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Provisional Peer-Reviewed Toxicity Values for

p,p′-Dichlorodiphenyldichloroethane (*p,p′*-DDD)
(CASRN 72-54-8)

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COMMONLY USED ABBREVIATIONS AND ACRONYMS[1]

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	*N*-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WBC	white blood cell

[1]Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV document.

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *p,p′*-DICHLORODIPHENYLDICHLOROETHANE (*p,p′*-DDD) (CASRN 72-54-8)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by at least two National Center for Environment Assessment (NCEA) scientists and an independent external peer review by at least three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

PPRTV assessments are eligible to be updated on a 5-year cycle to incorporate new data or methodologies that might impact the toxicity values or characterization of potential for adverse human-health effects and are revised as appropriate. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. Environmental Protection Agency (EPA) Superfund and Technology Liaison (https://www.epa.gov/research/fact-sheets-regional-science).

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. EPA programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVs

Questions regarding the content of this PPRTV assessment should be directed to the EPA Office of Research and Development's (ORD's) NCEA, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

p,p′-Dichlorodiphenyldichloroethane (*p,p′*-DDD), CASRN 72-54-8, belongs to the class of compounds known as aryl halides. It was formerly used as an insecticide, but all use has been banned in the United States due to concerns about human health, bioaccumulation, and toxicity to the aquatic environment (HSDB, 2010). *p,p′*-DDD is listed as a Superfund hazardous substance by the EPA and has been assigned a Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) Reportable Quantity of 1 pound (U.S. EPA, 2015), as well as being listed on the 2015 CERCLA Substance Priority List (ATSDR, 2016). It is also included on The Proposition 65 List (Cal/EPA, 2017a).

Commercial production of *p,p′*-DDD occurs by the condensation of dichloroacetaldehyde with chlorobenzene (O'Neil, 2013) or by the chlorination of ethanol to give 2,2-dichloro-vinylethyl ether, which is then condensed with 2 moles of chlorobenzene (NLM, 2010).

The empirical formula for *p,p′*-DDD is $C_{14}H_{10}Cl_4$ (see Figure 1). Table 1 summarizes the physicochemical properties of *p,p′*-DDD. *p,p′*-DDD is a crystalline solid at room temperature (NLM, 2010). *p,p′*-DDD's vapor pressure indicates that it will exist in both the vapor and particulate phases in the atmosphere. The estimated half-life of vapor phase *p,p′*-DDD in air by reaction with photochemically produced hydroxyl radicals is 2.5 days. *p,p′*-DDD's Henry's law constant indicates that it may volatilize from moist surfaces, although volatilization is expected to be attenuated by adsorption to suspended solids and sediment in the water column. Its low vapor pressure indicates that *p,p′*-DDD is not expected to volatilize from dry soil surfaces. The low water solubility and high soil adsorption coefficient for *p,p′*-DDD indicate that it will be immobile in soil, and it is therefore not expected to leach to groundwater or undergo runoff after a rain event. Hydrolysis is not expected to be an important fate process, as measured half-lives of 27 and 190 years have been reported at pH 7 and 3−5, respectively. Measured bioconcentration factor (BCF) values from 2,710–51,000 for *p,p′*-DDD suggest that bioconcentration in aquatic organisms is very high, and no biodegradation has been observed in screening and lab tests (NLM, 2010).

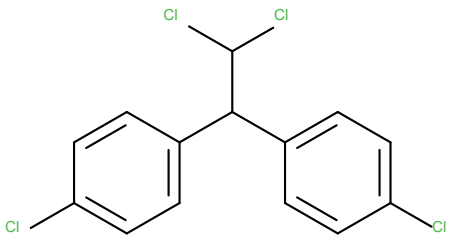


Figure 1. *p,p′*-DDD Structure

Table 1. Physicochemical Properties of *p,p′*-DDD (CASRN 72-54-8)

Property (unit)	Value
Physical state	Solid[a]
Boiling point (°C)	350[b]
Melting point (°C)	109.5[b]
Density (at 20°C)	1.476[a]
Vapor pressure (mm Hg at 25°C)	1.35×10^{-6} [b]
pH (unitless)	NA
pKa (unitless)	NA
Solubility in water (mg/L at 25°C)	0.09[b]
Octanol-water partition coefficient (log K_{ow})	6.02[b]
Henry's law constant (atm-m^3/mol at 25°C)	6.60×10^{-6} [b]
Soil adsorption coefficient K_{oc} (L/kg)	1.306 and 1.318×10^5 [a]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	4.3×10^{-12} (estimated)[b]
Atmospheric half-life (d)	2.5 (estimated)[b]
Relative vapor density (air = 1)	11[a]
Molecular weight (g/mol)	320[b]
Flash point (closed cup in °C)	NV

[a]HSDB (2010).
[b]U.S. EPA (2012b).

NA = not applicable; NV = not available; *p,p′*-DDD = *p,p′*-dichlorodiphenyldichloroethane.

A summary of available toxicity values for *p,p′*-DDD from EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for *p,p′*-DDD (CASRN 72-54-8)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2017a)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2017)
IPCS	NV	NA	IPCS (2017); WHO (2017)
Cal/EPA	NV	NA	Cal/EPA (2014a); Cal/EPA (2017a); Cal/EPA (2017b)
OSHA	NV	NA	OSHA (2006); OSHA (2011)
NIOSH	NV	NA	NIOSH (2016)
ACGIH	NV	NA	ACGIH (2016)
DOE (PAC)	PAC-1: 2.1 mg/m^3; PAC-2: 24 mg/m^3; PAC-3: 3,000 mg/m^3	Based on TEELs	DOE (2015)
USAPHC (air-MEG)	1-hr critical: 500 mg/m^3; 1-hr marginal: 250 mg/m^3; 1-hr negligible: 35 mg/m^3	Based on TEELs	U.S. APHC (2013)
USAPHC (water-MEG)	1-yr negligible: 0.41 mg/L	5 L intake rate; based on liver tumors	U.S. APHC (2013)
USAPHC (soil-MEG)	1-yr negligible: 5,160 mg/kg	Basis: cancer	U.S. APHC (2013)
Cancer			
IRIS (WOE)	Classification B2: probable human carcinogen	Based on an increased incidence of lung tumors in male and female mice, liver tumors in male mice, and thyroid tumors in male rats. *p,p′*-DDD is structurally similar to, and is a known metabolite of, *p,p′*-DDT, a probable human carcinogen.	U.S. EPA (1988b)
IRIS (OSF)	0.24 (mg/kg-d)$^{-1}$	Based on liver tumors in male CF-1 mice (Tomatis et al., 1974).	U.S. EPA (1988b)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2017)

Table 2. Summary of Available Toxicity Values for *p,p′*-DDD (CASRN 72-54-8)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
Cal/EPA (IUR)	0.000069 $(\mu g/m^3)^{-1}$	Based on U.S. EPA (1988b)	Cal/EPA (2014b)
Cal/EPA (ISF)	0.24 $(mg/kg\text{-}d)^{-1}$	Based on U.S. EPA (1988b)	Cal/EPA (2014b)
Cal/EPA (OSF)	0.24 $(mg/kg\text{-}d)^{-1}$	Based on U.S. EPA (1988b)	Cal/EPA (2014b)
ACGIH	NV	NA	ACGIH (2016)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; DOE = U.S. Department of Energy; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; USAPHC = U.S. Army Public Health Command.
[b]Parameters: ISF = inhalation slope factor; IUR = inhalation unit risk; MEG = military exposure guideline; OSF = oral slope factor; PAC = protective action criteria; TEEL = temporary emergency exposure limit; WOE = weight of evidence.

p,p′-DDD = *p,p′*-dichlorodiphenyldichloroethane; *p,p′*-DDT = *p,p′*-dichlorodiphenyltrichloroethane; NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in December 2015 and updated in July 2017 for studies relevant to the derivation of provisional toxicity values for *p,p′*-DDD (CASRN 72-54-8). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related data: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (Cal/EPA), U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Health Effects Assessment Summary Tables (HEAST),U.S. EPA Office of Water (OW),U.S. EPA TSCATS2/TSCATS8e,U.S. EPA High Production Volume (HPV),U.S. EPA National pesticide Information Retrieval System (NPIRS), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Japan Existing Chemical Data Base (JECDB), European Chemicals Agency (ECHA), Organisation for Economic Co-operation and Development (OECD) Screening Information Data Sets (SIDS), OECD International Uniform Chemical Information Database (IUCLID), OECD HPV, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), and Occupational Safety and Health Administration (OSHA).

REVIEW OF POTENTIALLY RELEVANT DATA

Tables 3A and 3B provide overviews of the relevant noncancer and cancer databases, respectively, for *p,p′*-DDD and include all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies as well as reproductive and developmental toxicity studies. The phrase "statistical significance," used throughout the document, indicates a *p*-value of < 0.05 unless otherwise specified. A carcinogenicity assessment for *p,p′*-DDD is available on IRIS (U.S. EPA, 1988b); therefore, cancer data are not discussed in detail below.

Table 3A. Summary of Potentially Relevant Noncancer Data for *p,p′*-DDD (CASRN 72-54-8)							
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
Human							
			1. Oral (mg/kg-d)				
Subchronic	One adult male volunteer, diet for 81 d. The pesticide was mixed with vegetable oil, emulsified with gum arabic and water, and taken with meals (no further detail on dosing was provided); reported dose: 5 mg/d	0.07[d]	No health effects noted in clinical chemistry or hematology parameters	NDr	NDr	Morgan and Roan (1974, 1971) (No NOAEL determination due to limited endpoints, limited experimental details, and single subject)	PR
			2. Inhalation (mg/m^3)				
ND							
Animal							
			1. Oral (mg/kg-d)				
Subchronic	8−12 M, Wistar rat, diet for 6 wk followed by 2-wk recovery; reported doses: 0 or 200 ppm	0, 18.4	Evidence of immunosuppression (reduced humoral and cell-mediated immunity) and decreased relative spleen weight	NDr	18.4	Banerjee et al. (1996) (Limited endpoints evaluated)	PR
Subchronic	5 M/5 F, Osborne-Mendel rat, diet for 6 wk followed by 2-wk recovery; reported doses: 0, 562, 1,000, 1,780, 3,160, or 5,620 ppm	0, 29.5, 52.5, 93.40, 165.8, or 294.9 (M); 0, 31.9, 56.7, 101.0, 179.2, or 318.7 (F)	NDr	NDr	NDr	NCI (1978) (Test article was 60% pure; only body weight and mortality were examined; few details on experimental results preclude the determination of critical effects and effect levels)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for *p,p′*-DDD (CASRN 72-54-8)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Subchronic	5 M/5 F, B6C3F$_1$ mouse, diet for 6 wk followed by 2-wk recovery; reported doses: 0, 251, 398, 631, 1,000, or 1,590 ppm	0, 27.2, 43.1, 68.3, 108, or 172.1 (M); 0, 29.4, 46.6, 73.9, 117, or 186.1 (F)	NDr	NDr	NDr	NCI (1978) (Test article was 60% pure; only body weight and mortality were examined; few details on experimental results preclude the determination of critical effects and effect levels)	PR
Subchronic	1 M, dog (breed not specified), diet for 29−60 d (control left untreated for 100 d); reported doses: 0, 80, or 200 mg/kg-d	0, 80, or 200	No observed effects	NDr	NDr	Cueto et al. (1958) (No NOAEL determination due to limited endpoints and low animal numbers)	PR
Chronic	50 M/50 F (20 controls/sex), Osborne-Mendel rat, diet for 78 wk followed by 34−35 wk of recovery; reported doses: 0, 1,647, or 3,294 ppm (M); 0, 850, or 1,700 ppm (F)	0, 69.21, 138.4 (M); 0, 39.3, 78.66 (F)	Depression of body weight (≥10%) in both sexes	NA	39.3 (F)	NCI (1978) (Test article was 60% pure. For endpoints evaluated at study termination, prolonged observation period may have allowed for recovery from toxic effects)	PR
Chronic	50 M/50 F (20 controls/sex), B6C3F$_1$ mouse, diet for 78 wk followed by 13−15 wk of recovery; reported doses: 0, 411, or 822 ppm	0, 42.3, 84.6 (M); 0, 42.6, 85.2 (F)	Depression of body weight (~14%) in females	42.6	85.2	NCI (1978) (Test article was 60% pure. For endpoints evaluated at study termination, prolonged observation period may have allowed for recovery from toxic effects)	PR
Chronic	60 M/60 F, CF-1 mouse, diet for 123 wk; reported doses: 0 or 250 ppm	0, 45.0 (M); 0, 46.1 (F)	Depression of body weight (>10%) in males	NDr	45.0	Tomatis et al. (1974)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for *p,p′*-DDD (CASRN 72-54-8)							
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
2. Inhalation (mg/m^3)							
ND							

[a]Duration categories are defined as follows: subchronic = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% lifespan for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dosimetry: Values are presented as ADDs (mg/kg-day) for *p,p′*-DDD, adjusted for purity of the administered material, where applicable [e.g., NCI (1978)].
[c]Notes: PR = peer reviewed.
[d]Intake of 5 mg/day for a male volunteer. ADD was calculated assuming a reference body weight of 70 kg (U.S. EPA, 1988e).

ADD = adjusted daily dose; F = female(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); NA = not applicable; ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; *p,p′*-DDD = *p,p′*-dichlorodiphenyldichloroethane.

Table 3B. Summary of Potentially Relevant Cancer Data for *p,p′*-DDD (CASRN 72-54-8)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses	Dosimetry[a]	Critical Effects	Reference (comments)	Notes[b]
Human					
ND					
Animal					
1. Oral (mg/kg-d)					
Carcinogenicity	50 M/50 F (20 controls/sex), Osborne-Mendel rat, diet for 78 wk followed by 34−35 wk of recovery; reported doses: 0, 1,647, or 3,294 ppm (M); 0, 850, or 1,700 ppm (F)	0, 20.26, 40.52 (M); 0, 10.73, 21.48 (F)	Treatment-related increases in the incidence of thyroid follicular cell adenomas or carcinomas in males	NCI (1978) (Test article was 60% pure)	PR
Carcinogenicity	50 M/50 F (20 controls/sex), B6C3F$_1$ mouse, diet for 78 wk followed by 13-15 wk of recovery; reported doses: 0, 411, or 822 ppm	0, 6.43, 11.8 (M); 0, 6.39, 12.8 (F)	Nonsignificant increase in hepatocellular carcinomas in both sexes	NCI (1978) (Test article was 60% pure)	PR
Carcinogenicity	60 M/60 F, CF-1 mouse, diet for 123 wk; reported doses: 0 or 250 ppm	0, 6.56 (M and F)	Significant increase in lung tumors in both sexes and liver tumors in males	Tomatis et al. (1974)	PR, IRIS
2. Inhalation (mg/m^3)					
ND					

[a]Dosimetry: The units for oral exposures are expressed as HEDs (mg/kg-day) for *p,p′*-DDD, adjusted for purity of the administered material, where applicable [e.g., NCI (1978)]. HED = animal dose (mg/kg-day) × $(BW_a \div BW_h)^{1/4}$, where DAF = dosimetric adjustment factor, BW_a = animal body weight, and BW_h = human body weight (U.S. EPA, 2011b). Reference body weights recommended by U.S. EPA (1988e) were used to calculate the DAFs: 70 kg for humans; 0.514 kg (M) and 0.389 kg (F) for Osborne-Mendel rats in a chronic-duration study; 0.0373 kg (M) and 0.0353 kg (F) for B6C3F$_1$ mice in a chronic-duration study; 0.134 kg (M). No strain-specific reference body weights were available for CF-1 mice; instead, average rat body weights in a chronic-duration study were used (0.0317 kg for M and 0.02875 kg for F).
[b]Notes: IRIS = used by the Integrated Risk Information System (U.S. EPA, 1988b); PR = peer reviewed.

BW = body weight; F = female(s); HED = human equivalent dose; M = male(s); ND = no data; *p,p′*-DDD = *p,p′*-dichlorodiphenyldichloroethane.

HUMAN STUDIES

Human studies of *p,p′*-DDD include one subchronic-duration study with a volunteer (Morgan and Roan, 1974, 1971), and several epidemiological investigations of associations between *p,p′*-DDD levels in biological media and adverse health effects (Tyagi et al., 2015; Freire et al., 2014; Guo et al., 2014; Al-Saleh et al., 2012; Boada et al., 2012; Freire et al., 2012; Su et al., 2012; Ociepa-Zawal et al., 2010; Son et al., 2010; Zumbado et al., 2010; Boada et al., 2007; Pant et al., 2007; Asawasinsopon et al., 2006; Damgaard et al., 2006; Perry et al., 2006; Dalvie et al., 2004a; Dalvie et al., 2004b; Pant et al., 2004; Pines et al., 1987; Saxena et al., 1983; Saxena et al., 1981; Saxena et al., 1980).

In a volunteer study of technical dichlorodiphenyltrichloroethane (T-DDT) and its metabolites (including *p,p′*-DDD), an adult male ingested 5 mg/day of *p,p′*-DDD for 81 days (Morgan and Roan, 1971). The pesticide was mixed with vegetable oil, emulsified with gum arabic and water, and taken with meals (no further detail on dosing was provided). Assuming a reference body weight of 70 kg (U.S. EPA, 1988e), the intake of *p,p′*-DDD was 0.07 mg/kg-day. Before, during, and after the treatment period, the man was given a battery of hematological and clinical biochemical tests (frequency and nature of testing not reported). No abnormalities were detected. Although no effects on hematological and clinical chemistry endpoints were observed, details of the test endpoints, frequency, and results were not reported, other endpoints were not assessed, and the study was conducted on a single volunteer with uncertain applicability to others; thus, the administered dose cannot be considered a no-observed-adverse-effect level (NOAEL).

