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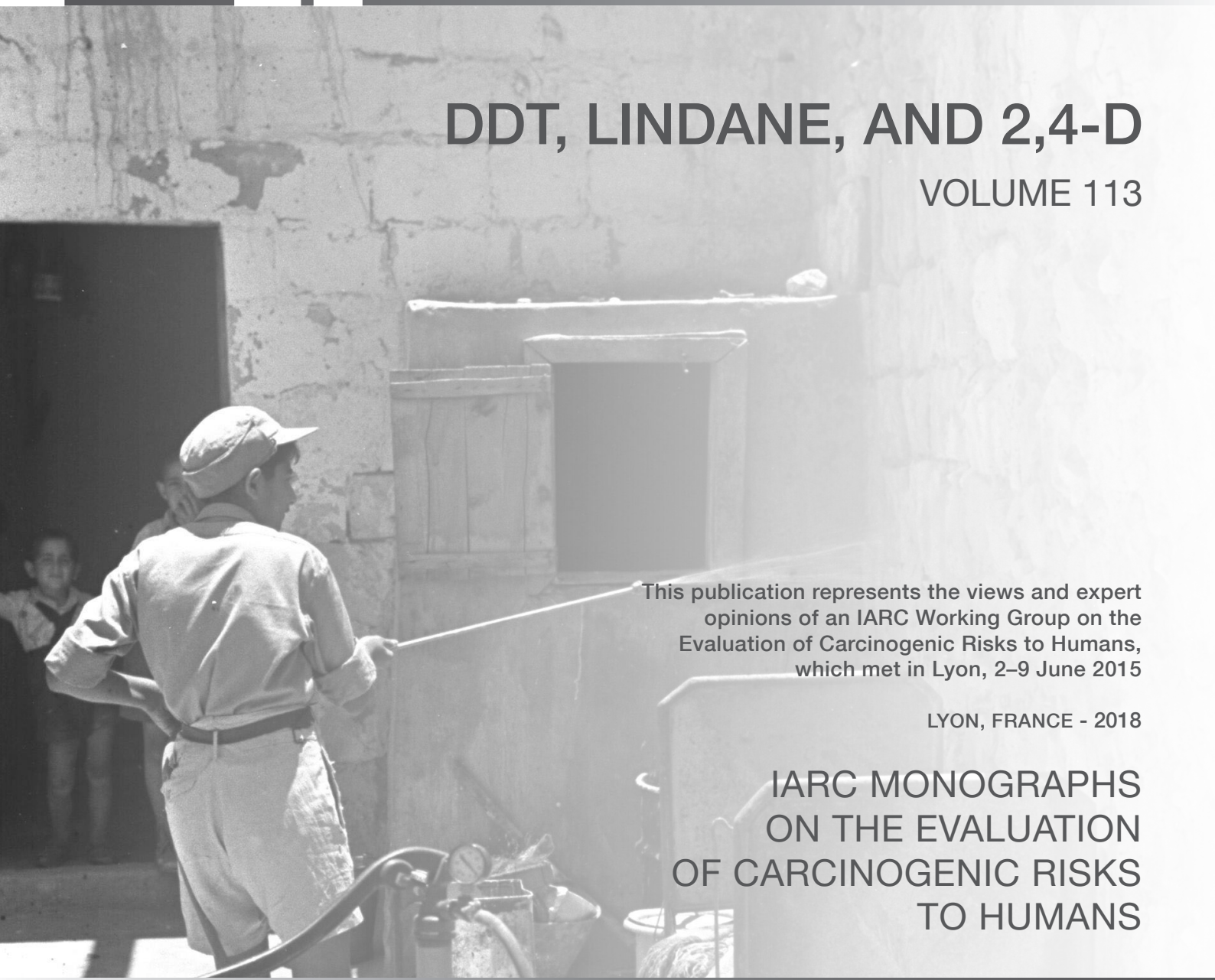

DDT, LINDANE, AND 2,4-D

VOLUME 113

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International Agency for Research on Cancer

World Health Organization

DDT

1. Exposure Data

1.1. Identification of the agent

1.1.1 Nomenclature

The term "DDT" (dichlorodiphenyltrichloroethane) refers to *para,para*′-DDT – 1,1′-(2,2,2-trichloro-ethylidene)bis (4-chloro benzene). The structure of DDT permits several different isomeric forms, such as *ortho,para*′-DDT (1-chloro-2-[2,2,2-trichloro-1-(4-chlorophenyl) ethyl]benzene). The term DDT is also applied to commercial products consisting predominantly of *p,p*′-DDT, but also containing smaller amounts of other compounds (WHO, 1989).

Chem. Abstr. Serv. Name: 1,1′-(2,2,2-trichloro-ethylidene)-bis(4-chlorobenzene)

Chem. Abstr. Serv. Reg. No.: 50-29-3

Preferred IUPAC Name: 1-chloro-4-[2,2,2-trichloro-1-(4-chlorophenyl)ethyl]benzene

Synonyms: dichlorodiphenyltrichloroethane; DDT; 1,1,1-trichloro-2,2-bis(*para*-chlorophenyl)ethane; α,α-bis(*para*-chlorophenyl)-β,β,β-trichloroethane; 1,1-bis(*para*-chlorophenyl)-2,2,2-trichloroethane; 2,2-bis(*para*-chlorophenyl)-1,1,1-trichloroethane; 4,4′-DDT; 4,4′-dichlorodiphenyltrichloroethane; *p,p*′-DDT; *para,para*′-dichlorodiphenyltrichloroethane; OMS 0016; 1,1,1-trichloro-2,2-bis(4,4′-dichlorodiphenyl)ethane; 2,2,2-trichloro-1,1-bis(4-chlorophenyl) ethane; trichlorobis(4′-chlorophenyl)ethane; TbisC-ethane; benzene, 1,1′-(2,2,2-trichloro-ethylidene)-bis(4-chloro-).

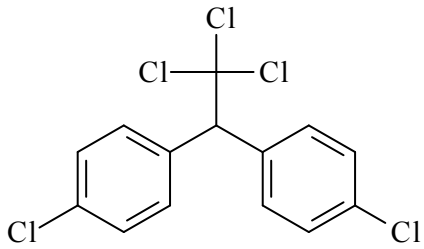
Trade Names: DDT has been used in many commercial product formulations. It is not possible to prepare an exhaustive list of all trade names that have been or are being used currently. Trade names specified below are presented as examples. Agritan; Arkotine; Benzochloryl; Bovidermol; Chlorophenothane; Chlorphenotoxum; Clofenotane; Detoxan; Dicophane; Didigam; Didimac; Estonate; Genitox; Gesafid; Parachlorocidum; Pentachlorin; Penticidum.

From NCBI (2015) and ChemIDplus (2015) unless otherwise specified.

The World Health Organization (WHO) specification for technical-grade DDT intended for use in public health programmes requires that the product contains a minimum of 70% *p,p*′-DDT (WHO, 2009). Technical-grade DDT typically also contains smaller amounts of other compounds such as *o,p*′-DDT, *p,p*′-DDD (1-chloro-4-[2,2-dichloro-1-(4-chlorophenyl) ethyl]benzene, also known as TDE), *o,p*′-DDE (1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene) (WHO, 1989). These other isomeric forms may add to the pesticide action of DDT since it is known that *o,p*′-DDT has insecticidal properties (Worthing & Walker, 1987). The structure and full chemical names of *p,p*′-DDT and its major metabolites are presented in Fig. 1.1. Technical-grade DDT has been formulated in almost every

conceivable form, including solutions in xylene and petroleum distillates, emulsifiable concentrates, water-wettable powders, granules, aerosols, smoke candles, and charges for vapourizers and lotions (WHO, 1989).

1.1.2 Structural and molecular formulae, and relative molecular mass



Structure from NIH (2015)

Molecular formula: $C_{14}H_9Cl_5$

Relative molecular mass: 354.49

1.1.3 Chemical and physical properties of the pure substance

See NCBI (2015)

Description: Colourless crystals or white powder, odourless or with weak aromatic odour

Solubility: Practically insoluble in water (0.055 mg/100 mL at 25 °C); soluble in acetone (58 g/100 mL), benzene (78 g/100 mL), benzyl benzoate (42 g/100 mL), carbon tetrachloride (45 g/100 mL), chlorobenzene (74 g/100 mL), cyclohexanone (116 g/100 mL), 95% alcohol (2 g/100 mL), ethyl ether (28 g/100 mL), and other organic solvents.

Octanol/water partition coefficient: log Pow = 7.48 (WHO, 1989)

Conversion factor for airborne concentrations: $mg/m^3 = 14.5 \times ppm$

1.2 Production and use

1.2.1 Production

The history of the development of DDT as a pesticide has been documented (Casida & Quistad, 1998; Jarman & Ballschmiter, 2012). Following the discovery of the insecticidal properties of DDT in 1939, DDT became a commonly used agent for insect control worldwide (both for public health and for agricultural uses), until agricultural uses were curtailed in various countries from the early 1970s (see Section 1.5 regulations).

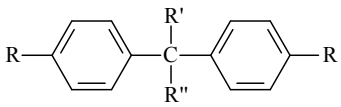
DDT is made industrially by condensing chloral hydrate with chlorobenzene in the presence of sulfuric acid. To prepare *o,p′*-DDT, an excess of chlorobenzene is condensed with 1-(2-chlorophenyl)-2,2,2-trichloroethanol in the presence of a mixture of 96% sulfuric acid and 25% oleum at 60 °C (Brooks, 1974).

Most DDT production can be assumed to have been technical-grade material that included 15–21% of *o,p′*-DDT, up to 4% of *p,p′*-DDD, and up to 1.5% of 1-(*p*-chlorophenyl)-2,2,2-trichloroethanol (Metcalf, 1955).

In the USA, peak production of DDT was reported in the early 1960s, with 56 000 tonnes produced in 1960 and 82 000 tonnes in 1962; DDT was registered for use on 334 agricultural commodities (Metcalf, 1955). Production then declined and by 1971 had dipped to about 2000 tonnes, shortly before DDT was banned (ATSDR, 2002).

In China, the cumulative production of DDT over 30 years until 1983 was reported to be 0.4 million tonnes, estimated to then account for 20% of the cumulative worldwide production (about 2 million tonnes) (ATSDR, 2002; Xin et al., 2011). During 2000–2003, average annual production in China was approximately 4500 tonnes and there were no DDT imports to China from other counties (Lin et al., 2009).

Fig. 1.1 Structure of *p,p'*-DDT and its major metabolites



Basic structure of *p,p'*-DDT related compounds

Name	Chemical name	R	R'	R"
DDT	1,1'-(2,2,2-trichloroethylidene)- bis[4-chlorobenzene]	- Cl	- H	- CCl_3
DDE	1,1'-(2,2-dichloroethenylidene)- bis[4-chlorobenzene]	- Cl	None	= CCl_2
DDD (also referred to as TDE)	1,1'-(2,2-dichloroethylidene)- bis[4-chlorobenzene]	- Cl	- H	- $CHCl_2$
DDMU	1,1'-(2-chloroethenylidene)- bis[4-chlorobenzene]-	- Cl	None	= CHCl
DDMS	1,1'-(2-chloroethylidene)- bis[4-chlorobenzene]	- Cl	- H	- CH_2Cl
DDNU	1,1'-bis(4-chlorophenyl)ethylene	- Cl	None	= CH_2
DDOH	2,2-bis(4-chlorophenyl)ethanol	- Cl	None	- CH_2OH
DDA	2,2-bis(4-chlorophenyl)- acetic acid	- Cl	- H	- COOH

Adapted from WHO (1989)

As assessed in 2007, DDT was produced in three countries - India, China and the Democratic People's Republic of Korea - with by far the largest amount then produced in India (van den Berg, 2009). Currently, DDT is produced only in India, from where it is exported as a pure (also called "technical") product, or as a commercially formulated product to other, mostly African, countries (UNEP, 2010; UNEP/WHO 2014).

[The Working Group noted that despite it being recognized that DDT being produced by many countries during the latter part of the twentieth century, no information on DDT production was available for most of these countries.]

1.2.2 Use

DDT has been, and is, primarily used as a pesticide. DDT is also used as an intermediate in the production of the pesticide dicofol (Kelthane), and in antifouling paint.

(a) Worldwide use as a pesticide

DDT was initially used by the military in World War II to control malaria, typhus, body lice, and bubonic plague. DDT was a key tool in malaria eradication efforts in Italy and the USA. In Italy, cases of malaria decreased from 400 000 in 1946 to virtually none in 1950. DDT was also used to manage an epidemic of typhus in Italy and Germany in 1943–1944 (Casida & Quistad, 1998; Jarman & Ballschmiter, 2012).

Historically, in addition to its public health uses, growers used DDT on a variety of food crops worldwide. In USA, some of the crops to which DDT was applied included beans, cotton, soybeans, sweet potatoes, peanuts, cabbage, tomatoes, cauliflower, brussel sprouts, corn, and other crops. DDT was also used to treat livestock and in buildings for pest control (EPA, 1975a).

The usage of DDT in the former Soviet Union was intensive in the 1950s and 1960s, and continued until the early 1990s. The total such use of DDT from 1946 till 1990 is estimated to

have been between 250 000 and 520 000 tons [254 000 and 528 000 tonnes] (Li et al., 2006).

Having been introduced as an agricultural chemical in the 1950s, DDT was used for that purpose in China until 1983 (Cai et al., 2008).

DDT is one of the 12 insecticides, and the only organochlorine compound, currently recommended by WHO for use in indoor residual spraying for disease vector control (WHO, 2011a). Currently, DDT represents some 71% of the global annual amount of insecticides used for vector control. In 2005, an estimated 5000 tonnes of DDT was used for disease vector control (Table 1.1). DDT is used mostly for malaria control, but 19% of the global share is sprayed to control transmission of leishmaniasis by sandflies (van den Berg et al., 2012).

As assessed in 1996, use of DDT and malathion was credited with reducing incident malaria in India to "only" 2 to 3 million cases per year (Sharma et al., 1996). In 2005, DDT was shown to be still useful for residual spraying in India, particularly in areas where the vectors are endophilic and not resistant, and its continued use in India was endorsed (Gunasekaran et al., 2005).

DDT has been used in China as an antimalarial agent, specifically in provinces where standing water in rice fields favours the breeding of *Anopheles anthropophagus* as a principal vector. Residual spraying of houses and cattle sheds was shown to reduce malarial prevalence (Xu et al., 1998). China has now stopped the use of DDT (UNEP/WHO, 2014).

In South Africa, spraying of DDT from 1945 to 1995 was highly successful in controlling the vectors of malaria, *Anopheles funestus* and *Anopheles arabiensis*, without emergent resistance. DDT was replaced by pyrethroids in 1995, but after 4 years, the incidence of malaria increased at least fourfold due to vector resistance to pyrethroids. In 2000, DDT was reintroduced and the incidence of malaria subsequently declined (Curtis, 2002). Currently, DDT is still used in South Africa and in a few other African countries for indoor residual spraying (Table 1.1). In 2009, India remained the largest user of DDT, with 78% of global use, the remainder being used in Ethiopia (15%), Mozambique (2%), Namibia (1.8%), South Africa (1.4%), Zimbabwe (1.2%), and Zambia, Madagascar, Eritrea, Swaziland, Uganda, and Mauritius (each < 1% of global use). Trends in the use of DDT have been associated with, and in some instances determined by, resurgence in malaria, as variously documented worldwide from the 1930s to the 2000s (Cohen et al., 2012). While the use of DDT declined in India in the 2000s, several countries in Africa, including Mozambique, Zambia, and Zimbabwe, significantly increased their DDT use until 2008 (Fig. 1.2; WHO, 2011b; van den Berg, 2009).

(b) Use as a chemical intermediate

DDT is used as a feedstock for the production of dicofol (Kelthane), an acaricide used for controlling mites that attack cotton, fruit trees, and vegetables. Dicofol is usually synthesized from technical DDT, which is first chlorinated and then hydrolysed to produce dicofol. DDT and reaction intermediates may remain in the dicofol product as impurities (Gillespie et al., 1994; Qiu et al., 2005).

In an assessment for the European Union in 2004, a single producer of dicofol within the European Union was identified; production was also indentified in China, Brazil, and India, with largest production volume (≈2000 tonnes/year) occurring in China (Ministerie van VROM, 2004).

Dicofol was introduced in China in the 1970s and, after discontinuation of DDT as an agricultural chemical, dicofol production became the major use of DDT. Use of DDT as an intermediate in dicofol production accounted for approximately 80% of the chemical used in China in 2002–2004, antimalarial usage and production of antifouling paint accounting for the balance. Difocol produced in China was reported to have

Table 1.1 Annual global production and use of DDT for vector control, in 2003, 2005, 2007, and 2009

Country	Quantity (1000 kg active ingredient)				Comment	Source
	2003	2005	2007	2009[c]		
DDT production						
China[a]	450	490	NA	NA	For export	Pd
India[b]	4100	4250	4495	NA	For malaria and leishmaniasis	Pd, WS, Dc
DPRK	NA	NA	5	NA	> 155 tonnes for use in agriculture	UNITAR
Global production	> 4550	> 4740	> 4500	NA		
DDT use						
Cameroon	0	0	0	NA	Plan to pilot in 2009	WHO
China	0	0	0	NA	Discontinued use in 2003	SC
Eritrea	13	15	15	12	Epidemic-prone areas	Qu, WHO
Ethiopia	272	398	371	781	Epidemic-prone areas	WHO, WS
Gambia	0	0	NA	NA	Reintroduction in 2008	Dc
India	4444	4253	3413	3399	For malaria and leishmaniasis	WHO, Dc
DPRK	NA	NA	5	NA	> 155 metric tonnes used in agriculture	UNITAR
Madagascar	42	0	0	NA	Plan to resume use in 2009	Qu
Malawi	0	0	0	NA	Plan to pilot in 2009	WHO
Mauritius	1	1	< 1	0.4	To prevent malaria introduction	Qu
Morocco	1	1	0	NA	For occasional outbreaks	Qu
Mozambique	0	308	NA	104	Reintroduction in 2005	WHO
Myanmar	1	1	NA	0.2	Phasing out	WS
Namibia	40	40	40	92	Long-term use	WHO
Papua New Guinea	NA	NA	0	NA	No recent use reported	SC
South Africa	54	62	66	70	Reintroduction in 2000	Qu, WHO
Sudan	75	NA	0	NA	No recent use reported	Qu, WHO
Swaziland	NA	8	8	7	Long-term use	WHO
Uganda	0	0	NA	NA	High Court prohibited use, 2008	SC, Dc
Zambia	7	26	22	NA	Reintroduction in 2000	WS, Qu, WHO
Zimbabwe	0	108	12	61	Reintroduction in 2004	WHO
Global use	> 4953	> 5219	> 3950	5127		

Dc, direct communication with national authorities; DDT, dichlorodiphenyltrichloroethane; DPRK, Democratic People's Republic of Korea; NA, not available; Pd, project proposals submitted to the Global Environment Facility; Qu, questionnaires on DDT by the Secretariat of the Stockholm Convention completed by national authorities; SC, documents published by the Secretariat; WS, workshop presentations by country delegates in the context of the Stockholm Convention. Further information was obtained from the World Health Organization (WHO) and United Nations Institute for Training and Research (UNITAR) reports, as indicated

[a] The figure for 2005 was extrapolated from the total production; in addition to production for vector control; DDT is produced for dicofol manufacture (≈3800 metric tonnes per year) and for antifoulant paints (≈200 metric tonnes per year)

[b] DDT is also produced for dicofol manufacture (≈280 metric tonnes per year)

[c] The data for 2009 were taken from WHO (2011b)

Adapted from van den Berg (2009)

Fig. 1.2 Trends in the global use of DDT, 2000–2009

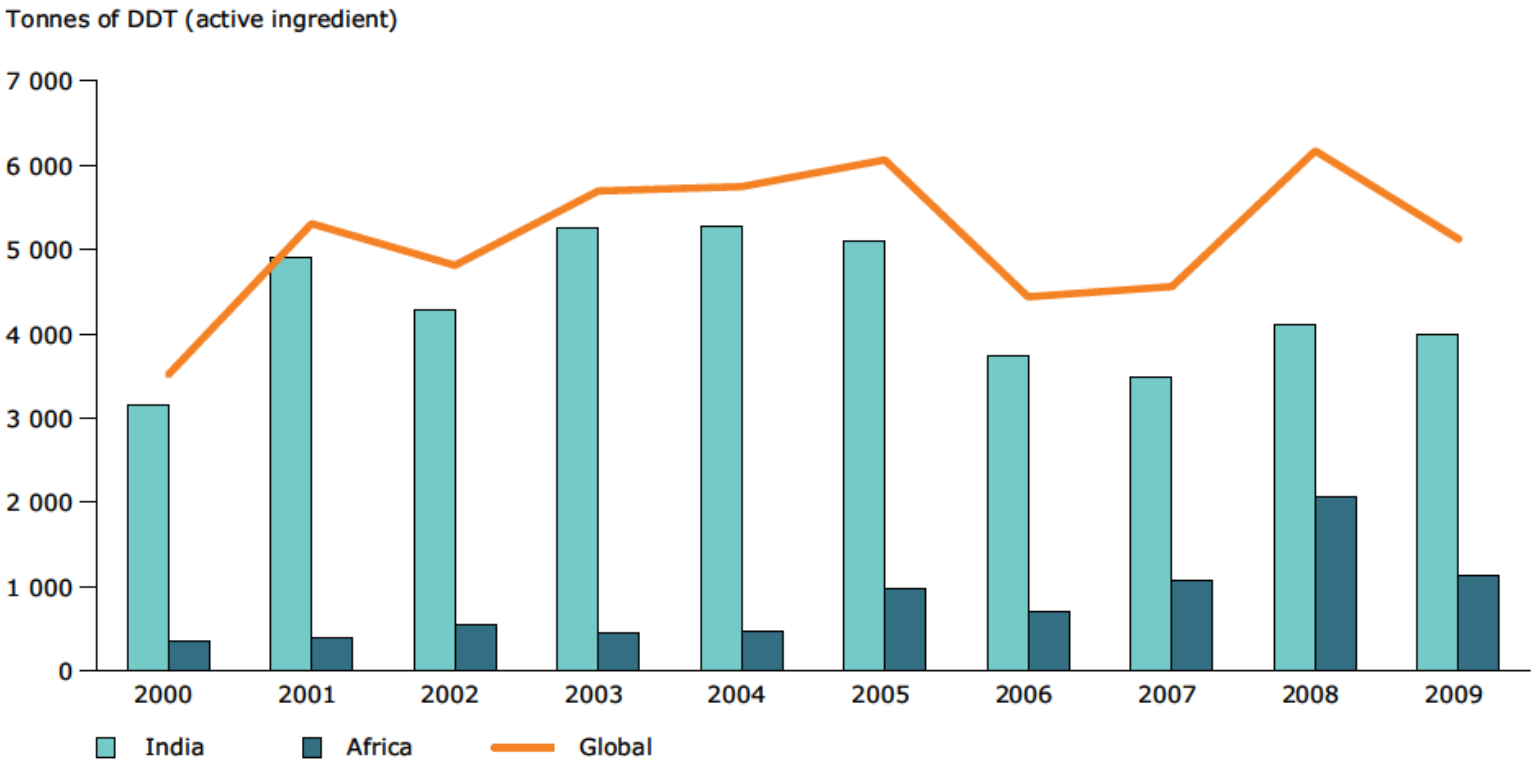


Figure compiled with data from van den Berg et al. (2012) 'Global trends in the use of insecticides to control vector-borne diseases', *Environ. Health Perspect*, (120):577–582 AND reproduced from Bouwman et al. (2013). DDT: fifty years since Silent Spring. Chapter 11. Late lessons from early warnings: science, precaution, innovation. Brussels, Belgium: European Environment Agency; pp. 272–91.

a high DDT content (on average, 20%) (Qiu et al., 2005; Global Environment Facility, 2006).

From the 1950s until 2009, DDT was used as an additive to antifouling paint produced in China (Xin et al., 2011). During 2000–2003, production of antifouling paint accounted for 4% of the DDT produced in China (Lin et al., 2009). By 2014, all uses of DDT in China were withdrawn; the only reported use of DDT as an intermediate in dicofol production was in India (UNEP/WHO, 2015).

1.3 Measurement and analysis

Methods for the analysis of organochlorine pesticides (OCPs) in a variety of environmental, biota, food, and human biological matrices have been well developed during the past several decades. These methods appear in both academic articles and in the standard operational procedures from various environmental and health agencies. The United States Environmental Protection Agency (EPA) (EPA, 2015a), the European Committee for Standardization (CEN/EU), the Japanese Industrial Standards (JIS), and agencies in other industrialized countries have developed comprehensive protocols for pesticide analysis. In particular, the EPA has posted an online index of pesticide analytical methods.

The analysis of DDT, its metabolites, and other OCPs involves extraction, clean-up, and instrumental analysis based on gas chromatography (GC) or gas chromatography-mass spectrometry (GC-MS) (EPA, 2015a). The available sample extraction and clean-up methods described above have generally provided recoveries of target OCP analytes in the range of 50–130%, depending on the sample matrix and analyte concentration. Regarding detection, gas chromatography-electron capture detection (GC-ECD) was widely used to quantify DDT, DDE, and other related isomers and metabolites in many media, especially in the 1970s until the 1990s, and is still a low-cost routine technique for most OCPs. One concern with GC-ECD methods is the potential for interfering non-target chemicals leading to misidentification or incorrect quantitation. GC-MS methods are now widely used have been used to identify and quantify DDT, DDE, and other related isomers and metabolites in many media. These include single quadruple MS detectors running in electron ionization mode with target analyses monitored by selective ion monitoring and GC coupled with high-resolution MS (HRMS) (Barr et al., 2003). These detection methods increase the confidence in confirmative analysis by decreasing matrix interferences, improving selectivity and, in the case of tandem MS and HRMS, showing higher signal-to-noise ratio, therefore improving the detection limits and selectivity.

1.4 Occurrence and exposure

The following summary of the literature is not a systematic review, but provides a descriptive narrative of the occurrence of and exposure to DDT and its metabolites in the environment and among the occupational and general population globally. Because DDT is a synthetic product that consists of variable quantities of several isomers, the term "ΣDDT" used here represents the sum of all isomers, total DDT, as reported by the authos.

DDT is a persistent organochlorine pesticide that together with its metabolites can have a half-life in soil of up to 30 years and in aquatic life of up to 150 years. DDT and its important metabolites for exposure assessment, DDE and DDD, are chemicals not known to occur naturally in the environment (see their structure, Fig. 1.1).

Historically, DDT was released to the environment during its production, formulation, and extensive use as a pesticide in agriculture and malaria-control applications. Although DDT was banned for use in many countries after 1972, it is still being used in some areas of the world for vector-control purposes (ATSDR, 2002).

Occupational exposures to DDT may occur in pesticide-manufacturing workers, commercial pesticide applicators, and historically occurred in farmers. Bystander exposure occurs during DDT application in homes for malaria control, if workers from manufacturing plants take home contaminated clothing, and historically occurred from field application in agriculture. DDT is widely distributed in the environment even decades after its use ended in most countries. General population exposures occur primarily through dietary intake, and as a result of contact with DDT in environmental media, including indoor environments. Where DDT remains in use for malaria control, there is the potential for associated human exposures. DDT and its metabolites are fairly ubiquitous in the atmosphere as a result of spraying operations in areas of the world where it is still used (ATSDR, 2002).

1.4.1 Occupational exposure

Detailed information on occupational exposure is given in Table 1.2

(a) Pesticide manufacturing

No studies reporting exposure measurements for workers manufacturing DDT pesticides were available to the Working Group. However, DDT has been reported to be used in the synthesis of the insecticide dicofol in China since 1978. Analytical studies have shown that DDT compounds, including *p,p′*-DDT and *p,p′*-DDE, may be contaminants in technical grades of difocol (Risebrough et al., 1986) with the potential for DDT to be released from difocol products. In a Chinese factory producing difocol with a closed-loop production system, ΣDDT was measured in workshop air (range, 1.88–17.53 μg/m^3) and worker inhalation doses were estimated (ΣDDT, 0.38–3.51 μg/kg bw per day) (Li et al., 2014a). Occupational hygiene assessment was conducted to assess the risks of workers involved in the demolition of a plant in which dicofol was manufactured between 1978 and 2004. Concentrations of ΣDDT were measured on process equipment surfaces and ranged between 5.4 and 37.5 g/m^2 (Luo et al., 2014).

(b) Agriculture

In North Carolina, USA, between 1995 and 1996, African-American farmers, most of whom were no longer working on a farm, presented with mean plasma DDE concentrations of 11.4 ng/mL (Cooper et al., 2004). In Bolivia, between 2010 and 2011, serum *p,p′*-DDE concentrations of 19.7 ng/mL (4788.7 ng/g lipid) were reported in agricultural workers (Mercado et al., 2013). In India, in a study carried out in 2009 among 30 agriculture, sheep-breeding and wool-shearing workers in rural Bangalore, the mean blood concentration of ΣDDT was 10.6 ng/mL (Dhananjayan et al., 2012).

(c) Malaria control

In Tzaneen, South Africa, median ΣDDT concentrations of 83.3 μg/g of lipid were reported among malaria-control workers (Dalvie et al., 2004a). In 2008 in northern Uganda, malaria-control workers had mean DDE/DDT concentrations in plasma collected post-spraying that ranged empirically from 24 to 128 ppb, with a mean of 77 ppb (Bimenya et al., 2010). In 1994, in the state of Veracruz, Mexico, workers employed to control vectors for malaria and dengue presented mean ΣDDT concentrations of 104.5 μg/g lipids in abdominal adipose tissue (Rivero-Rodriguez et al., 1997). In Mato Grosso, Brazil, between 1999 and 2000, malaria-control sprayers had median serum concentrations of ΣDDT, DDT, and *p,p′*-DDE of 135, 23.3, and 107.3 ng/mL, respectively (Dores et al., 2003). In the Amazon region of Brazil, malaria-control workers in 1997 had serum ΣDDT and *p,p′*-DDE concentrations of 231.5 and 156.9 ng/mL, respectively, levels that were much higher than those found in the general population in 2001, in which concentrations were

Table 1.2 Occupational exposure to DDT and its metabolites

Occupation	Country, collection date	Sampling matrix	Exposure		Comments	Reference
			Level [a]	Range		
Pesticide manufacture, closed-system, dicofol production	China, year NR	Air	NR	ΣDDT, 1.88–17.53 μg/m^3	Dicofol production with DDT as intermediate Estimated inhalation exposure range of 0.38–3.51 μg/kg bw per day	Li et al. (2014a)
Dicofol manufacture, demolition workers	China, around 2009	Dust on production equipment	NR	ΣDDT, 5.4–37.5 g/m^2	The factory produced difocol with DDT intermediate between 1978 and 2004	Luo et al. (2014)
Farmers	USA, North Carolina, 1995–1996	Plasma	*p,p′*-DDE, 7.7 ng/mL (median)	*p,p′*-DDE, 0.6–77.4 ng/mL		Cooper et al. (2004)
Farmers	Bolivia, Santa Cruz, 2010–2011	Serum	*p,p′*-DDE, 4788.7 ng/g lipid (median)	*p,p′*-DDE, 1197–35 131 ng/g lipid (25th–75th percentiles)		Mercado et al. (2013)
Agriculture and sheep wool-associated jobs	India, Bangalore city, Karmataka, (rural) 2009	Blood	*p,p′*-DDD, 3.01 ± 0.19; *p,p′*-DDE, 5.67 ± 1.21; *p,p*-DDT, 3.81 ± 1.51 ΣDDT, 10.6 ± 2.15 ng/mL	*p,p′*-DDD, < LOD–5.65; *p,p′*-DDE, < LOD–32.1; *p,p*-DDT, < LOD–48.3 ΣDDT, 6.72–51.7 ng/mL		Dhananjayan et al. (2012)
Malaria control, 1946–1950	Italy, Sardinia, 2000	Serum	DDT, 47; *p,p′*-DDE, 396 ng/g lipid (median)	DDT, 33–74. *p,p′*-DDE, 157–1045 ng/g lipid		Cocco et al. (2004)
Malaria-control workers, DDT spraying, mixing	South Africa, Tzaneen, Limpopo year NR	Serum	DDE, 52.4; DDD, 0.74; DDT, 28.2 ΣDDT, 83.3 μg/g lipid	DDE, 1.1–273.6; DDD, 0–3.1; DDT, 0.3–67.1 ΣDDT, 1.4–315 μg/g lipid	"DDT," "DDD", and "DDE" are used for the sum of the two respective *p,p′* and *o,p′* isomers	Dalvie et al. (2004a)
Malaria-control DDT weighing and spraying	Mexico, Veracruz, 1994	Abdominal adipose tissue	ΣDDT, 104.48 *p,p′*-DDT, 31; *o,p′*-DDT, 2.1; *p,p′*-DDE, 60.98; *p,p′*-DDD, 0.95 μg/g lipid (geometric mean)	ΣDDT, 10.56–665.56 *p,p′*-DDT, 0.72–344.98; *o,p′*-DDT, 0.07–29.74; *p,p′*-DDE, 9.57–298.42; *p,p′*-DDD, ND-3.51 μg/g lipid		Rivero-Rodriguez et al. (1997)
Malaria control DDT spraying	Brazil, Para state, 1997–2001	Serum	1997: ΣDDT, 231.5; *p,p′*-DDE, 156.9 2001: ΣDDT, 50.4; *p,p′*-DDE, 39.4 ng/mL	1997: ΣDDT, 5.3–3839.8; *p,p′*-DDE, 4.6–513.8 2001: ΣDDT, 3.3–357.9; *p,p′*-DDE, 2.3–284.1 ng/mL		Ferreira et al. (2011)

Table 1.2 (continued)

Occupation	Country, collection date	Sampling matrix	Exposure		Comments	Reference
			Level [a]	Range		
Malaria control DDT spraying	Brazil, Mato Grosso, 1999–2000	Serum	ΣDDT, 135.5; DDT, 23.3; *p,p′*-DDE, 107.3 ng/mL (median)	ΣDDT, 7.5–875.5; DDT, ND-476; *p,p′*-DDE, 7.5–518.5 ng/mL		Dores et al. (2003)
Malaria control DDT spraying	Uganda, Lango, 2008	Plasma	DDE/DDT, 77 ppb	DDE/DDT, 24–128 ppb	The mean value reported is a mean DDE/DDT; plasma samples analysed 6 months after one round of DDT spraying	Bimenya et al. (2010)
Electronic waste and fishery industry, e-waste cycling and fishery	China, Guangdong province (Guiyu town, Haojiang district), 2005	Serum	ΣDDTs: e-waste, 600; fishery, 2300 ng/g lipid (median)	ΣDDTs: e-waste, 210–1800; fishery, 380–5100 ng/g lipid	Exposure to ΣDDT was dominant in both e-waste and fishery industries compared with PCBs and other OCPs	Bi et al. (2007)
Textile	China, Anhui 1996–1998	Serum, preconception	ΣDDT, 27.9, *p,p′*-DDT, 1.42, *o,p′*-DDT, 0.16, *p,p′*–DDE, 26.24, *o,p′*-DDE, 0.09, *p,p′*-DDD, 0.21 ng/g lipid (median)	ΣDDT, 5.52–113.3, *p,p′*-DDT, 0.37–13.12, *o,p′*-DDT, 0.04–1.49, *p,p′*-DDE, 4.76–97.54, *o,p′*-DDE, 0.03–1.07, *p,p′*-DDD, 0.05–0.96 ng/g lipid	ΣDDT was positively associated with the risk of subsequent early pregnancy losses	Venners et al. (2005)

ΣDDT, total DDT corresponding to the sum of *o,p′*-DDE, *p,p′*-DDE, *o,p′*-DDD, *p,p′*-DDD, *o,p′*-DDT, *p,p′*-DDT; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; LOD, limit of detection; NR, not reported; OCPs, organochlorine pesticides; PCBs, polychlorinated biphenyl; ppb, parts per billion

[a] Arithmetic mean, except where otherwise stated

50.4 and 39.4 ng/mL, respectively (Ferreira et al., 2011). In Sardinia, Italy, workers who had participated in the 1946–1950 antimalarial campaign presented in 2000 with median serum DDT and *p,p′*-DDE concentrations of 47 and 396 ng/g lipid, respectively (Cocco et al., 2004).

(d) Other occupational exposures

In Guangdong province, China, in 2005, serum ΣDDT concentrations among electronic waste and fishery workers ranged from 210 to 5100 ng/g lipid (Bi et al., 2007). In Anhui, China, between 1996 and 1998, serum ΣDDT concentrations among female textile workers in China ranged from 5.52 to 113.3 ng/g lipid (Venners et al., 2005).

1.4.2 Environmental occurrence

Detailed information on environmental occurrence is given in Table 1.3.

(a) Water

The release of DDT to surface water still occurs in countries that rely on DDT for malaria control near open water. DDT also enters surface water as a result of dry and wet deposition from the atmosphere and direct gas transfer, contributing to the loading in rivers, deep wells, lakes, and oceans.

Concentrations of *p,p′*-DDE, *p,p′*-DDD, *p,p′*-DDT in water from the Nile delta ranged from 35 to 67, 19 to 33, and 24 to 31 ng/L respectively between 1995 and 1997 (Abbassy et al.,1999). In 2011 in South Africa, ΣDDT and residues were measured in Johannesburg in surface water (i.e. river and dam) as 14 day-measurement samples taken in spring and summer, and ranged from 0.026 to 0.549 ng/L (Amdany et al., 2014). Surface water sampled twice in 2012 from the Konya Basin in Turkey contained ΣDDT at concentrations ranging from not detected (ND) to 47 ng/L; *p,p′*-DDE represented the major metabolite measured, with concentrations ranging from ND to 37 ng/L (Aydin et al., 2013). Water samples taken monthly between 2009 and 2011 from the Karun river in Khuzestan Province, in the Islamic Republic of Iran, contained ΣDDT at mean concentrations of 32.2ng/L, with *o′,p′*-DDT and *p,p′*-DDT concentrations of 26 and 10.2 ng/L, respectively (Behfar et al., 2013). DDT concentrations in surface-water samples taken between August 1989 and October 1991 from southern Asia and Oceania ranged from 1.3 pg/L to up to 5 orders of magnitude higher (120 ng/L) measured in India (Iwata et al., 1994). Much higher ΣDDT concentrations were reported in a 20-year follow-up study in India. ΣDDT concentrations ranged from ND to < 163 × 106 ng/L at 45 surface-water sites, and from ND to 75 × 103 ng/L at 15 ground-water sites. Highest ΣDDT concentrations were measured in 2005 in the Ganges river, India (Sharma et al., 2014).

In the USA, no DDE was detected in 3251 samples obtained from 2001 to 2003 as a statistically selected, nationally representative sampling of small drinking-water systems (EPA, 2008). In the USA National Water Quality Assessment Program from 1992–2001, *p,p′*-DDE was detected in only 5.75% of 2013 samples from 83 agricultural surface water sites with only 0.29% being > 10 ng/L; and 2.02% detection frequency in 812 samples from 30 urban surface-water sites with none being > 10 ng/L (USGS, 2006). In central Poland, between 2002 and 2003, DDT concentrations in drinking-water ranging from 10.6 to 166 ng/L were reported in the vicinity of orchard areas (Badach et al., 2007). Little information was available in the open literature for Latin American countries or other European countries.

In Limpopo, South Africa, where DDT is still used for indoor residual spraying to control malaria vectors, ΣDDT was detected in potable water (tap water) with concentrations ranging from 600 to 7600 ng/L, while 83% of ΣDDT concentrations in exposed areas were < 2000 ng/L. In contrast, in control areas none of the tap-water samples contained residues of

Table 1.3 Environmental occurrence of DDT and its metabolites

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
South Africa, Johannesburg, 2011	Surface water	NR	ΣDDT, 0.026–0.549 ng/L	Measurements were done for 14 days in spring and in summer; concentrations of isomers also reported by site	Amdany et al. (2014)
Egypt, Nile Delta, 1995–1997	Surface water	NR	*p,p′*-DDE, 35–67, *p,p′*-DDD, 19–33 *p,p′*-DDT, 24–31 ng/L	Levels were reported for different seasons, 1995–1997	Abbassy et al. (1999)
Islamic Republic of Iran, Karun river in Khuzestan Province, August 2009 to March 2011	Surface water	ΣDDT, 36.2; *o,p′*-DDT, 26; *p,p′*-DDT, 10.2 ng/L	ΣDDT, 5.9–90.3; *o,p′*-DDT, ND–87.3; *p,p′*-DDT, 2.4–28 ng/L	There was significant correlation between *o,p′*-DDT and ΣDDT	Behfar et al. (2013)
Turkey, Konya closed basin, March and August 2012	Surface water	NR	ΣDDT, ND–47; *p,p′*-DDE, ND– 37; *p,p′*-DDD, ND–5; *p,p′*-DDT, ND–5 ng/L	Measurements taken in March and August; slightly higher levels of ΣDDT were found in March	Aydin et al. (2013)
Pakistan, River Chenab, Punjab, January–March 2013	Surface water	ΣDDT, 9.07 ng/L	ΣDDT, 1.90–20.6 ng/L		Mahmood et al. (2014)
Eastern and southern Asia and Oceania, August 1989 to October 1991	Surface water	NR	ΣDDT: India: 0.87–120, Thailand: 0.23–2.5, Viet Nam: 0.29–25; Malaysia: 1.7; Indonesia: 0.19–0.27; Solomon Islands: 0.062–21; Japan: 0.0065–0.016; Taiwan, China: 0.0095–0.19; Australia: 0.0013–1.1 ng/L		Iwata et al. (1994)
India, year NR NA	Surface water, ground water	NR	ΣDDT: Surface water: ND–16 367 × 10^3 Ground water: ND–75 × 103 ng/L	> 45 surface water sites, 15 ground water sites, approximately 20-year data; highest ΣDDT levels were measured in 2005 in the Ganges river	Sharma et al. (2014)
Poland, Warka-Grojec region Spring and autumn 2002–2003	Drinking-water	NR	DDT, 10.6–166.9 ng/L	Higher DDT levels were measured in autumn than in spring, and a higher percentage of samples was found contaminated in autumn (47.1%) than in spring (29.4%)	Badach et al. (2007)
South Africa, Limpopo Province February 2008	Drinking-water	NR	ΣDDT: exposed area: 600–7600 ng/L	83% of ΣDDT levels in exposed area: < 2000 ng/L; control area: < 500 ng/L [b]	Van Dyk et al. (2010)

Table 1.3 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Brazil, Cidade dos Meninos 2002–2003	Soil and sediments, water, pasture and vegetables	ΣDDT: soil and sediments: 188 × 10^3; pasture: 57.2 × 10^3; vegetables: 5100; water: NR ng/g or ng/L	ΣDDT: soil and sediments: < 30 × 10^3 to 465 × 10^3 ; water: ND–120; pasture: 9180–189 × 10^3; ΣDDT: vegetables: 3.22–7.01 ng/g or ng/L		Brilhante & Franco (2006)
China, Taihu lake 2006	Surface sediment	*p,p′*-DDT, 1.26, *p,p′*-DDD, 0.36, *p,p′*-DDE, 0.14, ΣDDT, 53.9 ng/g dw	ΣDDT, 0.25–375 ng/g dw	DDTs were detected in all sediment samples; benthic organisms were also employed for DDT environmental exposure levels	Zhao et al. (2009)
South Africa, Lake Sibaya, KwaZulu-Natal January–March 2012	Surface sediment	NR	ΣDDT, 0.8–123; *p,p′*-DDE, 1.8–42.8; *p,p′* DDD, 1.8–74.1; *p,p′*-DDT, < LOD–6.2 ng/g		Humphries (2013)
Thailand, tributaries of Mae Klong river; Mae Klong river basin 2003–2005	Surface sediment	NA	ΣDDT: Klong river: 80–1830; Klong river basin: < 1–6780 ng/g dw	DDT detection reflected a recent contamination in the study area	Poolpak et al. (2008)
Pakistan, River Chenab, Punjab January–March 2013	Sediment	ΣDDT, 40.3 ng/g	ΣDDT, 5.84–89.8 ng/g		Mahmood et al. (2014)
China Beibu Gulf and its tributary rivers 2010	Sediment	*p,p′*-DDT, 6.43; *o,p′*-DDT, 1.6; *p,p′*-DDE, 4.33; *p,p′*-DDD, 9.39; ΣDDT, 21.8 ng/g dw	*p,p′*-DDT, 0.19–44.1; *o,p′*-DDT, 0.07–10.1; *p,p′*-DDE, 0.08–19.2; *p,p′*-DDD, 0.16–52.2; ΣDDT, 0.59–126 ng/g dw	Concentrations of DDTs were higher than those reported in the sediments from other regions of the world	Xu et al. (2013b)
Eastern and southern Asia and Oceania August 1989 to October 1991	Sediment	NR	ΣDDT: India: 8.0–450; Thailand: 4.8–170; Viet Nam: 0.37–790; Malaysia: 1.8; Indonesia: 3.4–42; Papua New Guinea: 4.7–130; Solomon Islands: 9.3–750; Japan: 2.5–12; Australia: < 0.01–1700 ng/g dw		Iwata et al. (1994)
India	Sediment, soil	NR	ΣDDT: sediment: < 0.01–128 600, soil: 34–903 ng/g	Sediment from 20 sites; soil from 15 mostly agricultural areas; approximately 20-year data	Sharma et al. (2014)

Table 1.3 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Bahrain, Oman, Qatar and the United Arab Emirates (UAE) 2000 & 2001	Coastal sediment	NR	ΣDDT: Bahrain: 0.088–0.430; Oman: 0.7×10^{-3} to 0.0852; Qatar: 0.63×10^{-3} to 0.0367; UAE: ND–0.0519 ng/g dw		de Mora et al. (2005)
Canada Toronto 2002	Soil and sediment	NR	ΣDDT: soil: 1–18; sediment: 0.2–472 ng/g		Wong et al. (2009b)
Mexico, Culiacan Valley, Sinaloa 2007	Agricultural sediment	NR	ΣDDT, 1.1–25.95 ng/g dw	The Culiacan Valley is an extensive agricultural region characterized by a variety of crops with high-yield production; measurements were taken in the agricultural drainage system of the valley; highest measured concentration among the DDT-related compounds was for *p,p′*-DDE (20.19 ng/g dw)	García de la Parra et al. (2012)
Jordan, Humrat Al-Sahn, Jordan Valley 1998	Soil	NR	*p,p′*-DDE, ND–0.46; *p,p′*-DDD, ND–0.16; *o,p′*-DDT, ND–0.11; *p,p′*-DDT, ND–4.05 ppm	Mean values reported for five different sites	Al-Mughrabi & Qrunfleh (2002)
Brazil, Itirapina region at the Northeastern part of Sao Paulo 2005	Soil	*p,p′*-DDE, 5.16; *o,p′*-DDT, 0.47; *p,p′*-DDT, 0.5; *p,p′*-DDD, 0.48 ng/g dw	*p,p′*-DDE, 2.05–8.8; *o,p′*-DDT, 0.05–1.69; *p,p′*-DDT, 0.03–1.12; *p,p′*-DDD, < 0.01–1.23; ΣDDT, 0.12–11.01 ng/g dw		Rissato et al. (2006)
China, Beijing-Tianjin-Hebei Economic Zone and Bohai Bay Rim city Year NA	Surface soils	ΣDDT, 73.9 ng/g	ΣDDT, ND–2417 ng/g	Industrial area where technical DDT was highly produced	Li et al. (2011)
USA, Texas Year NR	Soil	NR	DDE, Palmview, ND–60; San Benito, 2–60; Harlingen, 1–20; McAllen, 10–50 ng/g	Soils were collected from elementary school yards in cities/towns in the state of Texas	Miersma et al. (2003)
South Africa, Limpopo February 2008	Outside soil	ΣDDT: exposed area: 25; control area: 21 ng/g dw	ΣDDT: exposed area: 5.7–59; control area: 2.1–93 ng/g dw		Van Dyk et al. (2010)

Table 1.3 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Eastern and southern Asia and Oceania August 1989 to October 1991	Air	NA	ΣDDT: India: 46–12 000; Thailand: 35–2600; Viet Nam: 1700–2400; Solomon Islands: 1300; Japan: 75; Taiwan, China: 230; Australia, 8.8–22 pg/m^3		Iwata et al. (1994)
Global 2005	Air	NA	*p,p′*-DDE: Delhi: 3600–6600; California: 210–460; Canary Islands: 190–250 pg/m^3	Reported from the first year of the Global Atmospheric Passive Sampling (GAPS) Network Highest and seasonably variable concentrations were detected at two agricultural sites near Delhi, India	Poo et al. (2009)
Mexico, Chiapas and Monterrey, and other Mexico sites 2005–2006	Air	ΣDDT, 558 pg/m^3	ΣDDT: southern Mexico sites: 239–2360; central sites: 15–750; Monterrey: 15; Chiapas: 2360 pg/m^3		Wong et al. (2009a)
USA, Canada, Mexico, and Belize 2000–2001	Air	NR	*p,p′*-DDT, 0.12–360; *p,p′*-DDE, 0.04–378; *p,p′*-DDD, 0.11–100 pg/m^3	The highest levels of DDT-related compounds were found in Mexico and Belize, which were about an order of magnitude higher than in the USA and southern Canada, and more than two orders of magnitude higher than in samples from the Arctic region	Shen et al. (2005)
China, Shanghai 2008–2011	Air	ΣDDT: air–gas phase: 4.78; air–particulate: 9.13 pg/m^3 (median)	ΣDDT: air–gas phase: ND–142.2, air–particulate: ND–120 pg/m^3	Estimated total daily uptake ΣDDT from food, dust and air 79.4 ng/day for children and 131.1 ng/day for adults > 95% from food	Yu et al. (2012)
South Africa, Limpopo Province February 2008	Indoor air	ΣDDT: exposed area: 3900; control area: 10 ng/m^3	ΣDDT: exposed area: 1100–8800; control area: 1.5–41 ng/m^3		Van Dyk et al. (2010)
China, Shanghai 2008–2011	Dust	ΣDDT: indoor dust: 29.8; outdoor dust: 5.7 ng/g (median)	ΣDDT: indoor dust: 0.15–179, outdoor dust: 0.16–107 ng/g	Estimated total daily uptake of ΣDDT from food, dust, and air was 79.4 ng/day for children and 131.1 ng/day for adults; > 95% from food	Yu et al. (2012)
South Africa, Limpopo Province February 2008	Floor dust	ΣDDT: in exposed area: 1200; in control area: 1.8 µg/m^2	ΣDDT: in exposed area: 8.3–4800; in control area: 0.1–8.9 µg/m^2		Van Dyk et al. (2010)

Table 1.3 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Singapore 2005	House dust	ΣDDT, 14 ng/g (median)	ΣDDT, < LOD–770 ng/g	ΣDDT represented *p,p′*-DDE, *p,p′*-DDD and *p,p′*-DDT	Tan et al. (2007)
Mexico, Chihuahua Year NR	House dust	NR	DDT, 1–9587; DDE, 1–797 ng/ g	Chihuahua is a north Mexican state where DDT was sprayed several years previously for malaria-vector control	Díaz-Barriga-Martinez et al. (2012)
USA, California 2001–2006	Carpet dust	*p,p′*-DDE, 9.4; *p,p′*-DDT, 16 ng/g (geometric mean)	NA	Exposure assessment to DDT and other organochlorines using residential carpet dust	Ward et al. (2009)
USA, Iowa, Los Angeles county, Detroit, and Seattle 1999–2001	Carpet dust	*p,p′*-DDE, 43; *p,p′*-DDT, 343 ng/g	NA		Colt et al. (2004)

[a] Arithmetic mean, unless otherwise stated

[b] DDT is still used in specific areas of South Africa for indoor residual spray to control malaria vectors. In this study, indoor air, floor dust, outside soil, and drinking-water were sampled for measurement of DDT and related compounds in summer, 2 months after indoor residual spraying

ΣDDT, total DDT corresponding to the sum of *o,p′*-DDE, *p,p′*-DDE, *o,p′*-DDD, *p,p′*-DDD, *o,p′*-DDT, and *p,p′*-DDT; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; LOD, detection limit; dw, dry weight; NA, not applicable; ND, not determined; NR, not reported

ΣDDT at above the detection limit of 500 ng/L (Van Dyk et al., 2010).

