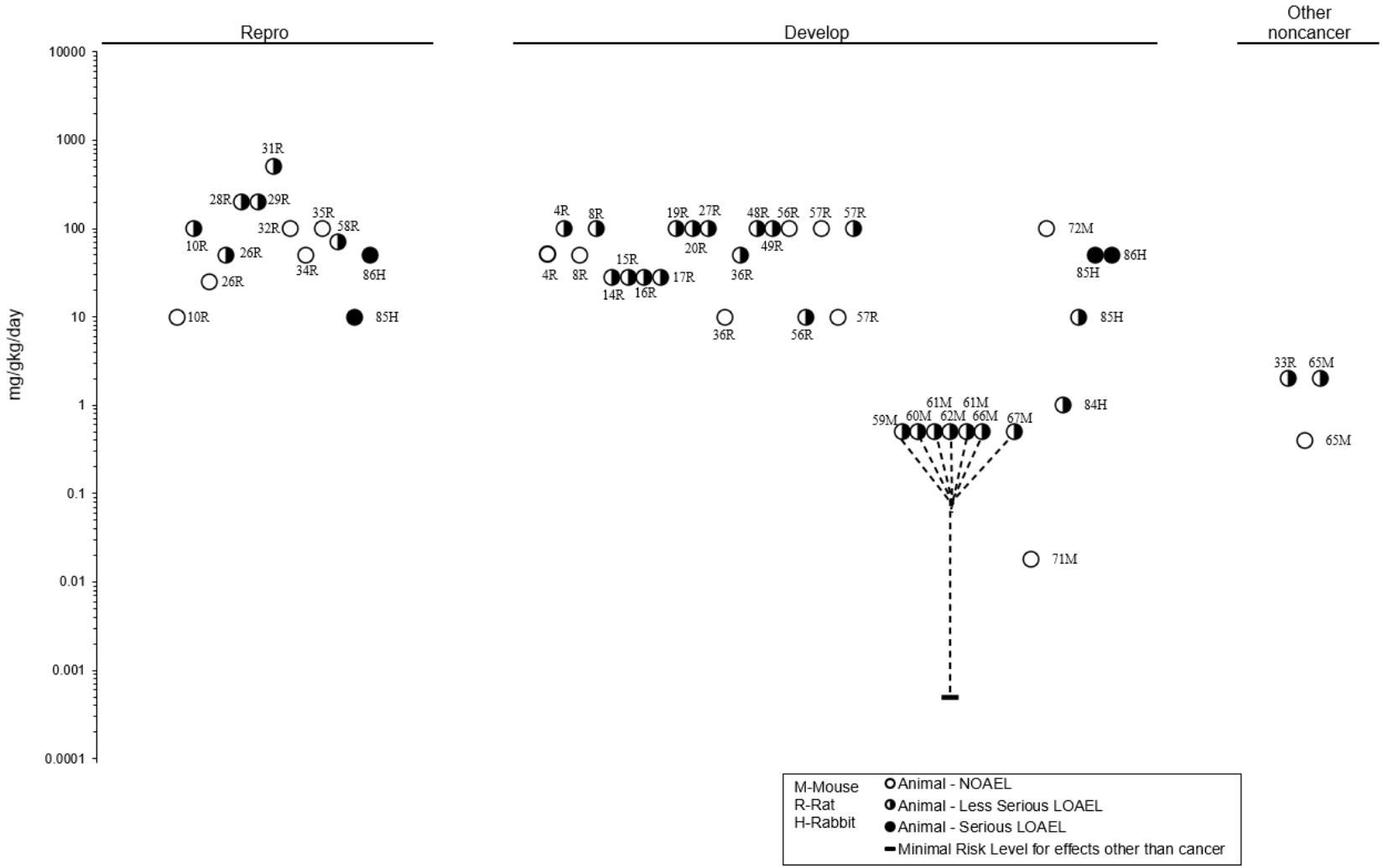


Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Intermediate (15-364 days)