ANIMAL STUDIES

Oral Exposures

Subchronic-Duration Studies

Banerjee et al. (1996)

The effects of dietary *p,p′*-DDD exposure on humoral and cell-mediated immune response were evaluated in Wistar rats. Groups of 8−12 male rats were given either the control diet or a diet containing 200 ppm *p,p′*-DDD (purity 99%) for 6 weeks (equivalent to 18.4 mg/kg-day[2]), during which general condition, food consumption, and body weights were recorded weekly. Half of each group was immunized by subcutaneous administration of 3 mg ovalbumin 3 weeks before the end of the exposure period; the other half was not challenged with ovalbumin. At the end of the exposure period, rats were sacrificed and blood samples were collected. The liver, spleen, and thymus from each animal were removed and weighed. The humoral immune response was quantified by measuring immunoglobulin levels (Immunoglobulin M [IgM] and Immunoglobulin G [IgG]), estimating the albumin:globulin (A:G) ratio and measuring the ovalbumin antibody titer by enzyme-linked immunosorbent assay (ELISA). Cell-mediated response was assessed in vivo, by quantifying the delayed type hypersensitivity reaction (measuring footpad thickness after ovalbumin challenge), and in vitro by measuring leukocyte and macrophage migration inhibition. The latter tests assess whether chemical exposure results in suppression of lymphokine production.

Exposure to *p,p′*-DDD had no effect on mortality, food intake, body weight, or relative liver or thymus weights, but significantly ($p < 0.05$) reduced relative spleen weight by 14%;

[2]Dose estimates were calculated using a reference body weight of 0.217 kg and a reference food consumption of 0.020 kg/day for male Wistar rats in a subchronic-duration study (U.S. EPA, 1988e).

absolute spleen weights were not reported (Banerjee et al., 1996). With regard to humoral immune responses, treatment with *p,p′*-DDD had no effect on the serum A:G ratio, but significantly ($p < 0.05$) reduced the levels of IgG, IgM, and the titer of antiovalbumin antibody in serum by 15, 24, and 35%, respectively, compared to controls. Treatment with *p,p′*-DDD significantly reduced cell-mediated immune responses; delayed type hypersensitivity reactions (increase in footpad thickness) and tests of inhibition of migration of leucocytes and macrophages were suppressed by 24, 24, and 25% (respectively) compared to controls.

The only dose tested (18.4 mg/kg-day) was identified as a lowest-observed-adverse-effect level (LOAEL) for evidence of immunosuppression and potential effects on spleen weight in rats; no NOAEL could be identified from these data.

NCI (1978)

In preparation for a chronic cancer bioassay, NCI (1978) conducted a range-finding dietary toxicity study of DDD in Osborne-Mendel rats and $B6C3F_1$ mice. Technical-grade DDD (60% *p,p′*-DDD) in corn oil was mixed with feed and administered ad libitum to groups of five male and five female rats per concentration for 6 weeks, followed by a 2-week observation period. The test material contained 19 impurities contributing 40% of the total dose; none of the impurities were identified. Diets containing 0, 562, 1,000, 1,780, 3,160, or 5,620 ppm technical-grade DDD were fed to rats (corresponding to *p,p′*-DDD doses of 0, 29.5, 52.5, 93.40, 165.8, or 294.9 mg/kg-day in males, and 0, 31.9, 56.7, 101.0, 179.2, or 318.7 mg/kg-day in females[3] after adjustment for 60% purity). Only mortality and body-weight changes were evaluated; no animals were necropsied.

No deaths were observed in rats exposed to *p,p′*-DDD concentrations up to 3,160 ppm; no information was reported on mortality at 5,620 ppm. Mean body weights were reduced in male rats exposed to 1,780 ppm (9% lower than controls) and 3,160 ppm (10% lower), and in female rats exposed to 1,000 ppm (39% lower) and 1,780 ppm (4% lower); neither statistical analysis nor raw data were presented. No data on body-weight changes at other doses were reported. This study included low animal numbers, examined few endpoints, and provided incomplete reporting on body-weight changes, preventing the identification of potential target organ effects and associated effect levels.

In the mouse study, groups of five male and five female mice were exposed to dietary *p,p′*-DDD for 6 weeks, followed by a 2-week observation period; test material and study protocol were as described above for rats. Mice received diets containing 0, 251, 398, 631, 1,000, or 1,590 ppm (0, 27.2, 43.1, 68.3, 108, or 172.1 mg/kg-day *p,p′*-DDD in males, and 0, 29.4, 46.6, 73.9, 117, or 186.1 mg/kg-day *p,p′*-DDD in females[3] after adjustment for 60% purity). Mortality was observed in male mice of all but the 631-ppm exposure group (data and details not reported); no deaths occurred among control males. Mortality was also observed in female mice exposed to 1,000 and 1,590 ppm, but not in other groups (data not reported). *p,p′*-DDD did not affect mean body weights in the exposed mice; mean body-weight gain in male and female mice exposed to

[3]Dose estimates were calculated using reference values for food consumption and body weight (U.S. EPA, 1988e). Reference body weights for Osborne-Mendel rats in a subchronic-duration study: 0.263 kg (males) and 0.201 kg (females). Reference food consumption for Osborne-Mendel rats in a subchronic-duration study: 0.023 kg/day (males) and 0.019 kg/day (females). Reference body weights for $B6C3F_1$ mice in a subchronic-duration study: 0.0316 kg (males) and 0.0246 kg (females). Reference food consumption for $B6C3F_1$ mice in a subchronic-duration study: 0.0057 kg/day (males) and 0.0048 kg/day (females).

concentrations up to 631 ppm exceeded weight gain in controls (details not reported). Because incidence data for mortality effects associated with *p,p′*-DDD exposure were not reported and few details were provided, reliable frank effect levels (FELs) cannot be established. The study also suffers from deficiencies in protocol design (low animal numbers and few endpoints examined) that preclude the identification other effect levels.

Cueto et al. (1958)

Technical-grade DDD was separated into different fractions and each fraction was tested for adrenocorticolytic activity in male dogs (breed not specified) via dietary administration. A single dog received 80 mg/kg-day of purified *p,p′*-DDD for 29 days, and another dog received the same dose for 80 days; a third dog was treated with 200 mg/kg-day for 30 days, and a fourth dog was left untreated for 100 days as a control. The endpoints examined included general appearance, periodic tests of adrenal activity and, after necropsy, examination of adrenal histopathology. No other organ system was evaluated. Treatment with *p,p′*-DDD at either dose level had no effect on the physical state of the dogs. In tests of adrenal activity administered after 4 and 20 days of treatment, the dog treated with 200 mg/kg-day of *p,p′*-DDD and the control dog exhibited the same effects in response to an injection of adrenocorticotropic hormone: there were similar decreases in the eosinophil count and similar increases in the plasma level of 17-hydroxycorticosteroids. At termination, no treated dogs showed evidence of adrenal histopathology. This study is inadequate to establish effect levels due to limited endpoints evaluated and very low animal numbers.

Chronic-Duration/Carcinogenicity Studies

NCI (1978)

A carcinogenicity bioassay of *p,p′*-DDD was conducted by NCI (1978) in Osborne-Mendel rats and B6C3F$_1$ mice. Technical-grade DDD (60% *p,p′*-DDD) in corn oil was mixed with feed at varying concentrations and administered ad libitum. The test material contained 19 impurities, contributing 40% of the total dose; none of the impurities were identified. Nominal concentrations, durations of exposure at these concentrations, and weighted average concentration and dose estimates over the 78-week exposure period are provided in Table B-1. As the table indicates, the exposure concentration was increased once in rats and twice in mice, as the animals tolerated the exposures well. Rats were observed for 34 or 35 weeks after exposure termination and prior to sacrifice. Mice were observed for 13−15 weeks after the 78-week exposure period and prior to sacrifice. Time-weighted average technical-grade DDD concentrations given to rats were 0, 1,647, or 3,294 ppm (corresponding to *p,p′*-DDD doses of 0, 69.21, or 138.4 mg/kg-day[4] after adjustment for 60% purity) in males and 0, 850, or 1,700 ppm (corresponding to *p,p′*-DDD doses of 0, 39.3, or 78.66 mg/kg-day[4] after adjustment for 60% purity) in females. Mice received weighted-average technical-grade DDD concentrations of 0, 411, or 822 ppm (corresponding to *p,p′*-DDD doses of 0, 42.3, or 84.6 mg/kg-day in males and 0, 42.6, or 85.2 mg/kg-day in females[4] after adjustment for 60% purity).

[4]Dose estimates were calculated using the reference values for food consumption and body weight (U.S. EPA, 1988e). Reference body weights for Osborne-Mendel rats in a chronic-duration study: 0.514 kg (males) and 0.389 kg (females). Reference food consumption for Osborne-Mendel rats in a chronic-duration study: 0.036 kg/day (males) and 0.030 kg/day (females). Reference body weights for B6C3F$_1$ mice in a chronic-duration study: 0.0373 kg (males) and 0.0353 kg (females). Reference food consumption for B6C3F$_1$ mice in a chronic-duration study: 0.0064 kg/day (males) and 0.0061 kg/day (females).

Body-weight and food-consumption measurements, clinical observations, and palpations for masses were conducted weekly for 10 weeks and monthly thereafter; mortality checks were performed daily (NCI, 1978). Necropsy was performed on all animals, but organ weights were not recorded. Histopathologic examination was initially limited to control animals, animals with visible tumors and at least 10 males and females with no gross pathological findings from each group. Later in the study, the protocol was altered to include tissues from other animals; however, the study authors did not indicate how the other animals were selected, how many were included, or when the protocol change was initiated. Nearly 30 tissues were subjected to microscopic examination. The study authors noted that tissues were not examined from some animals that died early and that some animals were missing, cannibalized, or in an advanced state of autolysis, precluding histopathologic examination. Incidence of lesions was reported using the number of animals for which that specific tissue was examined as the number at risk, except where lesions were observed grossly or could appear at multiple sites (e.g., lymphoma), in which case, the number of animals necropsied was used.

The study authors reported that, beginning at Week 30 and continuing through termination of the exposure period, treated rats (not further specified) exhibited a slightly greater incidence of clinical signs of toxicity (hunched appearance and urine staining; data not reported) (NCI, 1978). Prior to 30 weeks and during the recovery period, there was no treatment-related effect on the incidence of clinical signs (data not reported), according to the study authors. *p,p′*-DDD treatment did not significantly affect probability of survival in either sex. There were clear treatment-related reductions in body weight, but the study authors did not present statistical comparisons of group mean body weights or raw data. Based on graphical presentation of the data, the greatest differences from control weights occurred between Weeks 60 and 75, when the mean body weights were about 10 and 20% lower than controls in low- and high-dose males (respectively) and about 20 and 30% lower in low- and high-dose females. Treatment with *p,p′*-DDD had no significant effect on the incidence of non-neoplastic lesions in rats in any tissue examined. A NOAEL cannot be determined from this study. The low dose (39.3 mg/kg-day in females) is a LOAEL for biologically significant reductions (>10%) in mean body weight in male and female rats.

An increased incidence of combined thyroid follicular-cell adenomas or carcinomas was observed in exposed male rats compared to controls that reached statistical significance at the low treatment dose. Based on the statistical analysis, the study authors reported an association between increased incidence of thyroid tumors and *p,p′*-DDD treatment. No other treatment-related effects on tumor frequency were found. This study was evaluated as part of the IRIS cancer assessment (U.S. EPA, 1988b), but was not used in deriving the oral slope factor (OSF).

In mice, *p,p′*-DDD treatment had no significant effect on probability of survival in either sex. Clinical signs occurred with the same frequency in treated and control animals. Exposure to *p,p′*-DDD had no effect on male body weight throughout the treatment period, but dose-related depression of body weight was observed in female mice after Week 30. The study authors did not present statistical comparisons of group mean body weights or raw data. Based on graphical presentation of the data, the body-weight reduction peaked at about 14% in the high-dose group between Weeks 60 and 75; in the low-dose group, body-weight decrements appeared to be <10% throughout the study. Treatment did not significantly increase the incidence of non-neoplastic lesions in any tissue in either sex. The low dose of 42.3 mg/kg-day *p,p′*-DDD is a NOAEL and

the high dose of 84.6 mg/kg-day *p,p′*-DDD is a LOAEL for body-weight depression in female mice.

The study authors reported increases in the incidence of hepatocellular carcinomas in mice treated with *p,p′*-DDD; however, the increase was not statistically significant in either sex. No other treatment-related effects on tumor frequency were observed. This study was evaluated as part of the IRIS cancer assessment (U.S. EPA, 1988b), but was not used in deriving the OSF.

Tomatis et al. (1974)

The carcinogenicity of *p,p′*-DDD was evaluated in CF-1 mice treated via the diet for a lifetime. The study authors administered *p,p′*-DDD in the diet (250 ppm) to 60 male and 60 female mice (6−7 weeks old) for up to 123 weeks; 101 male and 97 female mice were maintained on a control diet. The test compound was 99% pure and was dissolved in acetone prior to being mixed with powdered food and converted to pellets. It is not clear whether the control diet contained acetone. A dietary concentration of 250 ppm corresponds to an estimated *p,p′*-DDD dose of about 45.0 and 46.1 mg/kg-day for males and females, respectively.[5] Groups of four animals (sex not specified) were sacrificed either between Weeks 65 and 74 of treatment or between Weeks 94 and 118 of treatment for analysis of *p,p′*-DDD levels in the liver and interscapular fat (and sometimes in liver tumors and kidney; details not provided). All animals dying spontaneously or killed humanely were necropsied; remaining animals were sacrificed at 130 weeks of age. Histopathology evaluation was restricted to the lungs, heart, thymus, liver, kidneys, spleen, brain, and any organs with gross abnormalities.

Survival was not affected by *p,p′*-DDD (Tomatis et al., 1974). Survival to 90 weeks was 76 and 72% in treated males and females, compared with 67 and 73% in control males and females, respectively. There were no clinical signs of toxicity among mice treated with *p,p′*-DDD. The study authors reported neither a statistical comparison of body weights nor raw data; however, based on visual evaluation of body-weight curves (covering the period from the third to fourteenth month of age), body weights of the treated males were depressed by >10% relative to controls over the entire period of observation; body weights of treated females were unaffected by treatment. The only other possible effect was a fivefold increase in the incidence of myocardial necrosis in males, although the overall incidence was small (3/59 in treated animals vs. 1/98 in controls) and not statistically significant (*p*-value = 0.15 in Fisher's exact test performed for this review). The only dose of *p,p′*-DDD tested, 45.0 mg/kg-day, is a LOAEL for body-weight depression in male mice.

The study authors noted that the incidence of lung tumors was increased over controls in *p,p′*-DDD-exposed mice of both sexes; in addition, the incidence of liver tumors (hepatomas) was increased in male mice (Tomatis et al., 1974). This study was used in the derivation of the OSF for *p,p′*-DDD (U.S. EPA, 1988b).

[5]Based on reference values for food consumption and body weight (U.S. EPA, 1988e). No strain-specific reference body weights were available for CF-1 mice; instead, average reference body weight for mice in a chronic-duration study were used: 0.0317 kg (male) and 0.02875 kg (female). Average reference food consumption for mice in a chronic-duration study were also used: 0.0057 kg/day (male) and 0.0053 kg/day (female).

Inhalation Exposures

No studies on the effects in laboratory animals to *p,p′*-DDD exposure via inhalation have been identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)
Short-Term-Duration Oral Studies with Considerable Limitations

Powers et al. (1974)

Eleven mongrel dogs and four purebred Beagle dogs were administered gelatin capsules containing technical-grade DDD (characterized by the study authors as 90% *p,p′*-DDD and 5−8% *o,p′*-DDD, other impurities unspecified) dissolved in corn oil. The dogs were given daily doses of 100 mg/kg for 6-day periods, or 200 mg/kg on alternative days for up to 30 days. In total, dogs received doses ranging from 600 mg/kg (6 × 100 mg/kg) to 3,000 mg/kg (15 × 200 mg/kg). Control groups (consisting of 6 mongrels and 2 Beagles) of various sizes were maintained. Upon sacrifice, the adrenal glands were weighed (in some cases), and/or examined with light and electron microscopy. The study authors reported histopathology findings in the adrenals of treated dogs, including degenerative vacuolation, especially in the inner cortex, mitochondrial swelling, cellular necrosis, and dilatation of smooth endoplasmic reticulum. Because the test material in this study included the potent adrenocorticolytic DDD isomer, *o,p′*-DDD, and potentially other contaminants, it is not possible to determine whether any of the adrenal effects are attributable to *p,p′*-DDD exposure. The study is inadequate to establish effect levels.

Genotoxicity

Genotoxicity data for *p,p′*-DDD have been summarized by ATSDR (2002a), WHO (2011), and IARC (1991). *p,p′*-DDD was negative in tests for reverse mutation in bacteria with or without activation. *p,p′*-DDD was also negative in tests for unscheduled deoxyribonucleic acid (DNA) synthesis in primary rat, mouse, and hamster hepatocytes. Weak positive results were found for chromosomal aberrations (CAs) in Chinese hamster B14F28 cells. Recent studies evaluating the potential genotoxicity of *p,p′*-DDD are limited to evaluations of DNA damage and micronucleus formation in zebra mussel hemocytes and human peripheral blood lymphocytes, and positive results were observed in both test systems (described in Table 4A and summarized below).

DNA damage and micronuclei (MN) were reported in *Dreissena polymorpha* (zebra mussel) hemocytes following 48, 96, and 168 hours of exposure to *p,p′*-DDD in water at 0.1, 2, or 10 µg/L (Binelli et al., 2008). Analysis using single cell gel electrophoresis (SCGE) alkaline comet assay revealed a dose- and time-related increase in DNA breakage, measured using tail-length-to-comet-head ratio (LDR) and tail intensity. MN were also induced in hemocytes collected from exposed zebra mussels, increasing with both exposure time and concentration.

DNA damage and MN were also reported in assays conducted in human peripheral blood lymphocytes following in vitro exposure to *p,p′*-DDD at 3.9 µg/mL for 1, 6, or 24 hours (Gerić et al., 2012). DNA strand breaks, detected in a standard comet assay, were significantly increased after 24 hours of exposure. Oxidative DNA damage, as measured by 8-hydroxy-2′-deoxyguanosine (8OHdG) formation in a modified comet assay, did not occur. Significant increases in the frequency of MN, numbers of nucleoplasmic bridges, and nuclear buds were reported after 24 hours, as analyzed using a cytokinesis-block micronucleus assay.