(b) Soil and sediment

DDT and other persistent OCPs are found in soil and sediment samples from all regions of the globe, and residues are widely distributed in all types of soil (Table 1.3). For example in 2003, soils from elementary school yards in cities/towns within the state of Texas, USA, were reported to contain DDE at concentrations between 1 and 60 ng/g (Miersma et al., 2003). Soil sampled in 1998 from Humrat Al-Sahn in Jordan had levels of *p,p′*-DDE, *p,p′*-DDD, *o,p′*-DDT, and *p,p′*-DDT which ranged from ND to 0.46 ppm, ND to 0.16 ppm, ND to 0.11 ppm, and ND to 4.05 ppm, respectively (Al-Mughrabi & Qrunfleh, 2002). In Canada, in 2002, ΣDDT concentrations ranging from 1.0 to 18 ng/g were detected in soil in suburban Toronto (Wong et al., 2009b). In Sao Paulo, Brazil, ΣDDT concentrations in soil ranged from 0.12 to 11.01 ng/g dry weight (Rissato et al., 2006). In a review by Sharma et al. (2014), mean ΣDDT concentrations ranged from 34–903 ng/g in soil at 15 mainly agricultural sites in India. DDT concentrations exceeding 100 ng/g have been reported in sediment from several countries in Asia; the highest concentrations of ΣDDT, > 100 000 ng/g, were measured in India (Iwata et al., 1994; Sharma et al., 2014).

(c) Residential dust

In Chihuahua, Mexico, DDT and DDE concentrations quantified in household dust ranged from 1 to 9587 ng/g and 1 to 797 ng/g, respectively (Díaz-Barriga Martinez et al., 2012). In Singapore, the median ΣDDT concentration in 31 samples of house dust was 14 ng/g dust, with a range of below the limit of detection to 770 ng/g dust (Tan et al., 2007). In a study in California, USA, in 2001–2006, geometric mean concentrations of *p,p′*-DDE and *p,p′*-DDT detected in samples of carpet dust were 9.4 and 16 ng/g dust, respectively (Ward et al., 2009). In carpet-dust samples collected from the homes of 513 control subjects in Detroit, Iowa, Los Angeles, and Seattle, USA, between 1999 and 2001, mean concentrations of *p,p′*-DDE and *p,p′*-DDT were 43 and 343 ng/g dust (Colt et al., 2004).

(d) Air

A study on the atmospheric distribution of OCPs in North America between 2000 and 2001 reported that concentrations were in the range of 0.12–360 pg/m^3 for DDT, 0.04–378 pg/m^3 for DDE, and 0.11–100 pg/m^3 for DDD; the highest levels of DDT-related substances found in Mexico and Belize which about an order of magnitude higher than in the USA and southern Canada, and more than two orders of magnitude higher than in samples from the Arctic region (Shen et al., 2005). A study from the Global Atmospheric Passive Sampling Network reported that DDE concentrations were below the limit of detection at most sites. DDE concentrations at a background site in the Canary Islands in 2005 were between 190 and 250 pg/m^3, and at a rural site in California, USA, were in the range of 210–460 pg/m^3, but higher levels (3600–6600 pg/m^3) were detected at two agricultural sites near Delhi, India (Pozo et al., 2009). In Mexico, the highest concentration of ΣDDT was found in Chiapas (2360 pg/m^3) and the lowest in Monterrey (15 pg/m^3). In general terms, levels measured between 2005 and 2006 tended to be higher in the southern and central parts of Mexico (Wong et al., 2009a). In Limpopo, South Africa, in 2008, the mean ΣDDT concentration measured in indoor air was 3900 ng/m^3 (Van Dyk et al., 2010).

Between 1989 and 1991, ΣDDT concentrations were measured in air samples from urban and estuarine areas of eastern and southern Asia and Oceania; highest concentrations were measured in India (46–12 000 pg/m^3), followed by Thailand (35–2600 pg/m^3) and Viet Nam (1700–2400 pg/m^3) (Iwata et al., 1994).

(e) Food

DDT and its metabolites have been detected in many foods and in many countries. Generally, ΣDDT concentrations were higher in food containing more fat (see Table 1.4).

In Limpopo, South Africa, in 2008, mean ΣDDT concentrations were measured in vegetables (mean ΣDDT, 43 ng/g), chicken meat (mean ΣDDT, 700 ng/g), chicken fat (mean ΣDDT, 240 × 104 ng/g), and chicken liver (mean ΣDDT, 1600 ng/g) (Van Dyk et al., 2010). In Ethiopia between February and April 2008, ΣDDT mean concentrations in fish ranged from 0.89 to 172 ng/g wet weight (Deribe et al., 2013). In Ethiopia in 2010, mean ΣDDT concentrations in cows' milk samples from three study sites ranged from 269 to 477 ng/g milk fat (Gebremichael et al., 2013).

Dairy products in Jordan were analysed for DDT and its metabolites between 2001 and 2007, and only *p,p′*-DDE was detected. Mean *p,p′*-DDE concentrations ranged from 0.006 to 0.064 mg/kg fat (Salem et al., 2009). Edible fish from the Shadegan marshes in the south-western part of the Islamic Republic of Iran sampled in 2007 had a mean concentration of ΣDDT of 330 ng/g lipid weight, with levels ranging from 43 to 1590 ng/g lipid weight (Davodi et al., 2011).

The main source of human exposure to DDT in the Americas and Europe is dietary consumption of contaminated meat, fish, poultry, and dairy products. In the United States Total Diet Study for the years 1986–1991, mean dietary intakes of ΣDDT ranged from 0.009 to 0.0448 µg/kg bw per day across age and sex groups (Gunderson, 1995).

The Canadian Total Diet Study in 1998 reported that DDE was present in 25.8% of composite samples, with a mean level of 1.2 ng/g wet weight (ww) of prepared food; and reported values in dairy products of 0.71–3.48 ng/g ww, meat and meat products of 0.37–1.14 ng/g ww, and fish and fish products of 0.43–6.69 ng/g ww (Rawn et al., 2004). In Mexico, a ΣDDT concentration of 1.53 ng/g in cows' milk was reported in Chiapas in in 2011 (Gutiérrez et al., 2012), while a DDT concentration of 0.27 ng/g milk fat was reported in Hidalgo in 2010 (Gutiérrez et al., 2013). Also in Mexico, in Veracruz, a ΣDDT concentration of 539 ng/g lipid was reported in bovine meat (Pardío et al., 2012). On the east coast of Brazil, ΣDDT concentrations of 0.93 and 2.47 ng/g w/w were reported in blue shark and swordfish, respectively (de Azevedo e Silva et al., 2007).

The European Union report on pesticide residues in food indicated that only 368 out of 53 493 samples from 27 countries contained DDT or its metabolites, mostly in cows' milk and swine meat (EFSA, 2015).

In Asia, dietary exposure from food consumption, e.g. vegetables, fruits, and food of animal origin and animal products, was conducted to monitor dietary exposures and establish whether DDT concentrations had declined after DDT use was banned. In China, Yu et al. (2013) report dietary intake of DDTs (unspecified) for three time periods before (1970 and 1992) and after the ban (2005–2007) on DDT use on food crops. The range in estimated mean intakes across two cities and five age groups was 125–240 µg/kg per day in the 1970s, 21.6–50.2 µg/kg per day in 1992, and 2.69–4.95 µg/kg per day in 2005–2007. The decrease in estimated intakes between the 1970s and 2005/2007 was almost two orders of magnitude. In the 2007 Chinese Total Diet Study, *p,p′*-DDT was not detected in any foods, while the mean concentration of *p,p′*-DDE ranged from 0 to 13.3 ng/g across six food groups, with a maximum value of 53.4 ng/g in aquatic food products (Zhou et al., 2012). Marine fish were found to contain DDT at higher concentrations than freshwater fish in 2013 in China (Fang et al., 2015). Between 2008 and 2011, Yu et al. (2012) estimated the daily uptake of ΣDDTs from food, dust, and air to be 79.4 ng per day for children and 131.1 ng per day for adults, with > 95% of intake from food consumption. Chung et al. (2008) in 2005 reported the estimated daily

Table 1.4 Exposure to DDT and its metabolites in food

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Ethiopia Jimma, Asendabo, Serbo March–May 2010	Cows' milk	ΣDDT, 389 ng/g milk fat	ΣDDT, 269–477 ng/g milk fat		Gebremichael et al. (2013)
Mexico Hidalgo 2008- 2010	Cows' milk	*p,p′*-DDT, 2008: 0.22; 2010: 0.27 ng/g milk fat	NR		Gutiérrez et al. (2013)
Mexico Chiapas January to December 2011	Cows' milk	ΣDDT, 1.53 ng/g milk fat	NR		Gutiérrez et al. (2012)
India Haryana 1992–1993 and 1998–1999	Cows' milk	1992–1993: *p,p′*-DDT, 297.8; *p,p′*-DDE, 27.6; ΣDDT, 514 ng/mL 1998–1999: *p,p′*-DDT, 8; *p,p′*-DDE, 20.4; ΣDDT, 36.7 ng/mL	1992–1993: *p,p′*-DDT, 58.2–674.6; *p,p′*-DDE, 6.2–146.9; ΣDDT, 119.9–989.9 ng/mL 1998–1999: *p,p′*-DDT, < LOD–78; *p,p′*-DDE, < LOD–231.1; ΣDDT, 1.7–286.4 ng/mL	ΣDDT concentrations in cows' milk significantly declined (92.8%) from 1992–1993 to 1998–1999	Kaushik et al. (2011)
China Beijing and Shenyang 2005–2007	Cows' milk	Beijing: *p,p′*-DDT, 1.26 ± 1.83; *p,p′*-DDE, 0.804 ± 0.471 ng/g ww Shenyang: *p,p′*-DDT, 0.403 ± 0.264; *p,p′*-DDE, 0.575 ± 0.426 ng/g ww	NR		Tao et al. (2008)
China Beijing and Shenyang 2005–2007	Pork, chicken and crucian fish	*p,p′*-DDE: Beijing: pork: 1.19 ± 0.20; chicken: 0.54 ± 0.25; crucian fish: 2.98 ± 3.32 Shenyang: pork: 0.21 ± 0.1; chicken: 0.14 ± 0.04; crucian fish: 0.59 ± 0.20 ng/g	NR		Tao et al. (2008)

Table 1.4 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
South Africa Limpopo February 2008	Vegetables, chicken muscle, chicken fat; chicken liver	DDT: vegetables: 43; chicken muscle: 700; chicken fat: 240 000; chicken liver: 1600 ng/g	DDT: vegetables: 10–150; chicken muscle: 69–1400; chicken liver: 52–5600; chicken fat: 99–1 300 000 ng/g		Van Dyk et al. (2010)
Portugal October 2002-July 2003	Fish	*p,p′*-DDT: sardine: 30.1; mackerel: 109.9 *p,p′*-DDD: sardine: 3; mackerel: 51.9 ng/g ww	*p,p′*-DDT: sardine: 663.1; mackerel: 1540.2 *p,p′*-DDD: sardine: 22.3; mackerel: 852.2 ng/g ww (maximum)		Campos et al. (2005)
USA Aleutian Islands of Alaska 2004	Sockeye salmon	DDE, 6.9 ng/g w/w (median)	DDE, 0–56 ng/g w/w	Note that in this study the author stated that *p,p′*-DDE coeluted with PCB-85 under the gas chromatography conditions used for the analyses	Hardell et al. (2010a)
Brazil East Coast 2001	Fish	ΣDDT: blue shark: 0.93; swordfish: 2.47 ng/g w/w	ΣDDT: blue shark: 0.4–2.1; swordfish: 0.15–10.53 ng/g w/w		de Azevedo e Silva et al. (2007)
Mexico Veracruz Year NR	Bovine muscle	ΣDDT: A: 493.1; B: 539.8; C: 1121.7; D: 445.1 ng/g lipid	NR	Livestock originated from four (A–D) extensive breeding stock on commercial bovine producing farms located in the south-western agrarian zone of Veracruz. Between 28.6% and 66.7% of the samples were positive for DDT and/or its metabolites	Pardío et al. (2012)
China Hong Kong Special Administrative Region 2005	Food	ΣDDT, 0.145 µg/kg bw per day	NR	The mean and high EDIs among secondary school student consumers were 0.145 and 0.291 µg/kg bw per day Seafood (39%) and cereal and cereal products (20%) represented the major sources of dietary exposure to DDT and its metabolites Foodstuffs: cereal and cereal products, vegetables, fruits, meat, poultry, egg and their products, seafood, dairy products	Chung et al. (2008)
China Northern metropolis 2013	Vegetable and fish	NA	ΣDDT: vegetable: ND–10.4, fish: 0.77–25.0 ng/g fresh weight	EDI of ΣDDT from vegetable; fresh waterfish and marine fish were 1.13–10.4, 2–40.3 and 2.99–20.2 ng/kg bw per day, respectively	Fang et al. (2015)

Table 1.4 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Thailand 1989–1996	Food	DDT levels in 1989 and 1996: Meat and milk: 10– < 2; poultry and eggs: 15–5; fats and oils: 35–ND ng/g or ng/L	NR	In Thai total diet, highest DDT levels were found in meat and milk, poultry and eggs and fats and oils; these concentrations decreased in 1989–1996. The dietary daily intake of DDT showed a gradual decline in 1989–1996 from 0.042 to 0.005 µg/kg bw per day	Vongbuddhapitak et al. (2002)
Japan Fukuoka 1992–1993	Food	Fish and fish products: *p,p′*-DDE, 4.74; ΣDDT, 7.58 Meat and meat products: *p,p′*-DDE, 2.87; ΣDDT, 5.25 Eggs: *p,p′*-DDE, 1.28; ΣDDT, 1.28 Cheese: *p,p′*-DDE, 2.24; ΣDDT, 2.28 µg/kg	Fish and fish products: *p,p′*-DDE, < LOD–24.8; ΣDDT, < LOD–40.64 Meat and meat products: *p,p′*-DDE, 1.04–6.54; ΣDDT, 1.04–15.06 µg/kg	*p,p′*-DDE was widely detected in the foods analysed, and levels were high in foods high in fat. Fish, fish products, meat, eggs, milk and milk products were analysed as the major sources of ΣDDT. The EDI in Japan from food was 1.42 µg/day per person	Nakagawa et al. (1995)
Brazil Ponta Grossa lake 2008	Fresh-water fish	ΣDDT: liver: 105; muscle: 29.9 ng/g dw	ΣDDT: liver: 2–641. muscle: ND–210 ng/g dw		Bussolaro et al. (2012)
Jordan 2001–2007	Dairy products	*p,p′*-DDE: milk: 27; butter: 9; cheese: 64; labneh: 6; yoghurt: 32 µg/kg fat	Milk: 5–70, butter: 8–10; cheese: 5–430; labneh: 5–6; yoghurt: 6–60 µg/kg fat	*o,p′*-DDD, *p,p′*-DDD, *o,p′*-DDE, *o,p′*-DDT, *p,p′*-DDT were all ND	Salem et al. (2009)
Islamic Republic of Iran Shadegan Marshes October & November 2007	Fish	ΣDDT, 330 ± 335 ng/g lipid weight	ΣDDT, 43–1590 ng/g lipid weight	Concentrations of DDE > DDD > DDT	Davodi et al. (2011)
Islamic Republic of Iran Fereydoon-kenar, Wildlife Refuge Winter 2008	Liver and muscle tissue of birds	Liver: DDE, 19; DDT, 9.3 Muscle: DDE, 396.8; DDT, 2 ng/g ww	Liver: DDE, < LOQ–89; DDT, < LOQ-28 Muscle: DDE, 0.5–2199; DDT, < LOQ–7.5 ng/g ww	Values are the means of results from three different birds: pintail, common teal and maillard DDE = sum of *o,p′*-DDE and *p-p′*-DDE; DDT = sum of *o,p′*-DDT and *p-p′*-DDT	Rajaei et al. (2010)
Canada Yukon 1998	Food	*p,p′*-DDE, 1.2 ng/g ww	*p,p′*-DDE: dairy: 0.71–3.48. meat: 0.37–1.14; fish: 0.43–6.69 ng/g ww	Canadian total diet study; 25.8% of the food samples were positive for *p,p′*-DDE compared with 28.9% in 1992–1996	Rawn et al. (2004)

Table 1.4 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Ethiopia Lake Ziway, Rift Valley February–April 2008	Fish	ΣDDT, 18.02 ng g ww	ΣDDT, 0.89–171.96 ng/g ww	Mean reported for four different fish species. Levels reported for *p,p′*-DDT, *p,p′*-DDE and *p,p′*-DDD	Deribe et al. (2013)
USA 1986–1991	Food	NA	ΣDDT, 0.009–0.0448; *p,p′*-DDT, 0.0004–0.0011; *p,p′*-DDE, 0.0082–0.0441 µg/kg bw per day	Total diet study estimated across eight age groups	Gunderson (1995)
China Beijing, Shenyang 1970s, 1992, 2005–2007	Food	NA	1970s: 125–240; 1992: 21.6–50.2 2005–2007: 2.69–5.88 µg/kg per day	Temporal trend dietary intake	Yu et al. (2013)
China Shanghai 2008–2011	Food	ΣDDT (range of median): fish: 1.86–126.6; shellfish: 0.59–8.34; livestock: 0.2–0.5; poultry: 0.35–0.38 ng/g ww (median)	ΣDDT: fish: 0.51–340.1; shellfish: 0.1–13.2; livestock: 0.2–0.98; poultry: 0.06–0.93 ng/g ww	Estimated total daily uptake of ΣDDT from food, dust, and air was 79.4 ng/day for children and 131.1 ng/day for adults; > 95% from food	Yu et al. (2012)
China 2007	Food	*p,p′*-DDE: aquatic foods and aquatic food products, 13.3; meat and meat products, 3.65; eggs and egg products, 0.96; milk and milk products, 0.46; vegetables and vegetable products, 0.25 ng/g	*p,p′*-DDE: aquatic foods and aquatic food products, 1.21–53.4; meat and meat products, 0–13.3; eggs and egg products, 0–6.59; milk and milk products, 0–1.36; vegetables and vegetable products, 0–2.12 ng/g	Chinese total diet study; estimated average dietary exposure to ΣDDT was 0.016 µg/kg bw per day; authors stated that this represented a significant decrease compared with the past *p,p′*-DDE was the only DDT-related compound detected in food samples; aquatic foods and aquatic food products, meat and meat products and eggs and egg products were the major dietary sources of *p,p′*-DDE	Zhou et al. (2012)

ΣDDT, total DDT corresponding to the sum of *o,p′*-DDE, *p,p′*-DDE, *o,p′*-DDD, *p,p′*-DDD, *o,p′*-DDT, and *p,p′*-DDT; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; dw, dry weight; EDI, estimated daily intake; LOD, limit of detection; LOQ, limit of quantification; NA, not applicable; ND, not detected; NR, not reported; PTDI, the provisional tolerable daily intake; w/w, weight per weight; ww, wet weight

[a] Arithmetic mean, unless otherwise stated

intake of DDT and its metabolites, finding that the mean and maximum estimated daily intakes among secondary school students, 0.145 and 0.291 µg/kg bw per day, fell below the provisional tolerable daily intake of 10 µg/kg bw per day established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (Food and Agriculture Organization of the United Nations/World Health Organization). However, the reported average estimated daily intakes were one to three orders of magnitude higher than those reported in Australia (FSANZ, 2003), New Zealand (NZFSA, 2005), Japan (Maitani, 2004), and Thailand (Vongbuddhapitak et al., 2002).

1.4.3 Exposure in the general population

DDT and/or its metabolites, mainly *p,p′*-DDE, have been measured in serum in the general population (in adults and children) in all parts of the world. Infants can also be exposed to these compounds, which have been detected in cord blood, placenta, and breast milk. ΣDDT has been shown to accumulate in adipose tissue and has also been detected in hair. Detailed biological measurements of DDT and its metabolites in the general population are given in Table 1.5.

Globally there are strong downward trends in population levels of plasma or serum *p,p′*-DDT and *p,p′*-DDE due to the ban of most uses of DDT in many countries (Fig. 1.3).

In populations living in homes where there has been indoor residual spraying for malaria control, the corresponding decrease is less and current levels are about 60 times higher than in comparable areas not subject to malaria-vector control (Ritter et al., 2011).

In breast milk, total DDT concentrations of up to 380 000 ng/g lipid have been reported in India in 1982 and in Zimbabwe in 1993–1995 (Ramachandran et al., 1984; Chikuni et al., 1997). ΣDDT concentrations in breast milk have tended to decrease globally, but remain high in some countries (Table 1.5).

The United Nations Environment Programme (UNEP) and WHO (UNEP/WHO, 2013) have presented the results of a global survey on concentrations of persistent organic pollutants in human milk. Large global differences with respect to contamination by DDT and its metabolites during 2000–2012 were apparent; the five countries with higher levels of total DDT in ascending order were Haiti, India, Solomon Islands, Tajikistan, and Ethiopia, which reported levels well above 20 000 ng/g lipid. Lower levels were reported for the Nordic countries.

1.4.4 Exposure assessment in epidemiological studies on DDT

The key epidemiological studies evaluated in this monograph can be categorized as studies of occupational exposure in farmers and commercial applicators, and studies involving the general population using questionnaire- or biological-based exposure assessments to DDT. The present section provides an assessment of the strengths and weaknesses of the exposure assessment and assignment methods used in these studies. The absence of similar detailed discussions for other epidemiological investigations should not be construed to suggest that these studies are inferior. In fact, in many ways these studies have improved on pesticide-exposure assessment when compared with earlier studies.

(a) Occupational exposure

In studies of occupational exposure to DDT among farmers and commercial applicators, exposure assessment has relied on either retrospective reporting of DDT use and similar reporting of factors potentially affecting exposure, or on job-title and task review to determine the circumstances of DDT exposure (Cocco et al., 2005; Alavanja et al., 2014). In both types of study, semiquantitative exposure scores were derived using exposure algorithms.

Table 1.5 Biological measurements of DDT and its metabolites in the general population

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
USA 1994–1995	Serum	DDE, 0.637 ± 0.125 µg/g lipid	NR	Pretreatment concentrations in NHL patients (lipid-adjusted)	Baris et al. (2000)
USA North Carolina 1978–1982 and folllow up in 2003–2004	Serum	DDE: 1978–1982: 8.5; follow-up 2003–2004: 1.2 µg/L (median)	DDE: 1978–1982: 1.3–41; follow-up: 0.01–11 µg/L	Baseline: 1978–1982 (pregnant women) and follow-up organochlorine levels were compared	Vo et al. (2008)
USA Akwesasne Mohawk Nation 1996–2000	Serum	*p,p′*-DDE, 0.45 ± 0.35 ppb	NR	Male adolescents (age, 10 to < 17 years)	Schell et al. (2014)
Mexico Mexico City 1994–1996	Serum	DDE, 505.46; *p,p′*-DDT, 84.53 ng/g lipid	DDE, 0.004–4361.7; *p,p′*-DDT, 0.012–1262.7 ng/g lipid	Control women participating in a breast cancer case–control study	López-Carrillo et al. (1997)
Mexico Morelos 1999	Serum	*p,p′*-DDE, 21.8 ± 2.58; *p,p′*-DDT, 2.9 ± 2.84 ng/mL (geometric mean)	NR	Women of childbearing age	López-Carrillo et al. (2001)
Mexico Mexico City 1990–1995	Serum	*p,p′*-DDE, 2,51; *p,p′*-DDT, 0.23 µg/g lipid	*p,p′*-DDE, 0.97–6.05. *p,p′*-DDT, 0.04–0.33 µg/g lipid	Control women participating in a breast cancer case–control study	Romieu et al. (2000)
Mexico Chiapas 2002–2003	Serum	*p,p′*-DDE, 2.7; *p,p′*-DDT, 0.3 µg/g lipid (median)	NR	Levels in serum from mothers at delivery; this population was exposed for almost 40 years: DDT was used for agriculture until 1991 and for malaria control until 1998	Cupul-Uicab et al. (2010)
Mexico Sonora 2009	Serum	*p,p′*-DDE, 1.24; *p,p′*-DDT, 0.38 µg/L	*p,p′*-DDE, 0.25–10.3; *p,p′*-DDT, 0.25–1 µg/L	Children aged 6–12 years *p,p′*-DDE in serum was found in 100% of the children whereas *p,p′*-DDT was found in 25%	Meza-Montenegro et al. (2013)
Brazil Rio de Janeiro 2003–2004	Serum	Men: *p,p′*-DDE, 8.32; *o,p′*-DDT, 0.30; *p,p′*-DDT, 3.09; *p,p′*-DDD, 0.61 Women: *p,p′*-DDE, 9.64; *o,p′*-DDT, 0.42; *p,p′*-DDT, 3.2; *p,p′*-DDD, 0.66 ng/mL (median)	P25–P75 men: *p,p′*-DDE, 2.86–21.9; *o,p′*-DDT: < LOD–0.89; *p,p′*-DDT, 0.94–6.96; *p,p′*-DDD, 0.19–1.34 P25–P75 women: *p,p′*-DDE, 3.45–28.9; *o,p′*-DDT, < LOD–1.10; *p,p′*-DDT, 1.03–7.59; *p,p′*-DDD, 0.21–1.41 ng/mL	Levels in men and women in a heavily contaminated rural area in Brazil	Freire et al. (2013)

Table 1.5 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Saudi Arabia Riyadh NR	Serum	ΣDDT: diabetics: 18.3 ± 1.4; non-diabetics: 11.8 ± 1.3 ng/mL	NR	The study compared serum concentrations of DDT and its metabolites in diabetic and non-diabetic individuals	Al-Othman et al. (2015)
Tunisia Bizerte June 2011 to May 2012	Serum	*p,p′*-DDE, 168.8 ± 158; *p,p′*-DDT, 24.3 ± 18.8; ΣDDT, 213.1 ± 160 ng/g lipid	Maximum: *p,p′*-DDE, 950.4; *p,p′*-DDT, 71.5; ΣDDT, 994.6 ng/g lipid		Ben-Hassine et al. (2014)
Egypt Port Said region July 1999 to July 2000	Serum	DDE, 31 ng/g	DDE, 12–44 ng/g		Ahmed et al. (2002)
Benin Republique Borgou region 2011	Serum	*p,p′*-DDT, 32; *p,p′*-DDE, 607.2 ng/g total lipid (geometric mean)	*p,p*-DDT, 22.8–45; *p,p′*-DDE, 453–813.9 ng/g total lipid		Azandjeme et al. (2014)
South Africa KwaZulu November 1986 to November 1987	Serum	Range of means: *p,p′*-DDE, 103.4–127.1; *p,p′*-DDT, 31.4–47.5; ΣDDTs 140.9–174.6 µg/L	NR		Bouwman et al. (1994)
South Africa KwaZulu-Natal Province 2008	Serum	*o,p′*-DDE, 9; *p,p′*-DDE, 3840; *o,p′*-DDD, 8; *p,p′*-DDD, 26; *o,p′*-DDT; 168; *p,p′*-DDT, 2194 ng/g lipid (geometric mean)	o,*p′*-DDE, 7–10; *p,p′*-DDE, 3008–4902; *o,p′*-DDD, 6–9; *p,p′*-DDD, 20–32; *o,p′*-DDT, 127–221; *p,p′*-DDT, 1706–2823. ng/g lipid	Data reported for women living in malaria-endemic areas who were admitted for delivery at the local hospital	Channa et al. (2012)
South Africa Limpopo 2008	Serum	*p,p′*-DDE, 5900; *p,p′*-DDD, 1500; *o,p′*-DDD, 1500; ΣDDT, 7300 ng/g lipid	*p,p′*-DDE, 1200–23 000; *p,p′*-DDD; 800–3800; *o,p′*-DDD, 300–2700; ΣDDT, 1300–23 000 ng/g lipid	Sampling was done in February 2008 during the summer season 2 months after the IRS process was completed	Van Dyk et al. (2010)
Belgium Flanders 2003–2004	Serum	*p,p′*-DDE: boys, 104; girls, 84 ng/g lipid (median)	*p,p′*-DDE 10th-90th percentile: boys: 47–404; girls: 39–247 ng/g lipid	Serum measurements in adolescents (aged 14–15 years)	Den Hond et al. (2011)
France Ille-et-Vilaine Côte d'Or 2005–2007	Serum	*p,p′*-DDE, 84.8 ng/g lipid (median)	*p,p′*-DDE, 51.9–131.3 ng/g lipid	Women CECILE Study	Bachelet et al. (2011)
France 2006–2007	Serum	*p,p′*-DDE, 88.7; *p,p′*-DDT, 3.6 ng/g lipid (geometric mean)	*p,p′*-DDE, 72.5–108.6; *p,p′*-DDT, 2.6–5.1 ng/g lipid	French National Nutrition and Health Study	Saoudi et al. (2014)

Table 1.5 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Spain Barcelona 2002–2006	Serum	2002: *p,p′*-DDE, 491.2; *p,p′*-DDT, 37.2; 2006: *p,p′*-DDE, 233.6; *p,p′*-DDT, 20.3 ng/g lipid (geometric mean)	2002: *p,p′*-DDE, 421.3–572.7; *p,p′*-DDT, 31.9–43.5 2006: *p,p′*-DDE, 206.8–263.8; *p,p′*-DDT, 17.9–22.9 ng/g lipid		Porta et al. (2012)
Spain Ribera d'Ebre and Menorca 1997–1999 and 2001–2012	Serum	*p,p′*-DDE: Ribera d'Ebre: cord: 0.86; 4 years: 0.75; 14 years: 0.12 Menorca: cord, 1.03; 4 years, 0.81; 14 years, 0.33 ng/mL (median)	*p,p′*-DDE (25th–75th percentile): Ribera d'Ebre: cord, 0.50–1.68; 4 years, 0.38–1.32; 14 years, 0.09–0.19 Menorca: cord: 0.57–1.94; 4 years, 0.44–1.77; 14 years, 0.23–0.58 ng/mL	Follow-up of organochlorine compounds serum concentration in children from birth until adolescence. Three measurements: at birth (cord), age 4 years, and age 14 years	Gascon et al. (2015)
Spain Asturias, Navarra, Guipúzcoa, Murcia and Granada) 1992–1996	Serum	DDE, 822.1 ng/g lipid (geometric mean)	DDE, 779.2–867.2 ng/g lipid	Participants in the EPIC cohort; Murcia and Granada showed higher levels with geometric mean for *p,p*-DDE of 1287.2 and 957.4 ng/g lipid, respectively	Jakszyn et al. (2009)
Japan Akita prefecture, a rural area in northern Japan 1999	Serum	*p,p′*-DDE + *p,p′*-DDT, 6.3 ng/mL	*p,p′*-DDE + *p,p′*-DDT, 0.9–31 ng/mL		Hanaoka et al., (2002)
the Russian Federation Chapaevsk 2003–2005	Serum	*p,p′*-DDE median, 287 ng/g lipid	*p,p′*-DDE 10th-90th percentile, 122–866 ng/g lipid	Serum measurements in Russian boys aged 8 and 9 years; association with growth was evaluated	Burns et al. (2012)
Thailand a highland village at the north of Chiang Mai 2003–2004	Serum	*p,p′*-DDE, 4013, *p,p′*-DDD, 390.5; *p,p′*-DDT, 628.7 ng/g lipid (geometric mean)	*p,p′*-DDE, 1325–12 683; *p,p′*-DDD, 212–1162; *p,p′*-DDT, 225–3085 ng/g lipid	Measurements in adult men	Asawasinsopon et al. (2006b)

Table 1.5 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Greenland, Sweden, Poland, Ukraine Warsaw, Kharkiv June 2002 to May 2004	Serum	*p,p′*-DDE: Sweden: 820; Ukraine: 620; Poland: 360. Greenland: 300 ng/g lipid (median)	*p,p′*-DDE: Sweden: 92–14 000; Ukraine: 230–1800; Poland: 100–1100. Greenland: 26–1700 ng/g lipid	Part of the INUENDO Collaborative Project; measurements in women	Axmon et al. (2006)
Republic of Korea Uljin county 2006	Serum	*p,p′*-DDE, 376 ± 290.7; *p,p′*-DDD, 5.7 ± 3.7; *p,p′*-DDT, 23.8 ± 12.1; *o,p′*-DDT, 3.2 ± 2.8 ng/g lipid	NA		Son et al. (2010)
India Ahmedabad urban area Year NR	Serum	*p,p′*-DDE, 20.74; *o,p′*-DDT, 0.99; *p,p′*-DDD, 1.6; *p,p′*-DDT, 7.65; ΣDDT, 29.63 ng/mL (median)	p,*p′*-DDE, 10.43–38.33; *o,p′*-DDT, 0.42–2.41; *p,p′*-DDD, 0.77–4.43; *p,p′*-DDT, 3.66–24.06; ΣDDT, 21.17–54.47 ng/mL	Measurements in adult men	Bhatnagar et al. (2004)
India Delhi 1982	Serum	ΣDDT, 390 ng/mL (geometric mean)	ΣDDT, ND–4610 ng/mL		Ramachandran et al. (1984)
Thailand nationwide 2011	Serum	Males: *p,p′*-DDE, 1539; *p,p′*-DDT, 135 Females: *p,p′*-DDE, 1547; *p,p′*-DDT, 133 ng/g lipid (geometric mean)	Males: *p,p′*-DDE, 1242–1837; p,*p′*-DDT, 116–164 Females: *p,p′*-DDE, 1293–1806; *p,p′*-DDT, 112–147 ng/g lipid		Teeyapant et al. (2014)
Egypt Cairo and Nile Delta NR	Serum	Rural women: DDE, 17.3; ΣDDT, 18.3 Urban women: DDE, 9.7; ΣDDT, 9.9 ppb (geometric mean)	Rural women: DDE, 0–142.1; ΣDDT, 0–144.8 Urban women: DDE, 0.7–59.8; ΣDDT, 0.7–61.8 ppb	Interestingly, women with low DDE serum levels had breast-fed their children for an average of 18 months; women with no lactation history had much higher organochlorine levels than women who breast-fed	Soliman et al. (2003)
Republic of Korea Seoul, Pyuncheon, Anson and Jeju 2011	Serum	*p,p′*-DDE, 57.4; *p,p′*-DDT, 5.2; ΣDDT, 64.4 ng/g lipid (median)	25th–75th percentile: *p,p′*-DDE, 38.8–78.9; *p,p′*-DDT, 2.94–8.99; ΣDDT, 42.2–92.4 ng/g lipid	Pregnant women (n = 138) from five university hospitals; blood samples were collected on the day before delivery	Kim et al. (2013a)
New Zealand Nationwide 1996–1997	Serum	*p,p′*-DDE: 15–24 years: 646; 25–34 years: 771; 35–49 years: 1060; 50–64 years: 1310; 65+: 1780 ng/g lipid	NR	General trend of increasing concentration with age, and no consistent differences between the sexes, or between people of Maori and non-Maori ethnicity	Bates et al. (2004)

Table 1.5 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Peru Trujillo 2004–2005	Serum, cord blood	*p,p′*-DDE: 1st trimester: 581; 2nd trimester: 486; 3rd trimester: 418; cord: 383 *p,p′*-DDT: 1st trimester: 39; 2nd trimester: 32; 3rd trimester: 29; cord: 20 ng/g lipid (geometric mean)	*p,p′*-DDE: 1st trimester: 373–906; 2nd trimester: 310–762; 3rd trimester: 255–686; cord: 225–652 *p,p′*-DDT: 1st trimester: 26–59; 2nd trimester: 20–51; 3rd trimester: 18–45; cord: 12–33 ng/g lipid	Samples collected once per pregnancy trimester and at delivery in the cord blood; the detection of DDT and DDE in cord serum suggested substantial transfer of these compounds from mother to fetus	Adetona et al. (2013)
Saudi Arabia Al-Kahrj 2005–2006	Serum, cord blood, placental tissue	Cord: *p,p′*-DDE, 0.197; *p,p′*-DDD, 0.005; *p,p′*-DDT, 0.005 µg/L Maternal serum: *p,p′*-DDE, 0.551; *p,p′*-DDD, 0.002; *p,p′*-DDT, 0.008 µg/L Placenta: *p,p′*-DDE, 10.17; *p,p′*-DDD, 7.042; *p,p′*-DDT, 29.62 µg/kg dw	Cord: *p,p′*-DDE, 0–19.95; *p,p′*-DDD, 0–5.08; *p,p′*-DDT, 0–2.97 µg/L Maternal serum: *p,p′*-DDE, 0–29; *p,p′*-DDD, 0–0.90; *p,p′*-DDT, 0–3.4 µg/L Placenta: *p,p′*-DDE, 0–314, *p,p′*-DDD, 0–223; *p,p′*-DDT, 0–2038 µg/kg dw	Detection of DDT, DDD, and DDE in cord serum and placenta suggested substantial transfer of these compounds from mother to fetus	Al-Saleh et al. (2012)
Thailand Chiang Mai Province 2003–2004	Maternal and cord sera	Maternal/cord serum: *p,p′*-DDE, 1191/742; *p,p′*-DDD, 104/89.1; *p,p′*-DDT, 123/77.1 ng/g lipid (geometric mean)	Maternal/cord serum: *p,p′*-DDE, 58.3–7981/81.3–4265, *p,p′*-DDD, 16.8–527/24.1–309, *p,p′*-DDT, 18.0–1067/21.5–660 ng/g lipid	Comparison of concentrations of DDT and metabolites in maternal and cord serum	Asawasinsopon et al. (2006a)
Thailand Chiang Mai, Chiang Dao district 2003–2004	Maternal and cord sera	Maternal/cord sera: *p,p′*-DDE, 1793/1255; *p,p′*-DDT, 145/102; *p,p′*-DDD, 152/145 ng/g lipid (geometric mean)	Maternal/cord sera: *p,p′*-DDE, 208–27 169/146–23 185; *p,p′*-DDT, 11.6–2003/17–2363; *p,p′*-DDD, 11.1–2984/28.6–1800 ng/g lipid	Pregnant women from an agricultural and former malaria-endemic area; cord serum levels of *p,p′*-DDE, *p,p′*-DDT, and *p,p′*-DDD were approximately 70%, 62%, and 79% of maternal serum levels, respectively	Sapbamrer et al. (2008)
China Shanxi province 2005–2007	Placenta	Neural tube defects/controls: Σ*o,p′*-DDTs, 4.3/2.7; Σ*p,p′*-DDTs, 55/59; ΣDDTs, 60/61 ng/g lipid (median)	Σ*o,p′*-DDTs: 2–7.6; Σ *p,p′*-DDTs, 31–85; ΣDDTs, 35–98 ng/g lipid	Placental concentrations given for newborn infants with neural tube defects compared with healthy (control) newborn infants	Ren et al. (2011)

Table 1.5 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Italy Brescia, an urban polluted area 2006	Serum placenta adipose tissue	*p,p′*-DDE: serum: 112.3; placenta: 62.5; adipose tissue: 202 ng/g lipid (median)	*p,p′*-DDE, 5th–95th percentile: serum: 42–377; placenta: 24–226; adipose tissue: 76–730 ng/g lipid		Bergonzi et al. (2009)
Nicaragua Rio Atoya basin NR	plasma and cord blood	*p,p′*-DDE: maternal plasma: 7.12; cord blood: 6.39 ng/g	*p,p′*-DDE: maternal plasma: 0–35.23; cord blood: 0–9.35 ng/g	Women at delivery	Dorea et al. (2001)
USA New York 1991–1998	Plasma	DDE, 5.83 ng/mL	DDE, 0.02–23.67 ng/mL	Women with cystic disease (not lipid -adjusted)	Blackwood et al. (1998)
Mexico Quintana Roo State 2007	Plasma	*p,p′*-DDT, 2206; *p,p′*-DDE, 7828 ng/g lipid (geometric mean)	*p,p′*-DDT, 463.5–9046.3; *p,p′*-DDE, 490.8–57 712.4 ng/g lipid	Children aged 6–12 years living in three communities	Trejo-Acevedo et al. (2013)
Mexico Chiapas 2012	Plasma	*p,p′*-DDE, 24.66; *p,p′*-DDT, 14.71 ng/mL (geometric mean)	*p,p′*-DDE, 1.1–222.6; *p,p′*-DDT, 6.37–29.66 ng/mL	Middle-aged men and women; a high proportion of participants were engaged in agricultural work	Ruiz-Suárez et al. (2014)
South Africa Limpopo Province 2010–2011	Plasma	*p,p′*-DDT: unsprayed villages:0.31; non-DDT IRS homes: 1.4; DDT-IRS homes: 2.6 µg/L *p,p′*-DDE: unsprayed villages: 1.7; non-DDT IRS homes: 7.95; DDT-IRS homes: 8.5 µg/L (median)	*p,p′*-DDT: unsprayed villages: 0.11–0.86; non-DDT IRS homes: 0.5–3; DDT-IRS homes: 1.1–6.6 µg/L *p,p′*-DDE: unsprayed villages: 0.7–5.5; non-DDT IRS homes: 3.4–12; DDT-IRS homes: 4.65–18 µg/L	Median and ranges reported for DDT and DDE in three different exposure settings	Whitworth et al. (2014)
South Africa 7 sites NR	Plasma	Range of means for sites: *p,p′*-DDE, 41.1–5178; *p,p′*-DDT, 1.9–1797 ng/g lipid (geometric mean)	*p,p′*-DDE,15–14 482; *p,p′*-DDT, 0.9–5278 ng/g lipid	Measurements in maternal plasma at delivery from seven different communities: rural, urban, industrial, fishing, mining, coastal endemic malaria, inland endemic malaria; highest levels of DDTs were measured in the coastal malaria site (Indian Ocean) with geometric means of 5178 ng/g lipid and 1797 ng/g lipid for *p,p′*-DDE and *p,p′*-DDT, and 1966 ng/g lipid and 726 ng/g lipid for *p,p′*-DDE and *p,p′*-DDT in inland endemic malaria site	Röllin et al. (2009)

Table 1.5 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
South Africa Limpopo Province Year NR	Plasma	*p,p′*-DDT, 109 200 ± 106 600; *p,p′*-DDE, 246 200 ± 218 500 ng/g lipid	NR	Measurements in young men from a malaria area	de Jager et al. (2012)
Norway Vestvagoy in north-western coast of Norway 1997	Plasma	*p,p′*-DDE, 0.936 ng/g lipid (median)	*p,p′*-DDE, 0.15–5.075 ng/g lipid	Women	Furberg et al. (2002)
Central America Year NR	Serum	*p,p′*-DDE + *p,p′*-DDT, 3.25 ng/mL (geometric mean)	*p,p′*-DDE + *p,p′*-DDT, 0.3–64 ng/mL	Measurements in children from several countries in Central America, except Mexico; by far the highest levels were found in children living in Mexico, with levels of *p,p′*-DDE+ *p,p′*-DDT up to 390 ng/mL and a geometric mean of 50 ng/mL	Pérez-Maldonado et al. (2010)
Brazil Sao Paolo State 2007–2008	Blood	*p,p′*-DDE, 280; *p,p′*-DDT, 18 ng/g lipid (median)	*p,p′*-DDE, 126–645 ng/g lipid	Measurements in women at delivery	Rudge et al. (2012)
India Dibrugarb and Nagaon districts, Assam state. 2009–2010	Blood	ΣDDT: Dibrugarb: 417; Nagaon: 743 ng/mL (median)	ΣDDT: Dibrugarb: 4–4718; Nagaon: 7–9906 ng/mL		Mishra et al. (2011)
Sweden 1993–2007	Blood; adipose tissue	DDE: blood: 211; adipose tissue: 555 ng/g lipid (median)	DDE: blood: 16–3725; adipose tissue: 41–3900 ng/g lipid	Measurements in control individuals participating in different cancer studies; during 1993–2007, an annual decrease of 13.5% was found for DDE concentrations in both tissues	Hardell et al. (2010b)
Jordan Jordan University Hospital 1996	Adipose tissue	ΣDDT: 0–14 years: 2.6; 15–29 years: 3.9; 30–44 years: 3.8; 45–59 years: 4.6; 60 years and over: 4.6 ppm	ΣDDT: 0–14 years: 0.36–9.94; 15–29 years: 0.52–16.36; 30–44 years: 0.28–11.04; 45–59 years: 0.11–12.88; 60 years and over: 0.80–7.68 ppm	Means and ranges also reported for individual metabolites (*o,p′*-DDT, *p,p′*-DDT; *o,p′*-DDE, *p,p′*-DDE; *o,p′*-DDD, *p,p′*-DDD) in each age category and by sex Men stored higher amounts of ΣDDT than women; highest levels of ΣDDT were in men (4.3 ppm) and women (5 ppm) aged ≥ 60 years	Alawi et al. (1999)
India Delhi 1982	Adipose tissue	ΣDDT, 15 430 ng/g (geometric mean)	320–380 000 ng/g		Ramachandran et al. (1984)

Table 1.5 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Denmark NR 1993 –1997	Adipose tissue	DDE, 505 ng/g lipid (median)	DDE, 17–6693 ng/g lipid	Measurements in postmenopausal women. Adipose tissue concentrations of DDE were consistently positively associated with age and the consumption of fish with high fat content. Total lifetime duration of lactation had an inverse relationship	Vaclavik et al. (2006)
Mexico Veracruz 2009	Adipose tissue	Control/pregnant women: *p,p′*-DDE, 695 /421; *p,p′*-DDT, 67/42; ΣDDT, 873/474 ng/g lipid (median)	Control/pregnant women: *p,p′*-DDE, 12–6007/34–5220; *p,p′*-DDT, 5–675/6–1695 ng/g lipid	Measurements in control and pregnant women	Herrero-Mercado et al. (2010)
Poland Poznan NR	Adipose tissue	ΣDDT, 773 ng/g lipid (median)	ΣDDT, 258–3570 ng/g lipid	Values are concentrations in control women from a breast cancer study	Ociepa-Zawal et al. (2010)
USA New York 1991–1998	Breast cyst fluid/plasma	DDE: breast cyst fluid: 1.98; plasma: 4.83 ng/mL	DDE: breast cyst fluid: 0.111–2.35; plasma: 0.02–9.52 ng/mL	Women with cystic disease; highest levels found in one woman: 25.27 and 23.67 ng/mL DDE in breast cyst fluid and plasma, respectively	Blackwood et al. (1998)
Colombia Bogota NR	Breast milk	*p,p′*-DDE, 203 ng/g lipid (milk fat)	*p,p′*-DDE, 17–14 948 ng/g lipid (milk fat)	Measurements in breastfeeding mothers	Rojas-Squella et al. (2013)
Tunisia Bizerte 2010	Breast milk	*p,p′*-DDE, 371.2; *p,p′*-DDD, 92; *p,p′*-DDT, 271.2; ΣDDT, 805.9 ng/g lipid (median)	*p,p′*-DDE, 73.3–3470.8; *p,p′*-DDD, 10.8–1701.6; *p,p′*-DDT, 27.8–2147.3; ΣDDT, 125.8–4574.8 ng/g lipid		Ben-Hassine et al. (2012)
Tunisia 12 different regions 2003–2005	Breast milk	*p,p′*-DDE, 676; *p,p′*-DDD, 92; *p,p′* DDT, 256; ΣDDT, 1931 ng/g lipid	*p,p′*-DDE, 3–6800; *p,p′*-DDD, 2–2461; *p,p′*-DDT, 1–2499; ΣDDT, 8–7060 ng/g lipid		Ennaceur et al. (2008)
Islamic Republic of Iran Southern coast of the Caspian sea 2006	Breast milk	ΣDDT, 2554 ng/g lipid	ΣDDT, 70–18 370 ng/g lipid		Behrooz et al. (2009)
South Africa KwaZulu-Natal April–November 2002	Breast milk	ΣDDT, 83.22 ng/mL	ΣDDT, 3.52–1537.73 ng/mL	Mean value calculated based on mean values reported from six subgroups; *p,p′*-DDE, *p,p′*-DDD and *p,p′*-DDT levels also reported	Bouwman et al. (2006)