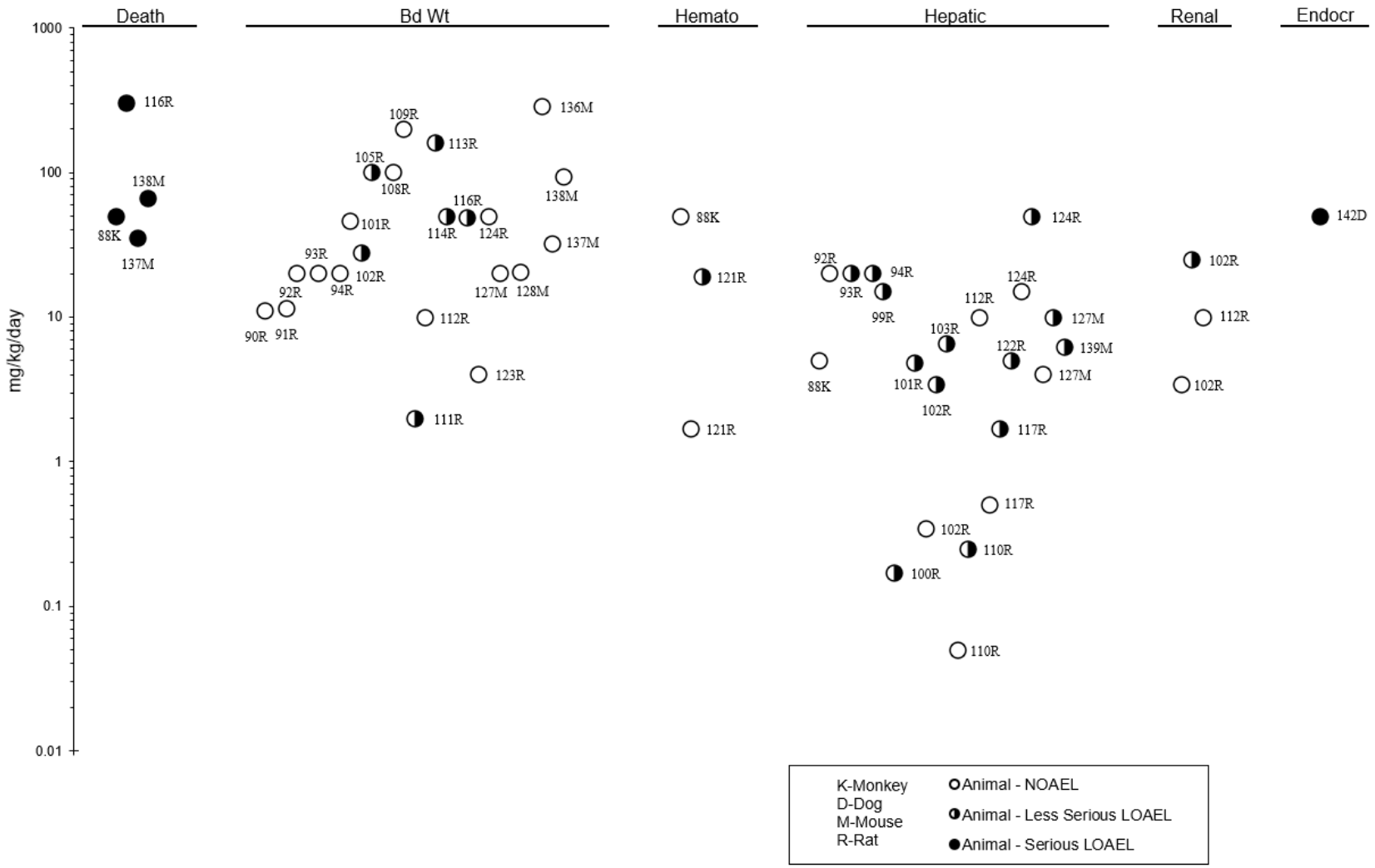


Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Intermediate (15-364 days)