Table 4A. Recent Studies of *p,p′*-DDD Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	Reference
Genotoxicity studies in nonmammalian eukaryotic organisms—in vivo exposure						
Micronucleus test	*Dreissena polymorpha* (zebra mussel) hemocytes; zebra mussel exposures were conducted under semistatic conditions for up to 168 hr. Hemolymph (100 µL) was extracted from the posterior adductor muscle of 10 mussels at 48, 96, and 168 hr after exposure initiation.	0 (untreated and solvent controls), 0.1, 2, or 10 µg/L	+	+	MN frequency was significantly increased ≥threefold over the respective controls at each dose and time period.	Binelli et al. (2008)
DNA damage (SCGE; comet assay)	*D. polymorpha* hemocytes; zebra mussel exposures were conducted under semistatic conditions for up to 168 hr. Hemolymph (100 µL) was extracted from the posterior adductor muscle of 10 mussels at 48, 96, and 168 hr after exposure initiation.	0 (untreated and solvent controls), 0.1, 2, or 10 µg/L	+	+	DNA damage was significantly increased in a dose- and time-related manner and exhibited progressive accumulation of DNA damage over time.	Binelli et al. (2008)
Genotoxicity studies in mammalian cells—in vitro exposure						
DNA diffusion assay	Human peripheral blood lymphocytes	0 (control), 3.9 µg/mL for 1, 6, or 24 hr	+	NDr	Cell viability was decreased from 25% of control at 1 and 6 hr, and to ~50% of control at 24 hr. Both apoptosis and necrosis were observed, but necrosis was the primary form of cell death.	Gerić et al. (2012)
DNA damage (alkaline comet assay)	Human peripheral blood lymphocytes	0 (control), 3.9 µg/mL for 1, 6, or 24 hr	+	NDr	Tail intensity was increased after 24 hr of exposure; the percentage of DNA in the tail was 9.28% compared to 1.81% (control).	Gerić et al. (2012)
DNA damage (FPG-modified comet assay; 8OHdG formation)	Human peripheral blood lymphocytes	3.9 µg/mL for 1, 6, or 24 hr	−	NDr	NA	Gerić et al. (2012)

Table 4A. Recent Studies of *p,p′*-DDD Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested[a]**	**Results without Activation[b]**	**Results with Activation[b]**	**Comments**	**Reference**
Cytokinesis-block micronucleus assay	Human peripheral blood lymphocytes	3.9 µg/mL for 1, 6, or 24 hr	+	NDr	*p,p′*-DDD induced significant increases in the number of micronucleated cells, and total number of MN, nucleoplasmic bridges, and nuclear buds after 6 and 24 hr of exposure. The CBPI was significantly decreased by 15% only at the 24-hr exposure.	Gerić et al. (2012)

[a]Lowest effective dose for positive results; highest dose tested for negative results.
[b]+ = positive; − = negative.

8OHdG = 8-hydroxy-2′-deoxyguanosine; CBPI = cytokinesis-block proliferation index; DNA = deoxyribonucleic acid; FPG = formamidopyrimidine-DNA glycosylase; MN = micronuclei; NA = not applicable; NDr = not determined; *p,p′*-DDD = *p,p′*-dichlorodiphenyldichloroethane; SCGE = single cell gel electrophoresis.

Supporting Human Studies

Epidemiology studies evaluating the association between adverse health effects and measurements of *p,p′*-DDD in biological fluids are described in detail in Table 4B. Maternal blood and placental levels of *p,p′*-DDD were significantly higher in cases of spontaneous abortion and preterm labor, but not the rate of still birth, when compared with full-term deliveries (Tyagi et al., 2015; Saxena et al., 1983; Saxena et al., 1981; Saxena et al., 1980). Decreased birth weight was associated with increased *p,p′*-DDD levels in cord blood serum (Guo et al., 2014) and decreased birth length was correlated with placental *p,p′*-DDD levels (Al-Saleh et al., 2012). Serum levels of *p,p′*-DDD were also associated with changes in reproductive hormones in adult males and females (Freire et al., 2014; Perry et al., 2006; Dalvie et al., 2004a). Infertility in men was associated with higher serum and seminal fluid concentrations of *p,p′*-DDD (Pant et al., 2007; Pant et al., 2004; Pines et al., 1987). Sperm effects, however, were not consistently observed in these studies (Pant et al., 2007; Pant et al., 2004; Pines et al., 1987). Other health outcomes that were reportedly associated with elevated serum *p,p′*-DDD concentrations include breast cancer (Boada et al., 2012), altered thyroid hormone status (Freire et al., 2012), decreased insulin-like growth factor-I (IGF-I) (Zumbado et al., 2010; Boada et al., 2007), and Type 2 diabetes (Son et al., 2010). Taken together, these studies suggest an association between *p,p′*-DDD exposure and reproductive or hormonal effects. However, in all of these studies, the participants had measurable levels of other chlorinated compounds, including DDE and DDT. Further, when *p,p′*-DDD levels in biological fluids are used as an estimate for exposure, it is not possible to determine whether the levels result from direct exposure to *p,p′*-DDD or from metabolism of DDT. As a consequence, none of the available human studies are suitable for use in deriving provisional toxicity values.

Table 4B. Epidemiology Studies Evaluating Associations between Health Effects and *p,p′*-DDD Levels in Biological Fluids and Tissues

Study Population	Outcome	Levels of *p,p′*-DDD in Biological Media[a]	Results and Notes	Reference
Pregnancy outcomes				
India; case-control study; pregnant women between 18−30 yr of age; 20 cases of spontaneous abortion or premature labor, 20 controls (full-term delivery)	Spontaneous abortion and preterm labor (12−32 wk of gestation)	Maternal blood: Controls = 6.5 ± 7.88 ppb; Cases = 39.65 ± 19.85 ppb Placenta: Controls = 4.85 ± 9.28 ppb; Cases = 16.72 ± 18.96 ppb	Maternal blood and placental levels of *p,p′*-DDD were significantly ($p < 0.001$) higher in cases of spontaneous abortion and preterm labor when compared with full-term deliveries.	Saxena et al. (1980)
India; case-control study; pregnant women between 18−32 yr of age; 10 cases of spontaneous abortion, 15 cases of preterm labor, 25 controls (full-term delivery)	Spontaneous abortion and preterm labor (weeks of gestation not specified)	Maternal blood: Controls = 6.9 ± 7.9 ppb; Preterm labor cases = 15.2 ± 12.5 ppb; Spontaneous abortion cases = 65.5 ± 129.4 ppb Placenta (also fetus for spontaneous abortion cases): Controls = 4.9 ± 8.3 ppb; Preterm labor cases = 10.7 ± 10.7 ppb; Spontaneous abortion cases = 20.6 ± 22.8 ppb	Maternal blood and placental levels of *p,p′*-DDD were significantly ($p < 0.001$) higher in cases of preterm labor and spontaneous abortion when compared with full-term deliveries.	Saxena et al. (1981)
India; case-control study; pregnant women (age not reported); 9 cases of stillbirth, 27 controls (full term delivery)	Stillbirth	Maternal blood: Controls = 5.3 ppb (SD not reported); Cases = 3.6 ppb Placenta: Controls = 5.0 ppb; Cases = 7.6 ppb Cord blood: Controls = 6.2 ppb; Cases = 4.1 ppb	Maternal blood, placental, and cord blood levels of *p,p′*-DDD were similar for stillbirth cases and controls.	Saxena et al. (1983)

Table 4B. Epidemiology Studies Evaluating Associations between Health Effects and *p,p′*-DDD Levels in Biological Fluids and Tissues

Study Population	Outcome	Levels of *p,p′*-DDD in Biological Media[a]	Results and Notes	Reference
Saudi Arabia; cross-sectional study of 1,578 mother-newborn pairs (mean maternal age of 28 yr)	Neonatal anthropometric measures	Maternal blood = 0.002 ± 0.030 µg/L Cord blood = 0.005 ± 0.135 µg/L Placenta (µg/kg dry wt.) = 7.042 ± 18.030; Placenta (µg/kg wet wt.) = 42.357 ± 110.792	Placental *p,p′*-DDD levels were correlated with decreased crown-heel length in neonates (regression analysis adjusted for many continuous and categorical variables).	Al-Saleh et al. (2012)
China; cross-sectional study of 81 mother-infant pairs (median maternal age of 29 yr)	Birth weight	Median serum (ng/g lipid): Maternal = 1.42; Cord = 0.73	A decrease in birth weight was associated with increased *p,p′*-DDD levels in cord blood serum (not statistically significant; multivariate linear regression adjusted for maternal age, maternal BMI at delivery, infant gender, and week of gestation).	Guo et al. (2014)
India; case-control study; pregnant women with a mean maternal age of 23 yr old; 50 cases of preterm birth (<37 wk gestation) and 50 controls (gestation of >37 wk)	Preterm birth (<37 wk gestation), placental weight, baby weight, period of gestation	Maternal blood (ppb): Controls = 1.13 ± 0.041; Cases = 1.74 ± 0.895 Placenta: Controls = 5.780 ± 4.8055; Cases = 7.663 ± 5.5670	Maternal blood levels of *p,p′*-DDD were significantly (p = 0.016) higher in cases of preterm labor; no significant correlation was observed between *p,p′*-DDD concentration and placental weight, baby weight, or gestation period.	Tyagi et al. (2015)
Sexual differentiation measures				
Denmark and Finland; nested case-control study of mother-child pairs (maternal age between 29−31 yr); 62 cases of cryptorchidism, 68 healthy controls	Cryptorchidism in male offspring	Breast milk (ng/g lipid): Controls (median) = 0.34; Cases (median) = 0.36	Breast milk concentrations of *p,p′*-DDD were similar between cryptorchidism cases and controls.	Damgaard et al. (2006)

Table 4B. Epidemiology Studies Evaluating Associations between Health Effects and *p,p′*-DDD Levels in Biological Fluids and Tissues

Study Population	Outcome	Levels of *p,p′*-DDD in Biological Media[a]	Results and Notes	Reference
Reproductive hormone levels				
South Africa; cross-sectional study of 50 male malaria control workers (mean age of 45 yr)	Hormone levels before and after gonadotropin-releasing hormone challenge (LH, FSH, E2, testosterone inhibin)	Serum level (µg/g lipid): 0.91 ± 0.68	A significant positive association was observed between serum *p,p′*-DDD levels, and baseline levels of testosterone and E2 (linear regression adjusted for age and basal SHBG).	Dalvie et al. (2004a)
China; prospective cohort study; 287 women between 20−34 yr of age	Levels of progesterone (measured as urinary PdG) and estrogen (measured as urinary estrone conjugates or E_1C)	Serum range (ng/g): 0.07−0.96	Higher serum *p,p′*-DDD levels were associated with lower log (PdG) levels across all phases of the menstrual cycle and lower E_1C levels during periovulation, and the luteal period (linear regression adjusted for age, age squared, BMI, BMI squared, education, shift work, stress, passive smoke, noise, and dust exposure).	Perry et al. (2006)
Brazil; cross-sectional study; 304 men and 300 women (mean age of 39 yr)	Serum levels of testosterone in men and E2, progesterone, prolactin, LH, and FSH in females	Median concentration in serum (ng/mL): Men = 0.61; Premenopausal women (*n* = 223) = 0.59; Peri/postmenopausal women (*n* = 77) = 0.87	A significant negative association was observed between serum *p,p′*-DDD levels, and LH and FSH concentrations in peri/postmenopausal women (multivariate regression adjusted for age, ethnicity, years at location, BMI, breastfeeding, smoking, and serum cholesterol and triglycerides).	Freire et al. (2014)

Table 4B. Epidemiology Studies Evaluating Associations between Health Effects and *p,p′*-DDD Levels in Biological Fluids and Tissues

Study Population	Outcome	Levels of *p,p′*-DDD in Biological Media[a]	Results and Notes	Reference
Male reproductive effects (fertility, semen analysis)				
Israel; case-control study; men between 25−45 yr of age; 29 cases of infertility (>5 yr history, sperm effects); 14 controls (fertile with at least one child <2 yr old)	Male fertility, semen analysis (sperm count, motility, and morphology)	Serum (ng/g): Control = 2.23 ± 3.0; Cases = 4.35 ± 4.74	Serum *p,p′*-DDD was significantly higher in infertile men compared to controls; no association between serum levels and sperm effects was noted.	Pines et al. (1987)
South Africa; cross-sectional study of 60 male malaria control workers (mean age of 45 yr)	Semen analysis (sperm count, density and motility)	Serum levels were not reported	No significant association between serum *p,p′*-DDD and semen parameters was observed.	Dalvie et al. (2004b)
India; case-control study of men; 45 cases of infertility (>1 yr history, mean age 31 yr); 45 controls (fertile; mean age of 29 yr)	Male fertility; semen analysis for fructose concentration (marker of seminal vesicle secretion), and activity of acid phosphatase and γ-glutamyl transpeptidase (markers of prostate function)	Seminal fluid concentration (µg/L): Controls = 12.1 ± 1.36 (SEM); Cases = 21.38 ± 2.12 (SEM)	The semen level of *p,p′*-DDD was significantly higher in infertile men compared to controls; in infertile men, *p,p′*-DDD levels in semen were significantly correlated with higher levels of fructose.	Pant et al. (2004)
India; case-control study of men; 50 cases of infertility (>1 yr history, mean age 30 yr); 50 controls (fertile, mean age of 29 yr)	Semen analysis (sperm count and motility)	Seminal fluid concentration (µg/L): Controls = 13.4 ± 1.09 (SEM); Cases = 20.74 ± 1.92 (SEM)	The semen level of *p,p′*-DDD was significantly higher in infertile men compared to controls; in infertile men, *p,p′*-DDD levels in semen were significantly correlated with decreased sperm count.	Pant et al. (2007)
Breast cancer				
Poland; case-control study of women between 37−87 yr of age (mean age of 58); 54 cases of breast cancer; 23 healthy controls	Breast cancer stage and grade	Breast adipose tissue (mg/kg fat): Controls = 0.025 ± 0.032; Cases = 0.031 ± 0.037	Levels of *p,p′*-DDD did not differ between cases and controls; no significant correlation was observed between breast adipose levels of *p,p′*-DDD and breast cancer stage or grade.	Ociepa-Zawal et al. (2010)

Table 4B. Epidemiology Studies Evaluating Associations between Health Effects and *p,p′*-DDD Levels in Biological Fluids and Tissues

Study Population	Outcome	Levels of *p,p′*-DDD in Biological Media[a]	Results and Notes	Reference
Spain; case-control study of women; 121 cases of breast cancer (mean age of 58); 103 healthy controls (mean age of 45)	Breast cancer risk	Serum (ng/g lipid): Controls = 21.8 ± 131.2; Cases = 440.3 ± 412.7	The serum level of *p,p′*-DDD was significantly higher in women with breast cancer compared to controls; breast cancer risk was slightly elevated (adjusted OR 1.008: 95% CI 1.001−1.015, $p = 0.024$; adjusted for age, BMI, menopausal status, lactation, and smoking habits).	Boada et al. (2012)
Thyroid hormone status				
Thailand; cross-sectional study of 39 mother-infant pairs (full term, normal delivery)	Thyroid hormone status in infants (measured in umbilical cord blood)	Serum (ng/g lipid): Maternal = 139 ± 115; Cord = 105 ± 63.0	No correlation was found between *p,p′*-DDD and thyroid hormone levels in cord serum.	Asawasinsopon et al. (2006)
Brazil; cross-sectional study of 193 children (<15 yr old)	Thyroid hormone status in children	Serum (ng/mL): Mean of levels above detection limit = 24.2	Total T3 levels and free T4 levels were positively associated with serum concentrations of *p,p′*-DDD (regression adjusted for age, gender, triglycerides, and cholesterol).	Freire et al. (2012)
Insulin-like growth factor-I (IGF-I)				
Spain; cross-sectional study of 176 men (mean age of 43 yr) and 247 women (mean age of 43 yr)	Serum concentrations of IGF-I	Median serum (ng/g fat): Men = 0.0 (19.3% of samples above the detection limit); Women = 0.0 (19.8% of samples above the detection limit)	IGF levels were lower in women aged 36−50 with detectable *p,p′*-DDD concentrations, compared to women of the same age group with nondetectable levels of *p,p′*-DDD ($p = 0.03$; IGF levels were adjusted for age, BMI, and IGFBP-3).	Boada et al. (2007)

Table 4B. Epidemiology Studies Evaluating Associations between Health Effects and *p,p′*-DDD Levels in Biological Fluids and Tissues

Study Population	Outcome	Levels of *p,p′*-DDD in Biological Media[a]	Results and Notes	Reference
Spain; cross-sectional study of children (ages 6−12 in females; 6−15 in males) and adolescents (ages 13−19 in females; 15−19 in males); 81 boys and 79 girls	Serum concentrations of IGF-I	Median serum (25th−75th percentile) (ng/g fat): Male children = 0.0 (0.0−0.0); Male adolescents = 0.0 (0.0−132.9); Female children = 0.0 (0.0−0.0); Female adolescents = 0.0 (0.0−0.0)	Detectable levels of *p,p′*-DDD in prepubertal male children were inversely associated with IGF-I levels ($p = 0.049$) (multivariate analysis adjusted for age, height, weight, and IGFBP-3; a categorical variable was included to account for the large number of samples with *p,p′*-DDD concentrations below the detection limit).	Zumbado et al. (2010)
Gallstone disease				
China; case-control study; 150 patients with gallstones, 150 age- and gender-matched controls	Gallstone disease	Median serum concentrations (µg/L): Controls = 0.369; Cases = 0.381	*p,p′*-DDD concentrations were similar between cases and controls; percent detectability was slightly higher in cases vs. controls (100 vs. 94.7%).	Su et al. (2012)
Type 2 diabetes				
Korea; case-control study; 40 diabetic patients (53% men, mean age of 57 yr) and 40 healthy controls (53% men, mean age of 57 yr)	Type 2 diabetes	Serum (ng/g lipid): Controls = 5.7 ± 3.7; Cases = 6.6 ± 3.6	*p,p′*-DDD concentrations were similar between cases and controls; association between serum concentration and Type 2 diabetes was observed at the highest tertile of exposure after adjusting for age, sex, BMI, alcohol consumption, and smoking (adjusted OR 3.6; 95% CI 0.08−16.3).	Son et al. (2010)

[a]Values represent mean ± SD unless otherwise indicated.

BMI = body mass index; CI = confidence interval; E2 = estradiol; FSH = follicle stimulating hormone; IGF = insulin-like growth factor; IGFBP-3 = IGF binding protein-3; LH = luteinizing hormone; OR = odds ratio; PdG = pregnanediol-3-glucuronide; *p,p′*-DDD = *p,p′*-dichlorodiphenyldichloroethane; SD = standard deviation; SEM = standard error of the mean; SHBG = sex hormone binding globulin; T3 = triiodothyronine; T4 = thyroxine.