Table 1.5 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
South Africa Thohoyando, a rural district in the Limpopo province April–November 2004	Breast milk	*p,p′*-DDE, 4580; *p,p′*-DDT, 1600; ΣDDT, 6320 ng/g lipid	*p,p′*-DDE, 98–13 600; *p,p′*-DDT, 20–6000; ΣDDT, 162–20 200 ng/g lipid		Darnerud et al. (2011)
South Africa KwaZulu-Natal & Limpopo 2008	Breast milk	ΣDDT at three sites, 18 000, 11 000 & 9500 ng/g lipid (milk fat)	ΣDDT, 106–140 000 ng/g lipid	Measurements from women in three DDT-sprayed villages	Bouwman et al. (2012)
South Africa Thohoyando, Limpopo Province 2004	Breast milk	NR	*p,p′*-DDE, 1–14 508; *p,p′*-DDD, ND–5901; ΣDDT, ND–8504 ng/g lipid	Values reported for 10 sites in Thohoyando area	Okonkwo et al. (2008)
Ethiopia Jimma, Asendabo, Serbo March–May 2010	Breast milk	Mean range: *p,p′*-DDE, 2520 – 4760; *p,p′*-DDD, 320–390; *p,p′*-DDT, 3550–12 200; ΣDDT, 6420–17 170 ng/g lipid	NR	Values reported for each of the three areas in which annual spraying with DDT for malaria control was common	Gebremichael et al. (2013)
Zimbabwe Seven sites in Kariba area February 1993 to April 1995	Breast milk	Mean range: *p,p′*-DDE, 1176–13 606; *p,p′*-DDT, 250–9080; ΣDDT, 1607–25 259 ng/g lipid	*p,p′*-DDE: 77–182 523; *p,p′*-DDT, 0–53 000; ΣDDT, 85–380 580 ng/g lipid	Vector-control programmes, agricultural activities, and possibly dietary habits (since DDT is also found in the urban population) were the main contributing factors towards high levels of DDT and DDT metabolites in breast milk	Chikuni et al. (1997)
Czech Republic Nationwide 2005–2009	Breast milk	*p,p′*-DDT, 7600; *p,p′*-DDE, 234 000 ng/g lipid (median)	NR	The Human Biomonitoring Project; preastfeeding primiparas *p,p′*-DDT and *p,p′*-DDE showed a downward trend, with median values decreasing respectively from 41 and 455 mg/kg milk fat in 1996, to 7.6 and 234 mg/kg milk fat in 2009	Cerná et al. (2012)
Cambodia Phnom Penh city (urban area), Meanchey (suburban area) 1999–2000	Breast milk	ΣDDT: urban area: 1100; suburban area: 860 ng/g lipid (median)	ΣDDT: urban area: 310–11 000, suburban area: 360–3800 ng/g lipid		Kunisue et al. (2004b)

Table 1.5 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
China Shanghai 2011–2012	Breast milk	*p,p′*-DDT, 6.4; *p,p′*-DDE, 207; ΣDDT, 221 ng/ g lipid (median)	*p,p′*-DDT, ND–160; *p,p′*-DDE, 42.6–1604; ΣDDT, 52–1643 ng/g lipid	ΣOCPs in this study were much lower than those in human breast milk samples collected in 2002 and 2007	Lu et al. (2015)
China Dalian and Shenyang 2002	Breast milk	Dalian: *p,p′*-DDE, 2000; *p,p′*-DDT, 130; ΣDDT, 2100 Shenyang: *p,p′*-DDE, 830; *p,p′*-DDT, 40; ΣDDT, 870 ng/g lipid	Dalian: *p,p′*-DDE, 710–5300; *p,p′*-DDT, 45–380; ΣDDT, 780–5400 Shenyang: *p,p′*-DDE, 110–3100; *p,p′*-DDT, 12–140; ΣDDT, 140–3200 ng/g lipid		Kunisue et al. (2004a)
Japan Osaka prefecture 1972–1998	Breast milk	1972: DDE, 1686; DDT, 538 1982: DDE, 2446; DDT, 171 1992: DDE, 510; DDT, 18.2 1998: DDE, 270; DDT, 17.8 ng/g lipid	1972: DDE, 640–2630; DDT, 130–1380 1982: DDE, 580–8967; DDT, 82–415 1992: DDE, 102–1318; DDT, 4.5–444 1998: DDE, 77–997; DDT, 4.3–122.7 ng/g lipid	Compared with peak levels found in 1972 (100%), concentrations of DDT and DDE in breast milk fell to about 3% and 16% in 1998, respectively	Konishi et al. (2001)
China Hong Kong SAR and Guangzhou 1999, 2000	Breast milk	Guangzhou: *p,p′*-DDE, 2850; *p,p′*-DDT, 700 Hong Kong SAR: *p,p′*-DDE, 2480; *p,p′*-DDT, 390 ng/g lipid	NA	In Hong Kong SAR, mean *p,p′*-DDT and *p,p′*-DDE levels (390 and 2480 ng/g lipid) from the present study (1999) were considerably lower than those reported 14 years previously (1985) (i.e. 2170 and 11 670 ng/g lipid)	Wong et al. (2002)
Indonesia Jarkata, Purwakarta, Bogor and Lampung 2001–2003	Breast milk	Jakarta: *p,p′*-DDE, 140; *p,p′*-DDT, 10; ΣDDT, 160 Purwakarta: *p,p′*-DDE, 430; *p,p′*-DDT, 17; ΣDDT, 440 Bogor: *p,p′*-DDE, 780; *p,p′*-DDT, 16; ΣDDT, 820 Lampung: *p,p′*-DDE, 860; *p,p′*-DDT, 8; ΣDDT, 910 ng/g lipid (median)	*p,p′*-DDE, 14–12 000; *p,p′*-DDT, < 2–2400; ΣDDT, 18–15 000 ng/g lipid	Study sites were Jakarta (major dumping site of municipal wastes, urban), Purwakarta (agriculture, rural), Bogor (city, suburban) and Lampung (coastal area, rural)	Sudaryanto et al. (2006)

Table 1.5 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Japan Fukuoka prefecture 2001–2004	Breast milk	Primipara: *p,p′*-DDE, 330; *p,p′*-DDT, 13; ΣDDT, 340 Multipara: *p,p′*-DDE, 220; *p,p′*-DDT, 10; ΣDDT, 230 ng/g lipid	Primipara: *p,p′*-DDE, 32–1100; *p,p′*-DDT, < 0.6–44; ΣDDT, 34–1100 Multipara: *p,p′*-DDE, 29–1100; *p,p′*-DDT, < 0.6–30; ΣDDT, 33–1100 ng/g lipid		Kunisue et al. (2006)
Republic of Korea Seoul and Pyungchon (residential area), Ansan (industrial) and Jeju (rural) 2011	Breast milk	*p,p′*-DDE, 106; *p,p′*-DDT, 7.11; ΣDDT, 114 ng/g lipid	*p,p′*-DDE, < LOQ–375; *p,p′*-DDT, < LOQ–51.7; ΣDDT, < LOQ–392 ng/g lipid		Lee et al. (2013)
Thailand Chiang Mai Province 1998	Breast milk	ΣDDT, 14 960 ng/g lipid (geometric mean)	ΣDDT, 3370–46 880 ng/g lipid	Participants were Hmong hill-tribe mothers living in an area formerly using DDT for malaria-vector control and in agriculture Estimated ΣDDT median daily intake among primipara infants was 63.2 µg/kg bw per day	Stuetz et al. (2001)
Viet Nam Hanoi and Hochiminh 2000–2001	Breast milk	Hanoi: *p,p′*-DDE, 1900; *p,p′*-DDT, 170; ΣDDT, 2100 Hochiminh: *p,p′*-DDE, 2000; *p,p′*-DDT, 265; ΣDDT, 2300 ng/g lipid	Hanoi: *p,p′*-DDE, 420–6300; *p,p′*-DDT, 34–6900; ΣDDT, 480–6900 Hochiminh: *p,p′*-DDE, 340–16 000; *p,p′*-DDT, 100–1000; ΣDDT, 440–17 000 ng/g lipid		Minh et al. (2004)
Thailand Chiang Mai City District 2002	Breast milk	*p,p′*-DDT, 600; *p,p′*-DDE, 3900; ΣDDT, 4800 ng/g lipid (median)	*p,p′*-DDT, 0–5300; *p,p′*-DDE, 700–24 700; ΣDDT, 900–30 100 ng/g lipid		Zimmermann et al. (2005)
Australia Melbourne and 12 other regions Melbourne: 1993; Melbourne plus other regions: 2002–2003	Breast milk	1993: *p,p′*-DDE, 280; *p,p′*-DDT, 12 2002–3: *p,p′*-DDE, 279; *p,p′*-DDT, 7 ng/g lipid (median)	NR		Mueller et al. (2008)

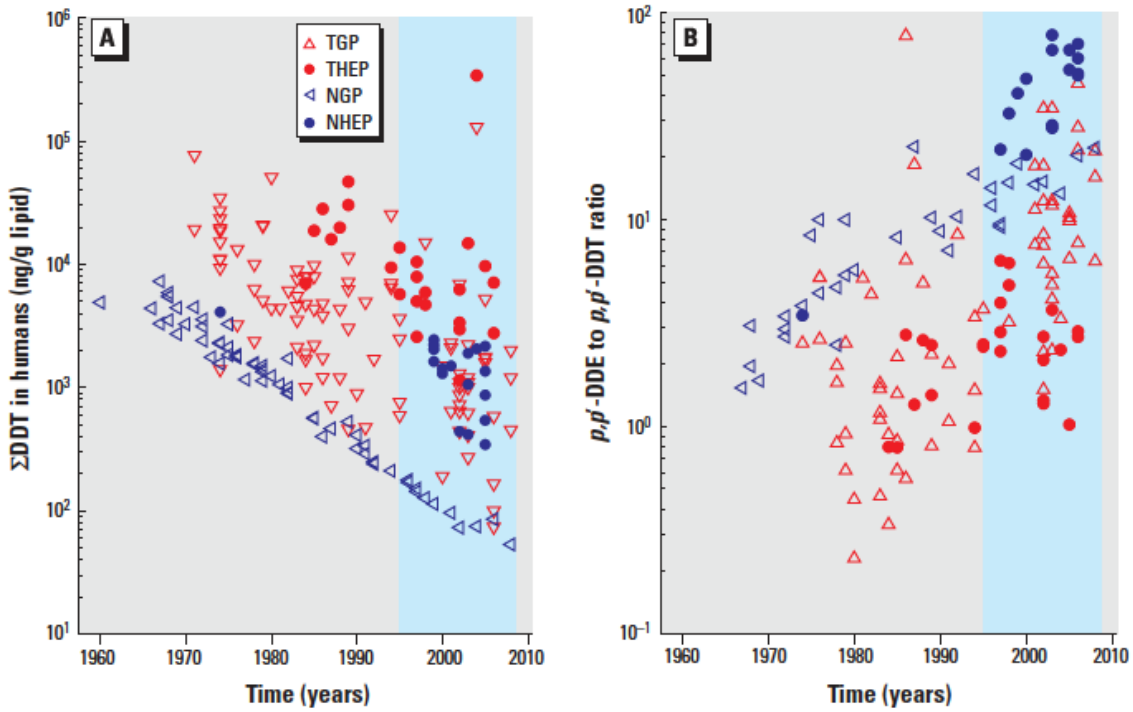
Table 1.5 (continued)

Location, collection date	Sampling matrix	Exposure		Comments	Reference
		Level[a]	Range		
Serbia South Bačka, Voyvodina 1983–2009	Breast milk	1983: ΣDDT, 3630 2009: ΣDDT, 108 ng/g lipid	1983: ΣDDT, 440–9730 2009: ΣDDT, 34–189 ng/g lipid		Vukavić et al. (2013)
China Beijing and Shenyang 2005–2007	Breast milk	Beijing: *p,p′*-DDT, 4.95; *p,p′*-DDE, 169; ΣDDT, 183 Shenyang: *p,p′*-DDT, 4.48; *p,p′*-DDE, 117; ΣDDT, 154 ng/g lipid	Beijing: *p,p′*-DDT, 1.21–17; *p,p′*-DDE, 30.2–1010; ΣDDT, 34.7–1050 Shenyang: *p,p′*-DDT, ND–14.6; *p,p′*-DDE, 15.65–763; ΣDDT, 18.74–833 ng/g lipid	Significant correlation between human milk concentration and daily dietary intake of DDTs; the dietary intake could explain 22% of the variation of DDTs in human milk	Tao et al. (2008)
Turkey Ankara (suburban area) Year NR	Breast milk	DDT, 223 ng/kg lipid	DDT, < LOD–1265.7 ng /g lipid		Yalçin et al. (2014)
Islamic Republic of Iran Ahvaz and Noushahr November 2007 to January 2008	Hair	ΣDDT, 23 ng/g	ΣDDT, 0.8–305 ng/g		Dahmardeh Behrooz et al. (2012)

ΣDDT, total DDT corresponding to the sum of *o,p′*-DDE, *p,p′*-DDE, *o,p′*-DDD, *p,p′*-DDD, *o,p′*-DDT, and *p,p′*-DDT; ADI, acceptable daily intake; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; dw, dry weight; EPIC, European Prospective Investigation into Cancer and Nutrition; EDI, estimated daily intake; IRS, indoor residual spraying; LOD, limit of detection; NA, not applicable; ND, not detected; NHL, non-Hodgkin lymphoma; NR, not reported; OCP, organochlorine pesticides; SAR, Special Administrative Region

[a] Arithmetic mean, unless otherwise stated

Fig. 1.3 Temporal trends in human biomonitoring data for DDT



(A) Trends in ΣDDT. (B) Trends in the *p,p′*-DDE to *p,p′*-DDT ratio. Blue shaded area marks the time period investigated in the integrated exposure assessment (1995–2008).
Reproduced from Ritter et al. (2011), *Environmental Health Perspectives*.

The Agricultural Health Study (AHS) of farmers and licensed pesticide applicators in Iowa and North Carolina, USA, estimated exposures to 50 pesticides, including DDT. Pesticide exposure information was ascertained from two phases of questionnaire administration. In the first phase (1993–1997), ever/never use of pesticides was ascertained for all applicators; detailed information on lifetime use of DDT use was obtained for 25 291 applicators from a self-administered questionnaire during phase 1. A follow-up questionnaire ascertained detailed pesticide information for the 5 years since enrolment in the study. For participants who did not complete the follow-up questionnaire, a multiple imputation procedure was used to impute exposure to specific pesticides. Information about factors potentially affecting exposure, such as spraying techniques and use of personal protective equipment, was also obtained by questionnaire. A semiquantitative exposure-assessment based on this information was developed in which estimated intensity was combined with years and annual frequency of use (Dosemeci et al., 2002). Cumulative exposure matrices of ever/never use, lifetime days of use, and intensity-weighted lifetime days of use and were created (Alavanja et al., 2014). The intensity score was based on development of an a priori exposure intensity algorithm. Several validity evaluations of the exposure assessment process were carried out. These included: (i) assessment of the reliability of reporting agricultural factors

by requiring completion of the enrolment questionnaires twice, approximately 1 year apart; (ii) confirmatory checks correlating the years in which a pesticide was reportedly used with dates of registered use of that particular pesticide; and (iii) comparison of the exposure algorithm with external exposure data. Agreement of reporting of ever/never use of specific pesticides and application practices was high, and generally ranged from 70% to > 90%. Agreement was lower (typically 50–60%) for duration or frequency of use of specific pesticides (Blair et al., 2000). The confirmatory checks on reported usage of specific pesticides established that the majority of respondents provided plausible responses for decade of first use and total duration of use (Hoppin et al., 2002). The exposure-intensity algorithm was evaluated in three studies (Coble et al., 2005; Acquavella et al., 2006; Thomas et al., 2010). When combined, these studies showed that the AHS algorithm had the capacity to separate the upper tertiles of exposure intensity from the lower.

[The Working Group noted that the AHS has collected detailed information on pesticide use and practices and through validation studies has shown this data to be appropriate for estimating historical exposure to pesticides. However, the validity studies were based on information reported at the time the exposure surveys were completed and would not necessarily reflect the recall of information for all aspects, in particular frequency and duration of use. The assessment of DDT exposure in the AHS is based on the baseline questionnaire (1993–1997) and relies on historical recall. Although DDT may be a pesticide the use of which is more readily recalled than others because of wide recognition and environmental and health concerns, the validity of recalled information is nonetheless unknown. Moreover, due to the persistent nature of DDT, it is likely that a certain proportion of farmer exposure is attributable to non-application circumstances, such as re-entry and contaminated work and home environments. Exposures related to non-application days may be collinear with reported lifetime days of application, but if not the non-application exposures could contribute to marked measurement misclassification. For example, Bakke et al. (2009) detected elevated urinary 2,4-D concentrations in corn farmers relative to non-farmers even on days when the farmers had not applied 2,4-D. These levels, although an order of magnitude lower than those recorded when applying 2,4-D, suggest a contribution of non-application days to cumulative annual exposure. This consideration is relevant when accounting for the fact that active applications by most farmers amount to only a few days during the growing season. Given the more persistent nature of DDT, it is reasonable to assume that similar concerns are in play for this pesticide.]

In the study of Cocco et al. (2005), based on workers exposed to DDT during antimalarial operations in Sardinia, Italy, estimated exposure was based on occupation held at the time of the antimalarial operations. Relevant occupations were those involving either direct exposure to DDT (i.e. applicators) and those involving the likelihood of bystander exposure (i.e. inspectors, warehouse workers, drivers). Dermal and inhalation exposure was estimated using the EUROPOEM model for applicators (van Hemmen, 2001), while for bystander situations only dermal exposure was estimated using the algorithm developed by Krebs et al. (2000).

[The Working Group noted that categorization specifying unexposed, directly exposed and bystander situations is appropriately based on job information. However, estimation of quantitative levels of exposure using the EUROPOEM model, whose scenarios are based on best practice (daily cumulative exposure range, 54–140 400 μg), might have underestimated the exposure to DDT from work practices as they occurred in 1946–1950 in the antimalarial campaigns in Sardinia. The validity of the assumption of no inhalation exposure for bystanders cannot be determined.]

(b) General population

In relevant studies based upon the general population, DDT exposure was assessed either by relying on data from questionnaires and/or biological monitoring.

(i) Questionnaire-based approaches

The studies relying on questionnaires collected varying information on jobs held, agricultural practices, and pesticide use. [The Working Group noted that these studies have employed standard accepted techniques in environmental and occupational epidemiology. As in all studies, self-reported exposure data are prone to inaccurate or biased recall that can lead to exposure misclassification. Due to the absence of confirmatory data on recall and exposure assignment, the validity of these exposure assessments could not be evaluated.]

(ii) Biomonitoring approaches

A number of relevant studies have relied on measurement of *p,p′*-DDE and/or *p,p′*-DDT in serum or plasma or in adipose tissue (see Table 1.4). The implicit rationale for monitoring levels of DDT and its metabolites in serum and adipose is the assumption that those levels would reflect past exposure and be indicative of differences in total exposures between individuals. However, this assumption has been questioned on the basis of long-term *p,p′*-DDT toxicokinetics and metabolism. Studies involving human ingestion of DDT have shown that *o,p′*-DDT is rapidly metabolized and excreted, and that when *p,p′*-DDT is compared with *p,p′*-DDE, the former is more rapidly metabolized and excreted, with the latter being the most persistent compound of this series (Morgan & Roan, 1974). In addition to chronic ingestion of *p,p′*-DDE from the diet and exposures from other environmental media, inter-individual differences in capacity to metabolize DDT may further complicate the interpretation of serum levels of *p,p′*-DDE. Thus, *p,p′*-DDE concentrations in human serum may not accurately reflect past exposure to *p,p′*-DDT, particularly in samples obtained decades after direct exposure to DDT (Perry et al., 2005; Wolff et al., 2005; Cohn et al., 2007). In addition, there are strong trends in population levels of *p,p′*-DDT and *p,p′*-DDE due to the ban of most uses of DDT (Fig. 1.3A; Ritter et al., 2011). The ratio of *p,p′*-DDE to *p,p′*-DDT is changing over time, with ratios around 1 recorded before 1980 and ratios of around 10 recorded in more recent time (2000–2010), the exception being populations living in homes with indoor residual spraying of DDT for disease-vector control (Ritter et al., 2011). This indicates that for many populations, direct exposures to DDT are unlikely and that current levels are predominantly attributable to *p,p′*-DDE in the diet and other environmental media (Fig. 1.3B).

[The Working Group noted that the ratio of *p,p′*-DDE to *p,p′*-DDT employed in the evaluated key epidemiological studies tended to range from 6 to 36, with lower ratios being reported for studies using measurements recorded in the more distant past, and higher ratios corresponding to more recent times. Studies with a higher ratio may indicate an earlier exposure and/or a predominant contribution of *p,p′*-DDE through diet and other environmental media. The Working Group also noted the high levels of *p,p′*-DDT and *p,p′*-DDE in the Persson et al. (2012) study for which no clear explanation was evident.]

1.5 Regulation

Regulation of pesticides typically involves restrictions inherent to registration or licensing for use and measures to limit exposure in an occupational and wider community context; the regulation of DDT is overwhelmingly concerned with its use being prohibited. Prohibition in many countries acknowledged, DDT is approved for use in limited circumstances and is therefore appropriately regulated as a pesticide in

that context. Moreover, many countries in which DDT is banned have adopted regulations concerning residues, and may specify limits in respect of occupational exposure.

1.5.1 International agreements

The Stockholm Convention on Persistent Organic Pollutants, signed in 2001, provided initially for the elimination of 12 chemicals, one of which was DDT (UNEP, 2002b). The Convention now addresses 22 chemicals. Within the convention, DDT is addressed in Annex B: Restriction, Part II (acceptable purpose – disease vector control in accordance with WHO recommendations), which has been published separately (Bouwman et al., 2013) and which, among other things, provides for establishment of a DDT register, and agreement between the parties to restrict usage of DDT and identify alternatives, and to report on and evaluate those circumstances where DDT usage continues to be approved.

International instruments variously addressing DDT also include the Basel Convention on the Control of Transboundary Movements of Hazardous Waste and Their Disposal, and the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade (Matthews et al., 2011).

Vector control is essential to malaria control, and as such is recognized by WHO, specifically with reference to 12 insecticides recommended for indoor residual spraying, including DDT – the only organochlorine compound in this context – until suitable alternatives are available (WHO, 2011a).

1.5.2 Transnational and national regulations

Based on the increasing amount of data on its toxicity, environmental persistence, bioaccumulation and potential for transboundary movement, restrictions on the use of DDT were adopted in different countries from the early 1970s (Bouwman et al., 2013).

Sweden was the first country to ban the use of DDT, beginning in January 1970 (Turusov et al., 2002).

In 1972, the EPA issued a cancellation order for DDT in the USA (EPA, 2015b). Prior to restrictions being adopted, DDT was variously registered in the USA, including application to livestock. The United States Department of Agriculture (USDA) had previously cancelled Federal registrations as of 1970 for several specified uses of DDT products, including on food crops, livestock and wood products (EPA, 1975b).

In the United Kingdom, use of DDT was severely restricted in 1964, and all use was prohibited from 1984 (Gillespie et al., 1994). In the former Soviet Union, the production and use of DDT in agriculture was officially banned in 1969–1970, but use for public health purposes (against mosquitoes, malarial plasmodia, fleas, lice, and ticks) was permitted until 1989 (Turusov et al., 2002).

From 1983, technical DDT was banned as an agricultural pesticide in China. As reported in 2005, China had requested specific exemptions for DDT under the Stockholm Convention (Wong et al., 2005). A national ban on use of DDT as an additive to antifouling paint was implemented in 2009 in China (Lin et al., 2009). By 2014, all uses of DDT in China were withdrawn (UNEP/WHO, 2014, 2015).

Granted usage of DDT for vector control in India, strict regulations to prevent diversion of DDT to agricultural uses are advocated (Gunasekaran et al., 2005).

As assessed in 2009, many countries that use DDT have inadequate legislation or lack capacity to implement or enforce regulations on pesticide management (Li et al., 2006; van den Berg, 2009; Aliyeva et al., 2013).

Despite bans on production and use, relevant national authorities may specify occupational exposure levels for DDT. In the USA, for example,

the National Institute of Occupational Safety and Health (NIOSH) has issued a recommended exposure level (REL, 0.5 mg/m^3 time-weighted average, TWA) and the American Conference of Governmental Industrial Hygienists (ACGIH) has put in place a threshold limit value (TLV, 1 mg/m^3 TWA for skin) for DDT (CDC, 2015), and such measures remain relevant to jurisdictions in which DDT continues to be used.

For the European Commission, maximum residue limits (MRL) for DDT and related compounds are specified for 378 products, almost all of which are 0.05 mg/kg, extending as high as 1 mg/kg for some products, e.g. coffee beans, spices, meat, and edible offal (European Commission, 2015).

In several countries regulations exist with respect to DDT and related substances in commercial dicofol. In the European Union, USA, and Canada, the limit for such content is 0.1% (Ministerie van VROM, 2004). Dicofol formulations sold in the United Kingdom were found to conform to this requirement (Gillespie et al., 1994). The use of dicofol in China has been banned on tea plant and vegetables. Having been reported at levels of 10% or more in the past, the DDT impurity in dicofol is now required by Chinese regulation to be no more than 0.5% of technical dicofol (Qiu et al., 2005).

2. Cancer in Humans

2.1 Cohort studies

Associations between exposure to DDT and several types of cancer have been extensively investigated in epidemiological studies. The pertinent studies reviewed by the Working Group are summarized here according to study design and cancer site. Several meta-analyses were also available to the Working Group. These are reviewed with the case–control studies for the cancers concerned, as most of the included studies had that design.

2.1.1 Cancer of the breast

See Table 2.1

The relationship between serum concentration of DDE [1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene], a main metabolite of DDT [1,1′-(2,2,2-trichloro-ethylidene)bis (4-chlorobenzene).], and cancer of the breast has been evaluated in case–control analyses of 10 prospective cohort studies (Wolff et al., 1993; Krieger et al., 1994; Hunter et al., 1997; Høyer et al., 1998; Dorgan et al., 1999; Helzlsouer et al., 1999; Ward et al., 2000; Raaschou-Nielsen et al., 2005; Cohn et al., 2007; Iwasaki et al., 2008; Cohn et al., 2015). These studies were performed in the USA, Denmark, Norway, and Japan. The duration of follow-up ranged from 1 month (Wolff et al., 1993) to 54 years (Cohn et al., 2015) after blood collection.

In addition, the relationship between DDT and breast cancer was evaluated in some of these studies (Høyer et al., 1998; Dorgan et al., 1999; Høyer et al., 2000; Ward et al., 2000; Høyer et al., 2002; Raaschou-Nielsen et al., 2005; Cohn et al., 2007; Iwasaki et al., 2008; Cohn et al., 2015).

The New York University Women's Health Study enrolled a cohort of 14 290 women from New York City, USA, between 1985 and 1991; these women donated a 30 mL blood sample while attending a mammography screening clinic (Wolff et al., 1993). During this period, women who were diagnosed with cancer of the breast 1–6 months after entry into the study were defined as cases. Controls were selected at random from all cohort members who were alive and free of cancer at the time of the cancer diagnosis in a case patient, matched on age at entry, number of blood donations, menopausal status, and day of menstrual cycle at the time of blood collection. Serum DDE and DDT concentrations were determined in a total of 58 cases and 171 controls.

Table 2.1 Cohort studies of cancer of the breast and exposure to DDT and its metabolites

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Wolff et al. (1993) New York, USA Enrolment, 1985–1991 Nested case–control	Cases: 58 women aged 35–65 yrs with breast cancer diagnosed 1–6 mo after entry Controls: 171 cohort members alive and free of cancer at the time of case diagnosis Exposure assessment method: personal monitoring; GC-ECD	Breast	DDE, 0.5–3.2 ng/mL 3.2–5.2 5.2–7.5 7.5–11.9 11.9–44.3	6 6 16 8 13	1.00 1.67 4.37 2.31 3.68	First-degree relative with cancer, lifetime lactation, age at first full-term pregnancy	From all prospective studies that have been performed so far, this is the only one that included prevalent cases Strengths: control for confounders, including lactation Limitations: prevalent cases; only one clinic as a source of women; no information on reluctant participants and losses in follow-up; no information on whether DDE measurements were performed before or after cancer treatment began; no information on lipid-adjusted DDE levels
Wolff et al. (2000a) New York Enrolment 1985–1991; follow-up to 1994 Nested case–control	Cases: 110 Controls: 213 Exposure assessment method: personal monitoring; GC-ECD	Breast	DDE: < 664 ng/g lipid 664–1172 1173–1934 > 1934 Trend-test *P* value: 0.99	31 30 24 25	1.00 0.81 (0.35–1.87) 0.6 (0.26–1.38) 1.3 (0.51–3.35)	Age at menarche, number of full-term pregnancies, age at first full-term pregnancy, family history of breast cancer, lifetime history of lactation, height), BMI, BMI-menopausal status interaction	Stratification by ER status showed no significant higher GM of DDE among controls Strengths: only incident cases included (see Wolff et al., 1993) Limitations: only women with 3 blood samples were included; short follow-up

Table 2.1 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Krieger et al. (1994) California, USA Enrolment 1964–1971; follow-up until 1990 Nested case–control study	Cases: race-stratified random sample of 150 cases from the cohort Controls: 150 women free of cancer up to the time of matched case patient's diagnosis, matched by race, date of joining the programme, year, and age at examination and length of follow up Exposure assessment method: personal monitoring; GC-ECD	Breast	5.33–29.68 DDE ng/mL 29.69–49.60 49.61–149.50 Trend-test *P* value: 0.431	NR NR NR	1.00 1.29 (0.67–2.47) 1.33 (0.68–2.62)	BMI, age at menarche, ever vs never pregnant, menopausal status at time of case patient´s diagnosis of breast cancer plus variables matched by design	Strengths: serum samples taken up to 26 yrs before diagnosis before DDT prohibition in USA Limitations: small sample size by race
Hunter et al. (1997) 11 USA states Enrolment 1976, follow-up June 1992 Nested case–control study	Cases: 236 incident cases with no previous cancer Controls: 236, matched by year of birth, menopausal status, month, time of day and fasting status at blood sampling and postmenopausal hormone use Exposure assessment method: personal monitoring; GC-ECD; plasma levels of DDE measured after adjustment for plasma cholesterol concentrations	Breast	DDE, ppb ≤ 2.78 > 2.78–4.54 > 4.54–6.26 > 6.26–9.46 > 9.46 Trend-test *P* value: 0.47	 61 54 35 43 43	 1.00 0.80 (0.45–1.43) 0.47 (0.25–0.9) 0.74 (0.40–1.36) 0.72 (0.37–1.4)	History of breast cancer in a mother or sister, history of benign breast disease, age at menarche, number of children and age at birth of first child, duration of lactation, BMI, plus variables matched by design	Strengths: well-designed study; control of key confounders; low attrition rate (5%) Limitations: DDE levels were measured 2–3 yrs before the end of follow-up

Table 2.1 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Laden et al. (2001a) 11 USA states Enrolment 1976, follow-up to 1994 Nested case–control study	Cases: 372; as in Hunter et al. (1997) plus 143 cases of invasive postmenopausal cancer diagnosed 1992–1994 Controls: 372 cancer-free women matched on year of birth, menopausal status, date and fasting status at blood collection and post-menopausal hormone use Exposure assessment method: personal monitoring; GC-ECD	Breast	DDE, µg/g lipid 0.007–0.427 0.428–0.703 0.708–0.955 0.955–1.441 1.466–6.054	 88 85 48 83 68	 1.00 0.95 (0.59–1.53) 0.51 (0.31–0.86) 0.91 (0.57–1.47) 0.82 (0.49–1.37)	History of breast cancer in mother or a sister, a history of benign breast disease, age at menarche, BMI at blood draw, number of children and age at birth of first child, and duration of lactation	Strengths: 98% completeness of follow-up Limitations: mostly premenopausal women
Dorgan et al. (1999) Columbia, Missouri Blood donation 1977 and 1987; follow-up to 1989 Nested case–control study	Cases: 105 histologically confirmed breast cancer cases up to 1989 Controls: 208; alive and free of cancer at the age of the case's diagnosis, matched on age, date of blood draw, history of benign breast disease and number of blood draws Exposure assessment method: personal monitoring; GC-ECD; serum cholesterol and triglycerides were measured	Breast	DDE, ng/g lipid 31–1377 1378–2355 2356–3500 3501–20 667 DDT, ng/g lipid 0–180 181–292 293–467 468–1724 Trend-test *P* value: 0.65	 33 32 14 26 29 29 33 14	 1.0 0.9 (0.5–1.7) 0.4 (0.2–0.8) 0.8 (0.4–1.5) 1.0 1.0 (0.5–2.0) 1.1 (0.6–2.1) 0.4 (0.2–1.0)	Height, weight, BMI, parity, age at menarche, menopausal status, exogenous estrogen use, history of breast cancer among first-degree relatives, education, and number of packs of cigarettes smoked per day	Strengths: up to 9.5 yrs of follow-up Limitations: study population were volunteers; relatively small sample size; no adjustment for lactation

Table 2.1 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Helzlsouer et al. (1999) Washington County, Maryland, USA Two cohorts enrolled in 1974 and 1989; follow up until 1994 Nested case–control study	Cases: cohort 1: 235; cohort 2: 105; county cancer registry Controls: cohort 1: 235; cohort 2: 105; women within the cohorts not diagnosed with cancer, matched by sex, race, age, menopausal status, date of blood donation Exposure assessment method: personal monitoring; serum DDE by GC-ECD	Breast	DDE ng/g (1974):			History of breast cancer, BMI at age 20 yrs or current age at menarche, age at first birth, duration of lactation plus matching variables	Strengths: serum collected up to 20 yrs before diagnosis; adjustment by key confounders Limitations: sample size limited for subgroup analyses
			< 1017.19	49	1.00		
			1017.20–1425.39	61	1.24 (0.72–2.13)		
			1425.40–1864.57	47	0.96 (0.55–1.67)		
			1864.58–2446.69	42	0.86 (0.49–1.51)		
			2446.70–10 795.91	36	0.73 (0.40–1.32)		
			DDE ng/g (1989):				
			< 816.3	38	1.00		
			816.4–1595.1	44	1.18 (0.65–2.13)		
			1595.2–10 065.6	23	0.58 (0.29–1.17)		

Table 2.1 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Cohn et al. (2007) Oakland, California, USA Enrolment between 1959–1967; follow-up to 1998 Nested case–control study	Cases: 129 from state cancer registry and vital records Controls: 129; matched to cases on birth year Exposure assessment method: personal monitoring; no lipid adjustment	Breast	*p,p′*-DDE, µg/L			None	Strengths: exposure measurements from stored serum samples reflecting early life exposures; long follow-up Limitations: small sample size (main results are based on 94 case–control pairs); no discussion of the effect of adjustment by correlated metabolites; no information on risk factors between the time of the pregnancy and development of breast cancer
			≤ 35.23	NR	1.0		
			35.23–58.49	NR	1.5 (0.8–2.6)		
			> 58.49	NR	1.1 (0.6–2.0)		
		Breast	*p,p′*-DDT, µg/L			None	
			≤ 8.09	NR	1.0		
			8.09–13.90	NR	1.4 (0.7–2.7)		
			> 13.90	NR	1.6 (0.8–3.0)		
		Breast	Age < 14 yrs in 1945			*p,p´*DDT, *p,p´*DDE and *o,p´*DDT, and women aged < 14 yrs in 1945	
			p,p′-DDE, µg/L				
			≤ 35.23	NR	1.0		
			> 35.23–58.49	NR	1.5 (0.6–3.4)		
			> 58.49	NR	0.9 (0.3–3.0)		
			p,p′-DDT, µg/L				
			< 8.09	NR	1.0		
			8.09–13.90	NR	2.5 (1.0–6.3)		
			> 13.90	NR	5.2 (1.4–19.1)		
Cohn et al. (2015) Oakland, California, USA 1959–1967 Nested case–control study	Cases: 103 from state cancer registry & vital records Controls: 315; cohort Exposure assessment method: personal monitoring	Breast	Concentration in mother's serum			Maternal cholesterol and triglycerides, maternal overweight in early pregnancy and maternal history of breast cancer	See Cohn et al. (2007) for details Strengths: long follow-up; DDT was measured during mothers'pregnancy Limitations: breast cancer risk factors in daughters were not considered
			Q1 DDE	NR	1.0		
			Q2	NR	1.3		
			Q3	NR	1.1		
			Q4	NR	1.3		
			Q1 DDT	NR	1.0		
			Q2	NR	1.9		
			Q3	NR	1.5		
			Q4	NR	2.2		
			Trend-test *P* value: 0.074				

Table 2.1 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Høyer et al. (2000) Copenhagen, Denmark First enrolment 1976–1978; follow-up until December 1992 Nested case–control study	Cases: 143 from Danish cancer registry Controls: 274 age-matched controls from the cohort Exposure assessment method: personal monitoring; GC-ECD; total lipid content was calculated	Breast	I DDE ng/g II III IV I DDT ng/g II III IV	NR NR NR NR NR NR NR NR	1.0 1.0 (0.5–2.0) 0.8 (0.4–1.6) 1.4 (0.7–2.8) 1.0 1.3 (0.4–4.5) 2.1 (0.6–7.0) 3.6 (1.1–12.2)	Weight changes	Parity, weight and HRT reported to be confounders but were not included in the final model Strengths: up to 8 yrs of follow-up; average concentration of two DDE measurements with a 5- yr interval was used Limitations: possibly inadequate control for breast-cancer risk factors; limited power, particularly for subgroups
Raaschou-Nielsen et al. (2005) Denmark Enrolment 1993–1997; follow-up to 2000 Nested case–control study	Cases: 409 from Danish cancer registry Controls: 409, cancer-free at age of case diagnosis matched by age, HRT & postmenopausal status Exposure assessment method: personal monitoring; gluteal adipose tissue; analysis by GC-MS	Breast	DDE, µg/kg lipids 15–282 283–507 508–903 904–6693 DDT, µg/kg lipids 6–14 14–20 20–31 31–159	 100 100 100 100 100 100 100 100	 1.0 1.0 (0.7–1.5) 0.9 (0.6–1.4) 0.7 (0.5–1.2) 1.0 0.8 (0.5–1.3) 1.4 (0.9–2.3) 0.6 (0.3–1.0)	Education, BMI, alcohol, number of childbirths, age at first delivery, lactation, HRT, history of benign breast disease	Strengths: largest prospective study with in adipose tissue measurements; ER status was determined Limitations: only postmenopausal women

Table 2.1 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Ward et al. (2000) Norway Enrolment 1991; follow-up to 1993 Nested case–control study	Cases: 150; random sample of eligible cases in the Norwegian cancer registry Controls: 150; alive and cancer-free at case diagnosis, matched by date of sample collection and date of birth Exposure assessment method: personal monitoring; high-resolution GC/high-resolution isotope dilution MS	Breast	Q1 DDE ng/g lipid	NR	1.0	None specified	Strengths: lipid-adjusted DDE values; ER status assessed Limitations: no BMI nor menopausal status information available; limited power; CIs not reported
			Q2	NR	0.7		
			Q3	NR	1.0		
			Q4	NR	1.2		
			Q1 DDT ng/g lipid	NR	1.0		
			Q2	NR	0.2		
			Q3	NR	0.5		
			Q4	NR	0.3		
Iwasaki et al. (2008) Japan Enrolment 1990–1993, follow-up to 2002 Nested case–control study	Cases: 139 from cancer registries, death certificates, hospitals Controls: 278 cohort members matched by age, public health centre area, area, date and time of blood collection, time of day of blood collection, and menopausal status Exposure assessment method: personal monitoring; GC isotope-dilution MS	Breast	DDE, ng/mL			Age at menarche, menopausal status at baseline, number of births, age at first birth, height (continuous), BMI, alcohol consumption	Strengths: up to 10 yrs of follow-up; control for confounders Limitations: no information on lactation; limited power; no lipid adjustment
			2.50	25	1.0		
			4.83	32	1.01 (0.47–2.19)		
			7.58	36	1.24 (0.60–2.53)		
			14.41	46	1.48 (0.70–3.13)		
			DDT, ng/mL				
			0.50	40	1.00		
			0.89	29	0.65 (0.32–1.32)		
			1.36	25	0.56 (0.26–1.22)		
			2.24	45	0.99 (0.47–2.08)		
			Trend-test *P* value: 0.25				

BMI, body mass index; CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; ER, estrogen receptor; GC-ECD, gas chromatography with electron capture detector; GC-MS, gas chromatography with mass spectrometry; GM, geometric mean; HRT, hormone replacement therapy; yr, year

Mean concentrations of DDE were statistically higher for cases of breast cancer than for control subjects (DDE in cases, 11.0 ± 9.1 ng/mL; DDE in controls, 7.7 ± 6.8 ng/mL; $P = 0.031$). After adjustment for first-degree family history of breast cancer, lifetime lactation, and age at first full-term pregnancy, the relative risk (RR) of cancer of the breast was found to increase by fourfold for an elevation in serum DDE concentrations from 2.0 ng/mL (10th percentile) to 19.1 ng/mL (90th percentile). [A major limitation of this study was the inclusion of prevalent cases. DDE measurements were not adjusted for lipids.]

In the same cohort, with an extended follow-up to 1994, only incident cases were considered. Cases with at least three annual blood samples were included and serum DDE concentrations were adjusted for lipids; 110 cases and 123 controls were included in the analysis (Wolff et al., 2000a). Geometric mean DDE concentration was 6.95 ng/mL among cases and 7.27 ng/mL among controls. The results did not confirm a significant increased risk of breast cancer in relation to DDE (odds ratio, OR, Q4 versus Q1, 1.30; 95% confidence interval, CI, 0.31–3.35). The authors also assessed whether changes of DDE over time were related to risk of cancer of the breast. The median half-life of DDE was estimated from the consecutive measurements to be 13 years among cases and 15 years among controls [reported to be non-significant, data not shown] and the risk of breast cancer was reported not to be associated with DDE half-life (data not shown). [A limitation of this study was that only women with three or more annual blood samples were included, and no key information about non-included women from the original cohort was provided. In addition, the follow-up was relatively short and the analysis thus had limited precision.]

Krieger et al. (1994) performed a nested case–control study among women in northern California, USA, who were members of the Kaiser Permanente Medical Care Program and who underwent a health examination, including giving a sample of blood between 1964 and 1969 and were followed up until 1990. Among the 2097 patients identified with cancer of the breast, 150 cases were randomly selected (50 white, 50 black, and 50 Asian) and matched to 150 controls by race, age, date of entry, and date of follow-up. Mean serum DDE concentration was 43.3 ± 25.9 ng/mL among cases, and 43.1 ± 23.7 ng/mL among controls. After adjustment for reproductive factors, menopausal status, and body mass index (BMI), no significant association was seen between risk of cancer of the breast and serum DDE concentrations for all subjects (OR, 1.33; 95% CI, 0.68–2.62; for the third versus first tertile of concentration), nor in ethnic subgroups: whites (OR, 2.38; 95% CI, 0.54–10.64); blacks (OR, 3.85; 95% CI, 0.93–16.05); or Asians (OR, 0.71; 95% CI, 0.23–2.18). [This was a well-designed study with a long follow-up period. Relevant confounders were adjusted. However, only 150 of more than 2000 available cases were selected for measurement of DDE and thus power was limited, especially for subgroup analyses.]

The Nurses' Health Study was established in 1976 and included more than 120 000 registered nurses in 11 states of the USA; participants were followed by questionnaire every 2 years and 32 826 provided a blood sample between 1989 and 1990. Findings on the association between cancer of the breast and plasma DDE concentrations were reported from follow-ups to 1992 (Hunter et al., 1997) and 1994 (Laden et al., 2001a). In the first follow-up, a total of 236 cases diagnosed within 3 years of blood collection were included. The same number of controls was selected from the cohort and matched by year of birth, menopausal status, month in which blood samples was returned, time of day blood sample was drawn, fasting status at blood sampling and hormone use among postmenopausal women. After adjusting for reproductive variables, BMI, and familial history of breast cancer and/or benign breast

disease, the risk of cancer of the breast tended to be lower and not statistically significant, among women with higher serum concentrations of DDE (Hunter et al., 1997). An extended follow-up to 1994 included 372 case–control pairs. Medians DDE concentrations were 768 ng/g lipid among cases, and 817 ng/g lipid among controls. The relative risks of breast cancer were below unity, but not statistically significant, among all groups of women compared with those with lowest levels of DDE (Laden et al., 2001a). [This was a well-designed study with good control for most relevant confounders, including reproductive factors and family history of breast cancer, and larger sample size compared with previous studies. Blood samples were taken after the start of follow-up, but 2–3 years before diagnosis for cases.]

Serum samples were obtained in 1976 from a cohort of 7712 women aged ≥ 20 years who participated in the Copenhagen City Heart Study and provided information and a blood sample (Høyer et al., 1998). Case ascertainment was achieved by linkage to the Danish cancer registry up to 1993. For each case, two women who were free of breast cancer and alive at the time of diagnosis and matched for age and date of examination were selected from the rest of the cohort; 240 cases with a valid serum sample and 447 age-matched controls were included in the analysis. Several potential confounders were tested, including reproductive variables, alcohol consumption, and physical activity, but only full-term pregnancies and weight were retained in final models, which showed no association between quartiles of DDE or DDT and breast cancer.

Participants in the same cohort study were invited for a second examination 5 years after recruitment; 155 cases and 274 controls from the previous study who had two serum sample available were included in a further study (Høyer et al., 2000). No significant association was found between breast cancer and the average concentration of *p,p′*-DDE in the two time periods; however, a 3.6-fold (95% CI, 1.1–12.2) risk of breast cancer was observed among women in the upper quartile of average *p,p′*-DDT serum concentration, with a significant trend. Elevated but non-significant odds ratios were observed for total DDT (OR, 2.4; 95% CI, 0.7–7.8 in the upper quartile). [Parity, weight, and use of hormone replacement therapy use were identified as confounders by the authors, but these were not included in the final model: it is possible that control for confounding was inadequate.]

Within the same cohort, a total of 161 cases with ER status information and 318 matched controls who were free of breast cancer were included in an analysis according to ER status (Høyer et al., 2001). ER status did not modify the association with breast cancer.

Finally, paraffin-embedded tumour-tissue specimens were retrieved for 162 cases and 316 controls from the same cohort and analysed for *p53* (*TP53*) tumour-suppressor gene mutation status (Høyer et al., 2002). No measure of DDT or DDE was associated with breast cancer, regardless of the presence of *p53* mutation. [Several analyses were carried out using data from this Danish study, but power was limited, particularly for subgroups.]

In another study in the USA, 7224 female volunteers donated blood to the Columbia, Missouri Breast Cancer Serum Bank between 1977 and 1987; active follow-up continued until 1989 (Dorgan et al., 1999). Among these women, 105 were diagnosed with histologically confirmed cancer of the breast, and two controls for each were selected, matched to each case on age, date of blood sampling, and history of benign breast disease at the time of enrolment. No association was found between risk of cancer of the breast and lipid-corrected concentrations of DDT or DDE. [This study had limited precision due to relatively small sample size. There was no adjustment for lactation history.]

Residents of Maryland, USA, who had participated in one of two studies conducted in 1974

and 1989 to obtain blood samples for a serum bank (the CLUE I and CLUE II studies) were invited to participate in a case–control study (Helzlsouer et al., 1999). Participants were followed up until 1994 by linkage with the county cancer registry. Of the 346 cases of cancer of the breast diagnosed, valid measurements of DDE were available for 340 cases, which were matched to 340 participating women without cancer of the breast by age, menopausal status, date of blood collection, and study. Taking into account relevant confounders, no association was found between breast cancer and DDE, including after stratifying for menopausal status, estrogen-receptor (ER) status, or polymorphism in *GSTM1*, *GSTT1*, *GSTP1*, *COMT*, or *CYP17*. [Although the sample size was adequate for the main analysis, it was limited for subgroup analyses.]