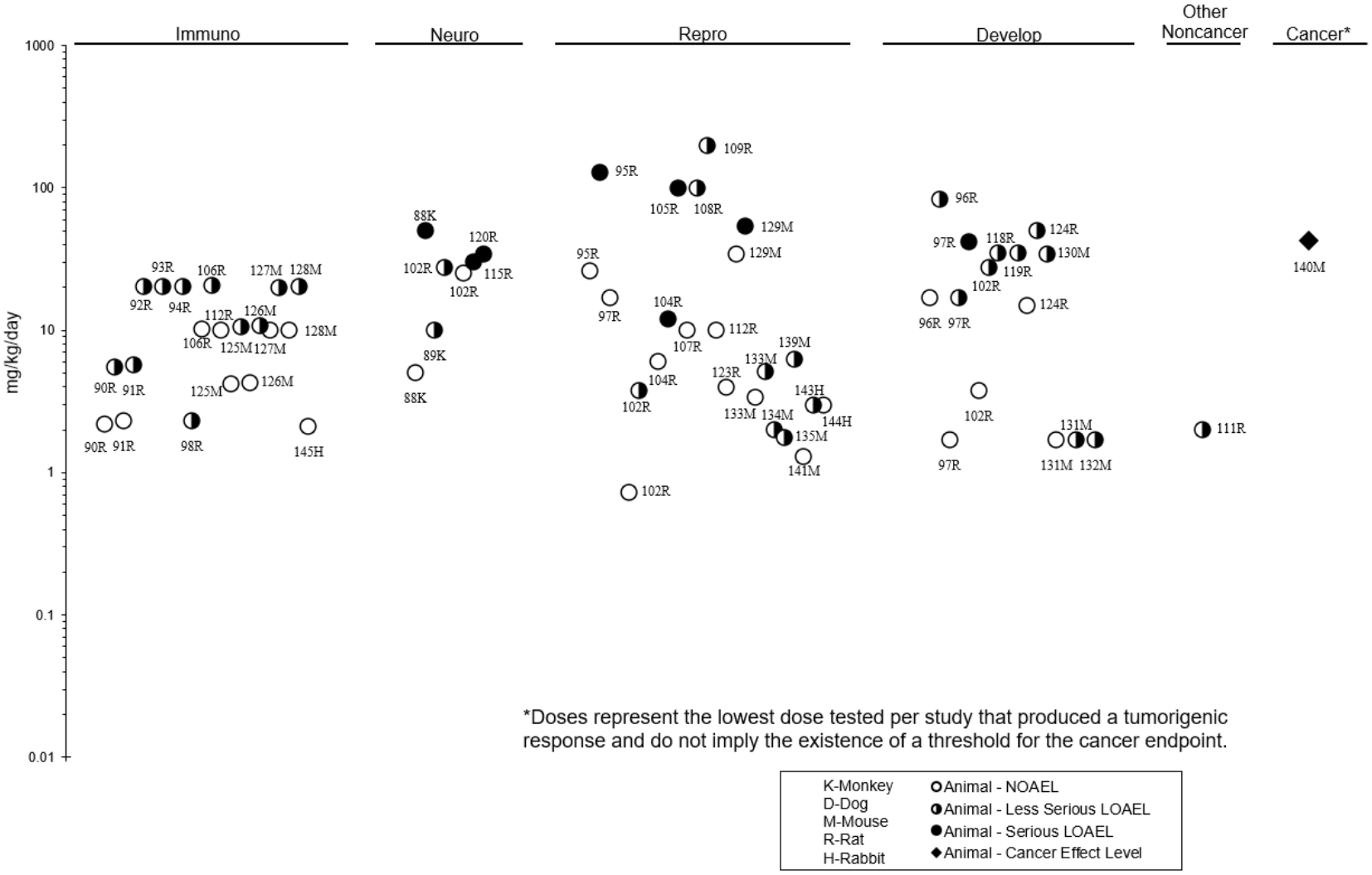


Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Chronic (≥365 days)