Metabolism/Toxicokinetic Studies

In a study of the toxicokinetics of DDT and its metabolites (including *p,p′*-DDD), an adult male volunteer ingested 5 mg/day of *p,p′*-DDD for 81 days (Morgan and Roan, 1974, 1971). The pesticide was mixed with vegetable oil, emulsified with gum arabic and water, and taken with meals (no further detail on dosing was provided). Serum and adipose levels of *p,p′*-DDD rose steadily during the exposure period, peaking at exposure termination at almost 80 ppb in serum and >4 ppm in adipose (based on visual examination of data presented graphically). Twenty-four percent of the ingested dose was stored in adipose tissue over the exposure period. After exposure was withdrawn, levels in both serum and adipose declined rapidly. Measurements taken 160 days after exposure termination showed no detectable *p,p′*-DDD in serum and levels reduced to almost 1 ppm in adipose. Approximately 68% of the total administered dose was excreted in the urine during the first year of the study (urine concentrations were measured monthly). *p,p′*-DDD has been detected in adipose tissue, breast milk, and placenta from many study populations of environmental exposure (Xu et al., 2015; Hernik et al., 2014; Man et al., 2014; Bedi et al., 2013; Song et al., 2013; Bergkvist et al., 2012; Cok et al., 2012; Wang et al., 2011; Azeredo et al., 2008; Shen et al., 2008; Bouwman et al., 2006).

The metabolism and excretion of *p,p′*-DDD have been studied in experimental animals. The primary urinary metabolite of *p,p′*-DDD in rats, mice, and hamsters is 2,2-*bis*(4′-chlorophenyl) acetic acid (DDA) (Gold and Brunk, 1984, 1983, 1982; Peterson and Robison, 1964). The intermediary metabolites (i.e., between *p,p′*-DDD and DDA) appear to differ by species. Studies in rats suggest that *p,p′*-DDD is rapidly detoxified to DDA through the following intermediates: 1-chloro-2,2-*bis*(4′-chlorophenyl)ethene (DDMU), 1-chloro-2,2-*bis*(4′-chlorophenyl)ethane (DDMS), 1,1-*bis*(4′-chlorophenyl)ethene (DDNU), 2,2-*bis*(4′-chlorophenyl)ethanol (DDOH), and 2,2-*bis*(4′-chlorophenyl)ethanal (DDCHO) (Peterson and Robison, 1964). Metabolism occurs in both the liver and kidney, and DDMU-epoxide is postulated as a possible reactive intermediate of *p,p′*-DDD in rats. Studies in mice and hamsters suggest that *p,p′*-DDD is preferentially metabolized to 2,2-*bis*(4′-chlorophenyl)acetyl chloride (DDA-Cl), which is hydrolyzed to DDA (Gold and Brunk, 1984, 1983, 1982). Formation of DDMU and DDMU-epoxide appears to be a minor pathway in mice and hamsters.

Mode-of-Action/Mechanistic Studies

A number of studies have investigated the hormonal activities of DDT and related compounds. When Gellert et al. (1972) injected groups of 11 or 12 mature ovariectomized Sprague-Dawley (S-D) rats with 0.1 or 10 mg/day of *p,p′*-DDD in dimethylsulfoxide (DMSO) for 7 days, there was no effect on uterine weight, uterine histology, cytology of vaginal smears, serum levels of luteinizing hormone, or follicle stimulating hormone. In castrated male Brl Han: WIST Jcl (GALAS) rats treated with 8, 40, or 200 mg/kg-day *p,p′*-DDD via gavage for 10 days, either with or without testosterone propionate, treatment with 200 mg/kg *p,p′*-DDD and testosterone propionate resulted in statistically significant decreases in seminal vesicle and bulbocavernosus/levator ani muscles, indicating antiandrogenic activity (Yamasaki et al., 2004). In in vitro assays, *p,p′*-DDD did not competitively inhibit binding of 17β-estradiol to the estrogen receptor (ER), but competitively inhibited binding of a synthetic androgen (R1881) to the rat androgen receptor (AR) (Kelce et al., 1995). In in vitro assays using yeast reporter gene systems, *p,p′*-DDD was unable to activate expression of the ER gene or the AR gene at concentrations $<10^{-4}$ M (Gaido et al., 1997). Using an in vitro human hepatoma cell reporter gene system,

Maness et al. (1998) found that *p,p′*-DDD did not stimulate expression of the human androgen receptor (hAR) gene, but did inhibit androgen-dependent expression of the hAR gene. *p,p′*-DDD gave positive results in an AR binding assay (Yamasaki et al., 2004). The results of these experiments suggest that *p,p′*-DDD possesses antiandrogenic activity.

Limited evidence suggests that *p,p′*-DDD binds to lung tissues and can be cytotoxic to lung cells. When Lund et al. (1989) intravenously (i.v.) injected radiolabeled *p,p′*-DDD into mice, autoradiography of solvent-extracted, whole-body sections revealed specific covalent binding in the alveoli of the lung, in the lateral nasal gland, and in the salivary glands. The results of the in vivo study suggest that pulmonary binding of *p,p′*-DDD can occur after i.v. exposure. An in vitro experiment in the same paper demonstrated that *p,p′*-DDD irreversibly bound to protein following incubation with S-9 fractions from murine lung or liver. The study authors concluded that covalent binding of *p,p′*-DDD in the lung was the result of in situ bioactivation. In an in vitro study, Nichols et al. (1992) incubated lung cells isolated from rabbits with *p,p′*-DDD, with or without 1-aminobenzotriazole (1-ABT, a suicide substrate inhibitor of cytochrome P450 [CYP450] monooxygenases). Cytotoxicity of *p,p′*-DDD to Clara cells especially, and to alveolar type II cells and alveolar macrophages to a lesser degree, was dependent on the presence of functional CYP450. Subsequently, Nichols et al. (1995) evaluated potential mechanisms for bioactivation of *p,p′*-DDD in cultured Clara cells of rabbits and a transformed human bronchial epithelial cell line (BEAS-2B). Both cell types were vulnerable to *p,p′*-DDD-mediated cytotoxicity and were protected by coincubation with 1-ABT, the inhibitor to CYP450. In another experiment, Nichols et al. (1995) found that cytotoxicity was reduced when human BEAS-2B cells, rabbit Clara cells, or rabbit pulmonary microsomes were incubated with *p,p′*-DDD that had a deuterium substitution at the C-1 position. The results indicated that the cytotoxicity of *p,p′*-DDD may be caused by its oxidation at C-1 mediated by CYP450 in the lung.

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer references values, respectively.

Table 5. Summary of Noncancer Reference Values for *p,p′*-DDD (CASRN 72-54-8)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)	Rat/M, F	Liver lesions	3×10^{-5}	NOAEL (HED)	0.01 (based on surrogate POD)	300	Laug et al. (1950) as cited in ATSDR (2002a) and U.S. EPA (1988d)
Screening chronic p-RfD (mg/kg-d)	Rat/M, F	Liver lesions	3×10^{-5}	NOAEL (HED)		300	Laug et al.(1950) as cited in ATSDR (2002a) and U.S. EPA (1988d)
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

F = female(s); HED = human equivalent dose; M = male(s); NDr = not determined;
NOAEL = no-observed-adverse-effect level; POD = point of departure;
p,p′-DDD = *p,p′*-dichlorodiphenyldichloroethane; p-RfC = provisional reference concentration;
p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

Table 6. Summary of Cancer Reference Values for *p,p′*-DDD (CASRN 72-54-8)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	An OSF of 0.24 $(mg/kg/day)^{-1}$ is available on IRIS (U.S. EPA, 1988b)			
p-IUR $(mg/m^3)^{-1}$	NDr			

IRIS = Integrated Risk Information System; NDr = not determined; p-IUR = provisional inhalation unit risk;
p-OSF = provisional oral slope factor; *p,p′*-DDD = *p,p′*-dichlorodiphenyldichloroethane.

DERIVATION OF ORAL REFERENCE DOSES

None of the human studies of *p,p′*-DDD are suitable for deriving provisional reference doses (p-RfDs). The human database includes an oral subchronic-duration study in a single male volunteer exposed to 0.07 mg *p,p′*-DDD/kg-day, with the study lacking detailed information on toxicity endpoints and experimental results (Morgan and Roan, 1974, 1971). Several epidemiological studies are available evaluating the potential association between biological measurements of *p,p′*-DDD, and reproductive or hormonal outcomes (see Table 4B). However, it is not possible to clearly attribute any effects reported in these studies to direct exposure to *p,p′*-DDD, due to confounding effects from concomitant exposure to other organochlorine compounds, and also because it is not possible to determine whether *p,p′*-DDD measured in biological tissues resulted from exposure to *p,p′*-DDD or from metabolism of DDT to *p,p′*-DDD in the human body.

Animal studies relevant to the derivation of p-RfD values include 6-week dose range-finding studies in rats and mice (NCI, 1978), a 6-week immunotoxicity study in rats

(Banerjee et al., 1996), a subchronic-duration adrenal toxicity study in dogs (Cueto et al., 1958), and chronic-duration studies in rats and mice (NCI, 1978; Tomatis et al., 1974) (see Table 3A).

The usefulness of the data from the NCI (1978) subchronic- and chronic-duration studies is compromised by the low purity of the technical-grade DDD tested. Only 60% of the product was *p,p′*-DDD and at least 19 impurities (unspecified) were present in the remaining 40%. In the subchronic dose range-finding studies, mortality was reported in exposed rats and decreases in body weight were noted in some exposed mice; however, low number of animals were included, limited endpoints were examined (body weight and mortality) and results were poorly reported, precluding the determination of critical effects and effect levels. The chronic-duration data are further compromised by the substantial adjustments in administered dietary level during the study and by the long post-treatment observation period, during which recovery from or reversal of effects could have occurred. Therefore, chronic-duration LOAELs (39.3−85.2 mg/kg-day) based on decreased body weights in rats and in female mice are not considered sufficiently reliable for the p-RfD derivation. Tomatis et al. (1974) also found reductions in body weight in male mice at a LOAEL of 45.0 mg/kg-day. The study was designed primarily as a carcinogenicity bioassay with sparse detail on noncancer effects, limiting its use for the assessment of long-term noncancer toxicity.

The 6-week immunotoxicity study by Banerjee et al. (1996) reported significant decreases in relative spleen weight and reduced humoral and cell-mediated immunity in male rats at a LOAEL of 18.4 mg/kg-day. In the absence of information on absolute organ-weight changes or spleen histopathology, the biological significance of the observed decreases in relative spleen weight are unknown. The study included relevant immune function assays (i.e., delayed-type hypersensitivity [DTH] reaction and ovalbumin-specific IgG and IgM measurements) indicative of an immunosuppressive effect, as well as, more general immune system tests (i.e., macrophage and lymphocyte migration) that provide equivocal evidence of immunotoxicity. However, the study suffers from methodological issues, such as the evaluation of limited endpoints and the use of one treatment dose, one species, and one sex (males). In the absence of additional supporting information, the findings of immunotoxicity with *p,p′*-DDD exposure are inconclusive. Therefore, the Banerjee et al. (1996) study, by itself, does not qualify as the basis for either a subchronic or chronic p-RfD. Finally, the adrenal toxicity study in dogs (Cueto et al., 1958) is not suitable for the p-RfD derivation due to the small number of animals used and few endpoints examined.

As a result of the limitations in the available oral toxicity data for *p,p′*-DDD, subchronic and chronic p-RfDs were not derived directly. Instead, screening subchronic and chronic p-RfDs are derived in Appendix A using an alternative surrogate approach.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

The absence of relevant inhalation data precludes derivation of provisional reference concentrations (p-RfCs) for *p,p′*-DDD directly. An alternative surrogate approach was attempted, but screening p-RfCs could not be derived due to a lack of inhalation toxicity values for potential surrogates (see Appendix A).

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

A B2 cancer classification (probable human carcinogen) is available for *p,p′*-DDD on IRIS (U.S. EPA, 1988b).

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of a Provisional Oral Slope Factor

An OSF of 0.24 $(mg/kg/day)^{-1}$ is available for *p,p′*-DDD on IRIS (U.S. EPA, 1988b).

Derivation of a Provisional Inhalation Unit Risk

Derivation of quantitative estimates of cancer risk following inhalation exposure to *p,p′*-DDD is precluded by the absence of inhalation data for this compound.

APPENDIX A. SCREENING PROVISIONAL VALUES

For the reasons noted in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, provisional toxicity values for *p,p′*-dichlorodiphenyldichloroethane (*p,p′*-DDD) could not be derived. However, information is available for this chemical, which although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the main documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Heath Risk Technical Support Center.

APPLICATION OF AN ALTERNATIVE SURROGATE APPROACH FOR NONCANCER VALUES

The surrogate approach allows for the use of data from related compounds to calculate screening values when data for the compound of interest are limited or unavailable. Details regarding searches and methods for surrogate analysis are presented in Wang et al. (2012). Three types of potential surrogates (structural, metabolic, and toxicity-like) are identified to facilitate the final surrogate chemical selection. The surrogate approach may or may not be route-specific or applicable to multiple routes of exposure. All information was considered together as part of the final weight-of-evidence (WOE) approach to select the most suitable surrogate both toxicologically and chemically.

Structural Surrogates (Structural Analogs)

An initial surrogate search focused on the identification of structurally similar chemicals with toxicity values from the Integrated Risk Information System (IRIS), PPRTV, Agency for Toxic Substances and Disease Registry (ATSDR), or California Environmental Protection Agency (Cal/EPA) databases to take advantage of the well-characterized chemical-class information. Under Wang et al. (2012), structural similarity for analogs is typically evaluated using U.S. EPA's DSSTox database (DSSTox, 2016), and the National Library of Medicine's (NLM's) ChemIDplus database (ChemIDplus, 2017). The Organisation for Economic Co-operation and Development (OECD) Toolbox was also used to calculate structural similarity using the Tanimoto method (a similar quantitative method used by ChemIDplus and DSSTox). Three structural analogs to *p,p′*-DDD were identified with available oral toxicity values and >50% similarity scores from at least two of the structure activity relationship (SAR) databases consulted: *p,p′*-dichlorodiphenyltrichloroethane (*p,p′*-DDT) (ATSDR, 2002a; U.S. EPA, 1988d), *p,p′*-dichlorodiphenyldichloroethylene (*p,p′*-DDE) (ATSDR, 2002a), and *p,p′*-dimethoxydiphenyltrichloroethane (methoxychlor) (ATSDR, 2002b; U.S. EPA, 1988c). No structural analogs with inhalation toxicity values were identified; therefore, the current surrogate analyses are specific to the assessment of repeated-exposure toxicity via the oral route.

Table A-1 summarizes the analogs' physicochemical properties and similarity scores. Overall, the structural similarity scores derived from ChemIDplus, DSSTox, and the OECD

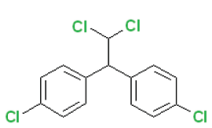
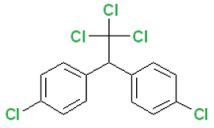
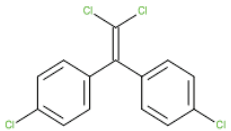
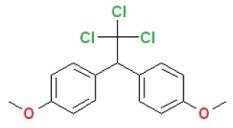
quantitative structure-activity relationship (QSAR) Toolbox were consistently highest for *p,p′*-DDT (71−96%) and lowest for methoxychlor (36−64.6%); structural similarity scores for *p,p′*-DDE were intermediate (56−67%). *p,p′*-DDD and the candidate surrogates are organochlorine compounds that share a basic chemical structure, consisting of a diphenylalkane structure containing three or more chlorine atoms. The para substitutions in the phenyl rings are important in determining the physicochemical properties and insecticidal activity of these compounds (Coats, 1990). In the case of *p,p′*-DDT, *p,p′*-DDD, and *p,p′*-DDE, the para substituents are occupied by chlorine atoms. Conversely, these moieties are replaced by methoxy groups in the methoxychlor compound, contributing to the less bioaccumulative properties of methoxychlor in animals and in the environment, compared to *p,p′*-DDT, *p,p′*-DDD, and *p,p′*-DDE (Kapoor et al., 1970).

In general, physicochemical properties for all four organochlorine compounds are similar (see Table A-1). Although water solubility is considered low (i.e., <1 mg/L), *p,p′*-DDD and the structural analogs are expected to be bioavailable by the oral route. These compounds exhibit moderate volatility (i.e., Henry's law constant of 10^{-3} to 10^{-7}) and low vapor pressure; however, they are expected to be bioavailable when inhaled (as a vapor or particulate matter).

Surrogate Summary and Evaluation

Based on comparable structural and physicochemical properties, *p,p′*-DDT and *p,p′*-DDE are considered suitable structural surrogates for *p,p′*-DDD. On the other hand, methoxychlor is a less suitable surrogate based on functional group differences (i.e., presence of *p,p′*-methoxy groups) that could affect the toxicokinetic properties and toxicity of this compound compared to *p,p′*-DDD and the structurally related *p,p′*-chlorinated analogs (*p,p′*-DDT and *p,p′*-DDE).

Table A-1. Physicochemical Properties of *p,p′*-DDD (CASRN 72-54-8) and Candidate Surrogates[a]

Chemical	***p,p′*-Dichlorodiphenyl dichloroethane (DDD)**	***p,p′*-Dichlorodiphenyl trichloroethane (DDT)**	***p,p′*-Dichlorodiphenyl dichloroethylene (DDE)**	***p,p′*-Dimethoxydiphenyl trichloroethane (Methoxychlor)**
Structure				
CASRN	72-54-8	50-29-3	72-55-9	72-43-5
Molecular weight	320	354	318	346
ChemIDplus similarity score (%)[b]	100	77	67	64.6
DSSTox similarity score (%)	100	96	61	52.1
OECD QSAR Toolbox similarity score (%)[c]	100	71	56	36
Melting point (°C)	109.5	108.5	89	87
Boiling point (°C)	350	260	336	346
Vapor pressure (mm Hg at 25°C)	1.35×10^{-6}	1.6×10^{-7} (20°C)	6×10^{-6} (extrapolated)	4.2×10^{-5} (estimated)
Henry's law constant (atm-m^3/mole at 25°C)	6.60×10^{-6}	8.32×10^{-6}	4.16×10^{-5}	2.03×10^{-7}
Water solubility (mg/L)	0.09	0.0055	0.04	0.1
Log K_{ow}	6.02	6.91	6.51	5.08
pKa	NA	NA	NA	NA

[a]Data were gathered from PHYSPROP for each respective compound unless otherwise specified (U.S. EPA, 2012b).
[b]ChemIDplus Advanced, similarity scores (ChemIDplus, 2017).
[c]OECD (2016).