The JANUS Serum Bank contains serum samples collected between 1973 and 1991 from almost 300 000 individuals undergoing routine health examinations in Norway. Cases of cancer of the breast were identified among 25 431 women who worked outside the home or lived on farms and were followed until 1993 through linkage with the Norwegian cancer registry (Ward et al., 2000). From the 272 cases diagnosed during this period, 150 women with a blood sample taken 2 or more years before diagnosis were randomly selected; an equal number of controls were matched to cases by date of sample collection and date of birth. Mean lipid-adjusted serum DDE concentrations were 1230 ng/g lipid among cases and 1260 ng/g lipid among controls. No association between DDE or DDT concentration and breast cancer was found. [This study was well designed, but had limited precision and did not consider confounding by BMI and menopausal status.]

Between 1993 and 1997, 29 875 Danish women aged 50 to 64 years were enrolled in a prospective study of diet and cancer and followed until December 2000 through linkage with Danish cancer registry (Raaschou-Nielsen et al., 2005). During this period, 409 women were diagnosed with postmenopausal cancer of the breast; each was matched to one randomly selected control-matched by age, postmenopausal status, and use of hormone replacement therapy, and *p,p′*-DDE and *p,p′*-DDT were measured in adipose tissue biopsies. Median DDE concentrations were 476.7 µg/kg lipids among cases and 507.1 µg/kg among controls. No association was found between concentrations of DDE or DDT and risk of cancer of the breast in the whole data set; however, a statistically significant inverse association with DDE was observed when the analysis was restricted to ER-negative (ER–) cases (OR, 0.1; 95% CI, 0.0–0.5 in the highest exposure group). [This was the largest nested case–control study with measurements in adipose tissue rather than serum. The inverse association of DDE among women with ER– tumours does not have a clear interpretation.]

The association of incident breast cancer with young adults' exposure to DDT before it was banned was investigated in a nested case–control study of California residents who provided serum samples for the Child Health and Development Studies between 1959 and 1967 (Cohn et al., 2007). These women would have been mostly aged < 20 years when DDT use peaked. Cases were 129 women who developed cancer of the breast before age 50 years, identified by linkage to the California cancer registry and California vital status records. An equal number of controls from the cohort were matched to cases on birth year. The median time from blood draw to diagnosis was 17 years, and mean age of cases at diagnosis was 44 years. No associations were reported between serum DDE or DDT concentrations and breast cancer in unadjusted analyses. Significant positive associations were found with *p,p′*-DDT after adjustment for *o,p′*-DDT and *p,p′*-DDE. These associations were strongest in the subset of women aged < 14 years in 1945. [This study was notable for providing data on early-life exposure to DDT during a time

when exposures were likely to have been higher. However, although breast-cancer risk factors including race, blood lipids, BMI, reproductive history, and breast feeding were evaluated, most models did not adjust for these factors. In addition, the Working Group considered that adjustment for multiple DDT congeners could introduce bias due to correlations among related metabolites, thus the non-adjusted results were taken to be more valid.]

In a further study based on this cohort, the incidence of cancer of the breast in 9300 daughters of women who provided blood samples in the original study was examined in relation to the mothers' prenatal exposure to DDT (Cohn et al., 2015). The methods of case and control selection were similar to those used in the parent study (Cohn et al., 2007). Daughters of the original participants were followed until 2012; 103 cases diagnosed before age 52 years and 315 controls provided serum samples and were included. Median *p,p′*-DDT concentrations were 13.18 ng/mL among cases and 12.98 ng/mL among controls. Mothers' perinatal serum concentration of *o,p′*-DDT was significantly associated with risk of breast cancer in the daughters in models adjusted for maternal lipids, overweight, and history of breast cancer (OR for Q4 versus Q1, 2.8; $P = 0.007$; P for trend, 0.053). Weaker positive and non-significant positive associations were observed for *p,p′*-DDT and DDE. [A major limitation of this study was that risk factors for breast cancer in daughters were not taken into account. As in the parent study, the Working Group gave less weight to models adjusted for multiple DDT metabolites.]

A total of 24 226 women aged 40–69 years in the Japan Public Health Center-based Prospective Study who responded to the baseline questionnaire and provided blood in 1990–1995 were followed until December 2002; 144 incident cases of breast cancer were identified (Iwasaki et al., 2008). Two matched controls for each case were selected from the cohort, and plasma DDT and DDE concentrations were measured for cases and controls. Median DDE concentrations were 7.04 ng/mL among cases versus 6.08 ng/mL among controls). After adjusting for reproductive variables, BMI, and alcohol consumption, the relative risk in the highest compared with the lowest quartile of *p,p′*-DDE was 1.48 (95% CI, 0.7–3.1) and for *p,p′*-DDT it was 0.99 (95% CI, 0.47–2.08). [This study was well-designed and considered most relevant confounders for cancer, but had limited power.]

2.1.2 Non-Hodgkin lymphoma

See Table 2.2

In all the cohort studies described below, a nested case–control analysis was used to investigate the relationship between non-Hodgkin lymphoma (NHL) and exposure to DDT.

Seventy-four cases of NHL (ICD-8 200 or 202) identified during follow-up from 1975 to 1994 of the CLUE I cohort from Washington County, Maryland, USA and 147 controls matched by race, sex, age and study-related factors were included in a nested case–control study (Rothman et al., 1997). Serum samples were collected before diagnosis. Four DDT-related compounds were measured and used to estimate total DDT concentration corrected for total lipids. Median concentrations of total lipid corrected DDT were 3150 ng/g lipid in cases and 2770 ng/g lipid in controls. There was no association between risk of NHL and quartiles of total DDT concentration (OR, 1.2; 95% CI, 0.5–3.0 for the fourth quartile compared with the first quartile) with adjustment, in addition to matching variables, for education, cigarette smoking, occupational exposure to suspected risk factors for NHL, and serum polychlorinated biphenyls (PCBs). [This study had the advantage that serum was collected at baseline before diagnosis.]

A later study using the same data set reported an analysis of the effect of *p,p′*-DDE on the risk of NHL found a slight increase in risk with the

Table 2.2 Cohort studies on cancers of the lympho-haematopoietic system and exposure to DDT and its metabolites

Reference, location, enrolment/ follow-up period, study-design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Rothman et al. (1997) Washington County, Maryland, USA 1975–94 Nested case–control study	Cases: 74 from county cancer registry Controls: 147 matched on race, sex, birthdate & study variables Exposure assessment method: personal monitoring; lipid-adjusted serum concentrations	NHL (200, 202)	ng/g lipid			PCBs	Strengths: large study; serum collected at baseline before diagnosis Limitations: no data on diet so could not evaluate influence of DDT from foods; limited precision
			180–1740	14	1.0		
			1760–2660	16	1.1 (0.4–2.7)		
			2690–4020	19	1.1 (0.4–2.7)		
			4140–20 500	25	1.2 (0.5–3.0)		
			Trend-test *P* value: 0.87				
Engel et al. (2007) USA 1975–94 Nested case–control study	Cases: 74; as in Rothman et al. (1997) Controls: 147 Exposure assessment method: personal monitoring; lipid-adjusted adjusted serum concentration	NHL (200, 202)	*p,p′*-DDE, median, ng/g lipid			Age, race, state, sex, educational level, smoking	See Rothman et al. (1997) for details
			912.2	17	1.0		
			1616.2	17	0.9 (0.4–2.2)		
			2443.8	14	0.8 (0.3–2.0)		
			4475.0	26	1.5 (0.7–3.2)		
			Early follow-up, 0–12 yrs				
			912.2	7	1.0		
			1616.2	11	1.6 (0.5–5.3)		
			2443.8	7	0.8 (0.2–2.8)		
			4475.0	15	2.1 (0.7–6.3)		
			Late follow-up: 13–19 yrs:				
			912.2	10	1.0		
			1616.2	6	0.4 (0.1–1.6)		
			2443.8	7	0.9 (0.2–3.6)		
			4475.0	11	1.1 (0.3–3.4)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study-design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Engel et al. (2007) USA Enrolment 1989–90, follow-up to 1994 Nested case–control study	Cases: 30; see Hunter et al. (1997) Controls: 78 Exposure assessment method: personal monitoring; serum concentrations adjusted for total lipids	NHL	*p,p′*-DDE, median, ng/g lipid 358.0 881.4 1788.9	 8 9 13	 1.0 1.2 (0.4–3.7) 2 (0.7–6.1)	Age	Strengths: large study sample Limitations: blood samples taken after start of follow-up; short follow-up period
Laden et al. (2010) USA Enrolment 1989–1990; follow-up NR Nested case–control study	Cases: 145; as in Hunter et al. (1997) Controls: 290 Exposure assessment method: personal monitoring; serum concentrations adjusted for total lipids	NHL	*p,p′*-DDE, median, ng/g lipid 343.6 779.6 1327.0 2325.2 Trend-test *P* value: 0.33	 30 43 27 45	 1.00 1.41 (0.76–2.60) 0.77 (0.39–1.52) 1.56 (0.82–2.97)	Smoking status, region	Strengths: large study Limitations: inconsistent results at different follow-up periods

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study-design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Engel et al. (2007) Norway Enrolment 1972–1978; follow-up to 1999 Nested case–control study	Cases: 190 from Norwegian cancer registry Controls: 190 Exposure assessment method: personal monitoring; exposure corrected for total lipids	NHL (200 202)	*p,p′*-DDE, median, ng/g lipid			Sex, age, smoking status, county	Strengths: clear diagnosis, long follow-up Limitations:
			2059.1	39	1.0		
			3247.2	50	1.4 (0.7–2.6)		
			4673.2	52	1.4 (0.7–2.6)		
			7513.0	49	1.4 (0.7–2.9)		
			Early follow-up, 2–16 yrs:				
			2059.1	17	1.0		
			3247.2	31	3.1 (1.1–8.6)		
			4673.2	28	2.4 (0.9–6.4)		
			7513.0	26	4.3 (1.2–15)		
			Late follow-up, 17–25 yrs:				
			2059.1	22	1.0		
			3247.2	19	0.8 (0.3–2.0)		
			4673.2	24	1.3 (0.5–3.2)		
			7513.0	23	0.8 (0.3–2.0)		
Bertrand et al. (2010) USA 1982–2003 Nested case–control study	Cases: 205; annual questionnaires, confirmed from medical records Controls: 409; cohort; matched on race, age, fasting status Exposure assessment method: personal monitoring; lipid-adjusted serum concentrations	NHL	ng/g lipid			Alcohol consumption, weight, smoking	Strengths: diagnoses confirmed using medical records; prospective measurement of serum Limitations: may be unmeasured confounding from dietary factors
			43–1045	37	1.00		
			> 1045–1741	37	0.97 (0.55–1.7)		
			> 1741–2523	52	1.4 (0.78–2.50)		
			> 2523–3595	29	0.71 (0.39–1.30)		
			> 3595–1897	50	1.30 (0.74–2.30)		
			Trend-test *P* value: 0.7				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study-design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Bräuner et al. (2012) Denmark Enrolment 1993–1997; follow-up to 2008 Nested case–control study	Cases: 239 from Danish cancer registry Controls: 245; random sample of the entire cohort Exposure assessment method: personal monitoring; concentrations in adipose tissue (see Raaschou-Nielsen et al., 2005)	NHL	*p,p′*-DDT, µg/kg lipids			Age, sex	Case–cohort analysis Strengths: adipose tissue used rather than blood (preferred indicator because it represents cumulative exposure) Limitations: did not adjust for co-exposure to other pesticides or PCBs; large number of samples were below the LOD
			6–15	29	1.00		
			15–22	32	1.06 (0.52–2.14)		
			22–36	35	1.03 (0.51–2.09)		
			36–49	23	1.21 (0.53–2.75)		
			49–460	18	1.64 (0.68–3.96)		
			68–390	59	1.00		
			390–680	53	0.83 (0.49–1.39)		
			p,p′-DDE, µg/kg lipids				
			680–1100	63	1.04 (0.62–1.73)		
			1100–1700	34	0.79 (0.43–1.46)		
			1700–8000	29	1.10 (0.57–2.14)		

CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; LOD, limit of detection; NHL, non-Hodgkin lymphoma; PCBs, polychlorinated biphenyls

concentration of *p,p′*-DDE (OR, 1.5; 95% CI, 0.7–3.2, adjusting for years of education, current smoking status), which was stronger in the earlier period of 0–12 years of follow-up (Engel et al., 2007). Neither analysis showed clear exposure–response trends.

An analysis of the association between NHL and serum *p,p′*-DDE concentrations in the previously described United States Nurses' Health Study (see Hunter et al., 1997) was also reported in the same paper by Engel et al. (2007). Thirty participants with incident NHL diagnosed between the date of blood collection and May 1994 (median follow-up, 1 year) were included as cases and 78 cohort members selected previously as controls for another study served as controls. A non-significant increased risk of NHL was found for increasing quartile of *p,p′*-DDE, with the odds ratio for the highest quartile being 2.0 (95% CI, 0.7–6.1).

After an extended follow-up of the Nurses' Health Study cohort [follow-up interval not specified] 145 cases of NHL were identified and two controls matched on age, race, month of blood draw, and fasting status were selected for each case (Laden et al., 2010). Median concentrations of *p,p′*-DDE were 996.2 ng/g lipid in cases and 1002.3 ng/g lipid in controls. No consistent pattern of association was observed for quartiles of total serum concentrations of *p,p′*-DDE after adjustment for potential confounders, including smoking and reproductive history. For all NHL combined, the odds ratio for the fourth versus the first quartile was 1.56 (95% CI, 0.82–2.97).

In the JANUS cohort described previously (see Ward et al., 2000), lipid-corrected concentrations of *p,p′*-DDE were available for 190 confirmed cases of NHL ascertained with follow-up to 1999 (Engel et al., 2007). An equal number of controls from the cohort were matched by age, sex, county, and date of examination. In the analysis, further adjustments were made for BMI and smoking status. The odds ratios for the association of NHL with *p,p′*-DDE was the same (1.4) for all quartiles above the first. For the early period of follow-up, 2–16 years, an increase in risk was reported for the second exposure quartile (OR, 3.1; 95% CI, 1.1–8.6) and for the fourth exposure quartile (OR, 4.3; 95% CI, 1.2–15.0) compared with the lowest quartile, with a significant upward trend across quartiles. However, no excess or trend was found for the later follow-up period, 17–25 years.

The Physicians' Health Study began in 1982 in the USA as a randomized trial for the primary prevention of cardiovascular disease and cancer in 22 071 male physicians aged 40–84 years at enrolment. A total of 14 916 participants provided a blood sample in 1982–84 (before randomization) and were followed until 2003 using annual questionnaires confirmed by review of medical records to identify newly diagnosed NHL (Bertrand et al., 2010). After exclusions, 205 cases with available blood samples were included. For each case, two controls matched on baseline by race, age, date of blood collection, and fasting status at blood draw were selected from the cohort. Lipid-corrected concentrations of *p,p′*-DDE in serum were determined for cases and controls. There was no significant association of NHL with *p,p′*-DDE, with the odds ratio in the highest quintile being 1.3 (95% CI, 0.74–2.3) in a multivariable adjusted analysis.

In a further study based on the Danish Diet, Cancer and Health study described previously (see Raaschou-Nielsen et al., 2005), NHL cases were ascertained among 57 053 persons followed until 2008 (Bräuner et al., 2012). Exposures of cases were compared with those of a random sample of the cohort in a case-cohort analysis that included 239 cases and 245 individuals from the cohort with measurements of *p,p′*-DDT and *p,p′*–DDE. The median concentration of *p,p′*-DDT was 24 µg/kg lipid for cases and 21 µg/kg lipid for controls; the median concentration of *p,p′*-DDE µg/kg lipid was 700 µg/kg lipid for cases and 640 µg/kg lipid for controls. There were suggestions of a monotonic dose–response relationship between risk of NHL and

p,p′-DDT concentration. The incidence rate ratio for the highest versus lowest exposure category was 1.64 (95% CI, 0.68–3.96). In a linear analysis, the incidence rate ratio for a one interquartile range increase in exposure to *p,p′*-DDT was 1.35 (95% CI, 1.10–1.66). There was no clear pattern of increased risk for *p,p′*-DDE. [Although measures were made of 8 pesticides and 10 PCB congeners, no adjustment was made for co-exposure. In addition, concentrations in a large number of samples were below the limit of detection.]

2.1.3 Cancer of the testis

See Table 2.3

McGlynn et al. (2008) reported the results of a case–control study on testicular germ cell tumours conducted among United States military personnel. The cases included in the analysis were 739 men who had donated blood to the Department of Defense Serum Repository between 1987 and 2002, and who were subsequently diagnosed with testicular germ cell tumour between 1988 and 2003. Controls were 915 men with a serum sample available in the repository, matched on birth year, ethnicity, and date of serum sample. Eleven organochlorine compounds, including *p,p′*-DDT and *p,p′*-DDE, were analysed in the serum. Data on other risk factors were collected by telephone interview. Testicular germ cell tumour was statistically significantly associated (*P* for trend, 0.0002) with increasing levels of *p,p′*-DDE (highest versus lowest quartile: OR, 1.71; 95% CI, 1.23–2.38). This association was apparent for seminoma (OR, 1.91; 95% CI, 1.22–2.99) and for non-seminoma (OR, 1.63; 95% CI, 1.10–2.42). *p,p′*-DDT was detected in only 20% of the subjects, and was not significantly associated with testicular germ cell tumour. [This was a well-conducted study with a large number of subjects, and high response rates. The use of prediagnostic serum samples was a major advantage of this study, as serum levels of organochlorine compounds are unlikely to be influenced by the disease.]

In a paper by Purdue et al. (2009), the authors reported the findings of a case–control study on testicular germ cell tumours that was nested within the previously described Janus Serum Bank cohort of Norway (see Ward et al., 2000). Cases were Janus cohort members who were diagnosed with testicular germ cell tumour between 1972 and 1999 through linkage with the Norwegian cancer registry. One male control from the cohort was matched to each case by region, time period, and age at blood draw. The analysis included 49 cases and 51 controls. Concentrations of 11 organochlorine insecticides, including *p,p′*-DDE, *p,p′*-DDT, and *o,p′*-DDT, and of 34 PCBs were measured in serum. In case–control comparisons, the odds ratio for testicular germ cell tumour increased with increasing serum *p,p′*-DDE concentration: the odds ratio for the highest to the lowest exposure tertile was 2.2 (95% CI, 0.7–6.5). A similar association was observed when restricting the analysis to seminoma cases. Elevated odds ratios were also observed for *p,p′*-DDT (OR, 2.1; 95% CI, 0.6–7.2 for the third versus the first quartile), but not for *o,p′*-DDT. [This was a small but well-conducted study. An important strength was the use of serum samples collected before diagnosis, minimizing the possibility that measurements were affected by the disease. Moreover, DDT had only recently been banned at the time of blood sample collection (1972–1978).]

In California, USA, Cohn et al. (2010) examined maternal serum concentrations of DDT-related compounds in relation to sons' risk of testicular cancer as assessed more than 30 years later in the Child Health and Development Studies (described previously, see Cohn et al., 2007). Of study participants who had serum samples, 15 sons were diagnosed with germ cell testicular tumour. The cases were matched to three controls each by race and year of birth; most analyses were not adjusted for other risk factors because

Table 2.3 Cohort studies of cancer of the testis and exposure to DDT and its metabolites

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
McGlynn et al. (2008) USA 1988–2003 Nested case–control study	Cases: 739 from Defence Medical Surveillance system Controls: 915 men with a sample in the registry matched on birth year, race/ethnicity, and date of sample Exposure assessment method: personal monitoring; GC-MS frequency for *p,p′*-DDT 20%	Testis (TGCT)	*p,p′*-DDE, µg/g			Age at blood donation, ethnicity, date of serum draw, age at reference date, cryptorchidism, family history of testicular cancer, height, BMI	Strengths: large study size; analysis of pre-diagnostic serum samples; high response rate; histologically confirmed tumours Limitations: some participants could not be contacted due to military deployment; adjustment for self-reported BMI; multiple comparisons
			≤ 0.157	186	1.00		
			0.158–0.250	167	1.01 (0.75–1.36)		
			0.251–0.390	146	1.00 (0.73–1.38)		
			> 0.390	236	1.71 (1.23–2.38)		
			Trend-test *P* value: 0.0002				
		Testis (seminoma)	*p,p′*-DDE, µg/g				
			≤ 0.157	59	1.00		
			0.158–0.250	68	1.17 (0.76–1.78)		
			0.251–0.390	57	0.98 (0.62–1.54)		
			> 0.390	128	1.91 (1.22–2.99)		
			Trend-test *P* value: 0.0008				
		Testis (non-seminoma)	*p,p′*-DDE, µg/g				
			≤ 0.157	127	1.00		
			0.158–0.250	98	0.98 (0.69–1.39)		
			0.251–0.390	89	1.10 (0.76–1.59)		
			> 0.390	108	1.63 (1.10–2.42)		
			Trend-test *P* value: 0.0044				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
McGlynn et al. (2008) USA 1988–2003 Nested case–control study (cont.)		Testis (TGCT)	*p,p′*-DDT, µg/g				
			≤ 0.029	630	1.00		
			0.0210–0.259	27	0.81 (0.49–1.35)		
			0.260–0.397	40	1.27 (0.81–2.01)		
			> 0.397	37	1.13 (0.71–1.82)		
			Trend-test *P* value: 0.5				
		Testis (seminoma)	*p,p′*-DDT, µg/g				
			≤ 0.029	260	1.00		
			0.0210–0.259	11	0.59 (0.29–1.19)		
			0.260–0.397	19	1.20 (0.67–2.14)		
			> 0.397	22	1.30 (0.73–2.30)		
			Trend-test *P* value: 0.4				
		Testis (non-seminoma)	*p,p′*-DDT, µg/g				
			≤ 0.029	369	1.00		
			0.0210–0.259	16	1.02 (0.55–1.9)		
			0.260–0.397	21	1.39 (0.79–2.42)		
			> 0.397	15	0.94 (0.50–1.77)		
			Trend-test *P* value: 0.86				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Purdue et al. (2009) Norway enrolment 1972 – 1978; follow-up 1999 Nested case–control study	Cases: 49 from Norwegian cancer registry Controls: 51 men from the Janus cohort matched by region, time period and age at blood draw Exposure assessment method: personal monitoring	Testis	*o,p′*-DDT:			Region, age at blood donation, time period of blood draw, total lipids	Strengths: use of serum samples collected before diagnosis – DDT had only recently been banned at the time of blood sample collection (1972–1978); completeness of the Norway cancer registry Limitations: small study size
			Tertile 1	16	1.0		
			Tertile 2	11	0.8 (0.2–2.6)		
			Tertile 3	21	1.4 (0.4–4.5)		
			p,p′-DDT:				
			Tertile 1	11	1.0		
			Tertile 2	20	2.3 (0.7–7.2)		
			Tertile 3	18	2.1 (0.6–7.2)		
			p,p′-DDE:				
			Tertile 1	11	1.0		
			Tertile 2	18	1.8 (0.6–5.5)		
			Tertile 3	20	2.2 (0.7–6.5)		
		Testis (seminomas)	*p,p′*-DDE:				
			Tertile 1	10	1.0		
			Tertile 2	10	1.0 (0.3–3.8)		
			Tertile 3	14	2.2 (0.5–8.7)		
Cohn et al. (2010) California, USA Enrolment 1959–1967; follow-up to 2000 Nested case–control study	Cases: 15 from california cancer registry Controls: 45 from cohort, matched by race and birth year Exposure assessment method: personal monitoring	Testis	Interquartile range			None	Strengths: assessment of exposure in utero from perinatal blood samples; maternal blood samples taken during time period of DDT use Limitations: very small study size; number lost to follow-up is not known; no adjustment for TGCT risk factors
			p,p′-DDT	15	0.70 (0.26–1.64)		
			p,p′-DDE	15	0.19 (0.04–0.62)		
			o,p′-DDT	15	0.77 (0.37–1.33)		
			p,p′-DDT/ *p,p′*-DDE ratio	15	3.56 (1.34–11.88)		
			Trend-test *P* value: 0.34				

BMI, body-mass index; CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; GC-ECD, gas chromatography with electron capture detector; GC-MS, gas chromatography-mass spectrometry; TGCT, testicular germ cell tumour; yr, year

of small numbers. Concentrations of *p,p′*-DDT, *o,p′*-DDT, and *p,p′*-DDT in mothers' serum were inversely associated with testicular cancer in univariate analyses; however, after adjustment for *p,p′*-DDE, the odds ratio for *p,p′*-DDT was increased to 4.81 (95% CI, 0.92–48.62). The odds ratio for *p,p′*-DDE in the same model was 0.08 (95% CI, 0.01–0.41). Testicular cancer cases had significantly higher DDT/DDE ratios than their matched controls ($P < 0.05$). [Direct measurements of three DDT-related compounds from maternal serum obtained 1–3 days after delivery was a strength of this study; however, the risk estimate for cancer of the testis associated with DDE concentration was extremely low in this population, and adjusting for DDE in this data may have introduced bias in risk estimates for DDT]. Since cancer of the testis is relatively rare and only 15 exposed cases were available for analysis, risks estimates were unstable and excessively sensitive to DDE adjustment. In addition, there was no adjustment for other risk factors. The results must therefore be considered with caution.]

2.1.4 Cancer of the liver

See Table 2.4

A nested case–control study was conducted among the participants in the Nutritional Intervention Trial in Linxian, China, to evaluate the association between DDT and primary cancer of the liver (McGlynn et al., 2006). Compared with the coastal regions of China, which have a high incidence of cancer of the liver attributed in part to aflatoxin exposure, Linxian has a relatively low incidence of cancer of the liver and low exposure to aflatoxin. The trial consisted of 29 584 women and men aged 40–69 years at enrolment (1986–1991). A 10 mL blood sample was collected from each participant at baseline. The cases included 168 individuals who developed cancer of the liver in 2001, and the control group included 385 individuals frequency-matched on age and sex who were alive and had never had cancer of the liver. In multivariable models controlled for hepatitis B surface antigen (HBsAg) status, serum DDE concentration and other covariates, the risk of developing liver cancer increased with increased serum DDT concentration (OR for quintile 5 versus quintile 1, 3.8; 95% CI, 1.7-8.6; *P* for trend, 0.002). The odds ratio for the same comparison without adjustment for DDE was 2.0 (95% CI, 1.1–3.9; *P* for trend, 0.049). In contrast there was no statistically significant association between liver cancer and DDE concentration, regardless of adjustment for DDT. The association between high serum DDT concentration and liver cancer was stronger among individuals with DDE concentrations below the median (OR, 3.55; 95% CI, 1.45–8.74) compared with those with DDE concentrations above the median (OR, 1.70; 95% CI, 0.97–2.98). [Risks may be particularly increased among persons exposed directly to DDT (resulting in a higher ratio of DDT to DDE) or alternatively may be associated with an individuals' ability to metabolize DDT and DDE. The odds ratios were not adjusted for alcohol drinking or exposure to aflatoxin.]

In Haimen City, China, a prospective study to identify environmental and genetic risk factors for hepatocellular carcinoma (HCC) in addition to hepatitis B virus (HBV) infection enrolled 83 794 people between February 1992 and December 1993 (Persson et al., 2012). Pre-diagnostic blood samples were collected at baseline and used to determine lipid-corrected DDT concentrations. Information on multiple risk factors and HBV infection status was determined based on HBsAg. Participants were actively followed until September 2000, and then passively followed via death-certificate determination. Incident cases of HCC were diagnosed by histology and/or liver imagining, α-fetoprotein elevation (> 400 ng/mL), clinical criteria, or by death certificate with post-mortem interviews of family members. HCC cases ($n = 488$) and controls ($n = 492$) were frequency-matched by

Table 2.4 Cohort studies of cancer of the liver and exposure to DDT and its metabolites

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
McGlynn et al. (2006) Linxian, China baseline 1984–85; follow-up 2001 Nested case–control study	Cases: 168; multiple methods Controls: 385; frequency-matched on age and sex Exposure assessment method: personal monitoring; *p,p′*-DDT and *p,p′*-DDE in serum	Liver (HCC)	DDT, ng/g lipid			Age, sex, HBsAg status, commune of residence	Strengths: pre-diagnostic blood samples; high DDT/DDE levels in Chinese population; controlling for other well-known risk factors for liver cancer Limitations: not all liver tumours histologically diagnosed; exposure to aflatoxin (AFB1) not known; no adjustment for alcohol drinking
			< 265 (Q1)	26	1.0		
			265–382 (Q2)	35	1.3 (0.7–2.5)		
			383–521 (Q3)	34	1.4 (0.7–2.6)		
			522–787 (Q4)	33	1.4 (0.7–2.7)		
			> 787 (Q5)	40	2.0 (1.1–3.9)		
			Trend-test *P* value: 0.049				
		Liver (HCC)	DDT, ng/g lipid			Age, sex, HBsAg status, commune of residence, DDE	
			< 265 (Q1)	26	1.0		
			265–382 (Q2)	35	1.5 (0.8–2.7)		
			383–521 (Q3)	34	1.7 (0.9–3.3)		
			522–787 (Q4)	33	2.1 (1.0–4.3)		
			> 787 (Q5)	40	3.8 (1.7–8.6)		
			Trend-test *P* value: 0.0024				
		Liver (HCC)	DDE, ng/g lipid			Age, sex, HBsAg status, commune of residence	
			< 1767 (Q1)	27	1.0		
			1767–2443 (Q2)	27	1.0 (0.5–1.9)		
			2444–3478 (Q3)	48	1.7 (0.9–3.1)		
			3479–5458 (Q4)	47	1.8 (1.0–3.3)		
			> 5458 (Q5)	19	0.7 (0.3–1.5)		
			Trend-test *P* value: 0.75				

Table 2.4 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
McGlynn et al. (2006) Linxian, China baseline 1984–85; follow-up 2001 Nested case–control study (cont.)		Liver (HCC)	DDE, ng/g lipid			Age, sex, HBsAg status, commune of residence, DDT	
			< 1767 (Q1)	27	1.0		
			1767–2443 (Q2)	27	1.0 (0.5–1.9)		
			2444–3478 (Q3)	48	1.7 (0.9–3.1)		
			3479–5458 (Q4)	47	1.9 (1.0–3.1)		
			> 5458 (Q5)	19	0.8 (0.3–1.7)		
			Trend-test *P* value: 0.75				
Persson et al. (2012) Haimen, China Enrolment 1992–1993; – follow-up to 2000 Nested case–control study	Cases: 473; HCC diagnosis ascertained by histology and/or liver imaging, alpha-fetoprotein elevation, clinical criteria, or by death certificate with post-mortem interviews of family members Controls: 488; frequency-matched by age, sex, residence area Exposure assessment method: personal monitoring	Liver (HCC)	*p,p′*-DDT, ng/g lipid			Age, sex, area of residence, HBsAg, family history of HCC, history of acute hepatitis, smoking, alcohol, occupation, continuous serum level of *p,p′*-DDE	Strengths: prospective design; completeness of follow up; large numbers; prediagnostic serum samples; adjustment for HBV chronic infection Limitations: no assessment of aflatoxin B1 exposure
			≤ 261	112	1.00		
			262–404	99	1.26 (0.65–2.46)		
			404–545	74	0.86 (0.41–1.80)		
			545–810	76	1.29 (0.57–2.92)		
			≥ 810	112	2.96 (1.19–7.40)		
			Trend-test *P* value: 0.04				
		Liver (HCC)	*p,p′*-DDE, ng/g lipid			Age, sex, area of residence, HBsAg, family history of HCC, history of acute hepatitis, smoking, alcohol, occupation, continuous serum level of *p,p′*-DDT	
			≤ 10 000	140	1.00		
			10 000–14 746	81	0.70 (0.36–1.35)		
			14 746–21 579	93	0.73 (0.36–1.46)		

Table 2.4 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Persson et al. (2012) Haimen, China Enrolment 1992–1993; – follow-up to 2000 Nested case–control study (cont.)			21 579–32 222	66	0.77 (0.35–1.70)		
			≥ 32 222	93	0.81 (0.33–2.03)		
			Trend-test *P* value: 0.79				
			DDT tertile 2	7	1.5 (0.5–4.9)		
			DDT tertile 3	7	1.8 (0.5–6.2)		
			Trend-test *P* value: 0.34				

BMI, body-mass index; CI, confidence interval DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; yr, year

age, sex, and area of residence. In a multivariate analysis adjusted for alcohol drinking, HBsAg, and other risk factors, the highest quintile of serum *p,p′*-DDT concentration was associated with an increased risk of HCC (OR, 2.96; 95% CI, 1.19–7.40) and there was a significant linear trend in the exposure-response relationship (*P* for trend, 0.04). There was no association with *p,p′*-DDE.

2.1.5 Other cancer sites

See Table 2.5

Sawada et al. (2010) reported the findings of a nested case–control analysis of cancer of the prostate nested within the Japan Public Health Center-based Prospective Study, a population-based cohort that included 65 657 men aged 40–69 years at baseline in 1990–1993, of whom 14 203 provided blood samples. During follow-up until 2005, 201 cases were identified from major hospitals, cancer registries, and death certificates. Two controls per case were matched by age, area of residence, date and time of blood sampling, and duration of fasting at blood collection. Concentrations of OCPs and PCBs were measured in plasma. No association between incidence of cancer of the prostate and concentration of *o,p′*-DDT, *p,p′*-DDT, or *p,p′*-DDE was observed (*P* for trend across quartiles of exposure distribution, 0.61, 0.45, and 0.65, respectively).

A prospective follow-up study enrolled 2283 adult residents of Charleston, South Carolina, USA in 1960. Venous blood samples were obtained from 919 subjects in 1974–1975 and analysed for *p,p′*-DDT and *p,p′*-DDE (Austin et al., 1989). In internal analysis using mortality until 1985, involving 209 deaths, a monotonic, but not statistically significant, rise in relative risk by tertile of exposure duration was observed for cancer of the respiratory tract. Adjusted relative risks relative to the lowest tertile of exposure were 1.5 (95% CI, 0.5–4.9) for tertile 2 and 1.8 (95% CI, 0.5–6.2) for tertile 3 (*P* for trend, 0.34). [Although follow-up was nearly complete, the small size of the cohort and the potential for residual confounding from smoking due to a lack of intensity and duration of smoking information limited the conclusions that can be made from the results of this study.]

2.1.6 Occupational cohort studies

See Table 2.6

(a) Non-Hodgkin lymphoma

The association between NHL and exposure to DDT was evaluated in the AHS by Purdue et al. (2007) and subsequently by Alavanja et al. (2014). Based on 523 incident cases of NHL among 54 306 study participants free of cancer at the time of enrolment, 98 participants with incident NHL, including multiple myeloma and chronic lymphocytic leukaemia (CLL), provided detailed data on DDT use before onset of disease (Alavanja et al., 2014). The primary use of DDT in this cohort occurred between the 1950s and the early 1970s. DDT was banned for use on crops in 1972 in the USA. Exposure assessment methods for the AHS are described in Section 1.4.4. Risk estimates were adjusted for age, state of residence, race, and total days of herbicide use. Ever use of DDT was not associated with total NHL (RR, 1.0; 95% CI, 0.8–1.3) or any NHL subtype; however, statistically significant positive exposure-response trends for total NHL were observed with lifetime days of DDT use (*P* for trend, 0.02)]. This positive association with total NHL was attenuated in analyses using an earlier definition of NHL that did not include multiple myeloma and CLL. In subtype analyses, the highest category of lifetime DDT use was associated with small B-cell lymphocytic lymphoma/CLL/mantle cell lymphoma (RR, 2.6; 95% CI, 1.3–4.8). The excess risk in this NHL subtype was, however, not significantly different to that for other NHL subtypes in the polytomous regression analysis.

Table 2.5 Cohort studies of cancer at other organ sites and exposure to DDT and its metabolites

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Sawada et al. (2010) Japan Enrolment 1990–1994; follow;up to 2005 Nested case–control study	Cases: 201 from hospitals, population-based cancer registries and death certificates Controls: 402 cohort members matched by age, area of residence, date and time of blood sampling, fasting at blood collection Exposure assessment method: personal monitoring; measurements made from blood samples taken at baseline	Prostate	*o,p′*-DDT, ng/g lipid			Smoking status, alcohol consumption, marital status, BMI, intake of green tea, intake of green tea and miso soup	Strengths: pre-diagnosis blood samples Limitations: response rate not known
			< 2.5	43	1.00		
			2.5–4.2	57	1.39 (0.79–2.44)		
			4.3–7.6	54	1.29 (0.71–2.34)		
			≥ 7.7	47	1.04 (0.54–2.03)		
			Trend-test *P* value: 0.61				
			p,p′-DDT, ng/g lipid			Smoking status, alcohol consumption, marital status, BMI, intake of green tea, intake of green tea and miso soup	
			< 24	41	1.00		
			24–40	64	1.51 (0.87–2.63)		
			41–63	50	0.92 (0.50–1.70)		
			≥ 64	46	1.0 (0.52–1.92)		
			Trend-test *P* value: 0.45				
			p,p′-DDE, ng/g lipid			Smoking status, alcohol consumption, marital status, BMI, intake of green tea, intake of green tea and miso soup	
			< 560	49	1.00		
			560–939	52	1.00 (0.60–1.66)		
			940–1599	47	0.89 (0.52–1.53)		
			≥ 1600	53	0.90 (0.52–1.54)		
			Trend-test *P* value: 0.65				

Table 2.5 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Austin et al. (1989) Charleston, South Carolina, USA 1974– 1985	919 residents with available blood sample at baseline (1974) Exposure assessment method: personal monitoring; total DDT calculated as a combination of *p,p′*-DDT and *p,p′*-DDE death certificate and expert committee	Respiratory tract:	DDT tertile 1	5		Age, sex, race, years of schooling, smoking status	Strengths: serum sampling in 1974 (high exposure period) Limitations: small study size; cancer mortality not incidence
			DDT tertile 2	7	1.5 (0.5–4.9)		
			DDT tertile 3	7	1.8 (0.5–6.2)		
			Trend-test *P* value: 0.34				

BMI, body-mass index; CI, confidence interval DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; yr, year

Table 2.6 Occupational cohort studies of exposure to DDT

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Alavanja et al. (2014b) Iowa and North Carolina, USA 1993–2011	57 310 certified private and commercial male pesticide applicators enrolled in the Agricultural Health Study Exposure assessment method: questionnaires administered 1993–1997 and 1999–2005	NHL	No exposure to DDT < 8.75 days of use 8.75–56 days of use > 56–1627.5 Trend-test *P* value: 0.02	152 43 28 27	1.0 1.3 (0.9–1.8) 1.1 (0.7–1.7) 1.7 (1.1–2.6)	Age, state, race, total herbicide days	Strengths: large prospective cohort study; pesticide applicators knowledgeable about use of specific pesticides; detailed exposure estimates Limitations: field verification of exposure estimates done on only a sample of applicators
Garabrant et al. (1992) USA Employment 1948–1971, follow-up dates NR Nested case–control study	Cases: 28; company death records Controls: 112 living cohort members matched by age, sex, & race Exposure assessment method: company records	Pancreas	Ever exposure Trend-test *P* value: 0.02	6	4.8 (1.3–17.6)	NR	Strengths: DDT manufacturing workers had relatively high exposure to DDT Limitations: small number of cases; exposure ascertainment by department and job title can allow for misclassification
Andreotti et al. (2009) Iowa and North Carolina, USA 1993–2004 Nested case–control study	Cases: 93; state cancer registries Controls: 82 503; cancer free cohort members Exposure assessment method: questionnaire	Pancreas	Ever use	6	0.4 (0.2–0.9)	Age, smoking, diabetes, applicator or spouse of applicator	Strengths: large prospective cohort of knowledgeable pesticide applicators Limitations: few exposed cases available for analysis
Beard et al. (2003) Australia 1935–1996	1999 workers and 1984 non-exposed workers; outdoor pest-control workers Exposure assessment method: company records; national death and insurance registers	Pancreas Leukaemia	Exposure duration < yrs ≥ 3 yrs Exposure duration < 3 yrs ≥ 3 yrs	 1 2 2 1	 5.27 (1.09–15.4) 1.35 (0.37–3.44) 2.57 (0.06–14.29) 1.52 (0.31–4.45)	Age and calendar period Age and calendar period	Strengths: DDT-exposed workers were compared with a non-exposed group of workers and with the general population Limitations: total exposed population was not large; limited exposure assessment

Table 2.6 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Cocco et al. (2005) Sardinia, Italy 1956–1999	4552 men exposed to DDT during antimalaria operation Exposure assessment method: JEM; algorithm based on the European Predictive Operator Exposure Model (EUROPOEM) database Sardinia and Italian mortality records	All cancers combined	Cumulative DDT exposure (mg)			Age, age at first exposure, ethnic origin	Strengths: documented exclusive exposure to DDT by job type and algorithm estimate Limitations: small numbers for some types of cancer
			Unexposed	228	1.0		
			0.01–21.6	154	1.1 (0.9–1.4)		
			21.7–531.4	133	0.9 (0.7–1.1)		
			531.5–2,755	134	0.9 (0.7–1.1)		
			> 2755	152	1 (0.8–1.2)		
		Stomach	Cumulative DDT exposure (mg)			Age, age at first exposure, ethnic origin	
			Unexposed	11	1.0		
			0.01–21.6	8	1.2 (0.5–3.0)		
			21.7–531.4	8	1.1 (0.5–2.8)		
			531.5–2755	13	1.7 (0.7–3.7)		
			≥ 2755	16	2.0 (0.9–4.4)		
			Trend-test *P* value: > 0.05				
Koutros et al. (2013) Iowa and North Carolina, USA 1993–2007	54 412; Agricultural Health Study Exposure assessment method: expert assessment	Prostate: total	Cumulative lifetime exposure to DDT				See Alavanja et al. (2014b) for details Strengths: large cohort study, in agricultural population thus high exposure prevalence, good exposure assessment
			Unexposed*	578	1.00	Age, state, smoking, fruit servings, leisure time physical activity in winter, race, family history	
			Q1*	96	0.98 (0.78–1.22)		
			Q2*	97	1.27 (1.02–1.58)		
			Q3*	96	1.27 (1.02–1.58)		
			Q4*	65	1.18 (0.95–1.34)		
			*Trend-test *P* value: 0.14				
		Prostate: aggressive	Cumulative lifetime exposure to DDT				
			Unexposed*	267	1.00	Age, state, smoking, fruit servings, leisure time physical activity in winter, race, family history	
			Q1*	47	1.06 (0.76–1.48)		
			Q2*	46	1.17 (0.85–1.61)		
			Q3*	46	1.56 (1.13–2.15)		
			Q4*	46	1.3 (0.94–1.80)		
			*Trend-test *P* value: 0.10				

CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; JEM, job–exposure matrix; NHL, non-Hodgkin lymphoma; NR, not reported; OR, odds ratio; yr, year

(b) Cancer of the prostate

Koutros et al. (2013) studied the association between total and aggressive cancer of the prostate with 48 pesticides, including DDT, in the AHS. In follow-up until 2007, there were 1962 incident cases of cancer of the prostate, of which 919 were classified as aggressive. Relative risks for the association between aggressive cancer of the prostate and cumulative lifetime exposure to DDT were greater than unity, but statistically significant only in the third quartile of exposure (RR, 1.56; 95% CI, 1.13–2.15). The relative risk in the fourth quartile was lower (RR, 1.30; 95% CI, 0.94–1.80) and there was no significant exposure-response trend (*P* for trend, 0.10). Similar findings were reported for total prostate cancer and for prostate cancer stratified by family history.

(c) Cancer of the pancreas

Garabrant et al. (1992) conducted a cohort study of mortality among 5886 chemical-manufacturing workers in the USA, which included a nested case–control study of exposure to DDT and cancer of the pancreas. There were 28 deceased cases of pancreatic cancer and 112 controls identified from the cohort matched on age, sex, and race, who were living at the time of the case's death. Only men were included. Next-of-kin of cases and controls were interviewed by telephone for lifestyle factors, occupational history, and past chemical exposures. Exposure histories were constructed from company records and interviews with co-workers that sought to determine whether a subject would have been exposed to specific chemical given their work location and job title. DDT was associated with pancreatic cancer in an ever versus never comparison (OR, 4.8; 95% CI, 1.3–17.6). Among workers with exposure duration greater than the median [not reported; mean exposure duration, 47 months] the risk was 7.4-times [95% CI not reported] that of those with no exposure. The risk also increased with time since first exposure. In models accounting for potential confounding by occupational and lifestyle factors, the odds ratio was 6.1 [95% CI not reported] (P = 0.02). [This study was quite small and included only deceased cases. Exposure assessment by location and job title may allow some misclassification.]

The potential link between the use of pesticides, including DDT, and cancer of the pancreas was evaluated in a nested case–control analysis (Andreotti et al., 2009) based on the AHS (see Alavanja et al., 2014),. Incident cases diagnosed through 2004 were included in this analysis (93 cases: 64 male applicators, 29 female spouses). Information on exposure was obtained from questionnaires administered at enrolment. Ever use of DDT by either applicators or spouses was inversely associated with cancer of the pancreas (OR, 0.4 [95% CI, 0.2–0.9]) when adjusted for age, cigarette smoking, diabetes, and applicator type (farmer, commercial applicator, non-certified applicator [spouse]). These results were not appreciably changed when the associations was limited to only certified applicators. [Although the analysis was able to control for age, applicator type, smoking history, and diabetes, only six DDT-exposed applicators were available for this evaluation, which limits the strength of the conclusion.]

(d) Studies of multiple cancer sites

Beard et al. (2003) studied mortality among 1999 men in New South Wales, Australia, who were part of an insecticide-application programme at some point during the period 1935–1996. Mortality and incidence of cancer was compared with that in a cohort of 1984 male outdoor workers not occupationally exposed to pesticides, and with the Australian population. A small portion of surviving subjects also completed a lifestyle morbidity questionnaire. Exposure to specific pesticides was estimated from records of when each pesticide was used and individual employment dates: 394 of the

pest-control workers were employed during the period of DDT use from 1955 to 1962. Results were reported for all cancers, prostate cancer, and leukaemia. Among workers employed ≥ 3 years during the period of DDT use, the standardized mortality ratio (SMR) for all cancers combined was 1.16 (95% CI, 0.92–1.46) relative to the national population. Mortality from cancer of the pancreas was more frequent in subjects exposed to DDT for < 3 years (SMR, 5.27; 95% CI, 1.09–15.40; 1 case); the association was weaker in those working for ≥ 3 years. Mortality from cancer of the pancreas was also compared in exposed workers and the unexposed cohort and gave largely similar results. A similar pattern was observed for leukaemia (SMR, 2.57; 95% CI, 0.06–14.29) among workers employed < 3 years. [The small number of exposed cases and the lack of information on exposure to individual pesticides limited the conclusions that could be drawn from this study.]

Cocco et al. (2005) investigated the association between exposure to DDT and cancer mortality in a cohort of 4552 men exposed to DDT as a part of antimalaria operation in Sardinia, Italy, during 1946–1950. Employment records and information on DDT use during the operation were used to develop individual estimates of average and cumulative exposure. Among applicators, an algorithm based on a European Predictive operator exposure model (EUROPOEM) database was used to estimate dermal and inhalation exposure to DDT. Apart from a short period when chlordane was used in unspecified areas, all the individuals were exposed only to DDT. Mortality of the cohort was analysed in comparison to the general Sardinian population and in internal comparisons to an unexposed subcohort. Relative to the general population, overall cancer mortality was decreased among DDT-exposed workers, mainly due to a low risk of cancer of the lung. The standardized mortality ratio for cancer of the stomach was 1.4 (95% CI, 0.7–2.7; 45 observed deaths) among exposed workers, while the standardized mortality ratios for all of the other cancer sites reported, including liver, pancreas, lympho-haematopoietic system, and leukaemia were unity or below. Similar patterns were observed among DDT applicators. In internal analyses, mortality from cancer of the stomach increased with increasing cumulative exposure to DDT (RR, 2.0; 95% CI, 0.9–4.4, in the highest quartile compared with unexposed workers), but the trend was not significant. Increased relative risks for cancer of the bladder, but no significant trend, were also observed in the higher categories of exposure to DDT (RR, 1.4; 95% CI, 0.7–3.4; for the fourth quartile compared with the unexposed). There was no indication of exposure-response relationships for other cancer sites. [Information on some important potential confounders for cancers of the lung and pancreas, such as tobacco use and alcohol consumption, were not individually available for study participants, and this may have resulted in a bias towards the null, since indirect evidence in the paper suggested that applicators smoked less than the comparison group.]

2.2 Case–control studies

The Working Group reviewed the available meta-analyses with the case–control studies for the cancers concerned, as most of the included studies had that design.