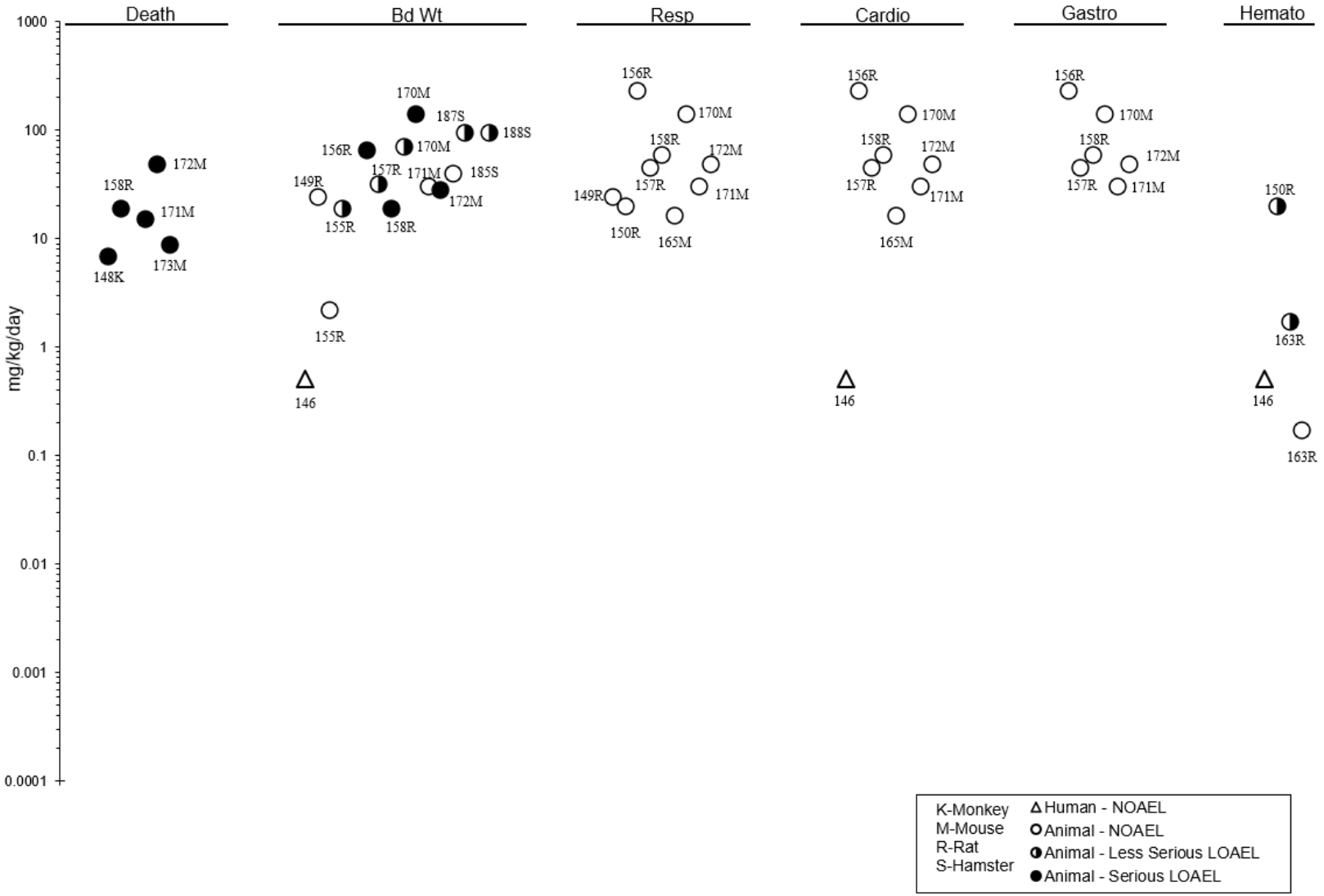


Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

Chronic (≥365 days)