NA = not applicable; OECD = Organisation for Economic Co-operation and Development; QSAR = quantitative structure-activity relationship.

Metabolic Surrogates

Table C-1 summarizes available toxicokinetic data for *p,p′*-DDD and the structurally similar compounds identified as potential surrogates.

Absorption

No data on the rate and extent of oral absorption are available for *p,p′*-DDD or *p,p′*-DDE; however, both *p,p′*-DDD and *p,p′*-DDE were detected in serum and adipose tissue from human volunteers ingesting 5 mg daily for 81 or 92 days, respectively, confirming that absorption did occur (Morgan and Roan, 1974, 1971). Additionally, oral absorption of *p,p′*-DDD and *p,p′*-DDE can be infered by the detection of parent chemicals and corresponding metabolites in excreta of exposed animals (see "Metabolism" discussion below). The maximum serum concentration (C_{MAX}) of *p,p′*-DDT was detected 3 hours after ingestion of a 20-mg dose by a volunteer, indicating that absorption was rapid (Morgan and Roan, 1974). The oral absorption of both *p,p′*-DDT and methoxychlor was confirmed in animal studies to be rapid and near complete (see Table C-1). Oral bioavailability is anticipated to be similar for the target compound and each of the potential surrogates based on comparable physicochemical properties (i.e., water solubility, K_{ow}).

Distribution

p,p′-DDD, *p,p′*-DDT, and *p,p′*-DDE have been detected in adipose tissue, breast milk, and the placenta of environmentally exposed humans (Xu et al., 2015; Hernik et al., 2014; Man et al., 2014; Bedi et al., 2013; Song et al., 2013; Bergkvist et al., 2012; Cok et al., 2012; Wang et al., 2011; Azeredo et al., 2008; Shen et al., 2008; Bouwman et al., 2006; ATSDR, 2002a). Data in human volunteers indicate that *p,p′*-DDD, *p,p′*-DDT, and *p,p′*-DDE persist in adipose tissue for several months to years following exposure (see Table C-1). Transplacental and lactational transfer of *p,p′*-DDT and *p,p′*-DDE have been demonstrated in laboratory animal studies (You et al., 1999; Woolley and Talens, 1971). Methoxychlor was detected in rat breast milk, but does not persist in rat adipose tissue (no human data are available) (Chapin et al., 1997; Harris et al., 1974; Kunze et al., 1950).

Metabolism

The primary metabolic pathway for *p,p′*-DDT involves initial dechlorination to *p,p′*-DDD or *p,p′*-DDE in the liver, although metabolism of *p,p′*-DDT via *p,p′*-DDD, proceeds faster than via the *p,p′*-DDE pathway (Morgan and Roan, 1971; Peterson and Robison, 1964). *p,p′*-DDD is further metabolized to 2,2-*bis*(*p*-chlorophenyl) acetic acid (DDA), which is the primary urinary metabolite detected following exposure to either *p,p′*-DDT or *p,p′*-DDD in humans, rats, mice, and hamsters (Gold and Brunk, 1984, 1983, 1982; Roan et al., 1971; Peterson and Robison, 1964). Table A-2 compares excreted metabolites in rodents for *p,p′*-DDD and the candidate surrogates. Metabolic disposition patterns in the mouse reveal remarkable similarities in the metabolism of *p,p′*-DDT and *p,p′*-DDD, providing further support for the suitability of *p,p′*-DDT as a metabolic surrogate of *p,p′*-DDD. Although possible reactive metabolites (e.g., 2,2-*bis*[4′-chlorophenyl]acetyl chloride [DDA-Cl] and 1-chloro-2,2-*bis*[*p*-chloro-phenyl]ethene [DDMU]-epoxide) can result from the biotransformation of *p,p′*-DDT to DDA, via *p,p′*-DDD (see Table C-1), this metabolic pathway is considered, for the most part, a detoxification pathway (Gold and Brunk, 1983).

p,p′-DDE is less metabolically active than *p,p′*-DDD and *p,p′*-DDT, as evidenced by the presence of *p,p′*-DDE as the major component in excreta from *p,p′*-DDE-exposed animals

(see Table A-2) and as the only urinary product recovered in a human subject exposed to *p,p′*-DDE (5 mg daily for 92 days) (Morgan and Roan, 1974). The inefficiency of *p,p′*-DDE metabolism appears to be related to the greater affinity of this compoud for fat storage in relation to *p,p′*-DDD and *p,p′*-DDT (Morgan and Roan, 1971). Nevertheless, metabolism of *p,p′*-DDE to DDA has been demostrated in rats with intraperitoneal (i.p.) injection (see Table A-2). Methylsulfonyl metabolites of *p,p′*-DDE (2- and 3-methylsulfonyl-DDE) have also been identified in humans and marine animals, and could represent an important metabolic pathway for *p,p′*-DDE (see Table C-1).

Table A-2. Summary of Metabolites for *p,p′*-DDD and Candidate Surrogates

Chemical	Route	Species	Metabolites and Other Excreted Products (%)	Reference
***p,p′*-DDD**	Oral: 100 mg/kg	Mouse	DDA (95%), parent compound (4%), 2-OH-DDA (1%), DDOH (<1%), DDE (<1%), and DDMU (<1%) in urine within 72 h[a]	Gold and Brunk (1982)
***p,p′*-DDT**	Oral: 500 mg/kg	Mouse	DDA (86%), DDE (9%), DDD (3%), 2-OH-DDA (1%), parent compound (<1%), DDMU (<1%), and DDOH (<1%) in urine within 72 h[a]	Gold and Brunk (1982)
***p,p′*-DDE**	Oral: 20 mg/kg i.p.: 200 mg/kg	Mouse Rat	Mostly excreted as parent compound in urine and feces within 72 h. Primary metabolite: 3′-OH-DDE Unchanged DDE was the major component in feces. Primary fecal metabolites: ring-hydroxylated products of DDE (3′-OH-DDE and 2′-OH-DDE), followed by DDA and DBP	Gold and Brunk (1986) Fawcett et al. (1987)
Methoxychlor	Oral: 50 mg/kg	Rat	*Mono*-hydroxy methoxychlor (30%), *bis*-hydroxy-methoxychlor (23%), *bis*-hydroxy-diphenylacetic acid and *bis*-hydroxy-benzophenone (11%), parent compound (8%), *bis*-hydroxy-dichloroethylene (1%) in urine and feces over an 11-d period[b]	Kapoor et al. (1970); ATSDR (2002b)

[a]Expressed as percent of excreted dose.
[b]Expressed as percent of the administered dose.

DBP = *bis*(4′-chlorophenyl)ketone; DDA = 2,2-*bis*(4′-chlorophenyl)acetic acid;
2-OH-DDA = 2-hydroxy-2,2-*bis*(4′-chlorophenyl)acetic acid;
2′-OH-DDE = 1,1,-dichloro-2-(4′-chlorophenyl)-2-(2″-hydroxy-4″-chlorophenyl)ethene;
3′-OH-DDE = 1,1,-dichloro-2-(4′-chlorophenyl)-2-(3″-hydroxy-4″-chlorophenyl)ethene;
DDMU = 1-chloro-2,2-*bis*(4′-chlorophenyl)ethene; DDOH = 2,2-*bis*(4′-chlorophenyl)ethanol; i.p. = intraperitoneal;
p,p′-DDD = *p,p′*-dichlorodiphenyldichloroethane; *p,p′*-DDE = *p,p′*-dichlorodiphenyldichloroethylene.

Contrary to *p,p′*-DDD, the primary metabolic pathway of methoxychlor in mice involves sequential *O*-demethylation, leading to the production of mono-hydroxy and *bis*-hydroxy methoxychlor (see Table A-2). The demethylated metabolites are believed to be involved in the reproductive effects of methoxychlor resulting from interaction of these compounds with steriod hormone receptors such as the estrogen and androgen receptors (Sumida et al., 2001; Charles et al., 2000; Maness et al., 1998; Bulger et al., 1978). Alternatively, dechlorination of methoxychlor results in the formation of *bis*-hydroxydiphenyl acetic acid,

bis-hydroxybenzophenone, and *bis*-hydroxy-dichloroethylene, which constitutes a minor metabolism pathway for this compound (see Table A-2).

Excretion

Excretion of *p,p′*-DDD and *p,p′*-DDT metabolites following oral exposure in humans occurs primarily through the urine (i.e., as DDA) (see Table C-1) and substantial urinary excretion has also been detected in animals (see Table A-2). *p,p′*-DDT may also be eliminated in feces, breast milk, and semen (as the parent compound and/or metabolites) (ATSDR, 2002a). In the rat, *p,p′*-DDE is excreted mostly unchanged via the urine and feces after oral exposure (Gold and Brunk, 1986), but preferential elimination via the feces has been documented after intravenous (i.v.) injection (34% of administered dose) (Mühlebach et al., 1991). Importantly, analysis of adipose tissue and urinary excretion in human volunteers with repeated-dose exposure to *p,p′*-DDD, *p,p′*-DDT, or *p,p′*-DDE showed slow rates of elimination of these compounds (see Table C-1). In contrast, methoxychlor and its metabolites were rapidly eliminated in mice via the feces (Kapoor et al., 1970).

Surrogate Summary and Evaluation

p,p′-DDT is a suitable metabolic surrogate for *p,p′*-DDD due to the fact that the primary metabolic pathway for *p,p′*-DDT is dechlorination to *p,p′*-DDD, as well as similarities in the rate and route of elimination (both materials persist in the body and are eliminated primarily as the shared downstream metabolite DDA in the urine). The other candidate surrogates are less suitable. Metabolism of *p,p′*-DDE is less efficient compared to *p,p′*-DDD and *p,p′*-DDT, in part, due to the greater capacity of *p,p′*-DDE for fat storage. Contrary to *p,p′*-DDT and the other candidate surrogates, methoxychlor appears to be efficiently metabolized and cleared from the body. In addition, the major metabolic pathway (*O*-demethylation) and pattern of metabolites for methoxychlor differ from *p,p′*-DDD and elimination is primarily via the feces.

Toxicity-Like Surrogates

Table A-3 summarizes available oral toxicity values for *p,p′*-DDD and the compounds identified as potential surrogates. Acute toxicity data for *p,p′*-DDD are limited to reported median lethal dose (LD_{50}) values of 113 mg/kg-day in rats and >5,000 mg/kg in hamsters; no further information was provided (ChemIDplus, 2017). Lethality data in hamsters were similar for *p,p′*-DDD, *p,p′*-DDT, and *p,p′*-DDE (LD_{50} >5,000 mg/kg). In rats, *p,p′*-DDD and *p,p′*-DDT displayed similar potency (LD_{50} = 113 and 87 mg/kg, respectively), but *p,p′*-DDE and methoxychlor were less acutely toxic (LD_{50} = 880 and 1,855 mg/kg, respectively).

As discussed in the main body of this document and shown in Table 3A, repeated-dose oral toxicity data for *p,p′*-DDD provide only limited information due to evaluation of few endpoints and/or use of a low-purity test compound (Banerjee et al., 1996; NCI, 1978; Tomatis et al., 1974; Cueto et al., 1958). Due to these limitations, sensitive target organs of toxicity could not be identified. Oral toxicity values for *p,p′*-DDT and *p,p′*-DDE are based on liver effects in rats, while oral toxicity values for methoxychlor are derived from reproductive effects in rats and rabbits (see Table A-3). These endpoints are discussed below, and a comparison of the dose-response data in experimental animals for these effects following oral exposure to *p,p′*-DDD and all potential surrogates is provided in Figures C-1 to C-7.

Among the candidate surrogates, the liver is a sensitive target organ of toxicity for *p,p′*-DDT and *p,p′*-DDE (see Figures C-1 and C-2). Non-neoplastic liver effects following

exposure to *p,p′*-DDT and *p,p′*-DDE include increased liver weight and hepatic lesions ranging from hepatocellular hypertrophy to fatty degeneration and necrosis. Liver toxicity has also been observed with methoxychlor exposure (see Figures C-1 and C-2); however, these effects (primarily increased liver weight and changes in serum and/or liver enzymes) occurred at high doses often associated with lethality (ATSDR, 2002b). Overall, potency for liver toxicity was *p,p′*-DDT > *p,p′*-DDE > methoxychlor. The only available study of *p,p′*-DDD that provided results for non-neoplastic endpoints was the chronic NCI (1978) cancer bioassay. This study found no effect on the incidence of liver lesions, but was limited by design as a cancer bioassay (e.g., treated rats and mice had respective 35- and 15-week untreated observation periods prior to necropsy; senescent changes in both species and liver tumors in mice may have obscured non-neoplastic changes). Nevertheless, *p,p′*-DDD, *p,p′*-DDT, and *p,p′*-DDE all produced liver tumors in experimental animals (see Figure C-3) and displayed similar carcinogenic potency based on estimated oral slope factors (OSFs) (see Table A-3). Conversely, evidence of liver carcinogenicity for methoxychlor was inconclusive (U.S. EPA, 1988c). Although a mode of action (MOA) for the liver tumors has not been established and it is unclear how the observed non-neoplastic liver effects may be related to development of tumors following *p,p′*-DDT and *p,p′*-DDE exposure, these findings suggest that the liver is a relevant target organ of toxicity for the *p,p′*-chlorinated chemicals (*p,p′*-DDD, *p,p′*-DDT, and *p,p′*-DDE).

Reproductive effects are produced by all three candidate surrogates, including decreased fertility, altered male sexual differentiation, and precocious puberty in females (see Figures C-4, C-5, and C-6). An increase in adverse pregnancy outcomes was also found for *p,p′*-DDT and methoxychlor, but not for *p,p′*-DDE (see Figure C-7). Potency was highest for *p,p′*-DDT. No reproductive or pregnancy outcomes data were available for *p,p′*-DDD. The mechanism of toxicity for the observed reproductive effects could be related to the endocrine disruption properties of these compounds. *p,p′*-DDD, *p,p′*-DDT, and *p,p′*-DDE are competitive inhibitors of the androgen receptor (AR) (Kelce et al., 1995) and may also possess weak estrogenic activity via interaction with the estrogen receptor (ER) (Soto et al., 1997; Singhal et al., 1970; Welch et al., 1969). Mechanistic studies suggest that hydroxylated metabolites of methoxychlor (e.g., *mono*- and *bis*-hydroxymethoxychlor and *bis*-hydroxy-dichloroethylene) are more potent agonists of the ER than the parent chemical (Sumida et al., 2001; Charles et al., 2000; Bulger et al., 1978; Bulger and Kupfer, 1978) and exert stronger antagonism towards the AR than methoxychlor (Maness et al., 1998). Thus, metabolic activation is thought to be important for the endocrine disrupting activity of this compound (ATSDR, 2002b).

Surrogate Summary and Evaluation

Based on comparisons of available toxicity data, *p,p′*-DDT and *p,p′*-DDE are potential toxicity-like surrogates for *p,p′*-DDD. The *p,p′*-chlorinated chemicals share similarities in overall toxicity profile, including LD_{50} values, long-term toxicity target organ (liver), carcinogenic potencies (OSFs), and a putative pathway for reproductive toxicity via modulation of steroid hormone receptors (e.g., ER and AR). Unlike *p,p′*-DDD and the other candidate surrogates, the major metabolic route (*O*-demethylation) for methoxychlor constitutes a bioactivation pathway for the critical effects of this compound (reproductive toxicity); therefore, methoxychlor is excluded from consideration as a potential toxicity-like surrogate for *p,p′*-DDD.