2.2.1 Cancer of the breast

(a) Exposure measured in blood

See Table 2.7

Twenty-two case–control studies of cancer of the breast and exposure to DDE or DDT were identified. Most studies adjusted for some or all of the standard reproductive and demographic risk factors for breast cancer, such as BMI, adult body-weight gain, family history, menopausal status, age at menarche, age at first birth, and lactation history. Some studies reported data for

Table 2.7 Case–control studies on cancer of the breast and exposure to DDT and its metabolites measured in blood or adipose tissue

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariate	Comments
Zheng et al. (2000) Connecticut, USA 1995–1997	Cases: 475; hospital pathology department and cancer centre Controls: 502; hospital patients with BBD (n = 347, response rate 71%) and 155 population-based by random-digit dialling (response rate, 61%) Exposure assessment method: biomarker; serum DDE, lipid-corrected gravimetric lipids; blood drawn post-diagnosis	Breast	DDE, ng/g lipid < 295.0 295.0–660.0 > 660.0 Trend-test P value: 0.58	 139 157 179	 1.00 1.05 (0.76–1.47) 0.96 (0.67–1.36)	BMI, menarche, lactation, FFTP age, parity, HRT, dietary fat, family income, family history, race, study site	Strengths: relatively large sample size Limitations: mainly hospital cases & controls, control groups combined; blood drawn after diagnosis

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariate	Comments
Demers et al. (2000) Quebec, Canada 1994–1997	Cases: 314; hospital Controls: 523; 219 hospital; 305 population Exposure assessment method: personal monitoring	Breast	DDE, ng/g lipid, population controls			Age, region, BMI, lactation, FFTP, fertility years, family history, BBD history	Strengths: relatively large sample size, some population controls Limitations: possible confounding as higher DDE in cases could be to more aggressive cancer; cases had lower BMI than controls and were younger; blood collected after surgery for cases & hospital controls
			184.4– < 282.5	52	0.75 (0.45–1.25)		
			282.5– < 427.8	56	1.06 (0.62–1.79)		
			427.8– < 680.0	67	0.86 (0.52–1.42)		
			≥ 680.0	72	1.00 (0.60–1.67)		
			DDT, ng/g lipid, population controls				
			6.0 – < 7.9	52	0.57 (0.34–0.95)		
			7.9 – < 10.6	50	0.5 (0.30–0.84)		
			10.6 – < 15.0	63	0.71 (0.43–1.19)		
			≥ 15.0	70	0.81 (0.48–1.37)		
			DDE, ng/g lipid, hospital controls				
			184.4 – < 282.5	41	0.85 (0.45–1.59)		
			282.5 – < 427.8	57	0.66 (0.37–1.19)		
			427.8 – < 680.0	36	1.54 (0.81–2.95)		
			≥ 680.0	40	1.36 (0.71–2.63)		
			DDT, ng/g lipid, hospital controls				
			6.0 – < 7.9	44	0.85 (0.45–1.59)		
			7.9 – < 10.6	36	1.06 (0.57–1.98)		
			10.6 – < 15.0	44	1.07 (0.59–1.94)		
			≥ 15.0	45	1.37 (0.73–2.56)		

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariate	Comments
Millikan et al. (2000) North Carolina, USA 1993–1996	Cases: 748 from atate cancer registry Controls: 659; driving license and Medicare lists Exposure assessment method: personal monitoring; plasma GC-ECD, lipid correction, *o,p*-DDT internal standardd	Breast	DDE, µg/g lipid All < 0.394 All 0.394–< 1.044 ≥ 1.044 African-Americans < 0.71 African-Americans 0.71–< 1.8 African-Americans ≥ 1.8 Whites < 0.30 Whites 0.30–< 0.66 Whites ≥ 0.66	 274 231 243 89 90 113 176 146 134	 1.00 1.05 (0.79–1.40) 1.09 (0.79–1.51) 1.00 1.12 (0.70–1.77) 1.41 (0.87–2.29) 1.00 0.97 (0.68–1.40) 0.98 (0.67–1.43)	Age, race (white/ black), menopause, BMI, parity, lactation, HRT use, income	292 African-American cases; 456 white cases Strengths: population-based, relatively large sample size Limitations: limited precision in stratified analysis
Gammon et al. (2002) Long Island, NY, USA 1996–1997	Cases: 646; hospital records Controls: 429; population (random-digit dialling and insurance records) Exposure assessment method: personal monitoring; serum, ECD, lipid-corrected	Breast	DDE, ng/g lipid < 306.91 306.91–515.00 515.01–798.24 798.25–1373.48 1378.49–11 818.78 DDT, ng/g lipid < 44.79 44.79–61.43 61.44–81.20 81.21–108.03 108.03–747.29	 122 110 127 123 150 129 96 123 134 133	 1.00 0.88 (0.58–1.32) 0.94 (0.63–1.43) 0.92 (0.60–1.42) 1.20 (0.76–1.9) 1.00 0.69 (0.44–1.07) 1.04 (0.66–1.63) 1.16 (0.75–1.80) 1.15 (0.74–1.79)	Age, race, fertility, BBD history	Strengths: population-based, large sample size Limitations: blood drawn after diagnosis
Gatto et al. (2007) Los Angeles, USA 1994–1998	Cases: 355 from cancer registry Controls: 327; random-digit dialling Exposure assessment method: personal monitoring; serum DDE	Breast	Serum DDE, µg/g lipid ≤ 0.44 > 0.44–0.73 > 0.73–1.15 > 1.15–1.91 > 1.91 Trend-test *P* value: 0.74	 61 62 76 81 75	 1.00 0.98 (0.59–1.62) 1.07 (0.65–1.75) 1.14 (0.69–1.88) 1.02 (0.61–1.72)	Age, BMI, Lactation, strata	African-American women only, ages 35–64 yrs Strengths: population-based, large sample of African-American women Limitations: timing of blood sampling not specified

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariate	Comments
Charlier et al. (2004) Liege, Belgium 2001–2002	Cases: 231; hospital Controls: 290; hospital, healthy screening patients Exposure assessment method: personal monitoring; DDE serum GC-MS/EI	Breast:	DDE > 0.5 ppb	176	2.21 (1.41–3.48)	Parity, lactation, menopause, HRT, family history	Strengths: sample size; blood draw before surgery Limitations: no BMI information; hospital-based controls
Itoh et al. (2009) Nagano, Japan 2001–2005	Cases: 403; hospital presurgery Controls: 403; women having medical checkups, matched for age, residence Exposure assessment method: personal monitoring; blood draw before surgery	Breast	Quartile median (ng/g lipid) *p,p′*-DDE: 160 300 490 1100 *p,p′*-DDT: 5.6 8.5 12.0 23.0 *o,p′*-DDT: 0.9 1.3 2.0 4.1	 116 89 107 91 136 79 97 91 103 100 122 78	 1.00 0.47 (0.24–0.92) 0.99 (0.48–2.02) 1.02 (0.46–2.26) 1.00 0.58 (0.27–1.25) 0.99 (0.47–2.07) 0.58 (0.27–1.25) 0.57 (0.25–1.29) 1.13 (0.53–2.38) 0.67 (0.30–1.50)	BMI, menopause, smoked fish intake, vegetable intake, family history, menarche, breast cancer history, screening, lactation, history of chemotherapy, FFTP, Age	Strengths: large sample, GC-MS method, presurgery ascertainment Limitations: controls may have medical conditions
López-Carrillo et al. (1997) Mexico City, Mexico 1994–1996	Cases: 141; hospital Controls: 141; hospital, non-gynaecology, non-oncology, matched on age and residence Exposure assessment method: biomarker	Breast	DDE, ng/g lipid < 242.11 242.11–509.25 > 509.25	 50 42 49	 1.00 0.60 (0.31–1.16) 0.76 (0.41–1.42)	Age, BMI, lactation, menopause, parity, family history, FFTP age	Strengths: blood sampled before treatment; control for major risk factors Limitations: controls were hospital-based

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariate	Comments
Olaya-Contreras et al. (1998) Bogota, Colombia 1995–1996	Cases: 153; hospital; incident primary cancer Controls: 153; non-cancer hospital controls, age-matched Exposure assessment method: biomarker; serum DDE ECD; blood drawn before chemotherapy	Breast	DDE, ng/mL 0.10–0.14 0.15–1.96 1.97–19.20 Premenopausal: 0.10–0.14 0.15–2.06 2.07–19.20 Postmenopausal: 0.10–0.19 0.20–1.90 0.91–19.00	 39 45 69 15 20 25 24 25 44	 1.00 1.20 (0.64–2.25) 1.95 (1.10–3.52) 1.00 1.40 (0.55–3.43) 2.46 (0.96–6.30) 1.00 1.14 (0.50–2.75) 1.85 (0.84–4.05)	Family history, BMI, parity, menopause, breast cancer history, lactation	Strengths: menopausal stratification Limitations: not lipid-adjusted; no stage information
Moysich et al. (1998) New York state, USA 1986–1991	Cases: 154; area hospitals, incident primary cancer Controls: 192; population (motor vehicle and health insurance rolls) Exposure assessment method: biomarker; serum, ECD	Breast	DDE, ng/g lipid 1st tertile 2nd tertile 3rd tertile	 54 46 54	 1.00 1.01 (0.56–1.86) 1.34 (0.71–2.55)	Age, education, family history, parity, BMI, lactation, FFTP age, years since pregnancy, fruit/vegetable intake, lipids	Postmenopausal women only Strengths: population-based Limitations: low participation rates; blood collected after surgery
Mendonça et al. (1999) Rio de Janeiro, Brazil 1995–1996	Cases: 177; hospital, admitted within 6 months of diagnosis Controls: 350; hospital visitors without breast cancer Exposure assessment method: biomarker; serum ECD	Breast	Serum DDE, ng/mL < 1.3 1.3–2.4 2.5–3.9 4.0–7.6 ≥ 7.6 Trend-test *P* value: 0.79	 29 32 35 37 29	 1.00 0.95 (0.49–1.80) 1.34 (0.68–2.60) 1.12 (0.58–2.10) 0.83 (0.4–1.60)	Age, lactation, education, parity, smoking, family history, breast size	OR in abstract differs from tables Strengths: NR Limitations: no adjustment for BMI or alcohol; not lipid-adjusted

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariate	Comments
Dello Iacovo et al. (1999) Naples, Italy 1997–1998 (cases), 1993–1998 (controls)	Cases: 170; hospital, first breast cancer surgery Controls: 195; community controls from ongoing cohort study Exposure assessment method: biomarker; fasting blood draw	Breast	Serum DDE, ng/mL < 6 6–10.2 > 10.2	 51 49 70	 1.00 0.84 (0.47–1.51) 1.24 (0.7–2.2)	Age, BMI, lactation, parity, serum lipids, education, smoking, menopause	Strengths: sizeable sample; > 30% having DDE > 10 ng/mL Limitations: cases and controls from different sources and not concurrent; criteria not stated for selection of controls; menopause not controlled
Romieu et al. (2000) Mexico City, Mexico 1990–1995	Cases: 120; public hospital network Controls: 126; age-stratified population sample Exposure assessment method: biomarker; lipid-corrected ECD	Breast	DDE, ng/g lipid 0.20–1.16 1.17–1.96 1.17–3.48 3.49–14.84 Trend-test *P* value: 0.06	 18 20 38 44	 1.00 1.06 (0.44–2.55) 1.75 (0.76–4.09) 2.16 (0.85–5.50)	Age, menarche, lactation, BMI, menopause	Strengths: high participation rates Limitations: smaller sample size; age difference in cases and controls could affect DDE/DDT risk; selection criteria for subsample not given
Wolff et al. (2000b) East Harlem, NY, USA 1994–1995	Cases: 175; hospital, presurgery Controls: 355; patients with benign breast disease (181) and patients seeking screening or minor procedures (175) Exposure assessment method: biomarker; serum DDE/DDT/ chlordane/PCB; ECD; most blood pre-surgery	Breast	DDE, µg/g lipid 0–0.44 0.45–1.03 > 1.04–12.90 Trend-test *P* value: 0.499 DDT, µg/g lipid 0–0.0207 0.0208–0.033 0.034–1.3 Trend-test *P* value: 0.241	 56 42 55 44 50 56	 1.00 0.80 (0.49–1.30) 0.93 (0.56–1.50) 1.00 1.19 (0.73–2.00) 1.34 (0.82–2.20)	Age, age-square, menopause, race, strata, lactation, HRT, parity	Control groups pooled for analysis Strengths: stage and receptor information, multiracial Limitations: hospital-based

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariate	Comments
Schecter et al. (1997) Hanoi, Viet Nam 1994	Cases: 21; hospital, histologically-confirmed invasive cancer Controls: 21; hospital; BBD Exposure assessment method: biomarker; serum; blood taken at diagnosis	Breast	DDE, ng/mL 3rd vs 1st tertile DDT, ng/mL 3rd vs 1st tertile	8 5	1.14 (0.23–5.68) 1.21 (0.15–9.65)	Menarche, parity, lactation, weight	DDE 16.7 ng/mL, DDT 2.4 ng/mL in controls Strengths: NR Limitations: BBD controls; cases likely at an advanced stage
Soliman et al. (2003) Egypt Period NR	Cases: 69; hospital, premenopausal Controls: 53; hospital visitors, age-matched Exposure assessment method: biomarker; serum; ECD; blood sampled pre-treatment	Breast	DDE (ppb) > 4.7	69	1.41 (0.63–3.19)	Age, lactation, residence	Strengths: highly exposed younger women Limitations: small sample size; limited control for potential confounders
Pavuk et al. (2003) Slovakia 1997–1999	Cases: 24; hospital, all had treatment Controls: 88; participants in another study Exposure assessment method: biomarker; serum gravimetric lipids, ECD	Breast	DDE, ng/g lipid 233–2582 2583–4388 4389–19 912 Trend-test *P* value: 0.10 DDT, ng/g lipid 29–81 82–136 137–562 Trend-test *P* value: 0.68	 8 2 14 8 3 13	 1.00 0.53 (0.08–3.27) 3.04 (0.65–14.3) 1 0.33 (0.06–1.7) 1.19 (0.27–5.23)	Age, menarche, education, alcohol intake, smoking	Strengths: NR Limitations: blood drawn after treatment and up to 2 yrs since diagnosis

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariate	Comments
Rubin et al. (2006) Alaska 1981–1987	Cases: 63; from Alaska Native Tumor registry with a prior banked serum sample Controls: 63; pair-matched cancer-free Alaska native women with a sample in the serum bank the same year as a case sample Exposure assessment method: biomarker	Breast	DDE (ppb) < 6.17 6.17–9.61 > 9.62	 15 18 30	 1.00 0.57 (0.15–2.19) 1.43 (0.46–4.47)	Parity, family history of breast cancer, ethnicity, triglycerides, cholesterol levels	Geometric mean DDE, 7.36 ng/mL in controls; Alaska native population Strengths: blood sampled years before diagnosis; wide range of exposure Limitations: small sample size; limited control for breast-cancer risk factors
van't Veer et al. (1997) Germany, the Netherlands, Northern Ireland, Switzerland, and Spain 1991–1992	Cases: 265; EURAMIC study, postmenopausal women age 50–74 Controls: 341; hospital, matched by centre and age Exposure assessment method: biomarker; needle aspirates from gluteal adipose tissue	Breast	DDE, µg/g ≤ 0.86 0.87- 1.89 1.89–3.46 > 3.46 Trend-test *P* value: 0.02	 73 75 63 54	 1.00 1.14 (0.62–2.12) 0.71 (0.38–1.34) 0.48 (0.25–0.95)	Age, centre, BMI, age at first birth, alcohol consumption	Strengths: women with substantial weight loss in the past year excluded Limitations: low response rates among controls
Liljegren et al. (1998) Sweden 1993–1995	Cases: 43; hospital Controls: 35; hospital, BBD Exposure assessment method: biomarker; frozen adipose tissue from surgery	Breast	DDE, ng/g lipid ≤ 700 > 700	 31 12	 1.0 0.4 (0.1–1.2)	Age, parity	Patients operated by one surgeon for malignant or benign breast diseases Strengths: ER status was determined Limitations: very small sample size

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariate	Comments
Zheng et al. (1999) Connecticut, USA 1994–1997	Cases: 304; patients with surgery for incident breast cancer and available tissue sample Controls: 186; surgical patients with incident BBD and available tissue sample Exposure assessment method: biomarker; GC; breast adipose tissue for cases and controls	Breast	DDE, ng/g lipid < 412.6 412.6–779.2 779.3–1355.9 ≥ 1356.0 Trend-test *P* value: 0.4	 65 85 71 83	 1 1.3 (0.7–2.2) 0.9 (0.5–1.6) 0.9 (0.5–1.5)	Age, BMI, lifetime months of lactation, age at menarche, age at FFTP, menopausal status, race, income 10 years before the disease diagnosis or interview	Women aged 40–79 yrs Strengths: relatively large sample size Limitations: based in only one hospital
Aronson et al. (2000) Ontario, Canada 1995–1997	Cases: 217; hospital: women scheduled for biopsy with subsequent diagnosis of cancer Controls: 213; as for cases but with nonmalignant diagnoses Exposure assessment method: biomarker; biopsy specimens obtained before diagnosis	Breast	DDE, µg/kg lipid ≤ 368 369–727 728–1389 > 1390	 55 59 54 49	 1.00 0.96 (0.55–1.68) 0.92 (0.51–1.67) 1.62 (0.84–3.11)	Age, study site, menopausal status, present use of HRT, ethnicity, BMI fat and alcohol intake	Strengths: control for multiple risk factors; tissue sampled before diagnosis Limitations: Based on only two hospitals; DDE analysis only for about 50% of eligible women

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariate	Comments
Ibarluzea et al. (2004) Spain 1996–1998	Cases: 198; hospital: women undergoing surgery for newly diagnosed malignant breast cancer Controls: 260; hospital: women undergoing non-cancer-related surgery (65% gall bladder) Exposure assessment method: biomarker; adipose tissue from breast for cases and abdomen for controls	Breast	DDE, ng/g lipid ≤ 201.72 201.73–397.67 397.68–675.97 ≥ 675.98	 33 40 29 19	 1.00 1.04 (0.59–1.84) 1.23 (0.69–2.17) 1.22 (0.68–2.21)	Age, reference hospital, number of children, age at FFTP, family history of breast cancer, and alcohol and tobacco consumption	Women aged 36–70 yrs Strengths: relatively good sample size, high response rates

BBD, benign breast disease; BMI, body-mass index; CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; ER, estrogen receptor; FFTP, first full-term pregnancy; GC-ECD, gas chromatography-electron capture detector; GC-MS/EI, gas chromatography-mass spectrometry- electron ionization; HRT, hormone replacement therapy; NR, not reported; OR, odds ratio; PCB, polychlorinated biphenyl; vs, versus; yr, year

DDT as well as for DDE, but the predominant findings were related to DDE. Most studies used blood serum; a few used plasma; one used whole blood. Unless otherwise indicated, DDE refers to p,p′-DDE and DDT to p,p′-DDT. These studies are described below in order of decreasing size. In addition, a pooled analysis of three case–control studies and two cohort studies also reviewed individually in this volume is described in this section (Laden et al., 2001b). Four studies reported incomplete study details (Charlier et al., 2003; Li et al., 2006a; Chang et al., 2008; Zhang et al., 2013) and were excluded from further review.

Seven studies with more than 200 cases and a similar number of controls were availabile to the Working Group; four were from the USA and the remaining three were from Canada, Belgium, and Japan (Demers et al., 2000; Millikan et al., 2000; Zheng et al., 2000; Gammon et al., 2002; Charlier et al., 2004; Gatto et al., 2007; Itoh et al.,2009). Three were population based, four hospital-based. Data collection occurred in the mid 1990s, except for Itoh et al. (2009), which began in 2001, and blood draw was generally soon after diagnosis and before treatment. The highest levels of DDE in blood serum were observed among black women in two studies in the USA, with an average of approximately 8 ng/mL among controls in both North Carolina (Millikan et al., 2000) and Los Angeles (Gatto et al., 2007).

Zheng et al. (2000) conducted a case–control study in Connecticut, USA. Cases (n = 475) were enrolled at a New Haven hospital and through a cancer centre that captured cases from a nearby county. Controls (n = 502) were frequency-matched on age, comprising 347 hospital patients with benign breast disease and 155 population-based controls sampled by random-digit dialling. Mean serum DDE concentration was 456 ng/g lipid in controls. Associations were null (OR, 0.96; 0.67–1.36; P for trend, 0.58) for the third versus first tertile of DDE concentration (P for trend, 0.58), adjusted for standard risk factors for breast cancer. Results were similar in analyses stratified by parity and breast feeding. [This was a large study, but blood was drawn after diagnosis and most controls were hospital-based and had benign breast disease, which shares risk factors with breast cancer. Data for DDT were not reported.]

Demers et al. (2000) undertook a hospital based case–control study in Québec, Canada. Cases (n = 314) were women with invasive cancer identified in 1994–1997 before treatment. Controls were surgical patients (n = 218) with no gynaecologic conditions and women randomly selected from insurance lists (305). Controls and cases were frequency matched on age and residence. Mean serum DDE was 463 ng/g lipid in controls; DDT was 12 ng/g lipid. Associations were null in analyses with population controls (e.g. OR, 1.00; 95% CI, 0.60–1.67; for DDE fifth versus first quintile); however, in analyses using hospital controls the odds ratio was non-significantly increased in the highest exposure categories (OR, 1.37; 95% CI, 0.71–2.63; for the fifth versus the first quintile). Similar patterns were observed for DDT. In case-case analyses, more aggressive cancer was more strongly associated with higher DDE concentration. [This was a large study, with some population-based controls. The Working Group was concerned that a significant proportion of aggressive cases could have higher organochlorine serum levels because of disease.]

Millikan et al. (2000) conducted a population-based case–control study of cancer of the breast among black and white women in North Carolina, USA. DDT exposures in this population in the southern USA were relatively high: mean plasma DDE concentrations among controls were 1690 ng/g lipid among black women, and 760 ng/g lipid among white women. Data for DDT were not reported. The risk of breast cancer increased with DDE concentration among black women (OR, 1.41; 95% CI, 0.87–2.29; for thirrd versus first tertile of DDE),

but not among white women (OR, 0.98; 95% CI, 0.67–1.43), or all women combined (OR, 1.09; 95% CI, 0.79–1.51). The risk was higher but imprecise among black women with BMI < 25 kg/m^2 (OR, 3.84; 95% CI, 0.98–15.08; third versus first tertile of DDE). Analyses across other strata, history of having lived or worked on a farm, parity, and lactation gave imprecise results. [This large population-based study included a large number of black women, with higher exposures than in many other studies. Participation was much lower in controls than cases, and the analyses by BMI strata suggested unresolved confounding from pharmacokinetic factors or chance.]

Gammon et al. (2002) reported on a study of cancer of the breast and exposure to organochlorine compounds in Long Island, New York, USA. Incident cases of breast cancer in 1996 and 1997 were identified from hospital pathology records, and age-matched population controls were sampled by random-digit dialling or from health insurance lists for those aged > 65 years. Data on the concentration of DDE and DDT in serum were available for a subset of cases and controls (643 cases and 427 controls for DDE; 633 cases and 418 controls for DDT). No increase in the risk of cancer of the breast was associated with the concentration of either DDE or DDT. Findings were similar in analyses stratified by BMI and tumour hormone-receptor status. [This large population-based study included many environmental risk factors, and results were stratified by suspected risk modifiers. Participation was lower in controls than cases.]

Gatto et al. (2007) studied the association of cancer of the breast and serum DDE concentration among African-American women in a population-based study in Los Angeles, USA. Organochlorine concentrations were measured in serum of a subset of the larger study (355 cases, 327 controls). The lipid-adjusted concentration of serum DDE was higher than in most studies (1250 ng/g lipid among controls); however, there was no association between risk of breast cancer and DDE concentration (OR, 1.02; 95% CI, 0.61–1.74; for fifth versus first quintile; *P* for trend, 0.74. [The large sample was population-based for cases and controls. Participation was lower in controls than cases. DDT was not reported. It was not clear whether blood was sampled before treatment.]

Charlier et al. (2004) studied the association between cancer of the breast and serum DDE concentration among 231 cases recruited from a hospital surgery unit and 290 age-matched controls seeking cytology screening in Belgium, 2001–2002. Blood was collected pre-surgery, and DDE was measured in serum by mass spectrometry. Both DDE and DDT levels were low compared with other studies (DDE, 310 ng/g lipid; DDT, 20 ng/g lipid among controls; other DDT isomers were not detectable). The odds ratio was 2.21 (95% CI, 1.41–3.48) for DDE concentration above the limit of quantification (0.5 ppb) and 1.24 (95% CI, 1.15–1.34) per ppb DDE in serum. Risk data for DDT were not reported. [Reasonably large sample size and blood draw before surgery were strengths of this study. Limitations included use of hospital controls and absence of BMI information. The Working Group noted that the risk estimates per unit of exposure exceeded those in most other studies; however, this was not readily explained by any aspect of the study design or methods.]

Itoh et al. (2009) recruited 403 consecutive patients with cancer of the breast from four hospitals in Japan, in 2001–2005. Control patients (n = 403) having medical checkups were matched for age and residence. Blood samples, collected before surgery for cases, were analysed for nine OCPs and PCBs. DDE and DDT levels in serum were low (370 and 9.9 ng/g lipid, respectively, in controls). After adjustment for multiple risk factors, no association or significant trend was found with the concentration of DDE, DDT, or *o,p′*-DDT. The odds ratio of for the fourth versus first *p,p′*-DDE quartiles was 1.02 (95% CI, 0.46–2.26). Stratified analyses by ER and

menopausal status were also null. [This large study used high-quality laboratory methods and obtained blood before surgery. Controls could have had medical conditions that affected DDE levels.]

[This group of large studies included two population-based studies with large numbers of African-American women who had higher DDT exposures than whites. Nevertheless, the range of exposures was modest; no median DDE levels exceeded 10 ng/mL. The Working Group noted that DDT blood levels in these studies were generally less than about 10% the concentration of DDE, consistent with past, not current, exposure. Several studies measured exposure to other pesticides or to PCBs in addition to DDT, but potential confounding from these exposures was generally not assessed. Blood sampling for cases occurred after diagnosis, but several studies reported that blood samples were obtained before treatment. Not all studies reported excluding metastatic or secondary cancer.]

An additional seven studies each with between 100 and 200 cases of cancer of the breast provided pertinent data (López-Carrillo et al., 1997; Moysich et al., 1998; Olaya-Contreras et al., 1998; Dello Iacovo et al., 1999; Mendonça et al., 1999; Romieu et al., 2000; Wolff et al., 2000b). The data were collected between 1986 and 1995; two studies were from the USA, four were from Latin America, and one was from Italy.

López-Carrillo et al. (1997) conducted a hospital-based case–control study in 1994–1996 in Mexico City, Mexico. Cases (n = 141) aged 20–79 years were recruited from participating hospitals and an equal number of age-matched cancer-free controls were selected from other hospital services. Mean serum concentrations of 505.5 ng/g lipid and 84.5 ng/g lipid were reported for DDE and DDT, respectively. DDE concentration was higher in cases and DDT was higher in controls, with neither difference being statistically significant. DDE level was not associated with the risk of cancer of the breast, including in models adjusted for multiple risk factors for breast cancer; the odds ratio for the third versus the first tertile of DDE was 0.76 (95% CI, 0.41–1.42). Analyses stratified by menopausal status gave similar results. No risk data were reported for DDT.

Olaya-Contreras et al. (1998) recruited women with incident breast cancer from a cancer-speciality hospital and controls from a hospital providing non-cancer care in Bogota, Colombia, during 1995–1996 (153 pairs). Blood samples for the cases were obtained before treatment; mean plasma DDE was 2.5 ng/mL among controls and was higher in cases than controls, regardless of menopausal status. The risk of breast cancer increased with plasma DDE concentration (OR, 1.95; 95% CI, 1.10–3.52; for the thirrd versus first tertile), but the trend was not statistically significant (P for trend, 0.09). DDD and DDT were measured, but results were not reported [DDE was not lipid-adjusted].

Moysich et al. (1998) studied the association between postmenopausal cancer of the breast with serum concentrations of several organochlorine compounds, including DDE, in a case–control study in the state of New York, USA. Women with incident, primary postmenopausal cancer of the breast were identified from hospitals, while the controls were postmenopausal women from the community sampled from motor-vehicle and health-insurance records. Data on DDE in serum and risk factors for cancer of the breast were available for 154 cases and 192 controls; blood samples were obtained after surgery for most cases. Among all women, the risk of breast cancer was increased in the highest category of DDE exposure (OR, 1.34; 95% CI, 0.71–2.55), but there was no significant exposure-response trend (P for trend, 0.25). Stronger associations, but no significant trend, were observed for women who had never lactated.

A case–control study in Rio de Janeiro, Brazil, enrolled women admitted to a national cancer hospital with a diagnosis of breast cancer within

6 months as cases, and female hospital visitors without breast cancer as controls (Mendonça et al., 1999). Cases and controls were interviewed in hospital and blood specimens were obtained (before surgery for most cases) and analysed for DDE and related compounds. DDE concentrations were available for 162 cases and 331 controls. No association between the risk of breast cancer and increasing serum DDE was observed (*P* for trend, 0.79). [The Working Group noted that the odds ratios reported in the abstract and tables did not match; the figures tabulated here are from Table 3 of the paper.]

Dello Iacovo et al. (1999) conducted a case–control study in Naples, Italy, among 170 women undergoing surgery for breast cancer in a cancer-speciality hospital and 190 controls from a cohort study on diet and cancer at the same hospital. Blood samples were analysed for several organochlorine compounds, including DDE and DDT. The odds ratios for breast cancer and serum DDE concentration were 0.84 (95% CI, 0.47–1.51) for 6.0–10.2 ng/mL, and 1.24 (95% CI, 0.70–2 20) for > 10.2 ng/mL, relative to a referent group with < 6.0 ng/mL. Data for DDT were not reported.

A hospital-based study in New York City, USA, included 175 women with incident breast cancer, a control group of 181 women having surgery or biopsies for benign breast disease, and a second control group of 175 women without either disease who were undergoing screening or minor procedures (Wolff et al., 2000b). Concentrations of organochlorines were determined in blood samples, most of which were collected before surgery. DDE concentration was not associated with the risk of breast cancer. However, risks were non-significantly increased for DDT (OR, 1.34; 95% CI, 0.82–2.2; in the highest exposure category. No significant trend was observed for either exposure indicator.

Romieu et al. (2000) measured serum DDE and DDT concentrations for a subsample of 120 cases of cancer of the breast and 126 controls from a larger study initiated in 1990 in Mexico City, Mexico. In the original study, cases were recruited from a network of hospitals affiliated with the government health system and controls were an age-stratified random sample of the general population. Levels of DDE and DDT in controls were 2510 ng/g lipid, and 230 ng/g lipid, respectively. The concentration of DDE was significantly higher in cases than in controls, while the concentration of DDT was non-significantly higher in controls. With adjustment for risk factors for breast cancer, but not DDT, the odds ratio for DDE was 2.16 (95% CI, 0.85–5.50) for the fourth compared with the first quartile (*P* for trend, 0.06). Similar odds ratios were observed in analyses stratified by menopausal status. Risk data were not reported for DDT.

Four smaller studies from several countries had comparatively high average serum or plasma DDE concentrations of up to 17 ng/mL (Schecter et al., 1997; Pavuk et al., 2003; Soliman et al., 2003; Rubin et al., 2006).

In a hospital-based study in Hanoi, Viet Nam, Schecter et al. (1997) measured serum DDE and DDT concentrations in 21 women with invasive cancer of the breast and 21 control women with fibrocystic breast disease. Mean DDE contentration in the controls was 16.7 ng/mL. Neither DDE nor DDT concentration was significantly associated with the occurrence of breast cancer. [While women in this study had relatively high exposures to DDE, the small sample size limited precision.]

Soliman et al. (2003) studied the association of serum organochlorine levels with cancer of the breast among 69 premenopausal women newly diagnosed with cancer of the breast from three centres in Egypt and 69 women hospital visitors selected as controls. Mean DDE concentration in controls was 17 ppb and was higher among rural than urban women. The odds ratio for DDE concentration above the median (4.7 ppb) was 1.41 (95% CI, 0.63–3.19). DDT concentrations were measured, but no risk data were reported.

[Exposures were relatively high in this population, but precision was limited.]

In a study in Slovakia, Pavuk et al. (2003) analysed the association between several organochlorines and cancer of the breast among 24 cases with diagnoses in 1997–1999 identified from a hospital oncology service and 88 controls participating in a cross-sectional study in the same district in 1998. All the cases had been treated before providing blood samples. For DDE, the odds ratio for the third versus first tertile of exposure was 3.04 (95% CI, 0.65–14.3; *P* for trend, 0.10). For DDT, the odds ratio was not notably increased. [The limitations of this study included blood collection up to 2 years after diagnosis and treatment, different sources for cases and controls, limited control for potential confounders, and limited precision.]

Rubin et al. (2006) measured DDE in banked serum samples collected from native women in Alaska, USA, in 1981–1987. Cases (n = 63) were women in the Alaska Native Tumor Registry with incident cancer of the breast cancer diagnosed up until 1995 and an earlier serum sample, Pair-matched controls were women with a sample in the same serum bank collected in the same year as a case's sample. In a multivariable model, the odds ratio for the third tertile of DDE exposure (> 9.62 ppb) was 1.43 (95% CI, 0.46–4.47). [This population had fairly high exposures to DDT and blood was sampled years before diagnosis; however, there was no adjustment for reproductive risk factors or BMI, and precision was limited.]

A pooled analysis of three of the case–control studies (Moysich et al., 1998; Wolff et al., 2000b; Zheng et al., 2000) and of the two cohort studies (Hunter et al., 1997; Helzlsouer et al., 1999) reviewed in this monograph included 1400 cases of cancer of the breast and 1642 controls from five different areas of the USA (Laden et al., 2001b). Median concentrations of DDE in serum or plasma ranged from 2.6 to 11.1 ng/mL across the five studies. In pooled case–control analyses adjusted for key breast cancer risk factors, there was no association between breast cancer risk and lipid-adjusted DDE concentration. [The pooled analysis included a wide range of DDE serum concentrations of > 10 ng/mL; the strengths of the pooled analysis, in addition to improved precision, included unified quality control during the course of the laboratory assays in four separate laboratories.]

(b) Exposure measured in adipose tissue

See Table 2.7

Seven case–control studies of the relationship between DDE or DDT concentration in adipose tissue and risk of cancer of the breast were available to the Working Group (van't Veer et al., 1997; Liljegren et al., 1998; Zheng et al., 1999; Aronson et al., 2000; Bagga et. al., 2000; Woolcott et al., 2001; Ibarluzea et al., 2004).

The European community multicenter study on antioxidants, myocardial infarction, and breast cancer (EURAMIC) study in Germany, the Netherlands, Northern Ireland, Switzerland, and Spain enrolled 265 postmenopausal women with cancer of the breast and 341 controls matched for age and centre in 1991–1992 (van't Veer et al., 1997). The mean DDE concentration in adipose tissue aspirates was 1.51 μg/g among controls and 1.35 μg/g among cases. After adjustment for BMI, age at first birth, and current alcohol drinking, odds ratios for cancer of the breast decreased with increasing DDE levels; women in the highest category of DDE exposure had an odds ratio of 0.48 (95% CI, 0.25–0.95). [This study had low response rates (22–50%) among controls, except for in Spain (91%).]

In a case–control study in Connecticut, USA (Zheng et al., 1999), 304 women with incident breast cancer and 186 control women with benign breast disease were enrolled beween 1994 to 1997. Cases and controls were aged 40–79 years and had had breast-related surgery at a single hospital and an available sample of breast adipose tissue. DDT and DDE concentrations were measured in

stored adipose tissue specimens. Age-adjusted geometric mean tissue DDE and DDT concentrations were similar for cases and controls (respectively, 736.5 ppb and 784.1 ppb for DDE; 51.8 ppb and 55.6 ppb for DDE). Analyses adjusted for reproductive and demographic risk factors did not indicate an association between adipose tissue levels of DDE or DDT and risk of breast cancer. [This study had a relatively large sample size, although it was based in a single hospital. The population may have overlapped with that of a study by Zheng et al. (2000) on breast cancer and DDT measured in blood.]

Liljegren et al. (1998) investigated the association between cancer of the breast and exposure to several chlorinated compounds, including DDE, in adipose tissue in a case–control study in surgical patients in Sweden. The population included 43 patients treated for malignant breast lesions and 35 treated for benign breast lesions by a single surgeon in 1993–1995. DDE concentration was measured in adipose tissue samples obtained at surgery. The concentration of DDE was higher among controls than among cases (1026 versus 767 ng/g lipid, respectively). Odds ratios adjusted for age and parity were below unity, but not statistically significant for all women, as well as for postmenopausal women and cases with ER-positive tumours. [Conclusions were limited by incomplete control for established risk factors, and small sample size.]

The relationship between risk of cancer of the breast and the concentration of DDE and other organochlorines was evaluated by Aronson et al. (2000) in a hospital-based case–control study in Ontario, Canada. Women aged < 80 years in 1995–1997 were enrolled at the time of biopsy. Through subsequent review of pathology records, 217 women with breast cancer and 213 control women, most with benign breast lesions, were identified. Concentrations of DDE and DDT were measured in biopsy tissue (geometric mean DDE concentration: cases, 693 µg/kg; controls, 596 µg/kg). For DDE, odds ratios adjusted for established risk factors were about unity except in the highest exposure category (OR, 1.62; 95% CI, 0.84–3.11; for concentrations ≥ 1390 µg/kg). This association was largely confined to premenopausal women. DDT concentrations were not associated with risk of breast cancer. In a further study in this population (Woolcott et al., 2001), breast cancer subtypes were defined by tumour characteristics, including ER status, progesterone receptor (PR) status, tumour size, and grade. Although the odds ratios did not differ significantly by subtype, DDE levels were higher with risk of ER-negative (OR, 2.4; 95% CI, 1.0–5.4) breast cancer than ER-positive breast cancer (OR, 1.1; 95% CI, 0.6–1.9) [This study included adjustments for multiple risk factors for breast cancer, including fat intake. However, participants were enrolled exclusively from two hospitals and only 50% of eligible women had enough adipose tissue available for analysis.]

Bagga et al. (2000) conducted a case–control study on the association betweem cancer of the breast and OCPs in breast adipose tissue among participants in a health plan in California, USA. The cases were 73 women with breast cancer and an equal number of women undergoing breast-reduction surgery were enrolled as controls, respectively. Concentrations of DDT and its metabolites were measured in adipose tissue obtained at biopsy. The concentration of DDE, but not DDE, was significantly higher in cases than in controls (800 versus 709 ng/g; $P = 0.006$). The association between risk of breast cancer and DDE and DDT concentrations was modelled using quadratic terms in logistic regression models adjusting for age. The coefficients were positive for both exposure metrics, but were not statistically significant. [This study was reported in a brief communication and details on the methods used were limited. Analyses did not control for important risk factors, and the modelling methods and results were not readily comparable with other studies.]

In Spain, Ibarluzea et al. (2004) carried out a case–control study with 198 women with cancer of the breast and 260 age- and hospital-matched control women. Cases were undergoing surgery for breast cancer and controls were receiving surgery for other, non-cancer conditions, mostly of the gall bladder. Concentrations of DDT and its metabolites, as well as those of several other chemicals, were measured in samples of breast or abdominal adipose tissue from cases and controls, respectively. Geometric mean DDE concentrations were 326.86 ng/g lipid among cases and 307.34 ng/g lipid among controls. Adjusted odds ratios were greater than unity in the two higher exposure groups (OR, 1.22; 95% CI, 0.68–2.21; for DDE ≥ 675.98 ng/g), but there was no significant trend with increasing exposure. In stratified analyses, increased risk was limited to postmenopausal women. Risk data were not reported for DDT. [This study had a relatively good sample size, and high response rates. There were no controls for lactation.]

(c) Other exposure assessment methods

In the Long Island Breast Cancer Study Project (LIBCSP), White et al. (2013) assessed self-reported acute exposure to a fogger truck (used in the area to spray DDT before it was banned in 1972) as a proxy measure of exposure to DDT in 1508 cases and 1556 controls. Among all women, 33% reported ever seeing a fogger truck at their residence before 1972. For women reporting such exposure, the odds ratio for breast cancer was 1.16 (95% CI, 0.98–1.37). Odds ratios were near unity for reported exposure before age 14 or age 20 years, or after 1972. Compared with other breast cancer subtypes, women with ER+PR+ tumours had an increased odds ratio for ever seeing a pre-1972 fogger truck (OR, 1.44; 95% CI, 1.08–1.93). Self-reported exposure to a fogger truck was not correlated with serum DDT or DDE concentrations. [There were low response rates among controls. Differential recall of exposure may have affected the results.]

(d) Meta-analyses

Four meta-analyses evaluated the association between cancer of the breast and DDT and/or DDE (Adami et al., 1995; López-Cervantes et al., 2004; Ingber et al., 2013; Park et al., 2014).

Forty-six studies on the association between cancer of the breast and exposure to DDT or DDE from 500 published studies screened through June 2012 were included in a meta-analysis by Ingber et al. (2013). The meta-odds ratio for DDE was 1.04 (95% CI, 0.94–1.15) and DDT was 1.02 (95% CI, 0.92–1.13). There was no indication of publication bias (Begg's *P*-value, 0.09; Egger's *P*-value, 0.14). Heterogeneity was moderate for DDE (I^2, 31.72%) and high (I^2, 64.5%) for DDT. Lipid-adjusted differences in mean concentration were significantly higher for DDE concentrations in cases versus controls (difference, 110.30 ng/g lipids; $P = 0.01$), while no differences were found for non-lipid adjusted estimates or for DDT.

A meta-analysis by Park et al. (2014) included 35 case–control studies (8160 cases and 9280 controls) on DDE exposure and cancer of the breast with nested, population-based, and hospital-based designs published in English until August 2012. The summary odds ratio for DDE was 1.03 (95% CI, 0.95–1.12). There was no evidence of publication bias (funnel plots were symmetric; Egger's test *P* value, 0.145) and moderate heterogeneity was indicated (I^2, 40.9; $P = 0.006$) overall. Subgroup meta-analysis indicated no significant association between exposure to DDE and risk of breast cancer by type of design, study years, biological specimens, and geographical region of the study.

Both the Park et al. (2014) and the Ingber et al. (2013) meta-analyses were largely consistent with the 2004 meta-analysis by López-Cervantes et al. (2004) which examined the scientific literature through February 2001 and by Adami et al. (1995), which reviewed the literature until 1993. A general conclusion of these reviews was that currently available studies do not support

the view that DDE increases the risk of breast cancer in humans (Fig. 2.1). [Many of the studies included in the available meta-analyses adjusted for common risk factors, such as age, BMI, family history of breast cancer, but few adjusted for breast feeding and diet, both of which have been related to DDT/DDE body burden. The Working Group concluded that adjustment for DDE in assessments of the risk of cancer associated with DDT is generally inappropriate because the practice produces variable effects on the risk estimate, depending on whether the exposure was from DDE in the diet or from DDT directly from application or manufacturing. Moreover, the age at exposure to chemicals such as DDE seems to be an important modifier in explaining the relationship between exposure and the risk of disease, for example, Cohn et al. (2007) reported that DDT was primarily associated with breast cancer in women potentially exposed before age 14 years. Unexamined variations in DDT metabolizing enzymes may also be an important determinant of increased risk of breast cancer.]

2.2.2 Lympho-haematopoietic cancers

See Table 2.8

Case–control studies of exposure to DDT and risk of lymphoma and leukaemia are grouped here by method of exposure assessment according to whether exposure was estimated from measurements in biological samples or by questionnaire or environmental monitoring. It should be noted that interpretation of the published literature was complicated by the change over time in the classification and coding systems for NHL and its subtypes.

(a) Studies based on biological samples

The hypothesis of immune system disturbances in modulating DDT-related risk of NHL, previously examined in relation to concurrent allergic conditions, was explored in three small Swedish case–control studies that measured the Epstein-Barr virus (EBV) early antigen (EBV EA) titre along with the lipid-adjusted plasma concentration of PCBs and organochlorines, including *p,p′*-DDE. The risk of hairy cell leukaemia was 6.6-fold (95% CI, 1.3–41.6) among subjects with above median plasma levels of *p,p′*-DDE and with an EBV EA titre above 40, while no association was observed in the overall study population (OR, 0.6; 95% CI, 0.2–1.5) (Nordström et al., 2000).

Similar results with respect to EBV EA were observed for total NHL in two further small studies by the same group (Hardell et al., 2001, 2009). For B-cell lymphoma subtypes, increased risk was associated with above median *p,p′*-DDE levels, independent of the EBV EA titre, for diffuse large B-cell lymphoma (OR, 2.8; 95% CI, 1.1–6.7), but not follicular lymphoma (Hardell et al., 2009). [While these studies highlighted the possible interaction between DDT body burden and immune factors, their small size and the heterogeneity of the exposure indicator in one study, limited the interpretation of the findings.]

A population survey on pesticide exposure was conducted in the USA by the EPA in 1970–87, during which organochlorine measurements were made in adipose tissue samples from surgical procedures or autopsy in a stratified random sample of the United States population. From the resulting database, 175 people with NHL and pesticide measurements were identified and matched by age, sex, hospital, and race to 481 control individuals in the database with diagnoses of myocardial infarction or accidental injury, but no cancer diagnosis (Quintana et al., 2004). DDT and DDE adipose tissue levels above the fourth quartile were associated with an increase in risk of NHL, which was non-significant for DDT (OR, 1.39; 95% CI, 0.78–2.47) and significant for DDE (OR, 1.99; 95% CI, 1.14–3.47). Although the trends were significant in both instances, risks below the upper quartile were near or below unity. [Organochlorines were measured post mortem or after diagnosis, which limited the interpretation. No further

information was available on conditions possibly associated with DDT and DDE body burden, apart from age, sex, geographical region of the patient's hospital, and race.]

De Roos et al. (2005) conducted a case–control study in four areas of the USA, including Iowa, Los Angeles County, and the cities of Chicago and Seattle, in 1998–2000, with 100 cases identified through the Surveillance, Epidemiology, and End results Program (SEER) cancer registries, and 100 population controls. Study subjects donated a blood sample before treatment was initiated and plasma samples were tested for 40 PCB congeners, and 13 OCPs. After adjusting by sex, study site, date of birth, and date of blood draw, risk of NHL did not increase with increasing quartile of plasma concentration of DDT (ORs, 1, 1.12, 1.02, 1.2, respectively; $P = 0.75$) or DDE (ORs, 1, 0.64, 0.33, 0.85, respectively; $P = 0.74$). No analysis was conducted for the individual lymphoma subtypes.

A similar design was applied in a population-based study of 422 NHL cases and 460 controls in British Columbia, Canada (Spinelli et al., 2007). After adjusting by age, sex, study area, education, family history of lympho-haematopoietic cancer, and ethnicity, risk of NHL showed a significant upward trend with *p,p′*-DDE blood concentration (*P* for trend, 0.027), although none of the individual risk estimates was statistically significant. Risk was mostly elevated for follicular lymphoma (OR, 1.8; 95% CI, 0.9–3.3), and a group of "other B-cell lymphomas" excluding follicular or diffuse large B-cell lymphoma (OR, 1.8; 95% CI, 1.0–3.2). No association was observed with DDT blood concentration (OR, 0.91; 95% CI, 0.68–1.20; for > 3.24 ng/g lipid). [The Working Group noted that this was the largest study of DDT and risk of NHL based on biomarkers (blood levels of DDE); subjects with > 10% body-weight loss before diagnosis were excluded from the study. However, the timing of blood draw, whether before or after treatment, might be reasons for caution in interpreting the results.]

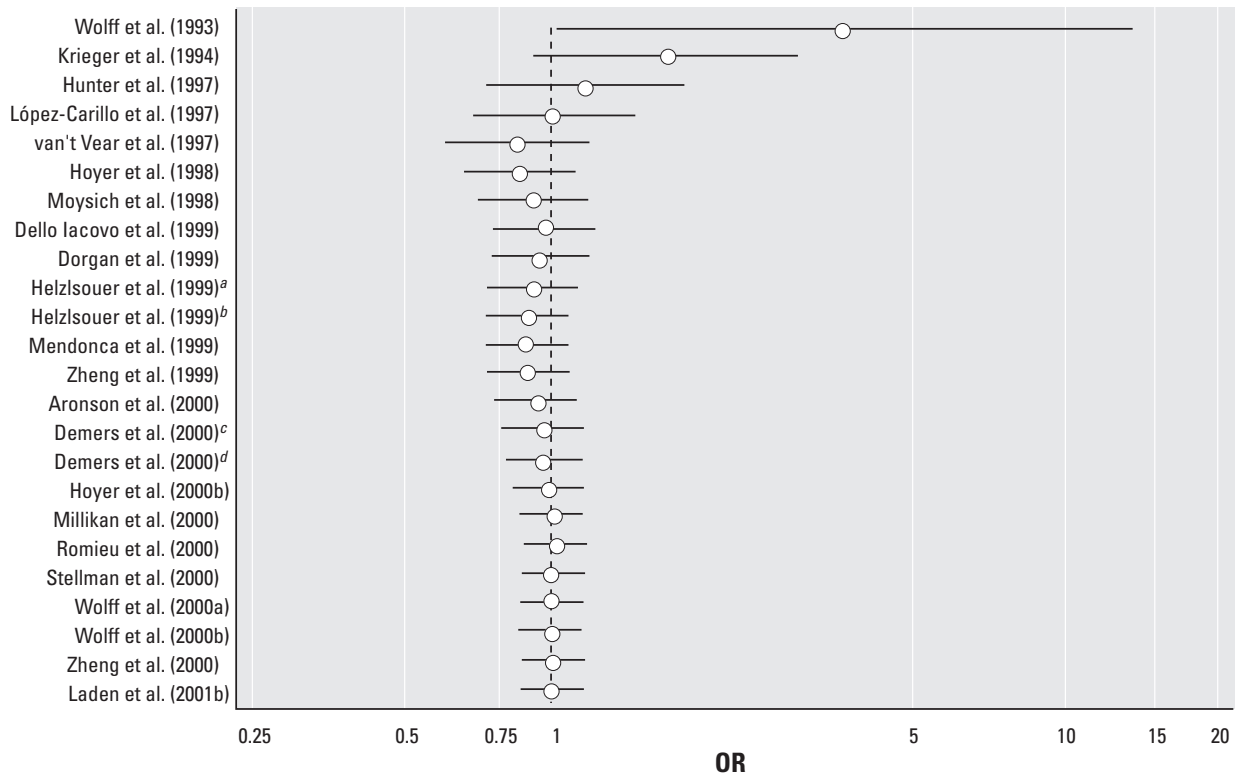
A multicentre European study of 174 NHL cases and 203 controls (Cocco et al., 2008) assessed exposure to 17 OCPs, including 6 DDT isomers, and 9 PCBs, in blood plasma. Analyses did not show an association between increasing blood *p,p′*-DDE concentration and risk of all NHL (*P* for trend, 0.48), or the subtypes, diffuse large B-cell lymphoma (*P* for trend, 0.48) and CLL (*P* for trend, 0.92), after adjusting by age, sex, education, and study centre. Analyses limited to subjects whose blood samples were taken before treatment did not modify the risk estimates.