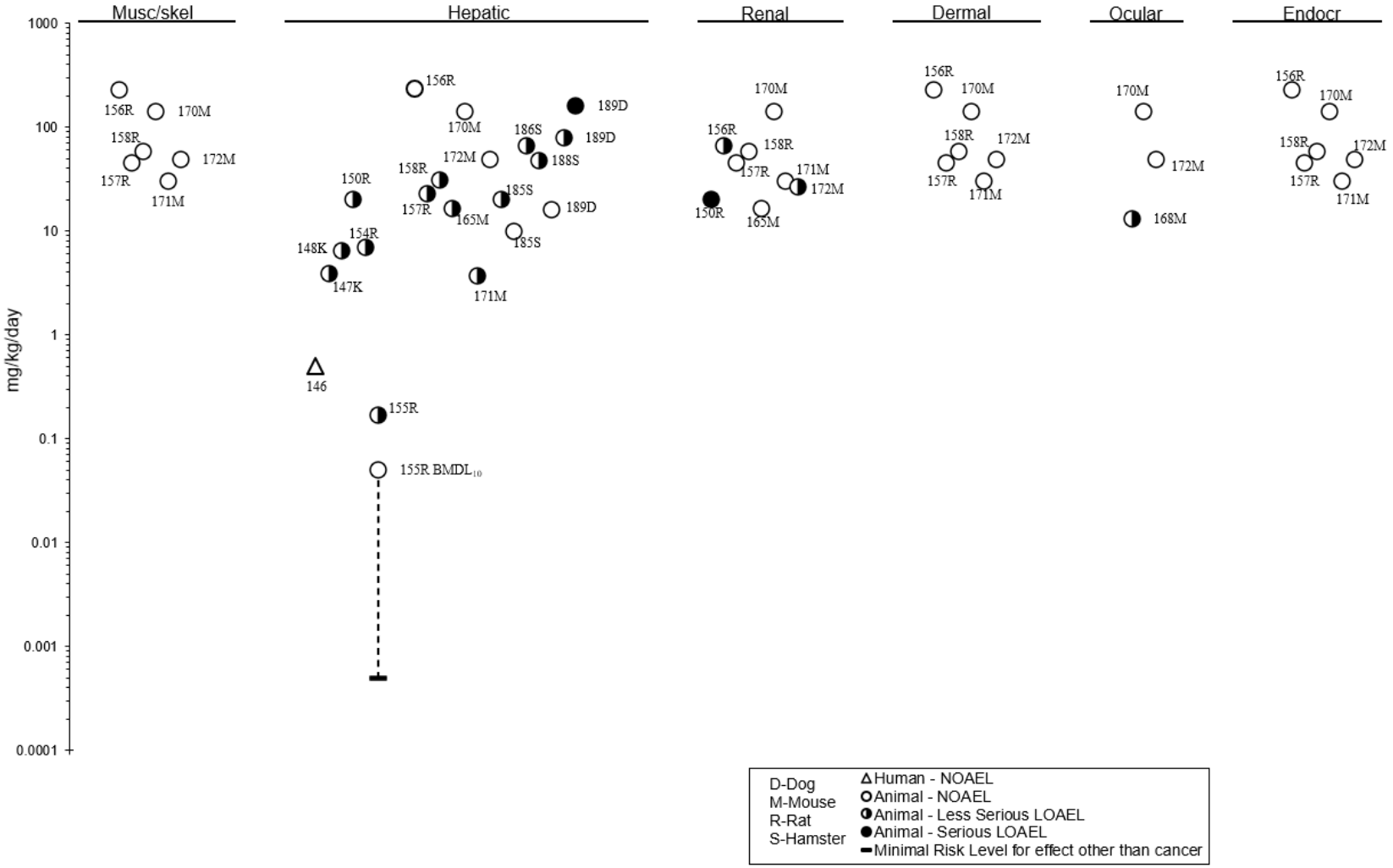
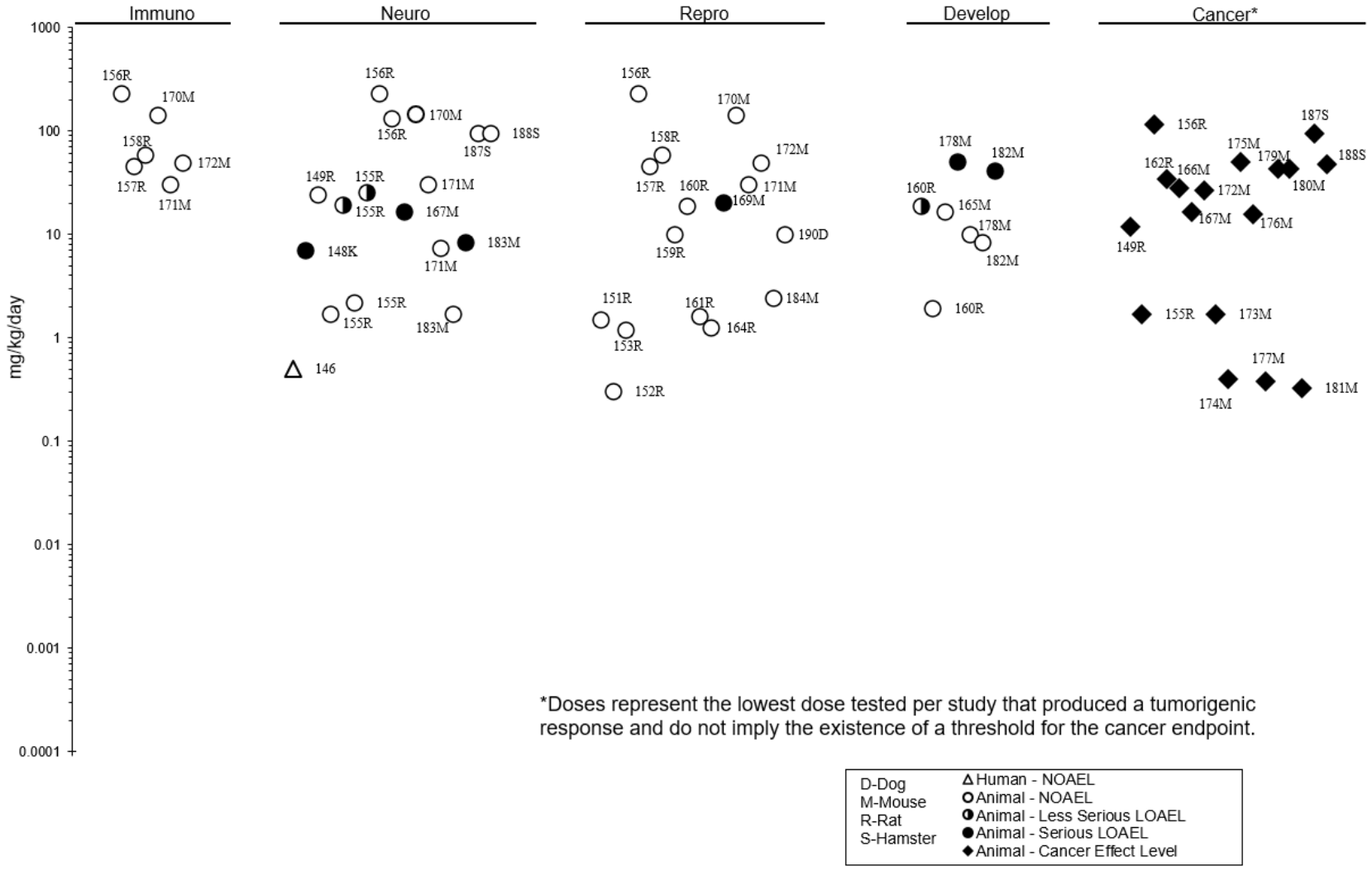


Figure 2-2. Levels of Significant Exposure to DDT, DDE, and DDD – Oral

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.