Table A-3. Comparison of Available Oral Toxicity Values for *p,p′*-DDD (CASRN 72-54-8) and Potential Surrogates

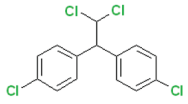
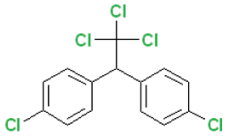
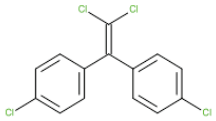
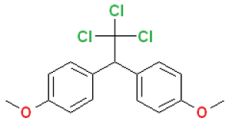
Name	*p,p′*-DDD	*p,p′*-DDT	*p,p′*-DDE	Methoxychlor
Structure				
CASRN	72-54-8	50-29-3	72-55-9	72-43-5
Subchronic oral toxicity values				
POD (mg/kg-d)	ND	0.05	1	5
POD type	ND	NOAEL	LOAEL (HED)	LOAEL
Subchronic UF_C	ND	100 (UF_A, UF_H)	3,000 (UF_A, UF_D, UF_H, UF_L)	1,000 (UF_A, UF_H, UF_L)
Subchronic p-RfD/MRL (mg/kg-d)	ND	5×10^{-4}	3×10^{-4}	5×10^{-3}
Critical effects[a]	ND	Liver lesions (centrilobular hepatocellular hypertrophy, cytoplasmic oxyphilia, and peripheral basophilic cytoplasmic granules)	Increased relative liver weight in adult male offspring exposed during gestation and via lactation	Precocious puberty in females (i.e., accelerated vaginal opening)
Other effects (in principal study)	ND	None (only liver and kidney histopathology were evaluated)	Effects at 50 mg/kg-d: Increased relative liver weight in exposed dams; decreased number of pups alive, and decreased weaning index at PND 21; delayed preputial separation in male offspring and early vaginal opening in female offspring; reductions in copulation index and fertility index in F1 generation; increases in relative adrenal weight and liver weight in F1 adult females	Females: Irregular or absent estrous cycles, decreased fertility, decreased gravid uterine weight, histopathological lesion in the ovaries (cysts), uterus (hyperplasia, metaplasia) and vagina (hyperplasia and cornification) at ≥50 mg/kg-d; decreased number of live pups per litter at 150 mg/kg-d Males: Delayed preputial separation and weight of testes and epididymis at ≥50 mg/kg-d

Table A-3. Comparison of Available Oral Toxicity Values for *p,p′*-DDD (CASRN 72-54-8) and Potential Surrogates

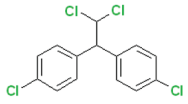
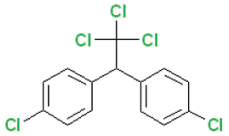
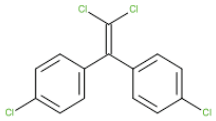
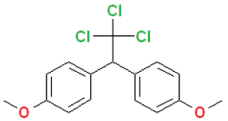
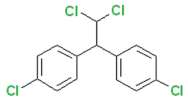
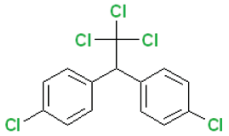
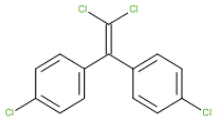
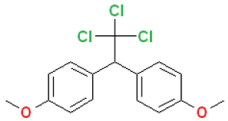
Name	*p,p′*-DDD	*p,p′*-DDT	*p,p′*-DDE	Methoxychlor
Structure				
CASRN	72-54-8	50-29-3	72-55-9	72-43-5
Species	ND	Rat	Rat	Rat
Duration	ND	27 wk	GD 6–PND 20	GD 14−PND 42
Route (method)	ND	Diet	Gavage	Gavage
Source	ND	ATSDR (2002a); U.S. EPA (1988d)	U.S. EPA (2017b)	ATSDR (2002b)
Chronic oral toxicity values				
POD (mg/k-d)	ND	0.05	1	5.01
POD type	ND	NOAEL	LOAEL (HED)	NOAEL
Chronic UF_C	ND	100 (UF_A, UF_H)	3,000 (UF_A, UF_D, UF_H, UF_L)	1,000 (UF_A, UF_D, UF_H)
Chronic RfD (mg/kg-d)	ND	5×10^{-4}	3×10^{-4} (screening p-RfD)	5×10^{-3}
Critical effects[a]	ND	Liver lesions (centrilobular hepatocellular hypertrophy, cytoplasmic oxyphilia, and peripheral basophilic cytoplasmic granules)	Increased relative liver weight in adult male offspring exposed as neonates	Excessive litter loss (i.e., spontaneous abortion)
Other effects (in principal study)	ND	See above	See above	Decreased maternal body-weight gain and increased clinical signs of toxicity (not specified) at ≥35.5 mg/kg-d
Species	ND	Rat	Rat	Rabbit
Duration	ND	27 wk	GD 6–PND 20	GDs 7−19
Route (method)	ND	Diet	Gavage	Gavage
Source	ND	U.S. EPA (1988d)	U.S. EPA (2017b)	U.S. EPA (1988c)

Table A-3. Comparison of Available Oral Toxicity Values for *p,p′*-DDD (CASRN 72-54-8) and Potential Surrogates

Name	*p,p′*-DDD	*p,p′*-DDT	*p,p′*-DDE	Methoxychlor
Structure				
CASRN	72-54-8	50-29-3	72-55-9	72-43-5
Carcinogenicity assessment				
Classification	B2; probable human carcinogen	B2; probable human carcinogen	B2; probable human carcinogen	D; not classified as to human carcinogenicity
OSF	2.4×10^{-1}	3.4×10^{-1}	3.4×10^{-1}	ND
Tumor type	Liver	Liver	Liver	ND
Species	Mouse	Mouse and rat	Mouse and hamster	ND
Route (method)	Diet	Diet	Diet	ND
Source	U.S. EPA (1988b)	U.S. EPA (1988d)	U.S. EPA (1988a)	U.S. EPA (1988c)
Oral acute lethality data				
Rat LD_{50} (mg/kg)	113	87	880	1,855
Hamster LD_{50} (mg/kg)	>5,000	>5,000	>5,000	ND
Source	ChemIDplus (2017)	ChemIDplus (2017)	ChemIDplus (2017)	ChemIDplus (2017)

[a]Exposure-response arrays were prepared to illustrate the dose-response relationship for liver and reproductive effects across the candidate surrogate compounds (see Figures C-1 to C-7).

GD = gestation day; HED = human equivalent dose; LD_{50} = median lethal dose; LOAEL = lowest-observed-adverse-effect level; MRL = minimal risk level; ND = no data; NOAEL = no-observed-adverse-effect level; OSF = oral slope factor; *p,p′*-DDD = *p,p′*-dichlorodiphenyldichloroethane; *p,p′*-DDE = *p,p′*-dichlorodiphenyldichloroethylene; *p,p′*-DDT = *p,p′*-dichlorodiphenyltrichloroethane; PND = postnatal day; POD = point of departure; p-RfD = provisional reference dose; RfD = oral reference dose; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor.

Weight-of-Evidence Approach

A WOE approach is used to evaluate information from potential candidate surrogates as described by Wang et al. (2012). Commonalities in structural/physicochemical properties, toxicokinetics, metabolism, toxicity, or MOA between potential surrogates and chemical(s) of concern are identified. Emphasis is given to toxicological and/or toxicokinetic similarity over structural similarity. Surrogate candidates are excluded if they do not have commonality or demonstrate significantly different physicochemical properties, and toxicokinetic profiles that set them apart from the pool of potential surrogates and/or chemical(s) of concern. From the remaining potential surrogates, the most appropriate surrogate (most biologically or toxicologically relevant analog chemical) with the highest structural similarity and/or most conservative toxicity value is selected.

The WOE approach used to select the surrogate compound for *p,p′*-DDD is based primarily on metabolic considerations, with supporting evidence from structural and toxicity surrogate analyses. As such, *p,p′*-DDT is identified as the final surrogate for *p,p′*-DDD based on the following WOE rationale:

1) *p,p′*-DDT is a metabolic precursor for *p,p′*-DDD, and both compounds exhibit similarities in metabolism pathways and in the rate and route of elimination (both materials persist in the body and are eliminated primarily as the shared downstream metabolite DDA in the urine).

2) *p,p′*-DDT is a toxicity-like surrogate for *p,p′*-DDD based on overall similarities in the toxicity profile of these compounds, including LD_{50} values, long-term toxicity target organ (liver), carcinogenic potencies (OSFs), and a putative pathway for reproductive toxicity via modulation of steroid hormone receptors (e.g., ER and AR).

3) *p,p′*-DDT displays the highest structural similarity (71–96%) to *p,p′*-DDD, according to structure-activity relationship evaluations from ChemIDplus, DSSTOX, and OECD Toolbox.

4) *p,p′*-DDE and methoxychlor are less suitable surrogate candidates for *p,p′*-DDD. *p,p′*-DDE is less metabolically active than *p,p′*-DDD and *p,p′*-DDT, which is related to its greater affinity for fat storage. Metabolism and elimination pathways for methoxychlor are different from *p,p′*-DDD, in part, due to the presence of *p,p′*-methoxy groups that allow for its efficient metabolism and clearance from the body. Furthermore, in contrast to *p,p′*-DDT and *p,p′*-DDD, metabolism of methoxychlor via *O*-demethylation is known to be a bioactivation pathway for the reproductive effects that form the basis of the oral toxicity values for this compound; therefore, methoxychlor is not considered an appropriate toxicity-like surrogate for *p,p′*-DDD.

ORAL TOXICITY VALUES

Derivation of a Screening Subchronic Provisional Reference Dose

Based on the overall surrogate approach presented in this PPRTV assessment, *p,p′*-DDT was selected as the surrogate for *p,p′*-DDD for derivation of a screening subchronic p-RfD. The study used to derive the ATSDR intermediate minimal risk levels (MRLs) and the IRIS chronic oral reference dose (RfD) (ATSDR, 2002a; U.S. EPA, 1988d) was a 27-week dietary study in

rats [Laug et al. (1950) as cited in ATSDR (2002a)]. ATSDR (2002a) described the study as follows:

> *Experimental design: Groups of male and female Osborne-Mendel rats (15/sex/group) were administered technical DDT (dissolved in corn oil) added to the diet at dosage levels of 0, 1, 5, 10, or 50 ppm for 15–27 weeks. This study was essentially designed to examine whether DDT accumulates in adipose tissue and to what extent, how age and dose level affect accumulation, and how rapidly it is eliminated. Seventy-seven rats were used for microscopic evaluation of only the liver and kidney. This was based on findings from a previous study from the same group (Fitzhugh and Nelson 1947) in which higher dietary levels of DDT had been used. Based on the previous findings, only the liver was expected to show microscopic changes. Although not explicitly stated, it is assumed that morphologic evaluations were conducted at the times when DDT levels in fat were determined (after 15, 19, 23, and 27 weeks of treatment).*
>
> *Effects noted in study and corresponding doses: These dose ranges were calculated as shown below in the discussion of conversion factors. There were no morphologic alterations in the kidneys. Liver alterations were noticed at the 5 ppm (0.25–0.5 mg/kg/day) dietary level of DDT and higher, but not at 1 ppm (0.05–0.09 mg/kg/day). Liver changes consisted of hepatic cell enlargement, especially in central lobules, increased cytoplasmic oxyphilia with sometimes a semihyaline appearance, and more peripheral location of the basophilic cytoplasmic granules. Necrosis was not observed. The severity of the effects was dose-related, and males tended to show more hepatic cell changes than females. Changes seen at the 5 ppm level (0.25–0.5 mg/kg/day) were considered by the authors as "minimal"; changes seen at the 50 ppm level (2.5–4.6 mg/kg/day) were slight, sometimes moderate; the authors do not comment about what they saw in the 10 ppm (0.5–0.9 mg/kg/day) group, presumably the results were intermediate to the doses above and below. The results from the kinetic studies revealed that accumulation of DDT in fat occurred at all dietary levels tested and that females stored more DDT than males; storage reached a maximum at 19–23 weeks; age did not affect the rate of DDT-accumulation; about 50–75% of DDT stored in fat remained after a 1-month DDT-free diet, and 25% remained after 3 months.*

The critical effect in this study was liver lesions in male and female rats exposed to technical-grade DDT (81% *p,p′*-DDT and 19% *o,p′*-DDT); the NOAEL of 1 ppm (0.05 mg/kg-day) was used at the point of departure (POD) for *p,p′*-DDT in ATSDR (2002a) and U.S. EPA (1988d), and is adopted as the surrogate POD for *p,p′*-DDD.

For the current assessment, the NOAEL of 0.05 mg/kg-day was converted to a human equivalent dose (HED) according to current (U.S. EPA, 2011b) guidance. In *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses body-weight scaling to the 3/4 power (i.e., BW$^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD from effects that are not portal-of-entry effects.

Following U.S. EPA (2011b) guidance, the POD for liver effects in male and female rats is converted to an HED through the application of a dosimetric adjustment factor (DAF) derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Using average reference BW_a values of 0.514 and 0.389 kg for Osborne-Mendel male and female rats, respectively, in a chronic-duration study and a reference BW_h of 70 kg for humans (U.S. EPA, 1988e), the resulting DAFs are 0.29 for males and 0.27 for females. The female DAF of 0.27 was applied to the NOAEL of 0.05 mg/kg-day because it yields the most health-protective POD (HED):

$$\begin{aligned} \text{POD (HED)} &= \text{NOAEL (mg/kg-day)} \times \text{DAF} \\ &= 0.05 \text{ mg/kg-day} \times 0.27 \\ &= 0.01 \text{ mg/kg-day} \end{aligned}$$

In deriving a screening subchronic p-RfD for *p,p′*-DDD, an interspecies uncertainty factor (UF_A) of 3 is applied because cross-species dosimetric adjustment was performed, and 10-fold uncertainty factors are applied to account for intraspecies variability (UF_H) and database deficiencies (UF_D) that reflect the lack of adequate repeated-dose toxicity data for *p,p′*-DDD. Thus, a composite uncertainty factor (UF_C) of 300 is used in the derivation of the screening subchronic p-RfD for *p,p′*-DDD.

$$\begin{aligned} \textbf{Screening Subchronic p-RfD} &= \text{Surrogate POD (HED)} \div UF_C \\ &= 0.01 \text{ mg/kg-day} \div 300 \\ &= \mathbf{3 \times 10^{-5} \text{ mg/kg-day}} \end{aligned}$$

Table A-4 summarizes the uncertainty factors for the screening subchronic p-RfD for *p,p′*-DDD.

Table A-4. Uncertainty Factors for the Screening Subchronic p-RfD for *p,p′*-DDD (CASRN 72-54-8)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following *p,p′*-DDD exposure. The toxicokinetic uncertainty has been accounted for by calculating an HED through application of a DAF as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_D	10	A UF_D of 10 is applied to reflect absence of adequate repeated-dose oral toxicity studies for *p,p′*-DDD.
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of *p,p′*-DDD in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because the principal study selected is a 27-wk study.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$

DAF = dosimetric adjustment factor; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; *p,p′*-DDD = *p,p′*-dichlorodiphenyldichloroethane; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Derivation of a Screening Chronic Provisional Reference Dose

p,p′-DDT was also selected as the surrogate for *p,p′*-DDD for the derivation of a screening chronic p-RfD. The principal study and POD for the IRIS chronic assessment for *p,p′*-DDT (U.S. EPA, 1988d) is the same used in the ATSDR (2002a) intermediate-duration MRL derivation (Laug et al., 1950) and the above derivation of a screening subchronic p-RfD for *p,p′*-DDD. Consistent findings of liver lesions induced by *p,p′*-DDT from a 2-year chronic dietary study in rats cited in the IRIS assessment (U.S. EPA, 1988d) provide further support for the use of the Laug et al. (1950) study to derive a surrogate chronic value for *p,p′*-DDD. Thus, the surrogate POD (HED) of 0.01 mg/kg-day identified in the 27-week rat study by Laug et al. (1950) is similarly adopted for the derivation of the screening chronic p-RfD for *p,p′*-DDD. Similar to the screening subchronic p-RfD derived above, a UF_C of 300 is applied.

$$\begin{aligned} \textbf{Screening Chronic p-RfD} &= \text{Surrogate POD (HED)} \div UF_C \\ &= 0.01 \text{ mg/kg-day} \div 300 \\ &= \mathbf{3 \times 10^{-5} \text{ mg/kg-day}} \end{aligned}$$

Table A-5 summarizes the uncertainty factors for the screening chronic p-RfD for *p,p′*-DDD.

Table A-5. Uncertainty Factors for the Screening Chronic p-RfD for *p,p′*-DDD (CASRN 72-54-8)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following *p,p′*-DDD exposure. The toxicokinetic uncertainty has been accounted for by calculating an HED through application of a DAF as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_D	10	A UF_D of 10 is applied to reflect absence of adequate repeated-dose oral toxicity studies for *p,p′*-DDD.
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of *p,p′*-DDD in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because the principal study selected for the chronic assessment is considered of chronic duration (>~90 d to 2 yr in typically used laboratory animal species).
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$

DAF = dosimetric adjustment factor; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; *p,p′*-DDD = *p,p′*-dichlorodiphenyldichloroethane; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

APPENDIX B. DATA TABLES

Table B-1. Group Sizes, Dietary Concentrations, and Dose Estimates for NCI (1978) Cancer Bioassay for *p,p′*-DDD

Group	Group Size	Nominal Concentration (ppm)	Duration at This Concentration (wk)	Untreated Duration (wk)	Weighted Average Concentration Technical-Grade DDD[a] (ppm)	Weighted ADD *p,p′*-DDD[b] (adjusted for purity) (mg/kg-d)
Male rats						
Control	20	0		111		0
Low dose	50	1,400 1,750 0	23 55	 34	1,647	69.21
High dose	50	2,800 3,500 0	23 55	 35	3,294	138.4
Female rats						
Control	20	0		111		0
Low dose	50	850 0	78	 35	850	39.3
High dose	50	1,700 0	78	 35	1,700	78.66
Male mice						
Control	20	0		90		0
Low dose	50	315 375 425 0	5 11 62	 13	411	42.3
High dose	50	630 750 850 0	5 11 62	 14	822	84.6

Table B-1. Group Sizes, Dietary Concentrations, and Dose Estimates for NCI (1978) Cancer Bioassay for *p,p′*-DDD

Group	Group Size	Nominal Concentration (ppm)	Duration at This Concentration (wk)	Untreated Duration (wk)	Weighted Average Concentration Technical-Grade DDD[a] (ppm)	Weighted ADD *p,p′*-DDD[b] (adjusted for purity) (mg/kg-d)
Female mice						
Control	20	0		90		0
Low dose	50	315 375 425 0	5 11 62	 14	411	42.6
High dose	50	630 750 850 0	5 11 62	 15	822	85.2

[a]Calculated by the study authors as the sum of concentration × time averaged over 78 weeks.
[b]Calculated using weighted average concentration, reference values for body weight, and food consumption from U.S. EPA (1988e); doses adjusted for 60% purity.

ADD = adjusted daily dose; *p,p′*-DDD = *p,p′*-dichlorodiphenyldichloroethane.