A small biomarker study was conducted in a French area polluted by emissions from an incinerator (Viel et al., 2011). Lipid-adjusted DDT and DDE serum concentrations were measured in 34 NHL cases and 1-to-1 matched blood donors: the results showed a 3% increase in risk of NHL for each 10 ng/g lipid increase in *p,p′*-DDE (95% CI, 0.99–1.08) and a 20% (95% CI, 1.01–1.45) increase for a 10 ng/g increase in *p,p′*-DDT level. [The Working Group noted that while the finding of detectable DDT blood levels in the years when this study was conducted was unexpected, the small study size and the lack of adjustment for the highly chlorinated organochlorines because of incinerator location in this contaminated area were reasons for caution in interpreting the results. The choice of blood donors as controls was a potential source of selection bias should those individuals might not be representative of the source population of the cases.]

(b) Questionnaire-based studies

Early case–control studies of human exposure to DDT took place in the late 1980s. Woods et al. (1987) conducted a case–control study of 576 NHL cases and 694 controls in Washington state, USA. Exposure data were obtained by interview with study participants or proxies, using a detailed questionnaire including a section on pesticides. Exposure assessment was supported by local

Fig. 2.1 Effect of *p,p′*-DDE on breast cancer risk from each study in a meta-analysis, according to *p,p′*-DDE (ng/g) body burden levels



[a] Biological samples taken in 1974.
[b] Biological samples taken in 1989
[c] Controls are population-based
[d] Controls are clinically based
From López-Cervantes et al. (2004)

experts in forestry, wood products, and agricultural industries. After adjusting for age, ever exposure to DDT was associated with increased risk of NHL (OR, 1.82, 95% CI, 1.04–3.20). [No trend was evaluated in this study.]

Occupational exposure to pesticides was also considered in a population-based case–control study of 121 Hodgkin lymphoma (HL) cases and 948 controls in Kansas, USA (Hoar Zahm et al., 1988). Information on use of insecticides, including DDT, was obtained by questionnaire. No association with the risk of HL was found for ever use of insecticides, but no data were reported for DDT, specifically.

Persson et al. (1989) interviewed 106 cases of NHL and 54 cases of HL identified through the register of patients diagnosed at the Department of Oncology at Orebro Medical Centre Hospital, Sweden, in 1964–1986, and still alive when the study was conducted. Cases of T-cell lymphoma and malignant histiocytosis were excluded. Controls were a sample of 275 subjects who had participated in earlier studies. Cases and controls self-reported about a list of occupational exposures, which included DDT, which had lasted a minimum of 1 year and occurred at least 5 years before interview. No case of NHL nor the corresponding controls reported exposure, while three cases of HL and three of their controls

Table 2.8 Case–control studies on cancers of the lympho-haematopoietic system and exposure to DDT and its metabolites

Reference, location follow-up/ enrolment period, study-design	Population size, description, exposure assessment method	Organ site (ICD-O)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Nordström et al. (2000) Sweden 1987–92	Cases: 54; national cancer registry Controls: 54; national population registry, matched for age, sex, & county Exposure assessment method: biomarker; lipid-adjusted concentrations in plasma	NHL (hairy cell leukaemia)	*p,p′*-DDE > median	19	0.6 (0.2–1.5)	Age, other occupational exposures, BMI	Strengths: based on national population; diagnoses validated by the cancer registry Limitations: small sample size
			p,p′-DDE above median & EBV EA < 40	9			
			p,p′-DDE above median & EBV EA ≥ 40	10			
Hardell et al. (2001) Sweden 1994–97	Cases: 82; hospital Controls: 83; hospital and population register Exposure assessment method: biomarker; OC concentrations in abdominal fat or plasma	NHL	*p,p′*-DDE > median	44	1.20 (0.60–2.50)	Age, sex, BMI, type of specimen	Strengths: assessment by EBV EA status Limitations: small study size; heterogeneous control group and tissue sampling material
			p,p-DDE > median & EBV EA ≤ 80	17	2.00 (0.64–6.50)		
			p,p-DDE > median & EBV EA > 80	18	2.90 (0.93–9.70)		
		NHL (B-cell lymphoma), low grade	*p,p*-DDE > median EBV EA ≤ 80	5	1.20 (0.23–7.80)		
			p,p-DDE > median & EBV EA > 80	11	4.4 (0.96–26.0)		
		NHL (B-cell lymphoma): high grade	*p,p*-DDE > median & EBV EA ≤ 80	9	1.60 (0.41–6.70)		
			p,p′-DDE > median & EBV EA > 80	7	1.80 (0.42–7.70)		

Table 2.8 (continued)

Reference, location follow-up/ enrolment period, study-design	Population size, description, exposure assessment method	Organ site (ICD-O)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Hardell et al. (2009) Sweden 2000–2002	Cases: 99; hospitals in 4 health service regions Controls: 99; population registries in the same regions, matched by age & sex Exposure assessment method: biomarker; lipid-adjusted concentration in plasma	NHL	*p,p′*-DDE > median	53	1.5 (0.8–2.9)	Age, sex, BMI	Strengths: population-based; pathology review Limitations: small study size
			p,p′-DDE > median & EBVEA ≤ 40	14	1.0 (0.4–2.7)		
			p,p′-DDE > median & EBVEA > 40	39	3.3 (1.4–7.7)		
		NHL (follicular)	*p,p′*-DDE > median	10	1.2 (0.4–3.5)		
		NHL (DLBCL)	*p,p′*-DDE > median	24	2.8 (1.1–6.7)		
Quintana et al. (2004) United States 1970–87	Cases: 175; NHL cases from national database of tissue samples with pesticide measurements Controls: 481; ondividuals in the database with diagnosis of accidental injuries or myocardal infarction Exposure assessment method: biomarker; OC concentration in surgical or autopsy fat tissue samples	NHL	DDT (ppm)			Age, sex, race, centre	Strengths: large database; random selection of subjects independent of diagnosis Limitations: exposure measurements post mortem or post diagnosis; limited information on potential confounders
			< 0.55	58	1.00		
			0.55–0.92	34	0.80 (0.47–1.35)		
			0.93–1.56	38	0.97 (0.56–1.70)		
			> 1.56	45	1.39 (0.78–2.47)		
			Trend-test *P* value: 0.04				
		NHL	DDE (ppm)				
			< 2.40	48	1		
			2.40–4.38	24	0.53 (0.29–0.96)		
			4.39–7.21	38	1.12 (0.64–1.98)		
			> 7.21	65	1.99 (1.14–3.47)		
			Trend-test *P* value: 0.002				

Table 2.8 (continued)

Reference, location follow-up/ enrolment period, study-design	Population size, description, exposure assessment method	Organ site (ICD-O)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
De Roos et al. (2005) Four states, USA 1998–2000	Cases: 100; SEER registries Controls: 100; Medicare records, random-digit dialling, matched by age, sex, race Exposure assessment method: biomarker; 36 PCB congeners & 14 OC pesticides or metabolites measured in plasma	NHL	*p,p′*-DDT, ng/g lipids			Sex, study site, birth date, date of blood draw	OCs detected in 30% or more study subjects Strengths: good statistical power; availability of pathology data; information on large number of possible confounders. Limitations: multiple comparisons; biomonitoring at the time of diagnosis
			≤ 3.7	18	1.00		
			> 3.7–5.9	23	1.12 (0.33–3.84)		
			> 5.9–9.9	32	1.02 (0.35–2.99)		
			> 9.9	27	1.20 (0.39–3.70)		
			Trend-test *P* value: 0.75				
		NHL	*p,p′*-DDE, ng/g lipids				
			≤ 254.5	35	1.00		
			> 254.5–450.5	25	0.64 (0.28–1.43)		
			> 450.5–872.5	11	0.33 (0.14–0.80)		
			> 872.5	29	0.85 (0.37–1.94)		
			Trend-test *P* value: 0.74				
Spinelli et al. (2007) British Columbia, Canada 2000–2004	Cases: 422; cancer registry Controls: 460; population (client registry of Ministry of Health) Exposure assessment method: lipid-adjusted plasma of 14 PCBs and 11 OC pesticides	NHL	DDE, ng/g lipid			Age, ethnicity, BMI	Time of blood collection not reported Strengths: large study size; exclusion of subjects with weight loss before diagnosis Limitations: low response among controls
			> 134.41–263.91	84	0.84 (0.56–1.25)		
			> 263.91–512.02	100	1.04 (0.70–1.56)		
			> 512.02–18 898	121	1.42 (0.92–2.19)		
			Highest vs lowest quartile	NR	1.40 (0.90–2.20)		
			Trend-test *P* value: 0.027				
		NHL (follicular)	DDE, highest vs lowest quartile	NR	1.8 (0.9–3.3)	Age, sex, study area, education, family history lymphopoietic cancer, ethnicity, BMI, farming jobs	
			Trend-test *P* value: 0.027				
		NHL (DLBCL)	DDE, highest vs lowest quartile	NR	0.6 (0.2–1.5)		
			Trend-test *P* value: 0.027				

Table 2.8 (continued)

Reference, location follow-up/ enrolment period, study-design	Population size, description, exposure assessment method	Organ site (ICD-O)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Spinelli et al. (2007) British Columbia, Canada 2000–2004 (cont.)		NHL, other histological type	DDE, highest vs lowest quartile	NR	1.8 (1.0–3.2)		
			Trend-test *P* value: 0.027				
		NHL					
			DDT, above vs below LOD	133	0.91 (0.68–1.20)		
			Trend-test *P* value: 0.491				
		NHL (DLBCL)					
			DDT above vs below DL	NR	1.0 (0.6–1.7)		
			Trend-test *P* value: 0.027				
		NHL (T-cell)	DDT				
			Above vs below LoD	NR	1.1 (0.6–2.1)		
			Trend-test *P* value: 0.027				
		NHL	DDT				
			Above vs below LOD	NR	1.0 (0.7–1.5)		
			Trend-test *P* value: 0.027				
		NHL (follicular)	DDE				
			Highest vs lowest quartile	NR	1.8 (0.9–3.3)		
			Trend-test *P* value: 0.027				

Table 2.8 (continued)

Reference, location follow-up/ enrolment period, study-design	Population size, description, exposure assessment method	Organ site (ICD-O)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Cocco et al. (2008) Spain, France, Germany 1998–2004	Cases: 174; resident in the referral area of the participating centres Controls: 203; population controls in Germany; hospital controls in Spain and France Exposure assessment method: biomarker; no difference in median OC levels by pre/post diagnostic sampling	NHL	ng/g lipid *p,p′*-DDE			Age, sex, education, study site	Epilymph study Strengths: Pathology review. Limitations: Limited sample size; low prevalence of exposure
			395.0–791.02	36	0.8 (0.4–1.5)		
			791.03–1431.07	43	0.9 (0.5–1.7)		
			> 1431.08	56	1.2 (0.7–2.4)		
			Trend-test *P* value: 0.48				
		NHL (DLBCL)	*p,p′*-DDE, ppb				
			395.0–791.02	8	0.7 (0.3–2.0)		
			791.03–1431.07	10	0.9 (0.4–2.6)		
			> 1431.08	14	1.3 (0.5–3.6)		
			Trend-test *P* value: 0.48				
		NHL (SLL/CLL)	*p,p′*-DDE, ppb				
			395.0–791.02	7	0.4 (0.1–1.1)		
			791.03–1431.07	13	0.6 (0.2–1.5)		
			> 1431.08	20	1.0 (0.4–2.5)		
			Trend-test *P* value: 0.92				
Viel et al. (2011) Besancon area, France 2003–05	Cases: 34; hospital Controls: 34; register of blood donors, matched by age, sex and date of blood draw Exposure assessment method: questionnaire; lipid-adjusted serum measurements of OC	NHL	10 ng/g increment			NR	Strengths: incident cases; well-defined area, questionnaire information was available; pathology was available Limitations: small study size; controls may not be representative of the base population; adjustment by PCB not considered
			DDE	NR	1.03 (0.99–1.08)		
			DDT	NR	1.20 (1.01–1.45)		

Table 2.8 (continued)

Reference, location follow-up/ enrolment period, study-design	Population size, description, exposure assessment method	Organ site (ICD-O)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Woods et al. (1987) Washington State, USA 1981–1984	Cases: 576; population-based cancer registry Controls: 694; random-digit dialling and social security records Exposure assessment method: questionnaire	NHL	Ever DDT	NR	1.82 (1.04–3.20)	Age	Strengths: large study size Limitations: multiple co-exposures; no trends evaluated; non consideration of confounders other than age
Persson et al. (1989) Sweden 1964–86	Cases: 160 (106 NHL, 54 HL); hospital Controls: 275; population Exposure assessment method: questionnaire; minimum duration of exposure, 1 yr; minimum latency, 5 yrs	NHL HL	Ever DDT Ever DDT	0 3	0 7.5 (0.8–70.0)	Age, sex, farming, fresh wood	Malignant histiocytosis and T-cell lymphoma were excluded Strengths: pathology was available Limitations: small size; only surviving cases included; reliance on self-reported exposure information
Flodin et al. (1988) Sweden 1975–84	Cases: 111; 5 hospitals Controls: 431; population Exposure assessment method: postal questionnaire; minimum exposure duration, 1 yr; minimum latency, 5 yrs	NHL (CLL)	Ever contact with DDT	6	6 (1.5–23)	Age, sex, other occupational exposures	Strengths: clinically and cytologically confirmed diagnoses Limitations: small size; only living cases included; reliance on self-report

Table 2.8 (continued)

Reference, location follow-up/ enrolment period, study-design	Population size, description, exposure assessment method	Organ site (ICD-O)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Eriksson & Karlsson (1992) Sweden 1982–86	Cases: 256; national cancer registry Controls: 256; national population registry, or national death registry of the causes of death, matched by age, sex, vital status, and county Exposure assessment method: postal questionnaire with telephone interview for subjects reporting farm work	MM	Days exposed to DDT Ever exposed Ever exposed, farming and forestry occupations only ≤ 5 days 6–20 days ≥ 21 days	 53 NR NR NR NR	 1.75 [1.07–2.86] 1.86 [0.92–3.75] 1.08 [0.35–3.37] 1.54 [0.77–3.10] 1.61 [0.53–4.93]	Co-exposures	Prevalence of exposure to DDT was unusually high Strengths: cases validated from cancer registry Limitations: overlapping exposures not considered; self-administered questionnaires
Brown et al. (1990) USA (Iowa and Minnesota) 1980–1983	Cases: 578; tumour registry (Iowa) and hospital records (Minnesota) Controls: 1245; population, matched by age, vital status and state Exposure assessment method: detailed questionnaires with supplemental interview on pesticide exposure	Leukaemia	DDT days/yr Ever use of DDT in crops 1–4 days/yr 5–9 10+ Ever use of DDT in animal breeding 1–4 days/yr 5–9 10+	 35 7 8 5 80 7 7 21	 1.2 (0.7–1.8) 0.7 (0.3–1.8) 2.4 (0.9–6.4) 1.0 (0.3–2.8) 1.3 (1.0–1.8) 0.6 (0.3–1.4) 1.1 (0.4–2.7) 2.1 (1.1–3.9)	Vital status, age, state, tobacco use, family history lymphopoietic cancer, high-risk occupations, high-risk exposures other than farming	Strengths: large size – pathology review. Limitations: overlap with exposure to other pesticides; self-report

Table 2.8 (continued)

Reference, location follow-up/ enrolment period, study-design	Population size, description, exposure assessment method	Organ site (ICD-O)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Cantor et al. (1992) USA (Iowa & Minnesota) 1980–83	Cases: 622; Iowa state health registry, Minnesota hospital and pathology records Controls: 1245; population Exposure assessment method: questionnaire; self report based on pesticide list	NHL	Ever use in animals Ever use in animals before 1965 Ever use in crops Ever use in crops before 1965	79 68 57 45	1.2 (0.9–1.7) 1.3 (0.9–1.8) 1.7 (1.2–2.6) 1.8 (1.1–2.7)	Vital status, age, state, cigarette smoking, family history of lympho-haematopoietic cancer, high-risk occupations, high-risk exposures	Strengths: good statistical power; availability of pathological information Limitations: multiple exposures; reliance on self-report
Baris et al. (1998) USA (Nebraska, Iowa, Minnesota, Kansas) 1983–1986	Cases: 993; cancer registry (Iowa & Kansas), hospitals and special surveillance (Nebraska & Minnesota) Controls: 2918; population, matched by state, race, sex, age and vital status Exposure assessment method: questionnaire; telephone or in-person interview	NHL	Use of DDT Ever 1–4 yrs 5–9 yrs 10–14 yrs ≥ 15 yrs ≤ 5 days/yr > 5 days/yr Ever, adjusted for 2,4-D & OPs 1–4 yrs, adjusted for 2,4-D & OPs 5–9 yrs adjusted for 2,4-D & OPs 10–14 yrs adjusted for 2,4-D & OPs ≥ 15 yrs adjusted for 2,4-D & OPs	 161 36 31 29 39 12 11 161 36 31 29 39	 1.2 (1.0–1.6) 1.1 (0.7–1.6) 1.4 (0.8–2.2) 1.1 (0.6–1.9) 1.5 (0.9–2.3) 1.0 (0.5–2.1) 2.1 (0.9–4.9) 0.9 (0.4–1.8) 0.9 (0.4–2.0) 1.0 (0.4–2.5) 0.9 (0.4–2.3) 1.2 (0.5–2.8)	Age, state of residence, respondent type (proxy/direct)	Pooled analysis of four case–control studies; men only; some states excluded from exposure–response analyses Strengths: large size; pathology review; exposure–response analysis Limitations: self-report; high proportion of proxy respondents, particularly among controls

Table 2.8 (continued)

Reference, location follow-up/ enrolment period, study-design	Population size, description, exposure assessment method	Organ site (ICD-O)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
De Roos et al. (2003) Midwestern USA 1979–86	Cases: 870; records of health registry, hospitals and pathology laboratories Controls: 2569; population controls from random-digit dialling and Medicare records Exposure assessment method: questionnaire; self report based on a list	NHL (200, 202)	Ever exposure to DDT Ever exposed to DDT only Ever exposed to DDT and chlordane	98 68 30	1.0 (0.7–1.3) 0.9 (0.6–1.3) 1.7 (0.7–3.2)	Age, study site, use of any pesticide in a list	Strengths: study size control for confounders assessment of multiple exposures Limitations: multiple comparisons, reliance on self-report, weakness in the exposure assessment
Assennato et al. (1995) Apulia, Italy 1987–89	Cases: 26; family physicians and pathology registers Controls: 74; other cancers, excluding sites associated with farm work Exposure assessment method: JEM; support from an agronomist	Lymphatic and haematopoetic	Ever exposed to DDT	7	4.18 (1.04–16.76)	Age, sex, respondent type (proxy/direct), smoking	Multiple exposure to different pesticides Strengths: detailed exposure assessment Limitations: extremely small study size
Nanni et al. (1996) Forli, Italy 1987–90	Cases: 61; ll incident cases of NHL and CLL in the study area Controls: 217; general population matched to cases by sex and age group Exposure assessment method: JEM; questionnaire and crop–exposure matrices	NHL (CLL)	DDT Ever used (recall) Ever used (JEM) 1 kg cumulative dose	 27 28 5	 1.74 (0.93–3.27) 1.70 (0.91–3.17) 1.22 (0.95–1.57)	Sex, age, family history lymphopoietic cancer, farming, herpes zoster, altitude	Strengths: pathological classification; more detailed exposure assessment Limitations: small size; number and type of controls is unclear; outdated classification of lymphoma; no results presented for exposure in crop farming without animal breeding

Table 2.8 (continued)

Reference, location follow-up/ enrolment period, study-design	Population size, description, exposure assessment method	Organ site (ICD-O)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
McDuffie et al. (2001) Canada (six provinces) 1991–1994	Cases: 517; Cancer registries and hospitals Controls: 1506; health insurance and voting records, matched by age & province Exposure assessment method: postal questionnaire with telephone follow-up on pesticides	NHL	Use of DDT 10+ hours/yr 1–2 days/yr 3+ days/yr	 32 18 14	 1.73 (1.08–2.76) 1.75 (0.96–3.21) 1.50 (0.77–2.91)	Age, province of residence, family history lymphopoietic cancer, medical history	Strengths: large size; pathology review. Limitations: self-reported exposure; low response rate; multiple comparisons
Pahwa et al. (2012) Six provinces, Canada 1991–94	Cases: 513; cancer registries & hospitals Controls: 1506; population Exposure assessment method: questionnaire; see McDuffie et al. (2001)	NHL	Use of DDT Ever Ever, no asthma, allergy or hay fever Ever, with asthma, allergy or hay fever	 33 18 15	 1.69 (1.07–2.67) 1.31 (0.73–2.36) 2.53 (1.17–5.47)	Age, province of residence, respondent type (proxy/ direct), diesel oil exposure	Same population as McDuffie et al. (2001) Strengths: analysis by concurrent immunological conditions; large size; pathology available Limitations: unknown proportion of refusals to participate; use of a postal questionnaire; lack of control for exposure to other pesticides

Table 2.8 (continued)

Reference, location follow-up/ enrolment period, study-design	Population size, description, exposure assessment method	Organ site (ICD-O)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Cocco et al. (2013) Six European centres 1998–2003	Cases: 2348; residents in the referral area of participating centres Controls: 2462; population and hospital controls Exposure assessment method: expert assessment; crop–exposure matrix	NHL (B-cell lymphoma)	Ever exposed to DDT	3	1.2 (0.2–5.9)	Age, sex, education, study site	Strengths: large study size; pathology review; detailed exposure assessment Limitations: low prevalence of exposure to individual chemicals
Colt et al. (2005) USA (Iowa, Los Angeles, Detroit and Seattle) 1998–2000	Cases: 603; cancer registries Controls: 443; population, frequency-matched on age, sex, race, and centre Exposure assessment method: environmental monitoring; vacuum sample of household carpet dust; measurement of DDT and derivatives, PCBs and other OC insecticides	NHL	DDE, 1 ng/g			Age, study site, education, sex	Strengths: study size; objective exposure measurements Limitations: other occupational and environmental (non-ousehold) sources of exposure not considered
			< LOD	304	1.0		
			> LOD	299	1.3 (1.0–1.7)		
			20.8–34.9	94	1.3 (0.8–1.8)		
			35–55.9	83	1.1 (0.7–1.6)		
			56–2450	122	1.6 (1.1–2.2)		
			Trend-test *P* value: 0.02				
			DDT, 1 ng/g				
			< LOD	197	1.0		
			> LOD	406	0.9 (0.7–1.2)		
			20.8–98.7	124	0.8 (0.6–1.2)		
			98.8–248	111	0.8 (0.5–1.1)		
			248.1–24 600	170	1.2 (0.8–1.6)		
			Trend-test *P* value: 0.09				
		NHL (follicular)	DDE > LOD	156	1.3 (0.9–2.0)		
			DDT > LOD	156	1.0 (0.7–1.6)		
		NHL (DLBCL)	DDE > LOD	189	1.3 (0.9–1.9)		
			DDT > LOD	189	0.8 (0.5–1.1)		
		NHL (T-cell)	DDE > LOD	36	2.6 (1.3–5.4)		
			DDT > LOD	36	2.8 (1.1–7.1)		
		Lymphatic and hematopoetic	DDE > LOD	206	1.2 (0.8–1.6)		
			DDT > LOD	206	0.8 (0.5–1.1)		

Table 2.8 (continued)

Reference, location follow-up/ enrolment period, study-design	Population size, description, exposure assessment method	Organ site (ICD-O)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Ward et al. (2009) USA (California) 2001–06	Cases: 184; paediatric clinical centres Controls: 212; birth certificate registries, individually matched on age, sex, race, Hispanic ethnicity, and maternal residence Exposure assessment method: environmental monitoring; vacuum sample of household carpet dust; measurement of DDT and derivatives, PCBs and other OC insecticides	Leukaemia (childhood ALL)	ng/g dust DDE > LOD detection limit 2.0–9.4 9.4–21.7 21.7–850.4	 145 38 59 48	 0.87 (0.51–1.50) 0.74 (0.39–1.41) 1.08 (0.58–2.02) 0.83 (0.43–1.59)	Age, sex, race, family income, year of enrolment	Strengths: pathology available; comprehensive recruitment of cases; high participation rate; objective measurement of exposure Limitations: other parental, occupational sources of exposure not considered; carpet dust measurements were missing for 10% of cases and 15% of controls

ALL, acute lymphoblastic/lymphocytic leukaemia; BBD, benign breast disease; BMI, body-mass index; CI, confidence interval; CLL, chronic lymphocytic leukaemia; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; EBV EA, Epstein-Barr virus early antigen; ER, estrogen receptor; FFTP, first full-term pregnancy; GC, gas chromatography; HRT, hormone replacement therapy; HL, Hodgkin lymphoma; JEM, job–exposure matrix; LOD, limit of detection; MM, multiple myeloma; NR, not reported; OC, organochlorine; OPs, organophosphates; PCB, polychlorinated biphenyl; SLL, small lymphocytic lymphoma; vs, versus; yr, year

did, resulting in non-significant although large excess risk in a multivariate analysis (OR, 7.5; 95% CI, 0.8–70).

Another study in Sweden focused on CLL, comparing 111 CLL cases identified in five hospitals in central and southern Sweden with 431 population controls from the same catchment areas. Exposures were assessed by postal questionnaire. Based on six cases, ever exposure to DDT was associated with a sixfold risk of CLL (95% CI, 1.5–23), after adjusting by age, sex, and other occupational exposures (Flodin et al., 1988).

A third study in Sweden, conducted in 1982–1986, focused on occupational and environmental risk factors for multiple myeloma (Eriksson & Karlsson, 1992). Cases were 256 patients with multiple myeloma who were identified through the Swedish cancer registry, individually matched by age, sex, vital status, and county to 256 controls selected from population registries or mortality registries. Exposure to DDT and other occupational exposures was assessed by mailed questionnaire, followed by a second in-person interview for subjects working on a farm or in other occupations potentially involving pesticides. Risk of multiple myeloma increased monotonically up to 1.6-fold with highest category of days of contact with DDT [95% CI, 0.53–4.93], although none of the individual risk estimates was statistically significant. When restricting the analysis to subjects working in agriculture or forestry, the risk was 1.86[(95% CI, 0.92–3.75). [The prevalence of farm work and exposure to DDT in this study population was unexpectedly high (farm work, 44%; ever exposure to DDT, about 12% among controls); a large proportion of interviews were conducted with next of kin; 90% confidence intervals of risk estimates were reported; a list of overlapping exposures, including phenoxy acids and livestock were evaluated individually, but no reciprocal adjustment was sought.]

[The Working Group considered that results from this group of studies were difficult to interpret as they were severely underpowered, referred to different pathological entities, and were further limited by the methodological concerns illustrated in preceding Working Group comments.]

Brown et al. (1990) included 578 cases of leukaemia identified from the Iowa, USA cancer registry and from hospital records in Minnesota between 1980 and 1983, and 1245 population controls matched by age, vital status, and state. All types of leukaemia, whether myeloid or lymphatic, acute or chronic, were included. Exposures were assessed by in-person interview, with a supplemental telephone interview concerning reported pesticide exposures. Risk of all leukaemia combined did not show a consistent trend when use of DDT in crop farming was considered; however, risk associated with the highest category of frequency of use (10+ days/year) was twofold (95% CI, 1.1–3.9) for DDT use in raising livestock. No substantial changes in the risk estimates were observed when a 20-year lag was applied to define exposure; risk was consistently elevated for both CLL or chronic myeloid leukaemia. [Interpretation was complicated by multiple exposures. Information was obtained by self-report or indirectly from next-of-kin in a substantial proportion of cases and controls.]

Another case–control study was conducted in the early 1980s in Iowa and Minnesota, USA, and included 622 NHL cases and 1245 controls (Cantor et al., 1992). This study evaluated the risk of NHL associated with ever exposure to DDT whether in disinfecting animals, or in crops, and whether occurring before 1965 or thereafter. The exposure assessment methods were similar to those used by Brown et al. (1990) with detailed questions on pesticide use. Regardless of whether exposure occurred before 1965 or thereafter, after adjusting by vital status, age, state, cigarette smoking, family history of lympho-haemopoietic cancer, high-risk occupations, and high-risk exposures, ever use of DDT on animals was

associated with a weak increase in risk, while there was a stronger association with ever use on crops (OR, 1.7; 95% CI, 1.2–2.6; for any use). [Information was indirectly obtained by next-of-kin for a substantial proportion of cases and controls.]

A pooled analysis of case–control studies on NHL conducted in the 1980s in four states in the USA (Baris et al., 1998) included the study by Cantor et al. (1992), and consisted of 993 histologically confirmed NHL cases and 2918 population controls, in part selected from mortality files, frequency-matched to cases by race, age, sex, and vital status at the time of interview. Next-of-kin interviews accounted for 32% of cases and 40% of the controls. Risk of NHL increased with days/year of use up to 2.1-fold (95% CI, 0.9–4.9) for the highest category (>5 days/year), However, when adjusting by exposure to 2,4-D and organophosphates, no increase in risk was observed for ever exposure (OR, 0.9; 95% CI, 0.4–1.8) and the dose–response curve was flattened (OR, 0.7; 95% CI, 0.0–15.0; for > 5 days/year). [This was the largest and most informative case–control study on NHL and occupational exposure to DDT, but information was indirectly obtained from next-of-kin in a substantial proportion of cases and controls.] A further analysis of the same data set was published in 2003 (De Roos et al., 2003), and included ever use of a list of 47 insecticides and herbicides. Any subject with missing information on any of the 47 pesticides was dropped from the analysis, and for the most frequently used pesticides, adjustments were made for multiple exposure using conventional and hierarchical logistic regression. Ever exposure to DDT was not associated with an increase in risk of NHL (OR, 1.0; 95% CI, 0.7–1.3), nor was reported use of DDT only (OR, 0.9; 95% CI, 0.6–1.3); however, a non-significant increase in risk was observed for the combined use of DDT and chlordane (OR, 1.7; 95% CI, 0.7–3.2; in conventional logistic regression).

In a small study in Italy that included 26 NHL cases and 74 controls, and was based partially on proxy interviews, ever exposure to DDT was attributed in seven cases using a crop–exposure matrix supported by a consultant agronomist (Assennato et al., 1995). The resulting odds ratio for exposure to DDT was increased more than fourfold (95% CI, 1.04–16.76).

In another small study in Italy (Nanni et al., 1996), cases of NHL and CLL combined (n = 61) and controls who were raising livestock were selected. The underlying hypothesis was that using insecticides in livestock might have involved higher exposure levels. Within this category, the authors explored risk associated with ever exposure to DDT using two strategies: self-report or using a job–exposure matrix (JEM). Either way, an approximate excess risk of 70% was observed when all NHL subtypes were combined with CLL (for the JEM: OR, 1.70; 95% CI, 0.91–3.17; for recall: 1.74 (95% CI, 0.93–3.27). When the analysis was limited to low-grade NHL combined with CLL, risks were elevated (based on JEM: OR, 2.16; 95% CI, 0.86–5.43; and based on the subjects' recall: OR, 2.33; 95% CI, 0.93–5.85). However, when calculating lifetime cumulative exposure, the excess risk among subjects with a cumulative exposure to ≥ 1 kg of DDT was 22% in respect to subjects with a lower cumulative exposure (OR, 1.22; 95% CI, 0.95–1.57). [This study used a more detailed exposure assessment, but the number and type of controls was unclear, the classification of lymphomas was outdated, and precision was limited.]

Risk of NHL risk related to exposure to DDT was also explored in a study in Canada that covered six provinces and gathered questionnaire data from 517 cases and 1506 population controls (Mc Duffie et al., 2001). Exposure to pesticides was assessed by questionnaire and detailed telephone interview with subjects who reported any exposure. More than 16% of cases and 12% of controls reported exposure to five or more chemicals, and it was mostly occasional,

with the highest exposure frequency set at ≥ 3 days/year and a median of 10 hours/year. DDT exposure above the median was associated with a significant increase in risk of NHL (OR, 1.73; 95% CI, 1.08–2.76), but risk did not increase by categories of exposure frequency. A subsequent analysis of the same data set explored the effect modification by concurrent asthma, allergy, or hay fever on the association between ever exposure to DDT and risk of NHL (Pahwa et al., 2012). The results showed that the excess risk associated with ever exposure to DDT was concentrated among subjects with a concurrent allergic condition (OR, 2.53; 95% CI, 1.17–5.47), while there was no association among those who did not report such conditions. [Major reasons for concern in interpreting findings from this study included reliance on self-reported exposures and a low response rate.]

DDT was evaluated in relation to overall lymphoma (including all B-cell and T-cell subtypes and HL) in a multicentre case–control study in six European countries (Cocco et al., 2013). Exposure to pesticides was estimated using a crop–exposure matrix and occupational histories collected by interview, which included a detailed questionnaire specific for the agricultural work. Data for DDT were reported only with respect to B-cell lymphoma. The prevalence of ever exposure to DDT was extremely low (about 0.01%) and the associated risk for all B-cell lymphomas was not elevated (OR, 1.2; 95% CI, 0.2–5.9).

(c) Environmental monitoring-based studies

Two studies in the USA examined environmental exposure to DDT by using a vacuum to sample carpet dust in the household of the study subjects (Colt et al., 2005; Ward et al., 2009). One study examined associations between organochlorines and NHL in adults in four areas covered by the SEER programme of the United States National Cancer Institute in 1998–2000 (Colt et al., 2005). The second study, conducted in northern and central California in 2001–2006, investigated associations between childhood leukaemia and PCBs and OCPs (Ward et al., 2009). Although both studies collected data more than 30 years after use of DDT was discontinued in the USA, the SEER study was characterized by an elevated frequency of detection of DDT in the carpet dust (cases, 67%; controls, 71%), that was higher than its major and most persistent derivative, DDE (cases, 50%; controls, 44%). A significant upward trend in risk of NHL was associated with DDE concentration in the carpet dust (*P* for trend, 0.02). There was no trend for DDT (*P* for trend, 0.09). In the analysis by individual NHL subtype, risk associated with DDE and DDT concentrations above the limit of detection was highest for T-cell lymphoma (ORs: 2.6; 95% 1.3–5.4; and 2.8; 95% CI, 1.1–7.1; respectively), while a non-significant 30% excess risk associated with DDE concentrations above the limit of detection was also observed for diffuse large B-cell lymphoma (OR, 1.3; 95% CI, 0.9–1.9) and follicular lymphoma (OR, 1.3; 95% CI, 0.9–2.0). [The Working Group noted that in this study risks were adjusted by age, sex, study site, and education, but not by occupation or rural/urban residence, which might have helped to discriminate possible alternative sources of the observed excess risk. In addition, it was not clear how DDT concentrations in carpet dust related to individual exposure in the etiologically relevant period.]

In a similar study of childhood leukaemia in California (Ward et al., 2009), which included family income and year of recruitment among the adjusting covariates, and used geographical mapping of rural areas and crops around the residence of study subjects, DDT was detected in 57% of dust samples, and DDE was detected in 82%. However, risk did not increase with increasing level of DDE (*P* for trend, 0.794), or DDT (*P* for trend, 0.709) in the carpet dust.

(d) Meta-analyses

Numerous meta-analyses and pooled analyses have evaluated associations between cancer risk and farmers' or farmworkers' occupational exposures to pesticides, but only one of these (Schinasi & Leon, 2014) examined associations of specific pesticides with NHL.

In that meta-analysis, Schinasi & Leon (2014), 44 papers published after 1980, with information about 21 pesticide chemical groups and 80 active ingredients were evaluated. [The Working Group noted that all of the reported results were from high-income countries.] Meta-risk ratio (meta RR) estimates and 95% confidence intervals using random effect models were computed, allowing between-study heterogeneity to contribute to the variance, and I^2 values, which represent the percentage of the total variance explained by study heterogeneity, and measures of inconsistency between studies were reported. Confidence limit ratios (CLRs, the ratio of the upper to the lower CI limits) were also reported as an indicator of precision. Sensitivity analyses were conducted to evaluate the robustness of results by potential sources of heterogeneity including study design, sex, geographical area, decade of cancer diagnosis, and source of the controls in the case–control studies

Seven papers contributed to the meta-analysis of DDT (Woods et al., 1987; Persson et al., 1993; Baris et al., 1998; Hardell et al., 2002; Purdue et al., 2007; Eriksson et al., 2008; Pahwa et al., 2012). The meta RR estimate for DDT with NHL overall was 1.3 (95% CI, 1.1–1.5; I^2 = 0%). The association with NHL subtypes was 1.4 (95% CI, 1.0–1.5) for B-cell lymphoma; 1.2 (95% CI, 0.9–1.7) for diffuse large B-cell lymphoma; and 1.5 (95% CI, 1.0–2.4) for follicular lymphoma (Schinasi & Leon, 2014).

[The Working Group noted that most of the available studies were on NHL overall and not NHL subtypes. Since NHL subtypes are believed to be etiologically heterogeneous, the lack of subtype-specific analyses in many of the previously published studies may be masking important associations in the available meta-analyses. Since the definition of NHL has changed over time, care must also be exercised in comparing findings from studies using older definitions of NHL with more recent studies based on the current understanding of NHL. The definition of NHL used by the SEER coding scheme is now based on the Pathology Working Group of the International Lymphoma Epidemiology Consortium (ICD-O-3 Interlymph modification) (Morton et al., 2007).]

2.2.3 Cancer of the prostate

See Table 2.9

In two studies on cancer of the prostate, exposure to DDT from agricultural work was assessed by experts or by means of JEM. These studies on occupational exposure are described first.

Settimi et al. (2003) investigated risk of cancer of the prostate in relation to exposure to pesticides in five areas in Italy using data from a hospital-based case–control study carried out between 1990 and 1992. The case group was composed of 124 patients with prostate cancer. The control group included 659 patients with other cancers. Exposure to 217 different pesticides, including DDT, was assessed by a team of agronomists using data obtained from crop-specific forms collected from subjects engaged in agricultural work, national statistics on pesticide use, supplier's records, and personal experience. Men ever exposed to DDT had an odds ratio for prostate cancer of 2.1 (95% CI, 1.2–3.8). Odds ratios in men exposed to DDT for ≤ 15 years or > 15 years were 2.1 (95% CI, 0.9–2.1) and 2.2 (95% CI, 1.1–4.8), respectively. [The Working Group noted the low specificity of exposure assessment, and that selection of controls with other cancers may have biased risk estimates.]

Band et al. (2011) conducted a case–control study on cancer of the prostate in British

Columbia, Canada. Cases were patients with prostate cancer ascertained by the population-based British Columbia cancer registry for the years 1983–1990 (n = 1153). Controls were patients with cancers at all other sites excluding lung and unknown primary (n = 3999), matched to the cases on year of birth and year of diagnosis. Information on lifetime job description, occupation, and industry titles, location, duration and time period of work, as well as alcohol and tobacco consumption was obtained from a self-administered questionnaire. Farmers' exposure to 180 pesticides was assessed using a JEM based on region, crop, task, and job title. Exposures via pesticide application were quantified using estimates derived from the North American Pesticide Handlers Exposure Database. A significant association was reported between prostate cancer and exposure to DDT (OR, 1.68; 95% CI, 1.04–2.70 for high-level exposure with reference to the unexposed group), with a dose–response trend (P for trend, 0.03). [This was a large case–control study. The use of a JEM for assessing exposure may have led to exposure misclassification, but exposure indicators were calculated over the lifetime.]

Several other studies reported on associations between cancer of the prostate and exposure to DDT and its derivatives as measured in biological samples. Ritchie et al. (2003) examined the relationship between serum concentrations of OCPs and prostate cancer in a population-based case–control study in Iowa, USA. Cases were 58 men diagnosed with prostate cancer between May 2000 and May 2001 who were enrolled at a university hospital and a smaller urology clinic. Controls were 99 men who received physical check-ups in the hospital. Concentrations of 48 organochlorinated compounds including *p,p′*-DDE and *p,p′*-DDT were measured in serum samples. Since the detection rate of *p,p′*-DDT was close to 0%, only *p,p′*-DDE (detection rate, > 99%) was investigated in relation to risk of prostate cancer. The odds ratio for *p,p′*-DDE in the highest exposure tertile when compared with the lowest was 1.08 (95% CI, 0.47–2.50). [This study was the first to investigate prostate cancer and biological measurements of organochlorine compounds, and was based on very small numbers of cases and controls.]

In another hospital-based case–control study on cancer of the prostate conducted at Örebro University hospital, Sweden, Hardell et al. (2006a) measured the levels of several chlorinated and brominated pollutants, including *p,p′*-DDE, in adipose tissue biopsy from the abdominal wall taken during surgery for 57 cases diagnosed with prostate cancer in 1997–1999, and 20 controls undergoing transurethral resection for benign hyperplasia. The odds ratio for prostate cancer among men with *p,p′*-DDE levels above the median was 2.30 (95% CI, 0.77–6.85). [The sample size of the study was small and choice of controls may have led to selection bias.]

Aronson et al. (2010) reported the results of a case–control study of cancer of the prostate in patients who had visited any of a group of five urologists in Kingston, Ontario, Canada, between 1997 and 1999. Cases were selected from men diagnosed with incident primary cancer of the prostate at biopsy (n = 79). A group of urological controls (n = 194) included men with non-cancerous urological disease (erectile dysfunction, prostatitis, benign prostate hyperplasia, haematospermia/haematuria, urinary obstruction/pain/ infection etc.), and a group of biopsy controls (n = 135) included men in whom no prostate cancer was detected at biopsy. Concentrations of 14 PCB congeners and 13 pesticides were measured in blood plasma. Odds ratios for *p,p′*-DDE and *p,p′*-DDT comparing the highest exposure tertile to the lowest were 0.73 (95% CI, 0.38–1.40) and 1.05 (0.55–2.00), respectively, indicating no association between risk of cancer and blood exposure levels at diagnosis. Results based on the urology control group only were similar. [This was a small study with limited statistical power to detect associations.]

Table 2.9 Case–control studies on cancer of the prostate and exposure to DDT and its metabolites

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Settimi et al. (2003) Italy (4 areas) 1990–1992	Cases: 124; local and university hospitals Controls: 659; hospital patients with other cancers Exposure assessment method: team of agronomists assessed exposure to pesticides based on interview data	Prostate	DDT: Ever exposed ≤ 15 yrs > 15 yrs	 20 16 4	 2.1 (1.2–3.8) 2.1 (0.9–2.1) 2.2 (1.1–4.8)	Age, family history of prostate cancer, interview (direct/ indirect)	Strengths: same study base for cases and controls; adjustment for main confounders Limitations: relatively small study size; low specificity of exposure assessment; cancer sites of controls possibly associated with exposure
Band et al. (2011) Canada, British Columbia 1983–1990	Cases: 1153; cancer registry Controls: 3999; other cancer patients from the same registry excluding lung cancer and cancer of unknown primary site Exposure assessment method: JEM for 1950–1998, including 45 animal and crops; information on exposure (quantitative or never/ever) to 139 pesticide active ingredients determined for type of work and time; quantification derived from models used for pesticide registration	Prostate	No exposure Low exposure High exposure Trend-test *P* value: 0.03 Ever vs never exposed Trend-test *P* value: 0.03	1104 19 30 49 	1.00 1.24 (0.71–2.16) 1.68 (1.04–2.70) 1.47 (1.02–2.12) 	Alcohol consumption, cigarette years, pipe years, education level, respondent type (proxy/direct)	Spearman correlation coefficient between DDT and lindane 0.72 Strengths: large size; histological confirmation-high response rates; lifetime cumulative exposure assessment Limitations: exposure misclassification due to the JEM; potential selection bias due to use of cancer controls; multiple comparisons (142 active chemicals evaluated); strong inter-correlations between exposures; no mutual adjustment

Table 2.9 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Ritchie et al. (2003) Iowa, USA 2000–2001	Cases: 58; university hospital and urology clinic Controls: 99; men receiving annual check-ups in the hospital Exposure assessment method: biomarker; detection rates for *p,p′*-DDE, > 99%; detection rates for *p,p′*-DDT, 0% cases; 2% controls (not investigated)	Prostate	*p,p′*-DDE (μg/g) ≤ 0.180 0.181–0.340 > 0.340	20 15 23	1 0.72 (0.31–1.71) 1.08 (0.47–2.5)	Age, body mass index, prostatis	Strengths: first study on prostate-cancer risk based on biological measurements of OC Limitations: very small numbers of cases; source population for the controls not well defined
Hardell et al. (2006a) Örebro, Sweden 1997–1999	Cases: 58; hospital Controls: 20; hospital (men undergoing transurethral resection for benign hyperplasia) Exposure assessment method: biomarker; chlorinated and brominated compounds measured in abdominal adipose tissue biopsy	Prostate	*p,p′*-DDE, < 291 ng/g lipid *p,p′*-DDE, > 291 ng/g lipid	15 42	1.0 2.3 (0.77–6.85)	Age, BMI	Strengths: adipose tissue biopsy; high response rate Limitations: small sample size
Aronson et al. (2010) Kingston, Ontario, Canada 1997–1999	Cases: 79; incident prostate cancer diagnosed by biopsy at urology clinics Controls: 329; men without prostate cancer seen at the same clinics (135 with biopsy, 194 without) Exposure assessment method: biomarker; 13 pesticides and 14 PCBs measured in plasma (LOD, 8 μg/kg lipid for DDT; 4 μg/kg lipid for DDE)	Prostate	*p,p′*-DDE, μg/kg lipid < 270 270–548.9 548.9–2362.3 Trend-test *P* value: 0.35 *p,p′*-DDT, μg/kg lipid < 5.3 5.3–8.4 8.4–49.1 Trend-test *P* value: 0.9	 27 27 24 24 28 26 	 1.00 0.97 (0.52–1.83) 0.73 (0.38–1.40) 1.00 1.19 (0.63–2.26) 1.05 (0.55–2.00)	Age, teenage physical activity, alcohol consumption, smoking pack-years	Strengths: PSA and DRE screening in cases and controls Limitations: very small number of cases; total response rates not available; controls with urological diseases possibly related to exposure

Table 2.9 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Emeville et al. (2015) Guadeloupe (French Caribbean) 2004–2007	Cases: 576; private and public urology clinics Controls: 655; free health screening programme Exposure assessment method: biomarker; *p,p′*-DDE measured in plasma (*p,p′*-DDT not investigated: detection frequency, 36.2%); LOD, 0.05 µg/L for *p,p′*-DDE and *p,p′*-DDT	Prostate (total)	*p,p′*-DDE, µg/L			Age, waist-to-hip ratio, type 2 diabetes, alcohol, total plasma lipid concentration	Strengths: largest study investigating associations between DDE and prostate cancer based on biological measurements of exposure Limitations: source population for the controls was not well defined; *p′,p′*-DDT not investigated; no adjustment for BMI
			< 0.79	106	1.00		
			0.79–1.62	96	0.96 (0.66–1.42)		
			1.63–2.89	111	1.05 (0.71–1.55)		
			2.90–5.18	104	1.02 (0.67–1.53)		
			> 5.19	159	1.53 (1.02–2.30)		
			Trend-test *P* value: 0.01				
		Prostate (aggressive/ advanced)	*p,p′*-DDE, µg/L				
			< 1.37	20	1.00		
			1.37–3.41	34	1.55 (0.85–2.85)		
			> 3.42	47	1.92 (1.04–3.54)		
			Trend-test *P* value: 0.06				
			DDT, 1–20 yrs of exposure	34	1.6 (0.9–4.6)		

BMI, body-mass index; CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DRE, digital rectal examination; JEM, job–exposure matrix; LOD, limit of detection; NR, not reported; OC, organochlorine; OPs, organophosphates; PCB, polychlorinated biphenyl; PSA, prostate-specific antigen; vs, versus; yr, year

Emeville et al. (2015) reported the results of a population-based case–control study of cancer of the prostate and plasma concentrations of DDE conducted in Guadeloupe (French Caribbean). The case group included 576 men with incident prostate cancer (81% of the cases with a blood sample available) identified from private and public clinics covering the entire territory of Guadeloupe. Controls were men aged 45 years or older selected from a free health screening programme open to the general population, and who had normal findings upon digital rectal examination and normal prostate-specific antigen (PSA) concentrations. Organochlorine compounds including *p,p′*-DDE and *p,p′*-DDT were measured in the blood samples via high-resolution gas chromatography, but only *p,p′*-DDE (detection frequency, 96.2% among controls) was investigated in relation to risk of prostate cancer. The odds ratio for men in the highest quintile of DDE concentration compared with men in the lowest quintile was 1.53 (1.02–2.30). There was an overall statistically significant trend ($P = 0.01$), which was mainly driven by the odds ratio in the highest exposure quintile, as the odds ratios in lower quintiles were close to the null. The odd ratio for cases with high-grade Gleason score was 1.92 (95% CI, 1.04–3.54) (worse prognostic value) for men in the highest tertile relative to men in the lowest tertile, but was not significantly different from the corresponding odds ratio for cases with low-grade Gleason score. [This was the largest study to date investigating associations between DDE and prostate cancer based on biological measurements of exposure; the source population for the controls was not well defined and may have introduced some selection bias.]

Lim et al. (2015) conducted a meta-analysis of studies of the associations between cancer of the prostate and measurements of persistent organic pollutants, including *p,p′*-DDE, in blood or adipose tissue. The analysis included four case–control studies and a nested case–control study reviewed in this Monograph and a cross-sectional study of the United States National Health and Nutrition Examination Survey (NHANES) study (Xu et al., 2010). The meta-odds ratio for cancer of the prostate with *p,p′*-DDE comparing high versus low concentrations was 1.41 (95% CI, 1.12–1.78). Based on four of the included studies, the odds ratio per 1 μg/g lipid of *p,p′*-DDE was 1.25 (95% CI, 0.86–1.84).

2.2.4 Cancer of the testis

See Table 2.10

Hardell et al. (2003) conducted a population-based case–control study on cancer of the testis in Sweden. Case patients and their mothers were recruited from 1997 to 2000 from urology or oncology departments of several hospitals in Sweden. Controls and their mothers were drawn from the Swedish population registry, age-matched with the cases (5-year age group) and control mothers were age-matched with case mothers (5-year age group). Persistent organic pollutants, including *p,p′*-DDE, were measured at diagnosis in the blood samples provided by 58 cases and 44 mothers of cases, and by 61 controls and 45 mothers of controls. The odds ratio for exposure to *p,p′*-DDE at above median concentration versus below median for male subjects was 1.7 (95% CI, 0.8–3.7), and 1.3 (95% CI, 0.5–3.0) for mothers of study subjects. Stratification of the case group by seminoma and non-seminoma did not reveal a notably different association with *p,p′*-DDE. In a later publication on the same study (Hardell et al., 2006b), results on *p,p′*-DDE in mothers were also presented separately by age group, showing increased odds ratios only among mothers younger than age 55 years at the time of diagnosis (OR, 2.3, 95% CI, 0.6–9.5). [This was the first study examining testicular cancer in relation to biological measurements of persistent organic pollutants. Selection biases were minimized by use of a population registry to select the controls and their mothers, and participation rates were high, but mothers' blood was sampled

only after case diagnosis (on average, at age 31 years) and the results were imprecise.]

Biggs et al. (2008) conducted a population-based case–control study on testicular germ cell tumours in Washington State, USA. The case group included 246 men aged 18–45 years with invasive testicular germ cell carcinoma diagnosed between 1999 and 2008, identified from the files of the cancer surveillance system, a part of the SEER programme of the United States National Cancer Institute. The control group included 630 men frequency-matched to the cases on 5-year age group, and selected using a random-digit dialling procedure. Concentations of 12 OCPs, including *p,p′*-DDT, *o,p*-DDT, *p,p′*-DDE, and 36 PCB congeners were measured from blood samples drawn at the date of enrolment in the study. The odds ratios for men exposed above the 85th percentile of exposure compared with men exposed below the median were 0.61 (95% CI, 0.32–1.14), 1.17 (95% CI, 0.68–2.00), 1.30 (95% CI, 0.67–2.53), and for *p,p′*-DDE, *p,p′*-DDT, and *o,p*-DDT, respectively. Analysis based on the continuous variables did not show any significant association between these compounds and testicular germ cell carcinoma. No interaction between *p,p′*-DDE levels and the androgen receptor genotype was observed. [In this study, the response rate for cases and controls was low; the use of post-diagnostic blood samples in this study may have distorted the results, despite the fact that odds ratios were adjusted for change in BMI between reference date and blood draw.]

In a hospital-based case–control study in Rome, Italy, Giannandrea et al. (2011) examined the association between serum levels of *p,p′*-DDE and cancer of the testis. Cases were 50 patients with testicular cancer recruited between October 2006 and September 2008 at the Laboratory of Seminology-Sperm Bank. The controls included 48 men recruited from the same department among men undergoing examination to ascertain their fertility status, and of approximately the same age and BMI as the cases. Only 26% of cases and 10% of controls had detectable serum *p,p′*-DDE concentrations (limit of detection, 0.2 ng/mL). For men with detectable levels of *p,p′*-DDE, the adjusted odds ratio for testicular cancer was 3.21 (95% CI, 0.77–13.30). [This was a small study. Choosing controls among men consulting for fertility problems could introduce bias. There was a large proportion of subjects under the limit of detection, possibly because the study was conducted long after the use of DDT was discontinued. There was no adjustment for total lipid concentration.]

2.2.5 Other cancer sites

See Table 2.11

(a) Cancer of the pancreas

Fryzek et al. (1997) conducted a case–control study in Michigan, USA, to investigate the relationship between cancer of the pancreas and exposure to pesticides. The case group included 66 patients diagnosed with this cancer in 1994 and 1995 in seven hospitals (response rate, 81%). The controls (n = 131) were frequency-matched on age, sex, ethnicity, and county of residence, and were identified by random-digit dialling (response rate, 27%). Exposure to pesticides and to DDT during leisure time activities and at work were assessed by questionnaire. Ever using DDT was associated with a non-statistically significant increased risk of cancer of the pancreas (OR, 1.6; 95% CI, 0.8–3.1). [Unlike most studies on this cancer, for which the prognosis is poor, this study was based on direct interviews of cases. However, the response rate for cases and controls was low and the use of questionnaire for assessing exposure to DDT may lead to recall bias.]

Hoppin et al. (2000) conducted a population-based case–control study on cancer of the pancreas in the San Francisco bay area, USA. Cases were 108 patients aged 21–85 years with pancreatic cancer, recruited using a rapid case ascertainment between October 1996 and May

Table 2.10 Case–control studies on cancer of the testis and exposure to DDT and its metabolites

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Hardell et al. (2003) Sweden 1997–2000	Cases: 58 (44 mothers); hospital urology and oncology departments Controls: 61 (45 mothers); population registry; matched by age Exposure assessment method: biomarker	Testis	*p,p′*-DDE > median	34	1.7 (0.8–3.7)	Age, BMI	Strengths: population controls; high participation rates, including mothers Limitations: small size; blood drawn from mothers after case diagnosis
			Seminoma	14	1.5 (0.5–4.5)		
			Non-seminoma	20	1.9 (0.8–3.7)		
			Mothers *p,p′*-DDE > median	22	1.3 (0.5–3.0)		
Biggs et al. (2008) Washington state, USA 1999–2008	Cases: 246; cancer registry Controls: 630; population; frequency-matched on age Exposure assessment method: biomarker; *p,p′*-DDT not detected in 6.7% of subjects, *o,p′*-DDT not detected in 42.3%, *p,p′*-DDE not detected in 0%; poor between-run reliability of the analytic method for several of the analyses	Testis (testicular germ cell tumours)	*p,p′*-DDE, pg/g			Age, ethnicity, change in BMI between reference date and blood draw, assay run number, serum lipids	Strengths: relatively large study size Limitations: use of post-diagnostic blood samples; low response rates of cases and controls
			≤ 1101	130	1.00		
			> 1101–2473	94	1.14 (0.78–1.67)		
			> 2473	21	0.61 (0.32–1.14)		
			Trend-test *P* value: 0.36				
			p,p′-DDT, pg/g				
			≤ 27	110	1.00		
			27–47	94	1.39 (0.96–2.02)		
			> 47	32	1.17 (0.68–2.00)		
			Trend-test *P* value: 0.3				
			o,p-DDT, pg/g				
			≤ 5	104	1.00		
			5–13	83	1.26 (0.83–1.91)		
			> 13	37	1.30 (0.67–2.53)		
			Trend-test *P* value: 0.28				

Table 2.10 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Giannandrea et al. (2011) Rome, Italy 2006–2008	Cases: 50; university laboratory and sperm bank Controls: 48; men with fertility examination in the same department as cases Exposure assessment method: personal monitoring	Testis (testicular cancer)	*p,p′*-DDE, < 0.2 ng/mL *p,p′*-DDE, ≥ 0.2 ng/mL DDT, 1–20 yrs of exposure	37 13 34	1.00 3.21 (0.77–13.30) 1.6 (0.9–4.6)	Mother's age at birth, education, parity	The late period of the study (2008) may explain the large proportion of subjects below the detection limit Limitations: small study; large proportion of subjects under LOD; selection of controls among men consulting for fertility problems may not be adequate if fertility is associated with DDT/DDE; no adjustment for total lipid concentration

BMI, body mass index; CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; JEM, job–exposure matrix; LOD, limit of detection; NR, not reported; OC, organochlorine; OPs, organophosphates; PCB, polychlorinated biphenyl; vs, versus; yr, year

1998, who were alive and provided a blood sample. Control subjects ($n = 82$) were frequency-matched on sex and age to the cases and identified using random-digit dialling and random samples from the Health Care Financing Administration lists. Detailed in-person interviews were conducted and blood samples were obtained for organochlorine analyses that included DDE, DDT, and 11 PCB congeners. DDE was detected in more than 50% of the samples. The odds ratio for DDE in the highest exposure tertile (≥ 1880 ng/g lipids) compared with DDE in the lowest (< 850 ng/g lipid) was 2.1 (95% CI, 0.9–4.7), and there was some indication of a dose–response trend (*P* for trend, 0.08). However, when adjusting for total PCBs, the odds ratio in the highest tertile decreased to 1.1 (95% CI, 0.4–2.8), whereas the association observed with PCBs was not modified by adjustment for DDE. [This was the first population-based study on pancreatic cancer using serum measurements of organochlorine chemicals.]

In a hospital-based case–control study of cancer of the pancreas in Sweden, Hardell et al. (2007) measured concentrations of organochlorine compounds in adipose tissue from 21 cases diagnosed between 1996 and 1999, and 59 controls undergoing surgery for benign prostate hyperplasia (20 men) or hysterectomy (39 women). For *p,p′*-DDE, the odds ratio for exposure above the median (controls, 261 ng/g lipid) adjusted for BMI at tissue sampling, age, and sex was 2.39 (95% CI, 0.73–7.78). The odds ratio was unchanged after consideration of loss of weight during the preceding year. [This was a small study with measurements of organochlorine compounds in the adipose tissue; the effect of the wasting syndrome characteristic of pancreatic cancer on organochlorine concentrations may have influenced the result.]

In a case–control (case–case) study in Spain evaluated the relation between levels of *p,p′*-DDT, *p,p′*-DDE, and PCBs, and mutations in codon 12 of the *K-ras* gene in patients with exocrine cancer of the pancreas (Porta et al., 1999). Cases of pancreatic cancer with wild-type *K-ras* ($n = 17$) were frequency-matched for age and sex to cases of pancreatic cancer with a *K-ras* mutation ($n = 34$). Serum concentrations of *p,p′*-DDT were significantly higher in pancreatic cancer cases with a *K-ras* mutation than in cases without a mutation (unadjusted odds ratio for upper tertile, 8.7 (95% CI, 1.6–48.5), *P* for trend , 0.005). For *p,p′*-DDE, the corresponding figures were 5.3 (95% CI, 1.1–25.2; *P* for trend, 0.03). These associations remained significant after adjusting for covariates, including smoking. A specific association was observed between glycine-to-valine substitution at codon 12 and both *p,p′*-DDT and *p,p′*-DDE concentrations. [The Working Group noted the small size of this study.]

(b) Cancer of the endometrium

Sturgeon et al. (1998) reported the results of a case–control study on cancer of the endometrium in five geographical areas of the USA. Cases were 90 women diagnosed with the disease in seven hospitals between 1987 and 1990. Controls with intact uterus matched on age, race, and areas of residence were selected from random-digit dialling or from the files of the Health Care Financing Administration. Among the 498 eligible cases and 477 eligible controls, only 90 sets of cases and matched controls had sufficient blood volume for organochlorine analyses. Among other organochlorine compounds, four DDT-related compounds (*o,p′*-DDT, *p,p′*-DDT, *o,p′*-DDE, *p,p ′*-DDE), as well as 13 other OCPs and 27 PCB congeners were measured in stored serum samples. Among these, *o,p′*-DDE was detected too infrequently for analysis, and only *p,p′*-DDT was higher in cases than in controls ($P = 0.03$). The odds ratio for women in the highest tertile of *p,p′*-DDT was 1.8 (95% CI, 0.7–4.4) compared with the women in the lowest tertile. Odds ratios were not increased for *p,p′*-DDE or for *o,p′*-DDT. [This was the first study examining the relationship between serum organochlorine

Table 2.11 Case–control studies on other cancers and exposure to DDT and its metabolites

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Fryzek et al. (1997) Michigan, USA 1994–1995	Cases: 66; 7 hospitals Controls: 131; population (random-digit dialling); frequency-matched by age group, sex, ethnicity and county Exposure assessment method: questionnaire	Pancreas	DDT Ever exposed Low exposure High exposure	 17 5 7	 1.6 (0.8–3.1) 1.1 (0.4–3.3) 1.7 (0.6–4.8)	None	Strengths: rapid identification of pancreas cancer cases allowing direct interviews; strict case definition Limitations: small study size; only living cases; low response rate in controls; possible recall bias when assessing exposure to DDT
Hoppin et al. (2000) San Francisco Bay Area, USA Oct–1998	Cases: 108; rapid case ascertainment Controls: 82; random-digit dialling and health care financing records, frequency-matched by sex and age Exposure assessment method: biomarker; measurements of DDE, DDT, PCBs and other OCs	Pancreas	DDE, ng/g lipid < 850 850–1880 ≥ 1880 Trend-test *P* value: 0.08	 30 37 41	 1.0 1.5 (0.7–3.3) 2.1 (0.9–4.7)	Age, race, sex	Strengths: direct interviews only; consideration of effects of cachexia on OC serum levels in sensitivity analyses; adjustment for exposure to PCBs Limitations: low response rates
Hardell et al. (2007) Sweden 1996–1999	Cases: 21; hospital Controls: 59; surgery patients (benign prostate hyperplasia, 20 men or hysterectomy, 39 women) Exposure assessment method: biomarker; OCs measured in adipose tissue	Pancreas	*p,p′*-DDE > median	14	2.39 (0.73–7.78)	BMI at tissue sampling, age, sex	Strengths: adipose tissue samples; 100% response rate in cases; consideration of BMI 1 yr and 10 yrs before tissue sampling Limitations: small study size

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Sturgeon et al. (1998) USA 198–1990	Cases: 90; 7 hospitals in 5 USA geographical areas Controls: 90; population, with intact uterus, matched by age, race, residence Exposure assessment method: biomarker; measurements of *o,p′*-DDT; *p,p′*-DDT, *o,p′*-DDE, *p,p′*-DDE; 13 other OC compounds & 27 PCBs	Endometrium	*p,p′*-DDE, ng/g lipids			Age, area of residence, weight, ethnicity	Strengths: first study examining the relation between serum OC concentrations and endometrial-cancer risk Limitations: small study size; low proportion of cases & controls with available blood samples
			256–943	27	1.0		
			954–1357	17	0.5 (0.2–1.2)		
			1359–2276	27	1.0 (0.4–2.5)		
			2391–10 486	19	0.7 (0.2–2.0)		
			o,p′-DDT, ng/g lipid				
			0	43	1.0		
			5–75.8	27	0.9 (0.4–2.1)		
			78.2–386.6	20	0.5 (0.1–1.9)		
			p,p′-DDT, ng/g lipids				
			0	41	1.0		
			31.6–98.2	15	0.6 (0.2–1.6)		
			99.0–278.0	34	1.8 (0.7–4.4)		
Weiderpass et al. (2000) Sweden 1996–1997	Cases: 154; hospital gynaecology and oncology departments in 12 counties Controls: 205; population, matched by age and with intact uterus Exposure assessment method: biomarker; 10 chlorinated pesticides, including DDT, and 10 PCBs measured in serum	Endometrium	*p,p′*-DDT:			Age, BMI	Strengths: population-based design; restriction to women who never used HRT; control for possible confounders- collection of blood samples immediately after diagnosis (no effect of cancer treatment) Limitations: relatively low participation rates
			quartile 1	NR	1.0		
			quartile 2	NR	1.1 (0.6–2.2)		
			quartile 3	NR	0.8 (0.4–1.6)		
			quartile 4	NR	1.1 (0.5–2.1)		
			Trend-test *P*-value: 0.95				
			p,p′-DDE:				
			quartile 1	NR	1.0		
			quartile 2	NR	0.9 (0.5–1.8)		
			quartile 3	NR	1.1 (0.6–2.0)		
			quartile 4	NR	1.0 (0.6–2.0)		
			Trend-test *P* value: 0.78				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Hardell et al. (2004) Sweden 1997–1998	Cases: 76; hospital, surgery for endometrial cancer Controls: 39; same hospitals, women having hysterectomy for endometrial hyperplasia Exposure assessment method: biomarker; *p,p′*-DDE and other OC compounds measured in adipose tissue collected during surgery	Endometrium	*p,p′*-DDE: < median ≥ median 50–75th percentile > 75th percentile	 21 55 32 23	 1.0 1.9 (0.8–4.8) 2.4 (0.8–6.8) 1.3 (0.4–4.1)	Age, BMI	Strengths: adipose tissue samples; high response rates Limitations: controls with benign disease (endometrial hyperplasia) possibly related to OC exposure; very small numbers
Zhao et al. (2012) Xiamen, China 2007–2009	Cases: 345; 3 hospitals Controls: 961; healthy control subjects recruited from the same three hospitals Exposure assessment method: biomarker; analytical methods not reported in detail	Liver (HCC)	*p,p′*-DDT, μg/L < 16.11 16.11–34.63 34.64–43.08 ≥ 43.09 Trend-test *P* value: 0 *p,p′*-DDE, μg/L < 2.62 2.62–6.84 6.85–10.55 ≥ 10.56 Trend-test *P* value: 0.00 001	 41 53 85 166 76 60 61 148	 1.0 1.3 (0.81–2.08) 2.08 (1.34–3.22) 4.07 (2.72–6.10) 1.00 0.79 (0.54–1.17) 0.81 (0.54–1.20) 1.96 (1.39–2.76)	Age, sex, education, alcohol consumption, smoking, aflatoxin, HBV, HCV	DDT/DDE ratio elevated (4.89) indicating recent exposure to DDT Strengths: large numbers; elevated levels of OC exposures; data on other risk factors for liver cancer Limitations: recruitment details for the controls not reported; details of exposure and covariate measurement not reported; DDE measurements not lipid-adjusted

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates	Comments
Howsam et al. (2004) Barcelona, Spain 1996–1998	Cases: 132; hospital Controls: 76; age-sex matched patients at the same hospital with other diseases Exposure assessment method: biomarker	Colon & rectum	*p,p′*-DDE, ng/g lipids			Age, sex, energy intake, BMI	Strengths: careful design, robust analytical methods, potential confounders examined in detail, study of interaction between OC values and K-ras and p53 mutations Limitations: use of hospital controls may introduce selection bias
			< 2574	38	1.00		
			2574–5565	49	2.17 (1.03–4.54)		
			> 5565	45	1.6 (0.79–3.25)		
			Trend-test *P* value: 0.19				
		Colon & rectum	*p,p′*-DDT, ng/g lipids				
			< 336	44	1.00		
			336–740	52	1.58 (0.74–3.36)		
			> 740	36	0.56 (0.27–1.17)		
			Trend-test *P* value: 0.12				
De Stefani et al. (1996) Uruguay 1993–1994	Cases: 270; 5 hospitals, men only Controls: 383; men with other cancers from the same hospitals Exposure assessment method: questionnaire	Lung	DDT, ever exposed	50	1.7 (1.0–2.8)	Age, residence, education, cigarette smoking, alcohol consumption	Overall response rate (all cancer sites), 97.4% Strengths: inclusion of all patients admitted to major hospital; high response rate; adjustment for major confounders Limitations: other cancers as controls; no indication of adjustment of other occupational lung carcinogens
			DDT, 1–20 yrs of exposure	34	1.6 (0.9–4.6)		

BBD, benign breast disease; BMI, body-mass index; CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HRT, hormone replacement therapy; JEM, job–exposure matrix; LOD, limit of detection; NR, not reported; OC, organochlorine; OPs, organophosphates; PCB, polychlorinated biphenyl; vs, versus; yr, year

concentrations and risk of endometrial cancer. The Working Group noted concerns about the potential for selection bias related to the small proportion of subjects with available blood samples and about the limited precision.]

Weiderpass et al. (2000) conducted a population-based case–control study on cancer of the endometrium in Sweden. Cases were 154 women with endometrial cancer diagnosed in 1996 and 1997 in gynaecology or gynaecological oncology departments in 12 Swedish counties and who had never used hormone replacement therapy. Controls were 205 age-matched women selected from the population register, who had never used hormone replacement therapy and who had not undergone hysterectomy. Four DDT and DDE compounds were measured in serum. No association was found between endometrial cancer and serum concentration of any of the four compounds. [This was a well-conducted study using a population-based design, in which only women who had never used hormonal treatment were included to examine the hormonal effects of environmental exposures on the endometrium.]

In a small hospital-based case–control study in Sweden, Hardell et al. (2004) compared concentrations of *p,p′*-DDE in adipose tissue from 76 cases with cancer of the endometrium, and 39 controls with endometrial hyperplasia undergoing surgery. The odds ratio for women with *p,p′*-DDE concentrations above the median compared with women with concentrations below the median was 1.9 (95% CI, 0.8–4.8), but the odds ratio decreased to 1.3 (95% CI, 0.4–4.1) for women in the highest exposure group (concentration > 75% percentile). [This was a very small study.]

(c) Cancer of the liver

Zhao et al. (2012) published the findings of a hospital-based case–control study of HCC in Xiamen, China. Cases diagnosed with HCC (n = 345) and healthy controls (n = 961) were recruited between 2007 and 2009 in three hospitals, from subjects who had been living for at least 10 years in Xiamen. Cases and controls were interviewed using a structured questionnaire. Organochlorine pesticides and PCB congeners were measured in blood serum samples taken after diagnosis. Higher concentrations of *p,p′*-DDT and *p,p′*-DDE were observed than in a previous study of cancer of the liver in Linxian (McGlynn et al., 2006; see Section 2.1.4). The odds ratio comparing the highest exposure quartile of *p,p′*-DDT to the lowest was 4.07 (95% CI, 2.72–6.10) with adjustment for risk factors including alcohol drinking, HBV, and hepatitis C virus (HCV) infection, and aflatoxin B1, and the dose–response trend was highly significant ($P < 10^{-5}$). Concentrations of *p,p′*-DDE was also associated with cancer of the liver (corresponding adjusted OR, 1.96; 95% CI, 1.39–2.76; *P* for trend, 10^{-4}). The authors also reported positive interactions of OCPs with other risk factors for HCC, particularly between *p,p′*-DDT and aflatoxin B1. [This was a large study on HCC in a region of high incidence of HCC, with intensive past use and limited current use of OCPs. The Working Group noted concerns about incomplete reporting of this study, particularly with respect to the selection of controls and measurement of covariates.]

(d) Cancer of the colon

Howsam et al. (2004) conducted a case–control study on organochlorine exposure and risk of cancer of the colorectum within a larger hospital-based study in Barcelona, Spain. Cases were a random sample of 132 patients with a new diagnosis of colorectal adenocarcinoma attending a university hospital between 1996 and 1998, frequency-matched on age, sex, and energy intake, to a sample of 76 controls with new diagnoses of other diseases at the same hospital. Organochlorine compounds were measured in blood samples obtained at diagnosis. Overall, as compared with subjects in the first exposure tertile of exposure distribution of *p,p′*-DDE, odds

ratios in the second and third exposure tertiles were 2.17 (95% CI, 1.03–4.54) and 1.30 (95% CI, 0.79–3.25), respectively (*P* for trend, 0.19). Corresponding values for *p,p′*-DDT were 1.58 (95% CI, 0.74–3.36) and 0.56 (95% CI, 0.27–1.17), *P* for trend, 0.12. *p,p′*-DDE significantly interacted with *p53* (*P* for interaction, 0.047) and *K-ras* gene mutations (*P* for interaction, 0.012). [DDT was only analysed in a subset of cases and controls from a larger study. The hospital-based design with other patients as controls was a potential source of selection bias.]

(e) Cancer of the lung

De Stefani et al. (1996) conducted a hospital-based case–control study in Montevideo, Uruguay, on occupational risk factors for cancer of the lung. The study was part of a large multisite case–control study: all incident cases of cancer occurring in men aged 30–75 years admitted in any of five major hospitals in Montevideo were included. The overall response rate was 97.4%. The paper reported results on lung cancer (*n* = 270 cases), using patients with cancer at other sites as the control group (*n* = 383), after excluding cancer sites that shared occupational etiologies with lung cancer. Cancers of the colorectum and prostate were the most common diagnoses among controls. Exposure to DDT was assessed from an occupational questionnaire, along with exposures to other occupational hazards. Ever being exposed to DDT was associated with an odds ratio of 1.7 (95% CI, 1.0–2.8) that increased to 2.0 (95% CI, 0.9–4.7) for men exposed to DDT for more than 20 years. The analysis by histological subtype indicated odds ratios of 1.3 (95% CI, 0.7–2.3), 3.6 (95% CI, 1.5–8.9), and 2.3 (95% CI, 1.2–4.7) for squamous cell cancer, small cell cancer, and adenocarcinoma of the lung, respectively. [Assessing exposure to pesticides from the questionnaire was the major limitation of this study; using a cancer reference group was also a limitation if the cancers used as controls shared common occupational exposures with cases of lung cancer.]

3. Cancer in Experimental Animals

The carcinogenicity of DDT in experimental animals was previously reviewed by the Working Group in 1973 (Some Organochlorine Pesticides; IARC, 1974) and in 1991 (Occupational Exposures in Insecticide Application, and Some Pesticides; IARC, 1991).

The Working Group previously classified DDT as having *sufficient evidence* of carcinogenicity in experimental animals (IARC, 1991). The Working Group for the present monograph reviewed all studies, including those published after 1991, and summarized those judged adequate for an evaluation of carcinogenicity. The findings of the pertinent studies are summarized in Table 3.1.

3.1 Mouse

3.1.1 Oral administration

ln a screening study on about 70 compounds, groups of 18 male and 18 female (C57Bl/6 × C3H/Anf) F_1 and (C57Bl/6 × AKR)F_1 mice (age, 7 days) were given daily single doses of *p,p′*-DDT [purity unspecified] at 46.4 mg/kg bw (maximum tolerated dose) by gavage until age 28 days, when the mice were transferred to a diet containing *p,p′*-DDT at a concentration of 140 mg/kg. Groups of 90 mice served as controls. About 30% of females of both strains died during the treatment. The surviving mice were killed at age 81 weeks. The incidence of hepatoma (benign or malignant, combined) was increased significantly in male and female mice of each strain, except in female (C57Bl/6 × AKR)F_1 mice, and the incidence of malignant lymphoma was significantly increased in (C57Bl/6 × AKR)F_1 females (NTIS, 1968; Innes et al., 1969).

In a five-generation study, *p,p′*-DDT-treated and control groups of male and female BALB/c mice from each of the five generations (F_1–F_5) were studied for tumour incidence. Groups of

mice from the F_1–F_5 generations (a total of 683 mice, including males and females) received a diet containing *p,p′*-DDT [purity unspecified] at a concentration of 2.8–3 mg/kg for 6 months, and other groups of mice from the F_1–F_5 generations (a total of 406 mice, including males and females) received a control diet. At experimental month 26, the incidence of pulmonary carcinoma was significantly increased in treated mice (all generations combined; 116/683 [$P < 0.001$]) compared with controls (5/406). The incidences of lymphosarcoma (all generations combined; 15/683 versus 1/406 controls [$P < 0.001$]), and leukaemia (all generations combined; control, 10/406; treated, 85/683 (64/683 in females) [$P < 0.001$]) were also significantly increased in treated mice (Tarján & Kemény, 1969). [The Working Group determined that the higher incidence of pulmonary carcinoma, leukaemia, and lymphosarcoma, attained significance in the F_2, F_3, and F_3 generations of treated mice, respectively, and subsequently increased in each succeeding generation.]

In a two-generation dose–response study, groups of 90–127 male and female CF-1 mice (including parent F_0, and offspring F_1) were fed a diet containing technical-grade DDT at concentrations of 0, 2, 10, 50, or 250 mg/kg, starting at age 6–7 weeks for the F_0 generation and continuing in the F_0 and F_1 for life. There was excess mortality from week 60 onwards among mice of the F_0 and F_1 generations that had received DDT at 250 mg/kg diet. The incidence (both generations combined) of hepatoma (benign or malignant, combined) was increased by exposure to DDT. The incidences were in males: 25/113 (controls), 57/124, 52/104, 67/127, and 82/103, respectively; and in females: 4/111 (controls), 4/105, 11/124, 13/104, and 60/90, respectively. The increase in the incidence of hepatoma over that in controls in male and female mice fed DDT at 250 mg/kg diet was significant [$P < 0.01$]. In females, the excess over that of the controls was also significant in the group fed DDT at 50 mg/kg diet [$P < 0.05$] (Tomatis et al., 1972).

In a continuation of the study byTomatis et al. (1972), the effects of the same doses of DDT were studied by Turusov et al. (1973) in six consecutive generations of CF-l mice [including the first two generations described by Tomatis et al. (1972)]. The experiment involved a total of 2764 exposed and 668 control animals. Exposure to all four levels of technical-grade DDT (2, 10, 50, 250 mg/kg diet) for life significantly increased the incidence (all generations combined) of hepatoma (benign or malignant, combined) in males. In females, the incidence of hepatoma was significantly increased after exposure at 10, 50, or 250 mg/kg, with a significant positive trend [$P < 0.001$]. Hepatoblastoma was observed at a significantly increased incidence in DDT-treated male mice: 3/328 in control males, and 5/354, 14/362, 12/383, and 25/350 in males treated at 2, 10, 50, and 250 ppm, respectively, with a significant positive trend [$P < 0.001$]. DDT did not significantly alter the incidence of tumours at sites other than the liver (Turusov et al., 1973).

In a two-generation study, 515 female and 430 male BALB/c mice were given diets containing technical-grade DDT at a concentration of 0, 2, 20, or 250 mg/kg for life. In females, the survival rates were comparable in all groups; in males, early deaths occurred in all groups as a consequence of fighting and because of toxicity (at the highest dose). In male and female (F_0 and F_1 combined) mice that survived more than 60 weeks, the incidences of liver cell tumours (benign or malignant, combined) were significantly increased in males and females fed diet containing DDT at 250 mg/kg (Terracini et al., 1973a). Confirmatory results were obtained in two subsequent generations of BALB/c female mice (F_2 and F_3) fed diets containing DDT at 250 mg/kg. Mice of the F_1, F_2 and F_3 generations, which were exposed to DDT both in utero and after birth for life, developed more liver cell tumours than did F_0 mice, which were exposed to DDT only after weaning [data presented only by graph, not by table or exact number] (Terracini et al., 1973b).

Table 3.1 Studies of carcinogenicity with DDT and its metabolites in mice, rats, hamsters, and monkeys

Species, strain (sex) Duration Reference	Route, dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Purity Comments
DDT				
Full carcinogenicity				
Mouse, (C57Bl/6 × C3H/Anf)F_1 (M) 80 wk Innes et al. (1969); NTIS (1968)	0, 46.4 mg/kg bw, by gavage (1×/day), age 7–28 days; subsequently in diet at 0, or 140 mg/kg 90, 18 mice	Hepatoma (benign or malignant, combined): 8/79, 11/18	[$P < 0.01$]	*p,p′*-DDT: purity, NR
Mouse, (C57Bl/6 × C3H/Anf)F_1 (F) 80 wk Innes et al. (1969); NTIS (1968)	0, 46.4 mg/kg bw, by gavage (1×/day), age 7–28 days; subsequently at 0, or 140 mg/kg diet 90, 18 mice	Hepatoma (benign or malignant, combined): 0/87, 4/18	[$P < 0.01$]	*p,p′*-DDT: purity, NR
Mouse, (C57Bl/6 × AKR) F_1 (M) 80 wk Innes et al. (1969); NTIS (1968)	0, 46.4 mg/kg bw, by gavage (1×/day), age 7–28 days; subsequently at 0, or 140 mg/kg diet 90, 18 mice	Hepatoma (benign or malignant, combined): 5/90, 7/18	[$P < 0.01$]	*p,p′*-DDT: purity, NR
Mouse, (C57Bl/6 × AKR) F_1 (F) 80 wk Innes et al. (1969); NTIS (1968)	0, 46.4 mg/kg bw, by gavage (1×/day), age 7–28 days; subsequently at 0, or 140 mg/kg diet 90, 18 mice	Hepatoma (benign or malignant, combined): 1/82, 1/18 Lymphoma: 4/82, 6/18	[NS] [$P < 0.01$]	*p,p′*-DDT: purity, NR
Mouse, BALB/c (M+F) 5 generations, for life Tarján & Kemény (1969)	0, 2.8–3 mg/kg diet for 6 mo for all 5 generations 406, 683 mice	Pulmonary carcinoma: 5/406, 116/683 Leukaemia: 10/406, 85/683 Lymphosarcoma: 1/406, 15/683	[$P < 0.001$] [$P < 0.001$] [$P < 0.001$]	*p,p′*-DDT: purity, NR Tumour incidences for each of the 5 generations at experimental month 26 were combined The increases in the incidence of pulmonary carcinoma, leukaemia or lymphosarcoma were consistent across all generations.
Mouse, CF-l (M) 2-generation for life Tomatis et al. (1972)	0, 2, 10, 50, 250 mg/kg diet for life for both generations 113, 124, 104, 127, 103 mice	Hepatoma (benign or malignant, combined): 25/113, 57/124, 52/104, 67/127, 82/103*	* [$P < 0.01$]	73–78% *p,p′*-DDT, 20% *o,p′*-DDT, 1% *m,p′*-DDT, 0.5–1.5% *p,p′*-TDE and 0.5% *p,p′*-DDE Tumour incidences for both generations were combined

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route, dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Purity Comments
Mouse, CF-1 (F) 2-generation for life Tomatis et al. (1972)	0, 2, 10, 50, 250 mg/kg diet for life for both generations 111, 105, 104, 104, 90 mice	Hepatoma (benign or malignant, combined): 4/111, 4/105, 11/124, 13/104*, 60/90**	* [$P < 0.05$]; ** [$P < 0.01$]	73–78% *p,p′*-DDT, 20% *o,p′*-DDT, 1% *m,p′*-DDT, 0.5–1.5% *p,p′*-TDE and 0.5% *p,p′*-DDE Tumour incidences for both generations were combined
Mouse, CF-1 (M) 6-generation for life Turusov et al. (1973)	0, 2, 10, 50, 250 mg/kg diet for life for all generations 328, 354, 362, 383, 350 mice	Hepatoma (benign or malignant, combined): 97/328, 179/354, 181/362, 214/383, 301/350 Hepatoblastoma: 3/328, 5/354, 14/362*, 12/383*, 25/350**	[$P < 0.01$ (all doses)] * [$P < 0.05$]; ** [$P < 0.01$]; [$P < 0.001$ (trend)]	73–78% *p,p′*-DDT, 20% *o,p′*-DDT, 1% *m,p′*-DDT, 0.5–1.5% *p,p′*-TDE and 0.5% *p,p′*-DDE Tumour incidences for all generations were combined
Mouse, CF-1 (F) 6-generation for life Turusov et al. (1973)	0, 2, 10, 50, 250 mg/kg diet for life for all generations 340, 339, 355, 328, 293 mice	Hepatoma (benign or malignant, combined): 16/340, 12/339, 32/355*, 43/328**, 192/293**	* [$P < 0.05$]; ** [$P < 0.01$]; [$P < 0.001$ (trend)]	73–78% *p,p′*-DDT, 20% *o,p′*-DDT, 1% *m,p′*-DDT, 0.5–1.5% *p,p′*-TDE and 0.5% *p,p′*-DDE Tumour incidences for all generations were combined
Mouse, BALB/c (M) 2-generation for life Terracini et al. (1973a)	0, 2, 20, 250 mg/kg diet for life for both generations 107, 112, 105, 106 mice	Liver cell tumours (benign or malignant, combined): 1/62, 3/48, 0/48, 14/31*	* [$P < 0.01$]; [$P < 0.001$ (trend)]	70–75% *p,p′*-DDT, 20% *o,p′*-DDT and 0.2–4% *p,p′*-TDE Incidence in mice that died after 60 wk Tumour incidences for both generations were combined
Mouse, BALB/c (F) 2-generation for life Terracini et al. (1973a)	0, 2, 20, 250 mg/kg diet for life for both generations 131, 135, 128, 121 mice	Liver cell tumours (benign or malignant, combined): 0/124, 0/130, 1/126, 71/115*	* [$P < 0.01$; [$P < 0.001$ (trend)]	70–75% *p,p′*-DDT, 20% *o,p′*-DDT and 0.2–4% *p,p′*-TDE Incidence in mice that died after 60 wk Tumour incidences for both generations were combined
Mouse, CF-1 (M) 2 years Walker et al. (1973)	0, 50, 100 mg/kg diet 47, 32, 32 mice	Liver cell tumours [benign or malignant, combined]: 6/47, 12/32*, 17/32**	* [$P < 0.05$]; ** [$P < 0.01$]; [$P < 0.001$ (trend)]	*p,p′*-DDT; purity, > 99.5%
Mouse, CF-1 (F) 2 years Walker et al. (1973)	0, 50, 100 mg/kg diet 47, 30, 32 mice	Liver cell tumours [benign or malignant, combined]: 8/47, 15/30*, 24/32*	* [$P < 0.01$]; [$P < 0.001$ (trend)]	*p,p′*-DDT; purity, > 99.5%
Mouse, CF-1 (M) 110 wk Thorpe & Walker (1973)	0, 100 mg/kg diet 45, 30 mice	Liver cell tumours [benign or malignant, combined]: 11/45, 23/30	$P < 0.01$	*p,p′*-DDT: purity, > 99.5%

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route, dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Purity Comments
Mouse, CF-1 (F) 110 wk Thorpe & Walker (1973)	0, 100 mg/kg diet 44, 30 mice	Liver cell tumours [benign or malignant, combined]: 10/44, 26/30	$P < 0.01$	*p,p′*-DDT: purity, > 99.5%
Mouse, Swiss (M) 80 wk Kashyap et al. (1977)	0 (untreated control), 100 mg/kg diet or 0.25 mg/animal by gavage 30, 30, 30 mice	Lymphoma: 2/26, 8/27*, 6/24	*[$P < 0.05$]	70.5% *p,p′*-DDT and 21.3% *o,p′*-DDT
Mouse, Swiss (F) 80 wk Kashyap et al. (1977)	0 (untreated control), 100 mg/kg diet or 0.25 mg/animal by gavage 30, 30, 30 mice	Lymphoma: 2/20, 8/22*, 8/24	*[$P < 0.05$]	70.5% *p,p′*-DDT and 21.3% *o,p′*-DDT
Mouse, B6C3F$_1$ (M) 91 wk NCI (1978)	0, 22, 44 mg/kg diet TWA for 78 wk 20, 50, 50 mice	Lymphoma: 0/19, 2/49, 1/50	NS	Technical-grade DDT; purity, about 70%, assumed to be *p,p′*-DDT Survival at 70 wk: 12/20, 20/50, 37/50
Mouse, B6C3F$_1$ (F) 92 wk NCI (1978)	0, 87, 175 mg/kg diet TWA for 78 wk 20, 50, 50 mice	Lymphoma: 0/20, 3/49, 7/46	$P = 0.026$ (trend), Cochran-Armitage test	Technical-grade DDT; purity, about 70%, assumed to be *p,p′*-DDT Survival at 70 wk: 20/20, 45/50, 36/50
Mouse, BALB/c (M) 75 wk Lipsky et al. (1989)	0 (control) or 175 ppm in the diet (0–16 wk), 125 ppm (16–24 wk) then 100 ppm (24–75 wk) 90, 90 mice	Hepatocellular adenoma: 0/10, 1/4 (at 52 wk) 2/36, 4/12 (at 75 wk) HCC: 1/36, 2/12 (at 75 wk) Hepatocellular adenoma or HCC (combined): 3/36, 5/12 (at 75 wk)	 [NS] [$P < 0.03$] [NS] [$P < 0.02$]	DDT: purity, 99%; the Working Group was unable to determine whether this was technical grade or *p,p′*-DDT Interim sacrifices at 2, 4, 8, 16, 24, 36, and 52 wk
Mouse, CF-1 (M) 65 wk 95 wk Tomatis et al. (1974a)	0 (control) or 250 ppm in the diet (15 or 30 wk treatment) 70, 60, 60 mice 0 (control) or 250 ppm in the diet (15 or 30 wk treatment) 83, 60, 60 mice	Hepatoma [not further classified]: 12/70, 13/60 (15 wk), 38/60* (30 wk) Hepatoma [not further classified]: 24/83, 25/60 (15 wk), 41/60* (30 wk)	* [$P < 0.01$] * [$P < 0.01$]	Technical-grade DDT: purity, NR

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route, dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Purity Comments
120 wk Tomatis et al. (1974a)	0 (control) or 250 ppm in the diet (15 or 30 wk treatment) 98, 60, 60 mice	Hepatoma [not further classified]: 33/98, 25/60 (15 wk), 37/60* (30 wk)	* [$P < 0.01$]	
Mouse, CF-1 (F) 65 wk	0 (control) or 250 ppm in the diet (15 or 30 wk treatment) 69, 60, 54 mice	Hepatoma [not further classified]: 0/69, 3/60 (15 wk), 4/54* (30 wk)	* [$P < 0.05$]	Technical-grade DDT: purity, NR
95 wk	0 (control) or 250 ppm in the diet (15 or 30 wk treatment) 72, 60, 55 mice	Hepatoma [not further classified]: 0/72, 11/60* (15 wk), 11/55* (30 wk)	* [$P < 0.01$]	
120 wk Tomatis et al. (1974a)	0 (control) or 250 ppm in the diet (15 or 30 wk treatment) 90, 60, 54 mice	Hepatoma [not further classified]: 1/90, 5/60* (15 wk), 11/54** (30 wk)	* [$P < 0.05$]; ** [$P < 0.01$]	
Mouse, Swiss (M) 80 wk Kashyap et al. (1977)	Skin application, 0 (untreated controls), 0.25 mg/animal, twice per wk 30, 30 mice	No significant increase	[NS]	70.5% *p,p′*-DDT and 21.3% *o,p′*-DDT
Mouse, Swiss (F) 80 wk Kashyap et al. (1977)	Skin application, 0 (untreated controls) or 0.25 mg/animal, twice per wk 30, 30 mice	No significant increase	[NS]	70.5% *p,p′*-DDT and 21.3% *o,p′*-DDT
Mouse, Swiss (M) 80 wk Kashyap et al. (1977)	Subcutaneous injection, 0 (untreated controls), or 0.25 mg/animal (2×/mo) 30, 30 mice	Liver cell carcinoma: 1/26, 3/28	[NS]	70.5% *p,p′*-DDT and 21.3% *o,p′*-DDT
Mouse, Swiss (F) 80 wk Kashyap et al. (1977)	Subcutaneous injection, 0 (untreated controls), or 0.25 mg/animal (2×/mo) 30, 30 mice	Liver cell carcinoma: 0/20, 7/26	[$P = 0.0123$]	70.5% *p,p′*-DDT and 21.3% *o,p′*-DDT
Co-administration with known carcinogens or modifying factors				
Mouse, dd (F) 8 wk Uchiyama et al. (1974)	0, 100 ppm in the diet 1 wk after start of DDT treatment (for 8 wk), 3-methylcholanthrene was applied for 4 wk in the uterus 39, 16 mice	Cervical epithelial carcinoma: 0/39, [3/16 (about 20%)]	[$P < 0.03$]	DDT, not further specified: purity NR

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route, dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Purity Comments
Mouse, B6C3F$_1$ (M) 43 wk Williams & Numoto (1984)	0, 50 ppm in the diet Initiated by NDEA at 20 ppm in drinking-water for 14 wk before DDT treatment (after 4 wk) for 25 wk 30, 30 mice	Hepatocellular adenoma or carcinoma (combined): 8/20, 14/21	[NS]	Technical-grade DDT: purity, 97.6%
Full carcinogenicity				
Rat, Osborne-Mendel (M+F) 24 mo Fitzhugh & Nelson (1947)	0, 100, 200, 400, 600, 800 ppm in the diet 36, 12, 36, 36, 48, 60 rats	"Low-grade" HCC: 4/81 (all treated groups) Liver nodular adenomatoid hyperplasias [adenoma]: 11/81 (all treated groups) No liver tumours in 20 controls	[NS] [NS]	81.8% *p,p′*-DDT and 18.2% *o,p′*-DDT Tumour incidence in rats that survived ≥ 18 mo
Rat, Osborne-Mendel (M) 2 yr Reuber (1978)	0, 200, 400, 600, 800 ppm in the diet 12, 12, 12, 24, 24 rats	HCC: 0/5, 6/21 (all DDT treatment groups) Liver neoplastic nodules [adenomas]: 0/5, 4/21 (all DDT treatment groups) Total liver tumours (HCC, neoplastic nodules, Küpffer cell sarcoma): 0/5, 11/21 (all DDT treatment groups) Lymphosarcoma: 0/6, 14/50 (all DDT treatment groups)	[NS] [NS] [$P < 0.05$] [NS]	81.8% *p,p′*-DDT and 18.2% *o,p′*-DDT The effective number of rats is the total number of rats that survived 84 wk or longer The effective number of rats is the total number of rats that survived 52 wk or longer
Rat, Osborne-Mendel (F) 2 yr Reuber (1978)	0, 200, 400, 600, 800 ppm in the diet 12, 12, 12, 24, 24 rats	HCC: 0/6, 4/12 (all DDT treatment groups combined) Ovary carcinoma: 0/6, 11/12 (all DDT treatment groups combined)	[NS] [$P = 0.0004$]	81.8% *p,p′*-DDT and 18.2% *o,p′*-DDT The effective number of rats is the total number of rats that survived 84 wk or longer The effective number of rats is the total number of rats that survived ≥ 89 wk
Rat, Osborne-Mendel (M, F) 2 yr Radomski et al. (1965)	0, 80 mg/kg diet 30 M and 30 F/group	Undifferentiated bronchogenic carcinoma (M+F): 2/60, 8/60	[$P < 0.05$]	DDT, not further specified: purity, NR

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route, dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Purity Comments
Rat, Osborne- Mendel (F) Up to 27 mo Deichmann et al. (1967)	0, 200 mg/kg diet 30 M and 30 F/group	No lung tumours	NS	DDT, not further specified: purity, NR
Rat, Wistar (M) 145 wk Rossi et al. (1977)	0, 500 mg/kg diet 36, 37 rats	Liver cell tumours [benign or malignant, combined]: 0/35, 9/27	[$P = 0.002$]	70–75% *p,p′*-DDT, 20% *o,p′*-DDT and 0.2–4% *p,p′*-TDE
Rat, Wistar (F) 145 wk Rossi et al. (1977)	0, 500 mg/kg diet 35, 35 rats	Liver cell tumours [benign or malignant, combined]: 0/32, 15/28	[$P < 0.0001$]	70–75% *p,p′*-DDT, 20% *o,p′*-DDT and 0.2–4% *p,p′*-TDE
Rat, Wistar (M) 60 wk Angsubhakorn et al. (2002)	0, 500 ppm in the diet (from wk 6–12) 30, 35 rats	Liver neoplastic nodules [benign]: 0/18, 1/19	[NS]	*p, p′*-DDT; purity, 86% Animals of age ≥ 1 year; weight, 400–500 g
Rat, F344 (M) 103 wk Shivapurkar et al. (1986)	0, 0.05% for 72 wk then fed un-supplemented diet 30, 30 rats	Liver neoplastic nodules [benign]: 2/28, 6/28 HCC: 1/28, 0/28	[NS] [NS]	DDT, not further specified: purity, NR Age NR; weight, > 50–60 g
Rat, Osborne-Mendel (M) 111 wk NCI (1978)	0, 321, 642 mg/kg diet TWA for 78 wk 20, 50, 50 rats	No significant increase	NS	Purity, about 70%; assumed to be *p,p′*-DDT Survival not affected
Rat, Osborne-Mendel (F) 111 wk NCI (1978)	0, 210, 420 mg/kg diet TWA for 78 wk 20, 50, 50 rats	Adrenal gland pheochromocytoma: 0/19, 0/38, 3/24 Thyroid follicular cell adenoma or carcinoma (combined): 1/19, 13/45*, 10/43 Thyroid follicular cell adenoma: 1/19, 10/45, 5/43 Thyroid follicular cell carcinoma: 0/19, 4/45, 6/43	$P = 0.031$ (trend), Cochran-Armitage test * $P = 0.032$	Purity, about 70%; assumed to be *p,p′*-DDT Survival not affected
Rat, MRC Porton (M) 144 wk Cabral et al. (1982a)	0, 125, 250, 500 mg/kg diet 38, 30, 30, 38 rats	Liver cell tumours [benign or malignant, combined]: 1/38, 0/30, 1/30, 2/38	[NS]	78.9% *p,p′*-DDT, 16.7% *o,p′*-DDT, 1.6% *p,p′*-DDE, 0.6% *p,p′*-TDE, 0.2% *o,p′*- DDE, 0.1% *o,p′*-TDE and 1.9% unknown
Rat, MRC Porton (F) 144 wk Cabral et al. (1982a)	0, 125, 250, 500 mg/kg diet 38, 30, 30, 38 rats	Liver cell tumours [benign or malignant, combined]: 0/38, 2/30, 4/30, 7/38*	$P < 0.001$ (trend), * [$P < 0.01$]	78.9% *p,p′*-DDT, 16.7% *o,p′*-DDT, 1.6% *p,p′*-DDE, 0.6% *p,p′*-TDE, 0.2% *o,p′*- DDE, 0.1% *o,p′*-TDE and 1.9% unknown