APPENDIX C. TOXICOKINETICS AND DOSE-RESPONSE INFORMATION FOR *p,p′*-DDD AND CANDIDATE SURROGATES

Table C-1. ADME Data for *p,p′*-DDD (CASRN 72-54-8) and Candidate Surrogates

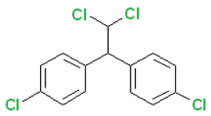
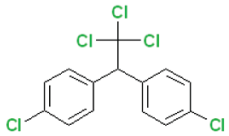
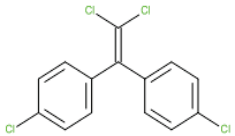
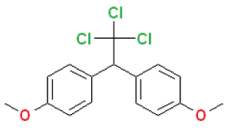
Chemical	*p,p′*-DDD	*p,p′*-DDT	*p,p′*-DDE	Methoxychlor
Structure				
CASRN	72-54-8	50-29-3	72-55-9	72-43-5
Absorption				
Rate and extent of oral absorption	Human (oral): Detected in serum and adipose tissue from a single volunteer ingesting 5 mg of *p,p′*-DDD daily for 81 d (rate and extent of absorption were not reported) (Morgan and Roan, 1974, 1971)	Human (oral): C_{MAX} was reached 3 hr after ingestion (Morgan and Roan, 1974) Rat (oral): 70−100% of dose was absorbed in rats (vegetable oil vehicle) over 24−48 hr (Keller and Yeary, 1980; Rothe et al., 1957)	Human (oral): Detected in serum and adipose tissue from a single volunteer ingesting 5 mg of *p,p′*-DDE daily for 92 d (rate and extent of absorption were not reported) (Morgan and Roan, 1974, 1971)	Mouse (oral): Rapid, >90% of oral dose absorbed (Kapoor et al., 1970)

Table C-1. ADME Data for *p,p′*-DDD (CASRN 72-54-8) and Candidate Surrogates				
Chemical	***p,p′*-DDD**	***p,p′*-DDT**	***p,p′*-DDE**	**Methoxychlor**
Distribution				
Extent of distribution	Human (oral): Detected in adipose tissue, breast milk, and placenta from many study populations of environmental exposure (ATSDR, 2002a); in a volunteer, 24% of the ingested dose was stored in adipose tissue (dosing described above) (Morgan and Roan, 1971)	Human (oral): Widespread distribution; many study populations of environmental exposure demonstrate adipose tissue storage, detection in breast milk and placental transfer (detected in cord blood) (ATSDR, 2002a); data from two volunteers ingesting 7.7 or 15.4 mg of *p,p′*-DDT daily for 183 d indicated that 54 or 68% of the dose was stored in adipose tissue, respectively (Morgan and Roan, 1971) Rat (oral): Widespread distribution to multiple organs; crosses the placenta; lactational transfer from dam to pup; stored in adipose tissue (Woolley and Talens, 1971)	Human (oral): Many study populations of environmental exposure demonstrate adipose tissue storage, detection in breast milk, and placental transfer (detected in cord blood) (ATSDR, 2002a); in a volunteer, 91% of the ingested dose was stored in adipose tissue (dosing described above) (Morgan and Roan, 1971) Rat (oral): Crosses the placenta; lactational transfer from dam to pup; stored in adipose tissue (You et al., 1999)	Rat (oral): Widespread distribution; not stored in adipose tissue; found in breast milk (Chapin et al., 1997; Harris et al., 1974; Kunze et al., 1950)

Table C-1. ADME Data for *p,p′*-DDD (CASRN 72-54-8) and Candidate Surrogates

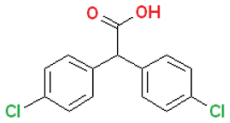
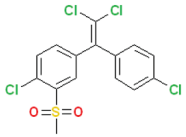
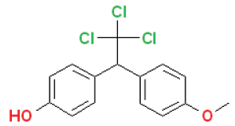
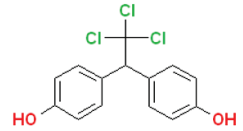
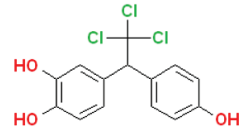
Chemical	*p,p′*-DDD	*p,p′*-DDT	*p,p′*-DDE	Methoxychlor
Metabolism				
Metabolic pathways and metabolites	Human, rat, mouse, and hamster (oral): Major urinary metabolite is DDA  Intermediary metabolites (i.e., between *p,p′*-DDD and DDA) may differ by species (see "Metabolism/Toxicokinetic Studies" section) Possible reactive intermediates include: DDA-Cl (formed by hydroxylation of chlorinated ethane side chain carbon in mice and hamsters)	Human, rat, mouse, and hamster (oral): Reductive dechlorination to *p,p′*-DDD occurs at a faster rate than dehydrodechlorination to *p,p′*-DDE (Morgan and Roan, 1971; Peterson and Robison, 1964) Further metabolism of *p,p′*-DDD by hydroxylation or oxidation yields DDA as the primary urinary metabolite of *p,p′*-DDT (see "*p,p′*-DDD" column for further details)	Human (oral): DDA was not detected in a human subject exposed to *p,p′*-DDE (Morgan and Roan, 1971) Rat (i.v): Metabolism of *p,p′*-DDE to DDA occurs in the following sequence: DDE→DDMU→DDNU→DDOH (Datta, 1970) Multiple mammalian species including human: 2- and 3-methylsulfonyl-DDE are formed following CYP450 oxidation to an arene oxide, GSH conjugation, excretion into bile, cleavage by microbial C-S lyase, methylation of thiols, reabsorption in the gut, and oxidation to form methyl sulfones that are distributed in the blood  Representative structure of 3-methylsulfonyl-DDE (Linderholm et al., 2007; Chu et al., 2003; Bergman et al., 1994; Bakke et al., 1982; Jensen and Jansson, 1976)	Mouse (oral): Sequential CYP450 demethylation to mono-hydroxy methoxychlor (1) and *bis*-4-hydroxy methoxychlor (2) (primary metabolites); *bis*-4-hydroxy methoxychlor may undergo ring hydroxylation to give tris-hydroxy methoxychlor (3) (1)  (2)  (3) 

Table C-1. ADME Data for *p,p′*-DDD (CASRN 72-54-8) and Candidate Surrogates

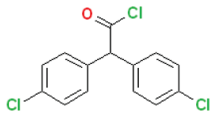
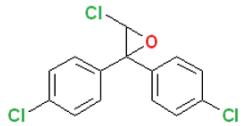
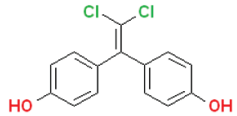
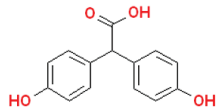
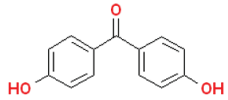
Chemical	*p,p′*-DDD	*p,p′*-DDT	*p,p′*-DDE	Methoxychlor
Continued:	Continued:  DDMU-epoxide (formed by dehydrodechlorination followed by oxidation in rats, mice, and hamsters)  (Gold and Brunk, 1984, 1983, 1982; Morgan and Roan, 1971; Peterson and Robison, 1964)	Continued:	Continued:	Continued: Metabolites resulting from dechlorination of methoxychlor: *bis*-hydroxy-dichloroethylene (4), *bis*-hydroxy-diphenyl acetic acid (5) and *bis*-hydroxybenzophenone (6) (4)  (5)  (6)  (ATSDR, 2002b; Kapoor et al., 1970)

Table C-1. ADME Data for *p,p′*-DDD (CASRN 72-54-8) and Candidate Surrogates

Chemical	*p,p′*-DDD	*p,p′*-DDT	*p,p′*-DDE	Methoxychlor
Excretion				
Rate of excretion	Human (oral): Detectable in urine within 24 hr of oral dosing (Morgan and Roan, 1971); adipose tissue analysis from a single volunteer (see dosing described above) showed complete elimination from fat within 9 mo of the termination of dosing (Morgan and Roan, 1971)	Human (oral): Detectable in urine within 24 hr of oral dosing (Morgan and Roan, 1971); reduction in DDT adipose storage occurs for at least 3.5 yr following the first dose (four human subjects who ingested 5, 10, or 20 mg/d of technical-grade DDT for up to 186 d) (Morgan and Roan, 1971) Comparison of elimination rates from fat showed the slowest elimination from humans, followed by monkeys, dogs, and rats (Morgan and Roan, 1974)	Human (oral): Adipose tissue analysis from a single volunteer (see dosing described above) showed minimal elimination of *p,p′*-DDE from lipid stores 8 mo after discontinuation of dosing (Morgan and Roan, 1971) Rat (i.v.): The total body burden t½ was 120 d (Mühlebach et al., 1991)	Mouse (oral): >90% of oral dose was excreted within 48 hr (Kapoor et al., 1970)

Table C-1. ADME Data for *p,p′*-DDD (CASRN 72-54-8) and Candidate Surrogates

Chemical	*p,p′*-DDD	*p,p′*-DDT	*p,p′*-DDE	Methoxychlor
Excretion routes	Human (oral): Urinary excretion of 69% of the total administered dose within a year of the first dose in a single volunteer (5 mg of *p,p′*-DDD daily for 81 d, urine concentrations were measured monthly) (Morgan and Roan, 1971)	Human and rat (oral): Urine (major route), also feces (via bile), semen, and breast milk (not quantified) (ATSDR, 2002a); urinary excretion of up to 10% of the total administered dose within 3.5 yr of the initial dose (20 mg of *p,p′*-DDT daily for 183 d, urine concentrations were measured monthly) (Morgan and Roan, 1971)	Human (oral): No urinary excretion was measured for up to 1 yr after the first dose in a single volunteer (5 mg of *p,p′*-DDE daily for 92 d, urine concentrations were measured monthly) (Morgan and Roan, 1971) Rat (i.v.): 34% of the administered dose was excreted in feces and 1% in urine (14 d after dosing); 10% of the excreted radioactivity was unchanged *p,p′*-DDE in the feces; no unchanged *p,p′*-DDE was detected in the urine (Mühlebach et al., 1991)	Mouse (oral): 90% in feces; 10% in urine (Kapoor et al., 1970)

ADME = absorption, distribution, metabolism, and excretion; C_{MAX} = maximum serum concentration; CYP450 = cytochrome P450; DDA = 2,2-*bis*(4′-chlorophenyl)acetic acid; DDA-Cl = 2,2-bis(4′-chlorophenyl)acetyl chloride; DDMU = 1-chloro-2,2-*bis*(4′-chlorophenyl)ethene; DDNU = 1,1-*bis*(4′-chlorophenyl)ethane; DDOH = 2,2-*bis*(4′-chlorophenyl)ethanol; GSH = glutathione; i.v. = intravenous; *p,p′*-DDD = *p,p′*-dichlorodiphenyldichloroethane; *p,p′*-DDE = *p,p′*-dichlorodiphenyldichloroethylene; *p,p′*-DDT = *p,p′*-dichlorodiphenyltrichloroethane.

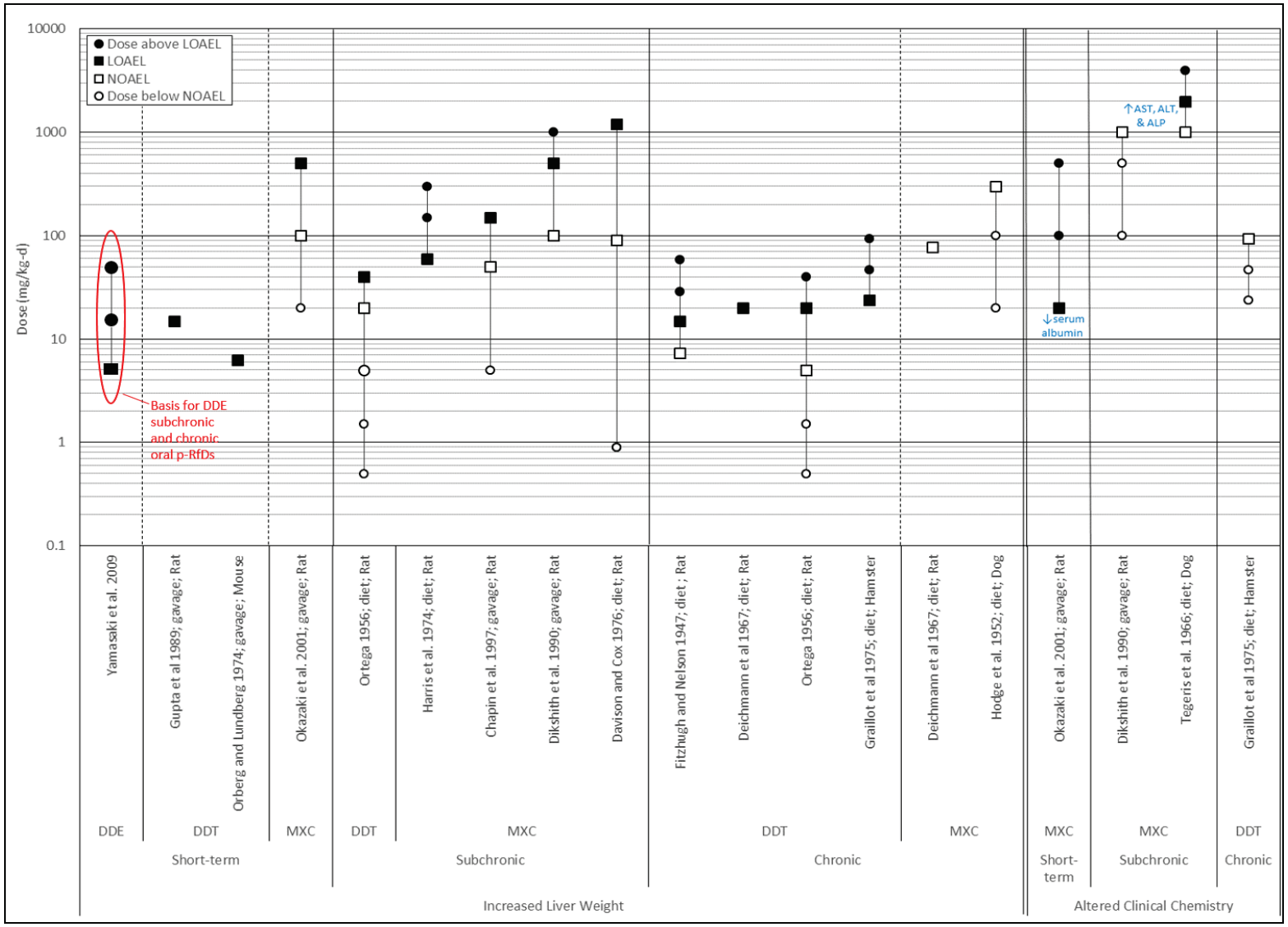


Figure C-1. Increased Liver Weight and Altered Liver Clinical Chemistry Following Oral Exposure to DDE, DDT, or Methoxychlor (MXC)

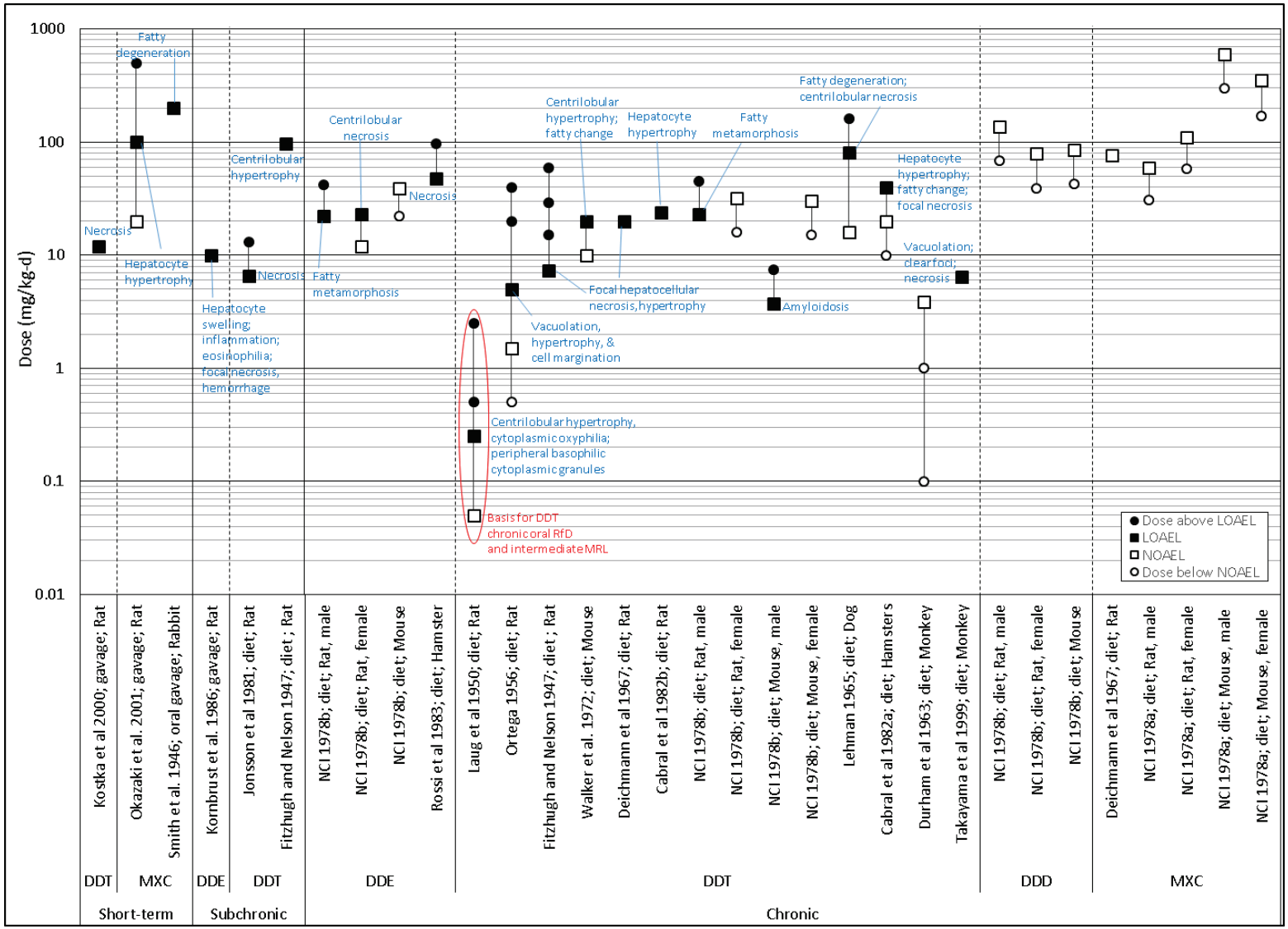


Figure C-2. Non-neoplastic Histopathological Changes in the Liver Following Oral Exposure to DDD, DDE, DDT, or Methoxychlor (MXC)

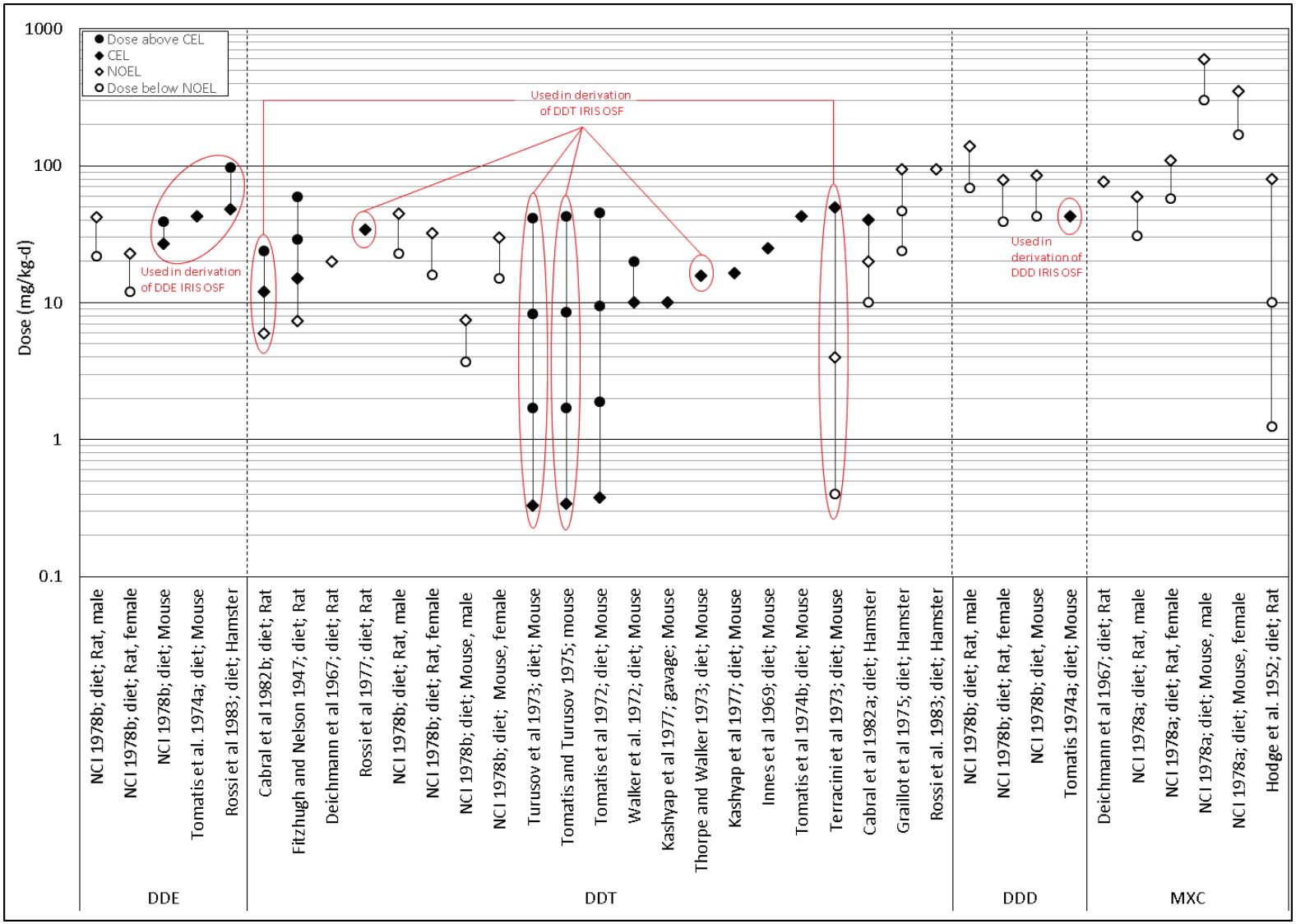


Figure C-3. Neoplastic Changes in the Liver Following Oral Exposure to DDD, DDE, DDT, or Methoxychlor (MXC)

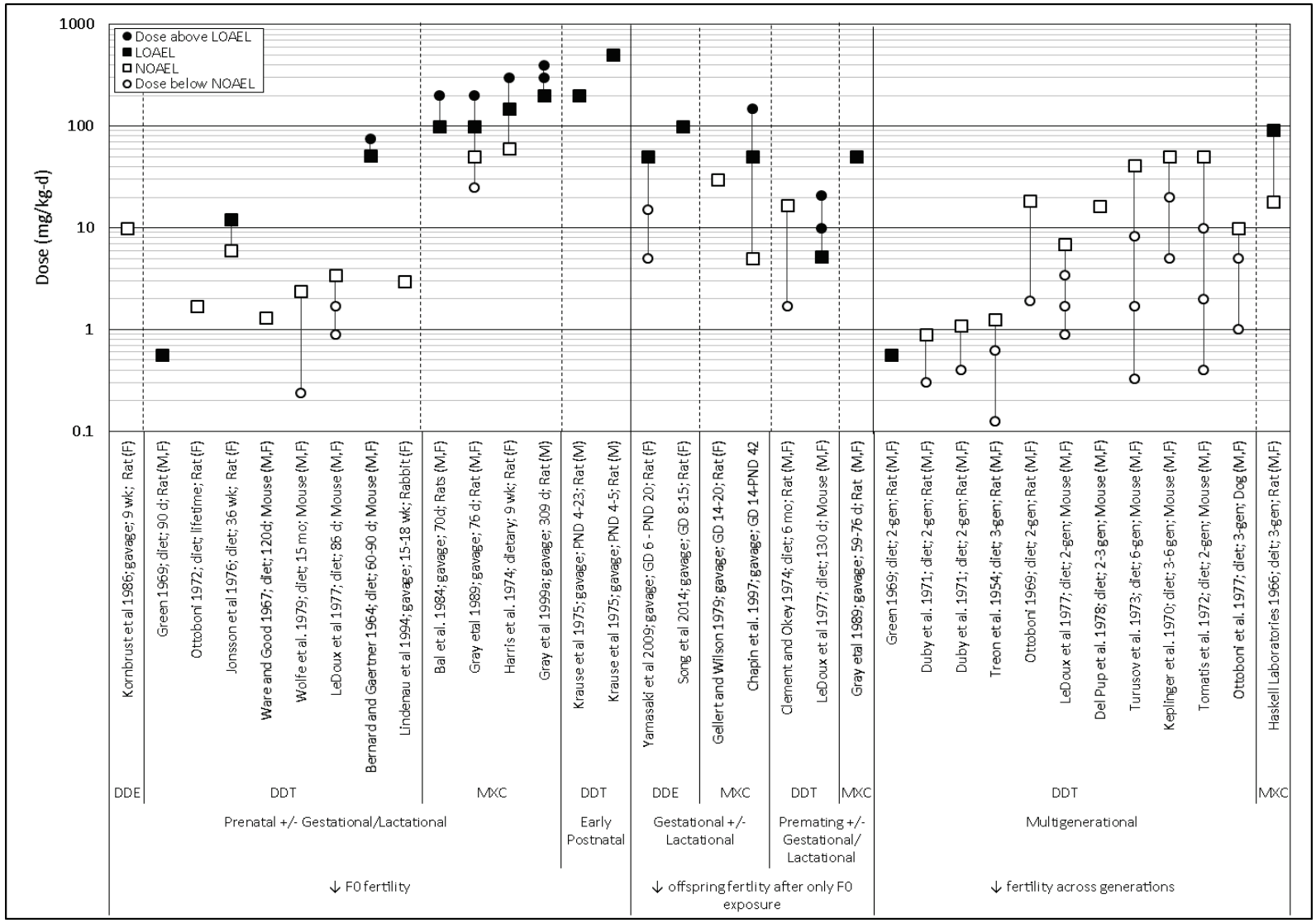


Figure C-4. Decreased Fertility Following Oral Exposure to DDE, DDT, or Methoxychlor (MXC)

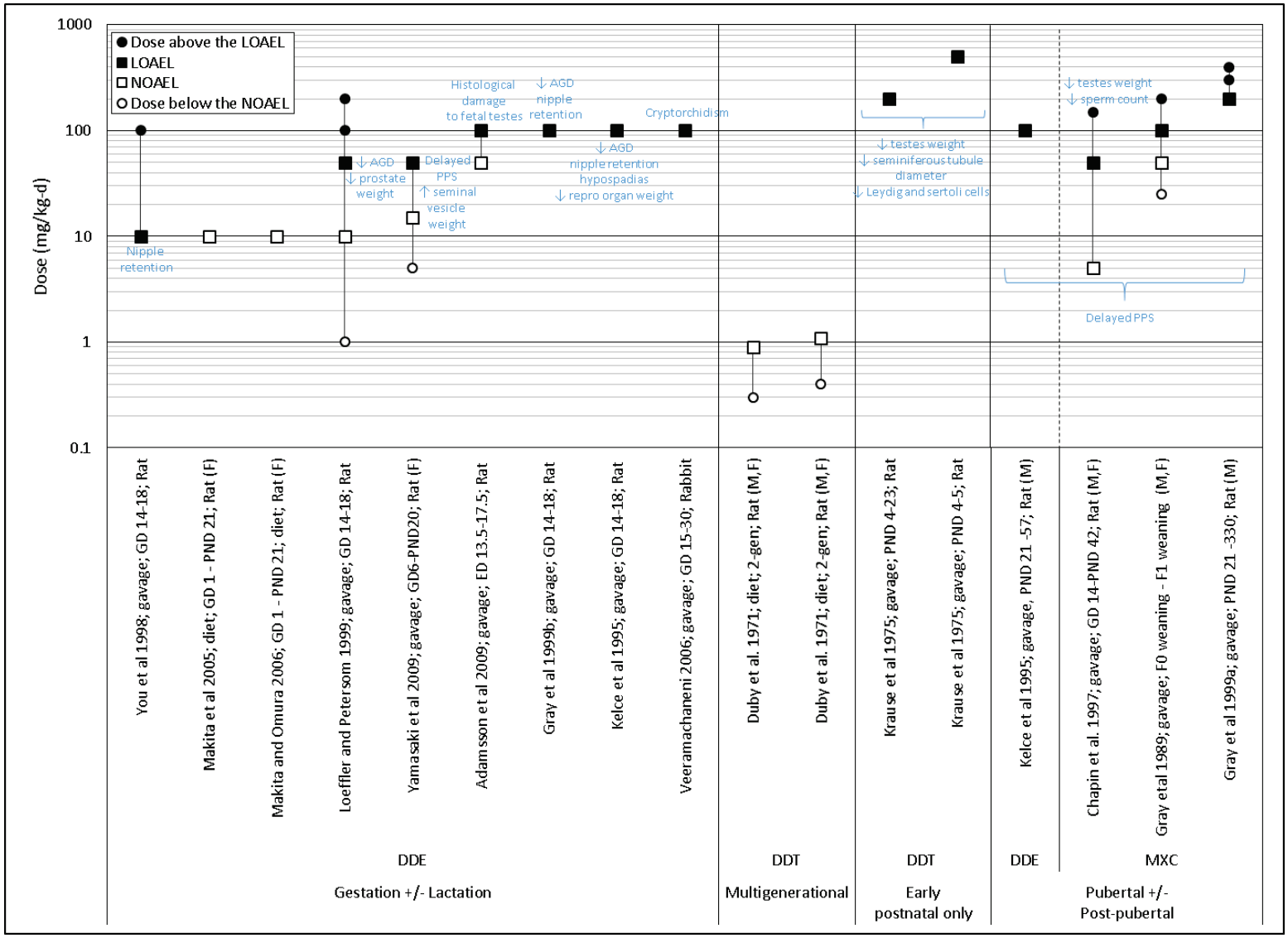


Figure C-5. Altered Male Sexual Differentiation Following Oral Exposure to DDE, DDT, or Methoxychlor (MXC)

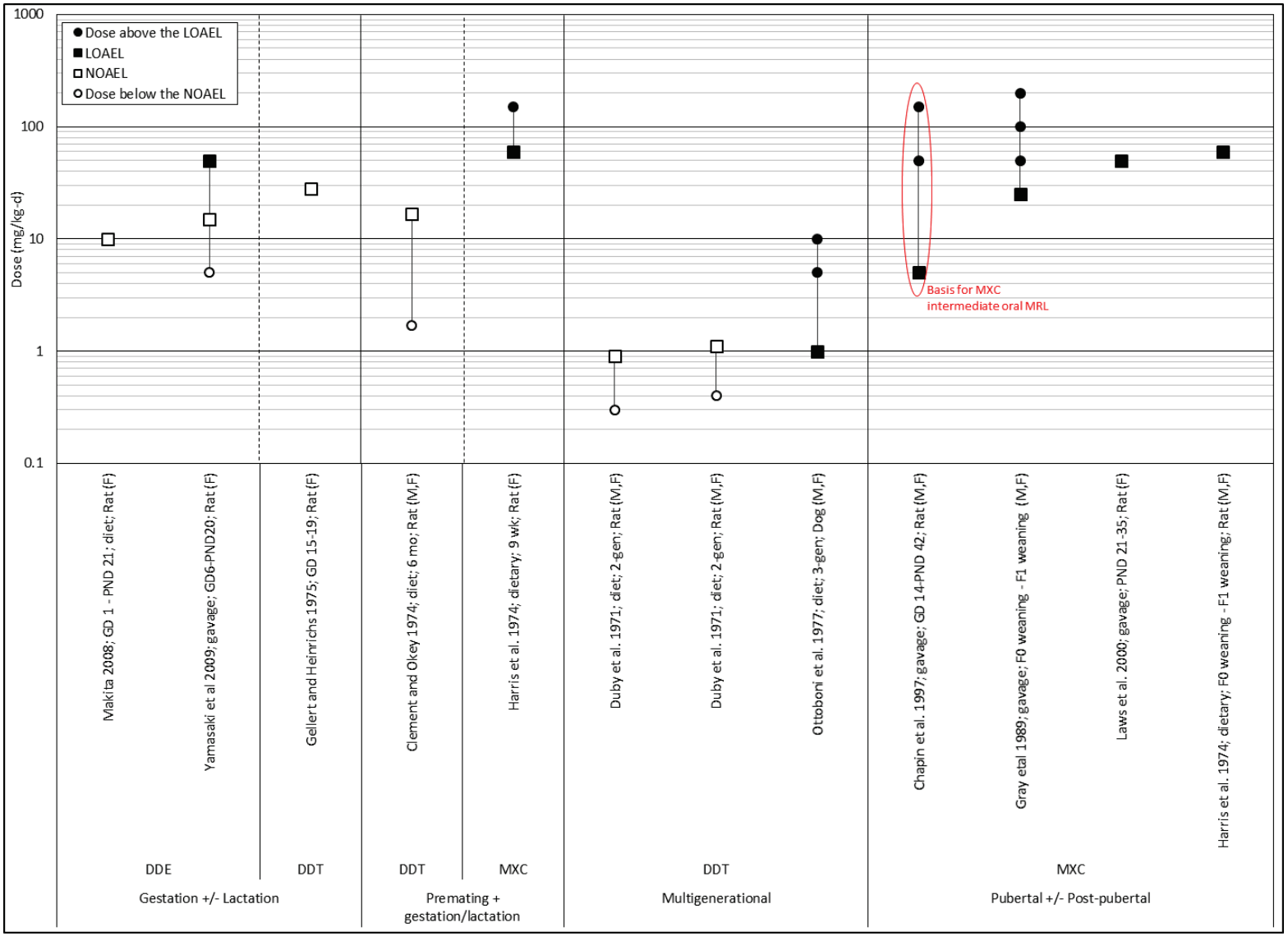


Figure C-6. Precocious Puberty in Females Following Oral Exposure to DDE, DDT, or Methoxychlor (MXC)

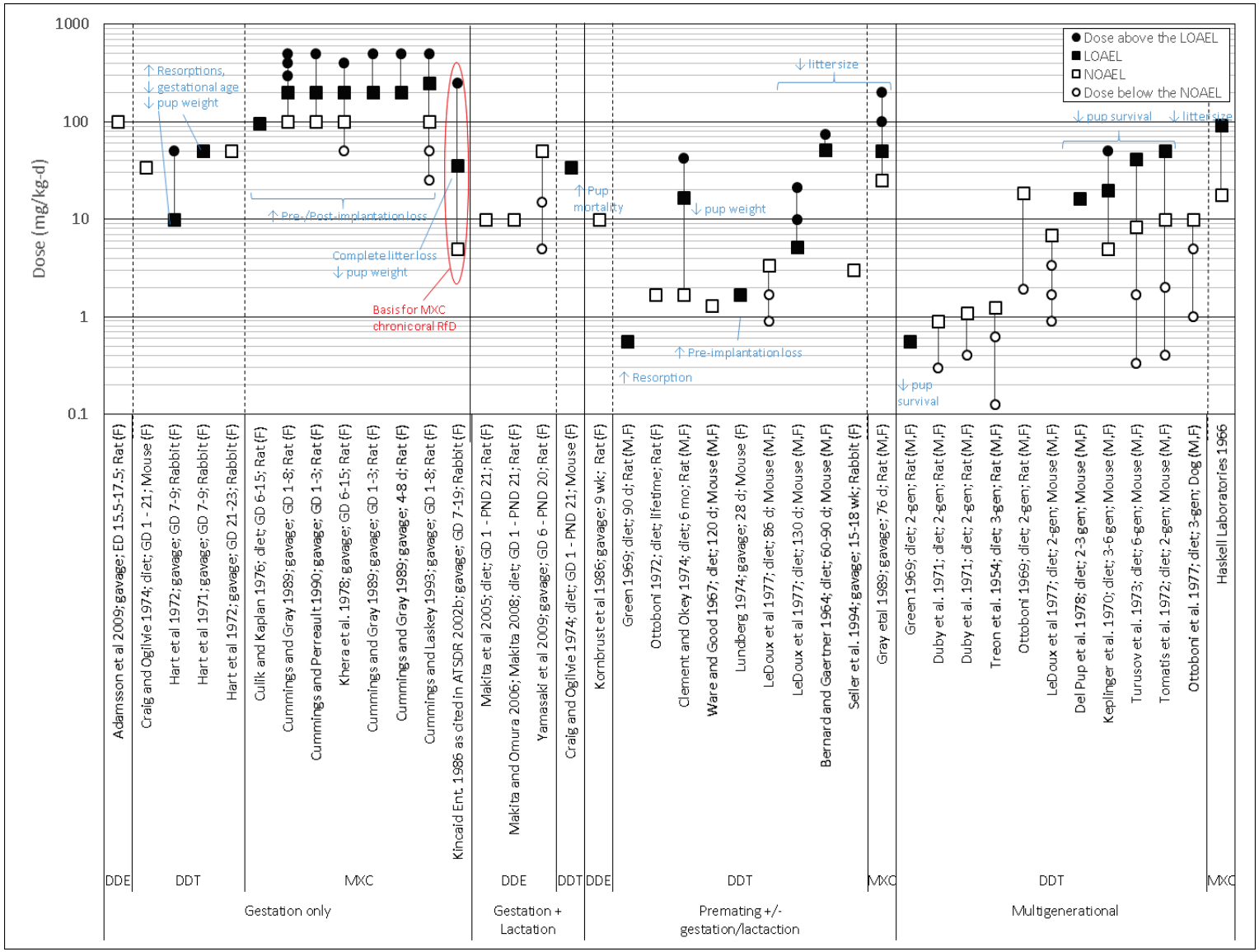


Figure C-7 Adverse Pregnancy Outcomes Following Oral Exposure to DDE, DDT, or Methoxychlor (MXC)

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