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route, dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Purity Comments
Rat, F344/DuCrj (M) 78 wk (satellite experiment) Harada et al. (2003)	0, 5, 50, 500 ppm in the diet 8, 8, 8, 7 rats	Hepatocellular adenoma: 0/8, 0/8, 0/8, 6/7*	* $P < 0.01$	*p,p′*-DDT: purity, > 98%
Rat, F344/DuCrj (F) 78 wk (satellite experiment) Harada et al. (2003)	0, 5, 50, 500 ppm in the diet 8, 8, 7, 8 rats	Hepatocellular adenoma: 0/8, 0/8, 0/7, 1/8	NS	*p,p′*-DDT: purity, > 98%
Rat, F344/DuCrj (M) 104 wk Harada et al. (2003)	0, 5, 50, 500 ppm in the diet (0, 0.17, 1.7, 19.1 mg/kg per day) 40, 40, 40, 40 rats	Hepatocellular adenoma: 0/40, 0/40, 5/40*, 22/40** HCC: 0/40, 0/40, 0/40, 14/40*	* $P < 0.05$; ** $P < 0.01$ * $P < 0.01$	*p,p′*-DDT: purity, > 98%
Rat, F344/DuCrj (F) 104 wk Harada et al. (2003)	0, 5, 50, 500 ppm in the diet (0, 0.21, 2.2, 25.2 mg/kg per day) 40, 40, 40, 40 rats	Hepatocellular adenoma: 0/40, 0/40, 0/40, 16/40* HCC: 0/40, 0/40 0/40, 2/40	* $P < 0.01$ NS (see comments)	*p,p′*-DDT: purity, > 98% The Working Group considered that the incidence of hepatocellular adenoma or carcinoma (combined) [16–18/40] was significantly increased in the high-dose group
Co-administration with known carcinogens or modifying factors				
Rat, Buffalo (M) 82 wk Angsubhakorn et al. (2002)	0, 100 ppm in the diet (from wk 1–20) Initiated by a single dose of AFB_1 at 5 mg/kg bw by gavage before DDT treatment for 20 wk 14, 19 rats	Liver neoplastic nodules [benign]: 1/14, 3/19	NS	*p, p′*-DDT: purity, 86%
Rat, Wistar (M) 60 wk Angsubhakorn et al. (2002)	0, 500 ppm in the diet (from wk 6–12) Initiated by AFB_1 at 4 ppm in the diet for 6 wk before DDT treatment 35, 43 rats	Liver neoplastic nodules [benign]: 9/29, 9/28 Malignant hepatic tumours: 8/29, 10/28 HCC: 6/29, 7/28 Cholangiocellular carcinoma: 1/29, 1/28 Hepato-cholangiocellular carcinoma: 1/29, 2/28	[NS] [NS] [NS] [NS] [NS]	*p, p′*-DDT: purity, 86% Animals of age ≥1 year; weight, 400–500 g

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route, dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Purity Comments
Rat, Wistar (M) 40 or 52 wk Nishizumi (1979)	0, 1.25 mg/rat by gavage, twice per wk for 12 wk Initiated by NDEA at 50 ppm in drinking-water for 2 wk before DDT treatment 1 wk after. The animals were killed at weeks 40 or 52 10, 10, 10, 10 rats	Liver tumours at 40 wk (> 5 mm): 0/8, 1/6 Liver tumours at 52 wk (> 5 mm): 0/8, 3/8	[NS] [NS]	Purity, NR
Rat, Sprague- Dawley (M) 389 days Peraino et al. (1975)	0, 0.05% in the diet Initiated by AAF at the dose of 0.02% in diet for 18 days, then 1 wk later were treated with DDT 120, 120 rats	Hepatocellular adenoma or carcinoma (combined): 31/108, 77/103	[$P < 0.0001$]	Technical-grade: 70% *p,p′*-DDT, 12% *o,p′*-DDT, 3% *p,p′*-TDE and 15% *p,p′*-DDE
Rat, F344 (M) 103 wk Shivapurkar et al. (1986)	0, 0.05% in the diet for 72 wk then fed un-supplemented diet Initiated by single i.p. injection of NDEA at 200 mg/kg bw before DDT treatment 30, 30 rats	Liver neoplastic nodules [benign]: 3/28, 1/28 HCC: 18/28, 28/28 Cholangioma or cholangiocarcinoma (combined): 0/28, 6/28	[NS] [$P < 0.0001$] [$P < 0.02$]	DDT, not further specified: purity, NR Age NR; weight, > 50–60 g
Rat, F344 (M) 43 wk Kushida et al. (2005)	0, 0.005, 0.5, 500 ppm in the diet Initiated by two i.p. injections of NDEA at 100 mg/kg bw with a 1-wk interval before DDT treatment 20, 20, 20, 20 rats	Hepatocellular adenoma: 11/20, 13/20, 10/20, 18/18* Multiplicity: 1.10, 0.95, 1.10, 11.44* tumours/rat HCC: 12/20, 7/20, 13/20, 18/18* Multiplicity: 1.00, 0.50, 0.90, 28.67* tumours/rat Hepatocellular adenoma or HCC (combined): 15/20, 14/20, 17/20, 18/18* Multiplicity: 2.10, 1.45, 2.00, 40.11* tumours/rat	* [$P < 0.002$] * $P < 0.01$, Dunnett's test * [$P < 0.01$] * $P < 0.01$, Dunnett's test * [$P < 0.05$] * $P < 0.01$, Dunnett's test	*p,p′*-DDT: purity, > 98%

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route, dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Purity Comments
Full carcinogenicity				
Hamster, Syrian golden (M) 120 wk Cabral et al. (1982b)	0, 125, 250, 500 mg/kg diet 40, 30, 31, 40 hamsters	Adrenal cortex tumours (mostly adenomas): 3/40, 4/30, 6/31, 8/39	[$P = 0.04$ (trend)]	78.9% *p,p′*-DDT, 16.7% *o,p′*-DDT, 1.6% *p,p′*-DDE, 0.6% *p,p′*- TDE, 0.2% *o,p′*-DDE, 0.1% *o,p′*-TDE and 1.9% unknown
Hamster, Syrian golden (F) 120 wk Cabral et al. (1982b)	0, 125, 250, 500 mg/kg diet 40, 30, 29, 40 hamsters	Adrenal cortex tumours (mostly adenomas): 0/39, 0/28, 1/28, 3/40	[NS]	78.9% *p,p′*-DDT, 16.7% *o,p′*-DDT, 1.6% *p,p′*-DDE, 0.6% *p,p′*- TDE, 0.2% *o,p′*-DDE, 0.1% *o,p′*-TDE and 1.9% unknown
Hamster, Syrian golden (M) 120 wk Rossi et al. (1983)	0, 1000 mg/kg diet 31, 35 hamsters	Adrenal gland tumours (mainly cortical adenoma): 8/31, 14/35	[NS]	70–75% *p,p′*-DDT, 20% *o,p′*-DDT and 0.2–4% *p,p′*-TDE
Hamster, Syrian golden (F) 120 wk Rossi et al. (1983)	0, 1000 mg/kg diet 42, 36 hamsters	Adrenal gland tumours (mainly cortical adenoma): 2/42, 10/36	[$P < 0.01$]	70–75% *p,p′*-DDT, 20% *o,p′*-DDT and 0.2–4% *p,p′*-TDE
Hamster, strain NR (M) 18 months Graillot et al. (1975)	0, 250, 500, 1000 mg/kg diet 30, 30, 30, 30 hamsters	Lymphosarcoma: 50.0%, 22.7%, 13.0%, 0%	NS (for increase)	Technical-grade DDT: 70% *p,p′*-DDT No other tumour types observed
Hamster, strain NR (F) 18 months Graillot et al. (1975)	0, 250, 500, 1000 mg/kg diet 30, 30, 30, 30 hamsters	Lymphosarcoma: 41.0%, 17.4%, 0%, 0%	NS (for increase)	Technical-grade DDT: 70% *p,p′*-DDT No other tumour types observed
Co-administration with known carcinogens or modifying factors				
Hamster, Syrian golden (M) 31 wk Tanaka et al. (1987)	0, 500 ppm in the diet for 30 wk Initiated by i.p. injection of NDMA at 6 mg/kg bw, then DDT 1 wk after 15, 15 hamsters	Hepatocellular adenoma: 1/15, 1/15	[NS]	Purity, NR

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route, dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Purity Comments
Full carcinogenicity				
Monkey, cynomolgus and rhesus (M+F) Up to 304 mo Takayama et al. (1999)	0 (control), 20 mg/kg bw in the diet for 130 mo 17, 24 monkeys	One HCC and one prostatic adenocarcinoma in two DDT-treated cynomolgus monkeys; and two leiomyoma of the uterus and one of the oesophagus in three other DDT-treated monkeys No tumours in controls		*p,p′*-DDT: purity, NR Treated: 13 cynomolgus monkeys and 11 rhesus monkeys Controls: 9 cynomolgus monkeys and 8 rhesus monkeys
DDD (TDE)				
Full carcinogenicity				
Mouse, CF-l (M) 123–124 wk Tomatis et al. (1974b)	0, 250 mg/kg diet 100, 60 mice	Hepatomas [benign or malignant, combined]: 33/98, 31/59 Lung tumours (adenoma or adenocarcinoma, combined): 53/98, 51/59	[$P < 0.05$] [$P < 0.0001$]	*p,p′*-TDE: purity, 99%
Mouse, CF-l (F) 123–124 wk Tomatis et al. (1974b)	0, 250 mg/kg diet 90, 60 mice	Hepatomas [benign or malignant, combined]: 1/90, 1/59 Lung tumours (adenoma or adenocarcinoma, combined): 37/90, 43/59	[NS] [$P < 0.0001$]	*p,p′*-TDE: purity, 99%
Mouse, B6C3F$_1$ (M) 90–92 wk NCI (1978)	0, 411, 822 mg/kg diet TWA for 78 wk 20, 50, 50 mice	HCC: 2/18, 12/44, 14/50	NS	TDE (principal component, 60%, assumed to be *p,p′*-TDE; 19 unidentified impurities)
Mouse, B6C3F$_1$ (F) 90–93 wk NCI (1978)	0, 411, 822 mg/kg diet TWA for 78 wk 20, 50, 50 mice	HCC: 0/20, 2/48, 3/47	NS	TDE (principal component, 60%, assumed to be *p,p′*-TDE; 19 unidentified impurities)
Rat, Osborne-Mendel (M) 111–112 wk NCI (1978)	0, 1647, 3294 mg/kg diet TWA for 78 wk 20, 50, 50 rats	Thyroid follicular cell adenoma: 0/19, 11/49*, 9/49* Thyroid follicular cell carcinoma: 1/19, 6/49, 3/49 Thyroid follicular cell adenoma or carcinoma (combined): 1/19, 16/49*, 11/49	* [$P < 0.05$], [$P < 0.05$ (trend)] NS * $P = 0.016$	TDE (principal component, 60%, assumed to be *p,p′*-TDE; 19 unidentified impurities)

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route, dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Purity Comments
Rat, Osborne-Mendel (F) 111–113 wk NCI (1978)	0, 850, 1700 mg/kg diet for 78 wk 20, 50, 50 rats	Thyroid follicular cell adenoma: 0/19, 6/48, 5/50 Thyroid follicular cell adenoma or carcinoma (combined): 2/19, 11/48, 6/50	[NS] NS	TDE (principal component, 60%, assumed to be *p,p′*-TDE; 19 unidentified impurities)
DDE				
Full carcinogenicity				
Mouse, CF-1 (M) 123–124 wk Tomatis et al. (1974b)	0, 250 mg/kg diet 100, 60 mice	Hepatoma [benign or malignant, combined]: 33/98, 39/53	[$P < 0.0001$]	*p,p′*-DDE: purity, 99%
Mouse, CF-1 (F) 123–124 wk Tomatis et al. (1974b)	0, 250 mg/kg diet 90, 60 mice	Hepatoma [benign or malignant, combined]: 1/90, 54/55	[$P < 0.0001$]	*p,p′*-DDE: purity, 99%
Mouse, B6C3F$_1$ (M) 92 wk NCI (1978)	0, 148, 261 mg/kg diet for 78–79 wk 20, 50, 50 mice	HCC: 0/19, 7/41, 17/47*	* $P = 0.001$; $P = 0.001$ (trend), Cochran-Armitage test	*p,p′*-DDE: purity, > 95%; 1 minor impurity Survival at 70 wk: 5/20, 35/50, 31/50
Mouse, B6C3F$_1$ (F) 92–93 wk NCI (1978)	0, 148, 261 mg/kg diet for 78 wk 20, 50, 50 mice	HCC: 0/19, 19/47*, 34/48*	* $P < 0.001$; $P < 0.001$ (trend), Cochran-Armitage test	*p,p′*-DDE: purity, > 95%; 1 minor impurity Survival at 75 wk: 19/20, 47/50, 28/50
Rat, Osborne-Mendel (M) 111 wk NCI (1978)	0, 437, 839 mg/kg diet TWA for 74–78 wk 20, 50, 50 rats	Thyroid follicular cell adenoma or carcinoma (combined): 3/20, 12/49, 10/47	NS	*p,p′*-DDE: purity, > 95%; 1 minor impurity
Rat, Osborne-Mendel (F) 111–112 wk NCI (1978)	0, 242, 462 mg/kg diet TWA for 73–78 wk 19, 50, 50 rats	Thyroid follicular cell adenoma or carcinoma (combined): 2/19, 9/48, 12/48	NS	*p,p′*-DDE: purity, > 95%; 1 minor impurity
Hamster, Syrian Golden (M) 120 wk Rossi et al. (1983)	0, 500, 1000 mg/kg diet 40–47 hamsters	Hepatocellular adenoma or HCC (combined): 0/10, 7/15*, 8/24*	* [$P < 0.05$]	*p,p′*-DDE: purity, 99% Hepatocellular tumours were mostly carcinomas
Hamster, Syrian Golden (F) 120 wk Rossi et al. (1983)	0, 500, 1000 mg/kg diet 43–46 hamsters	Hepatocellular adenoma or HCC (combined): 0/31, 4/26*, 5/24*	* [$P < 0.05$]	*p,p′*-DDE: purity, 99% Hepatocellular tumours were mostly carcinomas

AAF, 2-acetylaminofluorene; AFB$_1$, aflatoxin B$_1$; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; i.p., intraperitoneal; mo, month; NDEA, *N*-nitrosodiethylamine; NDMA, *N*-nitrosodimethylamine; NR, not reported; NS, not significant; TWA, time-weighted average; wk, week

Groups of 30–32 male and 30–32 female CF-1 mice (age, 4 weeks) were fed diets containing *p,p′*-DDT (purity, > 99.5%) at a concentration of 0, 50, or 100 mg/kg for 2 years. A control group consisted of 47 males and 47 females. A significant increase in the incidence of liver cell tumours (including simple nodular growth of parenchymal cells and areas of papilliform and adenoid growth of tumour cells) [benign or malignant hepatocellular tumours] was observed in all groups of treated males [$P < 0.05$] and females [$P < 0.01$] (Walker et al., 1973).

In a subsequent study, 30 male and 30 female CF-1 mice (age, 4 weeks) were fed a diet containing *p,p′*-DDT (purity, > 99.5%) at a concentration of 100 mg/kg for 110 weeks. Forty five males and 44 females served as controls. The mice were killed when the intra-abdominal masses reached a size that caused the mice to become anorexic or clinically affected. A significant increase ($P < 0.01$) in the incidence of liver tumours (including simple nodular growth of parenchymal cells, and areas of papilliform and adenoid growth of tumour cells) [benign or malignant, combined] (23/30 treated males and 26/30 treated females compared with 11/45 male and 10/44 female controls, respectively) was observed within 26 months (Thorpe & Walker, 1973).

Groups of 30 male and 30 female Swiss inbred mice (age, 6–8 weeks) were given diet containing technical-grade DDT at 100 mg/kg or a daily dose of DDT of 0.25 mg by gavage in olive oil for 80 weeks. Groups of 30 male and 30 female mice served as untreated controls. Survival and body-weight gains were not affected by treatment. The incidence of malignant lymphoma was increased in males (feeding, 8/27 [$P < 0.05$]; gavage, 6/24 [not significant]; controls, 2/26) and females (feeding, 8/22 [$P < 0.05$]; gavage, 8/24 [not significant]; controls, 2/20) (Kashyap et al., 1977). [The Working Group noted the inadequate number of animals used and lack of vehicle controls.]

Groups of 50 male and 50 female B6C3F$_1$ mice (age, 6 weeks) were fed diets containing technical-grade DDT for 78 weeks and were then held for 14 (male) or 15 (female) additional weeks before termination. Groups of 20 mice were fed a control diet for 91 (male) or 92 (female) weeks. Initially, males received diets containing DDT at 10 or 20 mg/kg and females received diets containing DDT at 50 or 100 mg/kg; after 9 weeks, these concentrations were gradually increased up to 25 and 50 mg/kg for males and 100 and 200 mg/kg for females because of the absence of toxicity. The time-weighted average dietary concentrations were 22 and 44 mg/kg for males and 87 and 175 mg/kg of diet for females. Survival in all groups of male mice was poor, possibly due to fighting. Survival of male mice at week 70 was 12/20 among controls, 20/50 at the lower dose, and 37/50 at the higher dose; terminal survival of female mice was 20/20 among controls, 45/50 at the lower dose, and 36/50 at the higher dose. There was no difference in body-weight gain between treated and control mice. The incidence of malignant lymphoma was increased only in females (males: controls, 0/19; lower dose, 2/49; higher dose, 1/50 (not significant); females: controls, 0/20; lower dose, 3/49; higher dose, 7/46 ($P = 0.026$, trend test) (NCI, 1978). [The Working Group noted the small number of controls, and that females received doses that were four times higher than those for males.]

Ninety male BALB/c mice [age, 8–10 weeks] were fed diets containing DDT (purity, 99%; Aldrich [The Working Group was unable to determine whether this was *p,p′*-DDT or technical-grade DDT]). The control group contained 90 male mice. Ten mice were killed after 2, 4, and 8 weeks of exposure to DDT at 175 ppm. The DDT concentration was lowered to 125 ppm and 6 mice were killed at 16 weeks because of toxicity. Due to increasing mortality, the DDT concentration was lowered to 100 ppm and 4 mice were killed at 24, 36, and 52 weeks, and 12 mice at 75 weeks. Ten mice from the control group were killed after 2, 4, 8, 16, 24, 36, and 52 weeks, and 20 mice were killed after 75 weeks. The incidence

of hepatocellular adenoma was: controls, 0/10; DDT, 1/4 at 52 weeks; and controls, 2/36; treated, 4/12 [$P < 0.03$] at 75 weeks. The incidence of HCC was: controls, 1/36; treated, 2/12 at 75 weeks. The incidence of hepatocellular adenoma or carcinoma (combined) was: controls, 3/36; treated, 5/12 [$P < 0.02$] at 75 weeks (Lipsky et al., 1989).

Six groups of 60 male and 54–60 female CF-1 mice (age, 9–10 weeks) were fed diets containing technical-grade DDT [purity not reported] at a concentration of 250 ppm for 15 or 30 weeks. Three control groups of 70–98 males and 69–90 females were fed a normal diet. The mice were killed at 65, 95, or 120 weeks. For the control groups, the incidences of hepatoma [not further classified] in males were 12/70 at 65 weeks, 24/83 at 95 weeks, and 33/98 at 120 weeks, and in females were 0/69 at 65 weeks, 0/72 at 95 weeks, and 1/90 at 120 weeks. For the 15-week treatment groups, there was no increase in the incidence of hepatoma in males, and for females the incidences were 3/60 at 65 weeks [not significant], 11/60 at 95 weeks [$P < 0.01$], and 5/60 at 120 weeks [$P < 0.05$]. For the 30-week treatment groups, the incidences of hepatoma for males were 38/60 at 65 weeks [$P < 0.01$], 41/60 at 95 weeks [$P < 0.01$], and 37/60 at 120 weeks [$P < 0.01$], and for females were 4/54 at 65 weeks [$P < 0.05$], 11/55 at 95 weeks [$P < 0.01$], and 11/54 at 120 weeks [$P < 0.01$] (Tomatis et al., 1974a).

3.1.2 Skin application

Groups of 30 male and 30 female Swiss inbred mice (age, 6–8 weeks) were given technical-grade DDT as a dose of 0.25 mg in 0.1 mL olive oil twice per week by skin application for 80 weeks. Groups of 30 males and 30 females served as untreated controls. Survival and body-weight gains were not affected by treatment, and no increase in tumour incidence was observed (Kashyap et al., 1977).

3.1.3 Subcutaneous injection

Groups of 30 male and 30 female Swiss inbred mice (age, 6–8 weeks) received technical-grade DDT at a dose of 0.25 mg by subcutaneous injection in 0.1 mL of olive oil twice per month for 80 weeks. Groups of 30 males and 30 females served as untreated controls. Survival and body-weight gain were not affected by treatment. The incidence of liver cell carcinoma was 7/26 [$P = 0.0123$] in treated females and 0/20 in control females, and 3/28 [not significant] in treated males and 1/26 in control males (Kashyap et al., 1977).

3.1.4 Co-administration with known carcinogens or other modifying factors

Groups of 30 male $B6C3F_1$ mice (age, 8 weeks) were given drinking-water containing *N*-nitrosodiethylamine (NDEA) at a concentration of 20 ppm for 14 weeks. After 4 weeks, the mice were fed diets containing technical-grade DDT (purity, 97.6%) at either 0 or 50 ppm for 25 weeks. At 43 weeks, the number of DDT-treated mice with hepatocellular adenoma or carcinoma (combined) was non-significantly increased compared with controls (NDEA, 8/20; NDEA/DDT, 14/21) (Williams & Numoto, 1984).

Groups of 39 and 16 female dd mice [age not reported; weight, 22–25 g] were fed DDT [not further specified, purity unspecified] at a concentration of 0 (control) or 100 ppm for 8 weeks (termination of the experiment). One week after the DDT treatment was started, a thread impregnated with 3-methylcholanthrene was inserted into the uterus and removed after 4 weeks. The incidence of carcinoma of the cervical epithelium was increased in DDT-treated mice compared with controls (controls, 0/39; DDT, [about 20%; 3/16, estimated; $P < 0.03$]) (Uchiyama et al., 1974).

3.2 Rat

3.2.1 Oral administration

In two long-term studies started at an interval of 1 year, a total of 192 male and female Osborne-Mendel rats (age, 3 weeks) received diets containing technical-grade DDT, as a powder or as a solution in corn oil, at various concentrations from 100 to 800 ppm for 24 months. A total of 36 male and female rats served as controls (corn oil only). Tumour incidences for all treated groups for both studies were pooled. Among the 81 treated rats that survived at least 18 months, four had "low-grade" HCCs (measuring 0.5–1.2 cm), and 11 had nodular adenomatoid hyperplasia (liver nodules measuring up to 0.3 cm [adenomas]). No liver tumours were found in 20 rats in the control group (Fitzhugh & Nelson, 1947). [The Working Group noted the inadequate reporting and that incidences for both studies were pooled, which made the study impossible to interpret.]

In a re-analysis of one of the two studies by Fitzhugh & Nelson (1947) (see above), Reuber (1978) reported that groups of 12 male and 12 female Osborne-Mendel rats (age, 3 weeks) were given diets containing technical-grade DDT (as a powder or as a solution in corn oil) at a concentration of 0, 200, 400, 600, or 800 ppm for 2 years. Tumour incidences for groups of treated rats were pooled. Hepatocellular carcinomas were present in 6 out of 21 male rats, liver neoplastic nodules [adenomas] in 4 out of 21 male rats, and a Küpffer cell sarcoma in 1 out of 21 male rats receiving DDT that survived for 84 weeks or longer. None of the five male rats in the control group had hepatocellular neoplasms. Neoplasms of the liver (all types) were seen in 11 out of 21 exposed male rats (54% [$P < 0.05$]). Half of the 12 liver neoplasms developed in male rats receiving DDT at 800 ppm. Four out of 12 (36%) exposed female rats (DDT concentration, 200–600 ppm) and 0 out of 6 female control rats that survived for 84 weeks or longer developed HCCs. Fourteen out of 50 male rats receiving DDT, and 0 of 6 male control rats that survived for 52 weeks or longer developed lymphosarcoma. Carcinomas of the ovary were seen in 11 out of 12 females (92% [$P = 0.0004$]) receiving DDT for 89 weeks or longer, compared with 0 of 6 controls (Reuber, 1978). [The Working Group noted the inadequate reporting, and that incidences in treated groups were pooled, which made the study difficult to interpret.]

In two studies of similar design reported by the same institute, groups of 30 male and 30 female Osborne-Mendel rats [age not reported] were exposed to diets containing DDT [not further identified, purity unspecified] at a concentration of 0 or 80 ppm from weaning for 2 years in the first study (Radomski et al., 1965), and to DDT [not further identified, purity unspecified] at a concentration of 0 or 200 ppm from weaning for up to 27 months in the second study (Deichmann et al., 1967). In the first study, undifferentiated bronchogenic carcinomas were seen in 2 out of 60 rats in the control group (male and females combined), and in 8 out of 60 rats (males and females combined) fed DDT at 80 ppm [$P < 0.05$]. In the second study, no tumours of the lung were observed.

Four groups of 36 or 37 male and 35 female outbred Wistar rats (age, 7 weeks) were fed diets containing technical-grade DDT at a concentration of 0 or 500 mg/kg of diet until age 152 weeks. Survival was not affected by the treatment. Body-weight gains were decreased [by 10–20%] in the treated groups when compared with the controls. The average dose of DDT was 34.1 mg/kg bw per day in males and 37.0 mg/kg bw per day in females. The incidence of liver cell tumours [benign or malignant, combined] was increased in treated males (9/27; controls, 0/35) [$P = 0.002$] and females (15/28; controls, 0/32) [$P < 0.0001$] (Rossi et al., 1977).

Groups of 50 male and 50 female Osborne-Mendel rats (age, 7 weeks) were fed diets containing technical-grade DDT for 78 weeks

and killed at 111 weeks. The initial concentrations of DDT were 420 or 840 mg/kg diet for males and 315 or 630 mg/kg diet for females. In females, these concentrations were decreased (after 26 weeks) to 158 and 315 mg/kg diet for females when signs of toxicity (tremors) appeared. In males, these concentrations were increased (after 12 weeks) to 500 and 1000 mg/kg diet, and then decreased (after 14 weeks) to 250 and 500 mg/kg diet (because of the signs of toxicity observed in females at the same time). The time-weighted average concentrations were 321 and 642 mg/kg diet for males and 210 and 420 mg/kg diet for females. Groups of 20 males and 20 females received a control diet. Compound-related mean body-weight depression was observed in male and female rats at the higher dose. Survival was not affected by the treatment. In females, there was a significant positive trend in the incidence of pheochromocytoma of the adrenal gland (0/19, 0/38, 3/24; $P = 0.031$) and a significant increase in the incidence of thyroid follicular cell adenoma or carcinoma (combined) at the lower dose (1/19, 13/45, 10/43; $P = 0.032$). There was no increase in the incidence of tumours that could be attributed to treatment with DDT in males (NCI, 1978). [The Working Group noted the small number of controls, and that dose levels were changed during the course of the study.]

Groups of 38 male and 38 female MRC Porton rats (age, 6–7 weeks) were fed a control diet or a diet containing technical-grade DDT at 500 mg/kg for 144 weeks. Additional groups of 30 male and 30 female rats were fed diets containing DDT at 125 or 250 mg/kg. Survival and body-weight gains were not significantly different between treated and control groups; survival at 80 weeks was > 70% in all groups except males at the highest dose (61%). The incidence of liver cell tumours [benign or malignant, combined] was significantly increased in female rats at the highest dose (controls, 0/38; lowest dose, 2/30; intermediate dose, 4/30; highest dose, 7/38 [$P < 0.01$]; trend test, $P < 0.001$). There was no significant increase in the incidence of any neoplasm in males (Cabral et al., 1982a).

Groups of 30 male Fischer 344 rats [age not reported; weight, 50–60 g] were fed with chow diet for 5 days, then were fed with chow diet with or without 0.05% DDT (Aldrich Chemical Co., [purity unspecified]) for 72 weeks, then fed un-supplemented diet until week 103. The incidence of liver neoplastic nodules [benign] was 2/28 in the controls, and 6/28 [not significant] in the group receiving DDT; while the incidence of HCC was 1/28 in the controls, and 0/28 in the group receiving DDT (Shivapurkar et al., 1986).

Groups of 30 or 35 male Wistar rats (age, at least 1 year; weight, 400–500 g) were given diets containing *p,p′*-DDT (purity, 86%) at a concentration of 0 or 500 ppm in experimental weeks 6–12, and then normal diet until the end of the study (60 weeks). Only one rat developed liver neoplastic nodules [benign] (control, 0/18; DDT, 1/19) (Angsubhakorn et al., 2002). [The Working Group noted the short duration of the experiment.]

Groups of 40 male and 40 female F344/DuCrj rats (age, 5 weeks) were fed diets containing *p,p′*-DDT (purity, > 98%) at a concentration of 0, 5, 50, or 500 ppm for 2 years. *p,p′*-DDT intake for males was estimated as 0, 0.17, 1.7 or 19.1 mg/kg per day, and for females was 0, 0.21, 2.2, or 25.2 mg/kg per day. Groups of 20 male and 20 female F344DuCrj rats were used for a satellite experiment with 6 males and 6 females for each dose level killed after 26 and 52 weeks of treatment, and with all surviving rats killed after 78 weeks of treatment. After 2 years, males and females at the highest dose (500 ppm) had whole body tremors in the late stages of treatment (weeks 70 to 104); however, there were no significant differences in mortality between treated and control groups. The mortality rates in the groups at 0, 5, 50, or 500 ppm at termination were 5/40, 10/40, 4/40, 7/40 for males, and 7/40, 13/40, 8/40, 7/40 for females, respectively. Mean body weights of males and females at the highest

dose were reduced by 12% and 25% during the study compared with controls, but those of other dose groups were similar to those of the controls. The incidences of hepatocellular adenoma at 104 weeks of treatment were significantly increased in males at 50 and 500 ppm (control, 0/40; 50 ppm, 5/40; 500 ppm, 22/40; $P < 0.05$ and $P < 0.01$, respectively) and females at 500 ppm (control, 0/40; 500 ppm, 16/40; $P < 0.01$). The incidence of HCC was also increased in males at 500 ppm (control, 0/40; 500 ppm, 14/40; $P < 0.01$), but not in females (control, 0/40; 500 ppm, 2/40) after 104 weeks of treatment. [The Working Group considered that the incidence of hepatocellular adenoma or carcinoma (combined) was significantly increased in treated female rats at 500 ppm.] In the satellite experiment, hepatocellular adenomas were observed in males and females at 500 ppm after 78 weeks of treatment (males: 6/7 versus 0/8 controls, $P < 0.01$; and females: 1/8) (Harada et al., 2003).

3.2.2 Co-administration with known carcinogens or other modifying factors

Groups of 14 or 19 male Buffalo rats (age, 6 weeks) were given a single oral dose of aflatoxin B_1 (AFB_1) at 5 mg/kg bw by gavage, followed by diet containing DDT (*p,p′*-DDT; purity, 86%) at a concentration of 0 or 100 ppm for 20 weeks, and then normal diet until the end of the study (82 weeks). Neoplastic nodules [benign] were observed in the liver (AFB_1 group, 1/14; AFB_1/DDT group, 3/19 [not significant]) (Angsubhakorn et al., 2002).

Groups of 35 or 43 male Wistar rats (age, at least 1 year; weight, 400–500 g), were given diets containing AFB_1 at a concentration of 4 ppm for 6 weeks, followed by a 6-week exposure to *p,p′*-DDT (purity, 86%) at a dose of 0 or 500 ppm, then normal diet until the end of the study (60 weeks). Neoplastic nodules [benign] were observed in the liver (AFB_1 group, 9/29; AFB_1/DDT group, 9/28 [not significant]). There was a slight [not significant] increase in the incidence of malignant hepatic tumours in the AFB_1/DDT-treated group (8/29 AFB_1 group; 10/28, AFB_1/DDT group) (Angsubhakorn et al., 2002).

A group of 120 male Sprague- Dawley rats (age, 22 days) were fed diet containing 2-acetylaminofluorene (AAF) at 0.02% for 18 days. After a pause of 1 week, the rats were then given diet containing technical-grade DDT at 0.05% for 389 days. A control group of 120 male rats was given AAF only. Average daily intake of DDT was estimated to be 50 mg/kg per day (by the 4th to 6th experimental month) or 20 mg/kg per day (by the 15th month). The incidence of hepatocellular adenoma or carcinoma (combined) was increased by treatment with DDT (AAF group, 31/108; and AAF/DDT group, 77/103, [$P < 0.0001$]) (Peraino et al., 1975).

A group of 30 male Fischer 344 rats [age not reported; weight, 50–60 g] were fed a chow diet for 5 days, then were injected with a single intraperitoneal dose of NDEA (200 mg/kg bw), then fed either the same chow diet as previously or the chow diet supplemented with 0.05% DDT (Aldrich Chemical Co., [purity unspecified]) for 72 weeks, then fed un-supplemented diet until 103 weeks. The incidence of hepatic tumours was increased by treatment with DDT: for liver neoplastic nodules [benign], there were 3/28 in the group receiving NDEA compared with 1/28 in the group receiving NDEA/DDT [not significant]; for HCC, there were 18/28 in the group receiving NDEA compared with 28/28 in the group receiving NDEA/DDT [$P < 0.0001$]; and for cholangioma or cholangiocarcinoma (combined), there were 0/28 in the group receiving NDEA compared with 6/28 in the group receiving NDEA/DDT [$P < 0.02$] (Shivapurkar et al., 1986).

Four groups of 10 male Wistar rats (age, 28 days) received drinking-water containing NDEA at a concentration of 50 ppm for 2 weeks, and (1 week later) were given DDT (Nakarai Chemical Co., Kyoto; [purity unspecified]) at a dose of 0 or 1.25 mg/rat (a solution of 0.1 mL of 1.25%

DDT) by gavage twice per week for 12 weeks. The rats were killed at 40 or 52 weeks. The incidence of liver tumours (> 5 mm) was 0/8 in the group receiving NDEA and 3/8 [not significant] in the group receiving NDEA/DDT at 52 weeks (Nishizumi, 1979).

Groups of 20 male F344 rats (age, 6 weeks) received two intraperitoneal injections of NDEA (100 mg/kg bw) with a 1-week interval, and then were fed diets containing *p,p′*-DDT (purity, > 98%) at a dose of 0 (control), 0.005, 0.5, or 500 ppm for 43 weeks. Final body weights were significantly decreased in the group receiving DDT at 500 ppm for 43 weeks compared with controls. Rats fed DDT at 500 ppm had significantly increased incidences and multiplicities of hepatocellular tumours. Tumour incidences and multiplicities were as follows: incidences of hepatocellular adenoma, 11/20 in NDEA controls, 13/20 in the group receiving DDT at 0.005 ppm, 10/20 at 0.5 ppm, and 18/18 at 500 ppm [$P < 0.002$]; the multiplicities of hepatocellular adenoma were 1.10, 0.95, 1.10, and 11.44 tumours per rat ($P < 0.01$); incidences of HCC were 12/20 in NDEA controls, 7/20 in the group receiving DDT at 0.005 ppm, 13/20 at 0.5 ppm, and 18/18 at 500 ppm [$P < 0.01$]; multiplicities of HCC were 1.00, 0.50, 0.90, and 28.67 tumours per rat ($P < 0.01$); the incidence of hepatocellular adenoma or carcinoma (combined) were 15/20 in NDEA controls, 14/20 in the group receiving DDT at 0.005 ppm, 17/20 at 0.5 ppm, and 18/18 at 500 ppm [$P < 0.05$]; and the multiplicities of of hepatocellular adenoma or carcinoma (combined) were 2.10, 1.45, 2.00, and 40.11 tumours per rat ($P < 0.01$) (Kushida et al., 2005).

3.3 Hamster

3.3.1 Oral administration

Groups of 30–40 male and 29–40 female outbred Syrian golden hamsters (age, 5 weeks) were fed diets containing technical-grade DDT at a concentration of 0, 125, 250, or 500 mg/kg. Survival of the treated hamsters at 52 weeks was similar to that of controls. The study was terminated at 120 weeks, when the last survivor was killed. There was no significant difference in tumour incidence between treated groups and controls; however, a significant positive trend was observed for the incidence of tumours of the adrenal cortex (mostly adenomas) in males (controls, 3/40; lowest dose, 4/30; intermediate dose, 6/31; and highest dose, 8/39; [*P* for trend, 0.04]), but not in females (controls, 0/39; lowest dose, 0/28; intermediate dose, 1/28; and highest dose, 3/40) (Cabral et al., 1982b).

Groups of 45 or 48 male and 46 or 48 female Syrian golden hamsters (age, 8 weeks) were fed diets containing technical-grade DDT at a concentration of 0 or 1000 mg/kg until age 128 weeks. Survival was 60% or greater in all groups at 80 weeks. Tumours of the adrenal gland (mainly cortical adenoma) occurred in 14/35 treated males compared with 8/31 male controls [not significant], and in 10/36 treated females compared with 2/42 female controls [$P < 0.01$] (Rossi et al., 1983).

Groups of 30 male and 30 female hamsters [strain unspecified; age at start, ~1 month] were given diets containing technical-grade DDT at a concentration of 0, 250, 500, or 1000 mg/kg for 18 months. No difference in body-weight gains between groups was observed. Mean survival time ranged, respectively, from 13.0 and 14.9 months in the male and female control groups, to 17.3 and 17.1 months in the groups of males and females at the highest dose. The incidence of lymphosarcoma was reduced from 50% in male controls and 41% in female controls to 0% in groups of males and females at the highest dose. No other tumour types were observed (Graillot et al., 1975).

3.3.2 Co-administration with known carcinogens or other modifying factors

Groups of 15 male Syrian golden hamsters (age, 6 weeks) were fed diets containing DDT at a concentration of 0 or 500 ppm (Nakarai Chemical Co., Osaka; [purity unspecified]) for 30 weeks. One week before DDT treatment, the hamsters were given an intraperitoneal injection of *N*-nitrosodimethylamine (NDMA) at 6 mg/kg bw. Hepatocellular adenomas were observed, but the incidence was not increased in hamsters treated with DDT (NDMA, 1/15; NDMA/DDT, 1/15) (Tanaka et al., 1987).

3.4 Monkey

Oral administration

A group of 13 cynomolgus monkeys and 11 rhesus monkeys (male and female newborns) were given diets containing *p,p′*-DDT (Aldrich Chemical Co., [purity not specified]) at a dose of 20 mg/kg bw for 130 months, followed by a control diet (without DDT). A control group of 9 cynomolgus monkeys and 8 rhesus monkeys received only the control diet. The monkeys were observed for up to 304 months. One HCC and one prostatic adenocarcinoma were reported in two DDT-treated cynomolgus monkeys. Two leiomyoma of the uterus and one of the oesophagus were reported in three other DDT-treated monkeys. No tumours were observed in the controls (Takayama et al., 1999).

3.5 Carcinogenicity of metabolites of DDT

3.5.1 DDD

(a) Mouse

Groups of 60 male and 60 female CF-1 mice (age, 6–7 weeks) were fed a diet containing *p,p′*-TDE [*p,p′*-DDD] (purity, 99%) at a concentration of 250 mg/kg until age 130 weeks; 100 males and 90 females served as controls. The incidence of hepatoma [benign or malignant, combined] was significantly increased in treated males (control, 33/98 (34%); treated, 31/59 (52%); [$P < 0.05$]), and the incidence of lung tumours (adenoma or adenocarcinoma, combined) was significantly increased in males and females compared with controls (male controls, 53/98 (53%); treated, 51/59 (86%) [$P < 0.0001$]; female controls, 37/90 (41%); treated, 43/59 (73%) [$P < 0.0001$] (Tomatis et al., 1974b).

Groups of 50 male and 50 female B6C3F$_1$ mice (age, 6 weeks) were fed diets initially containing technical-grade TDE (principal component, 60%; assumed to be *p,p′*-TDE [*p,p′*-DDD]; 19 unidentified impurities) at a concentration of 0, 315, or 630 mg/kg. The dietary concentrations of TDE were increased to 425 and 850 mg/kg due to lack of toxicity. The mice were fed DDT for 78 weeks and were killed at 90–93 weeks. The time-weighted average dietary concentrations of TDE were 411 and 822 mg/kg of diet. Additional groups of 20 males and 20 females were fed a control diet. Body-weight gain of treated females was reduced (beginning experimental week 30). Survival was not affected by treatment; terminal survival in males was 13/20 in the controls, 30/50 at the lower dose, and 27/50 at the highest dose; and in females was 18/20 in the controls, 41/50 at the lower dose, and 44/50 at the highest dose. There was no significant increase in the incidence of tumours (NCI, 1978). [The Working Group noted the small number of controls, and changes in dosing during the study.]

(b) Rat

Groups of 50 male and 50 female Osborne-Mendel rats (age, 7 weeks) were fed diets containing technical-grade TDE [*p,p′*-] (principal component, 60%; assumed to be *p,p′*-TDE [*p,p′*-DDD]; 19 unidentified impurities) for 78 weeks and were killed at 111–113 weeks. The initial dietary concentrations of TDE for male

rats of 1400 or 2800 mg/kg were increased to 1750 or 3500 mg/kg due to lack of toxicity. Females received diets containing TDE at 850 or 1700 mg/kg of diet throughout the study. The time-weighted average concentrations given to males were 1647 or 3294 mg/kg of diet. Additional groups of 20 males and 20 females were fed a control diet. Body-weight gains were substantially reduced in rats at the higher dose and somewhat reduced in rats at the lower dose compared with controls. Survival was not affected by treatment. Increased incidences of follicular cell adenoma of the thyroid gland were seen in males and females (males: controls, 0/19; lower dose, 11/49 [$P < 0.05$]; higher dose, 9/49 [$P < 0.05$]; [trend, $P < 0.05$]; female: controls, 0/19; lower dose, 6/48 [not significant]; higher dose, 5/50 [not significant]), and significance was reached for follicular cell adenoma or carcinoma (combined) only in males at the lower dose (males: controls, 1/19; lower dose, 16/49 ($P = 0.016$); higher dose, 11/49; females: controls, 2/19; lower dose, 11/48; higher dose: 6/50) (NCI, 1978). [The Working Group noted the small number of controls, and the changes in dosing for males during the study.]

3.5.2 DDE

(a) Mouse

A group of 60 male and 60 female CF-1 mice (age, 6–7 weeks) was fed a diet containing *p,p′*-DDE (purity, 99%) at a concentration of 250 mg/kg until age 130 weeks. The control group comprised 100 males and 90 females. An increased incidence of hepatoma [benign or malignant, combined] was found in treated males and treated females compared with controls (male controls, 33/98 (34%); treated males, 39/53 (74%) [$P < 0.0001$]; female controls, 1/90 (1%); treated females, 54/55 (98%) [$P < 0.0001$]) (Tomatis et al., 1974b).

Groups of 50 male and 50 female B6C3F$_1$ mice (age, 6 weeks) were fed diets containing *p,p′*-DDE (purity, > 95%; one minor impurity) for 78–79 weeks and were killed at 92–93 weeks. The initial dietary concentrations of 125 (lower dose) or 250 mg/kg (higher dose) were increased during the study to 150 or 300 mg/kg due to lack of toxicity. When toxicity became apparent, the concentrations in the diet were held constant, but the higher-dose diets were replaced by control diet every fifth week for the duration of the treatment period. The time-weighted average dietary concentrations were 148 and 261 mg/kg of diet for the groups at the lower and higher dose, respectively. Control groups of 20 males and 20 females were fed a control diet. Body-weight gain was reduced in treated females compared with controls. At 70 weeks, survival in males was 5/20 in controls, 35/50 at the lower dose, and 31/50 at the higher dose; at 75 weeks, survival in females was 19/20 in controls, 47/50 at the lower dose, and 28/50 at the higher dose. The incidences of HCC were significantly increased in males (0/19 in controls, 7/41 at the lower dose, and 17/47 at the higher dose; $P = 0.001$ for trend and for the group at the higher dose) and females (0/19 in controls, 19/47 at the lower dose, and 34/48 at the higher dose; $P < 0.001$ for the groups at the lower dose, higher dose, and for trend) (NCI, 1978). [The Working Group noted the small number of controls, the low survival of male controls, and the changes in dosing during the study.]

(b) Rat

Groups of 50 male and 50 female Osborne-Mendel rats (age, 7 weeks) were fed diets containing *p,p′*-DDE (purity, > 95%; one minor impurity) for 73–78 weeks and were killed at 111–112 weeks. The initial dietary concentrations of 675 or 1350 mg/kg for male rats, and of 375 or 750 mg/kg for females were reduced to 338 or 675 mg/kg of diet for males and 187 or 375 for females due to the onset of toxic signs. After 32–36 weeks, the higher-dose diets were replaced by control diet every fifth week for the duration of treatment period. The time-weighted average concentrations were 437 and 839 mg/kg

of diet for males, and 242 and 462 mg/kg of diet for females. Control groups of 20 males and 20 females were fed a control diet. Body-weight gains were somewhat reduced in all treated male and high-dose females compared with controls. Survival at 92 weeks was 16/20 in controls, 34/50 at the lower dose, and 26/50 at the higher dose in males, and 20/20 in controls, 42/50 at the lower dose, and 36/50 at the higher dose in females. There was no significant increase in tumour incidence in treated males and females (NCI, 1978). [The Working Group noted the small number of controls and the changes in dosing during the study.]

(c) Hamster

Groups of 40–47 male and 43–46 female Syrian golden hamsters (age, 8 weeks) were fed a control diet or a diet containing *p,p′*-DDE (purity, 99%) at a concentration of 500 or 1000 mg/kg until age 128 weeks. Survival was 50% or greater in all groups at 80 weeks. There were significantly increased incidences [$P < 0.05$] of hepatocellular adenoma or carcinoma (combined) [mostly carcinomas] in both groups of treated males and females: male controls, 0/10; males at the lower dose, 7/15; and males at the higher dose, 8/24; and female controls, 0/31; females at the lower dose, 4/26; and females at the higher dose, 5/24 (Rossi et al., 1983).

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetic data

4.1.1 Absorption, distribution, and excretion

(a) Humans

p,p′-DDT, *o,p′*-DDT, and their metabolites DDE, *p,p′*-DDD, and *o,p′*-DDD are highly lipophilic compounds. They are expected to be readily absorbed in exposed humans. The toxicokinetics of *p,p′*-DDT have been more extensively studied than those of *o,p′*-DDT. Absorption after inhalation exposure has not been directly measured experimentally in humans, but uptake has been estimated to be 100% for the gaseous phase and 44% for the particulate phase (Volckens & Leith, 2003). Uptake from direct dermal exposures to *p,p′*-DDT has been estimated to be around 10%, with about an order of magnitude lower for uptake from contaminated soil (Wester et al., 1990). Human experimental studies have confirmed *p,p′*-DDT absorption via the oral route, although urinary recovery is not complete in the timeframe of the studies because of the long excretion half-lives of the compounds (Morgan & Roan, 1971; Roan et al., 1971).

p,p′-DDT, *o,p′*-DDT, and their metabolites readily distribute through the body via lymphatic and blood circulation, preferentially concentrating in lipids due to their high lipophilicity (Morgan & Roan, 1970, 1971). In an analysis of human autopsy cases, concentrations of *p,p′*-DDT and DDE were highest in adipose tissue, with concentrations in blood, liver, and kidney proportion to their lipid content (Morgan & Roan, 1970). Levels of *p,p′*-DDT and DDE in the brain, however, were about an order of magnitude lower than would be expected based on lipid content alone (Morgan & Roan, 1970). *p,p′*-DDT and its metabolites have also been detected in breast milk and cord blood (Galetin-Smith et al., 1990; Minh et al., 2004), and have been found to be transported across the placenta to the fetus (Sala et al., 2001; Vizcaino et al., 2014). Due to their lipophilicity, *p,p′*-DDT and DDE remain sequestered in adipose tissue, with a long biological half-lives, estimated to be around 5 years for *p,p′*-DDT and almost 9 years for DDE (Smith, 1999; Wolff et al., 2000b). Due to these long half-lives, comprehensive mass-balance studies have not been performed in humans. Available data suggest that excretion of *p,p′*-DDT products after exposure occurs largely via the urine, with

p,p′-DDA (2,2-bis(4-chlorophenyl)-acetic acid) being the most commonly measured metabolite (Hayes et al., 1971; Roan et al., 1971). However, the excretion rate of *p,p′*-DDA may be more closely related to ongoing exposures than overall body burden (Roan et al., 1971). On the other hand, *o,p′*-DDT is rapidly excreted as urinary metabolites (Morgan & Roan, 1974).

(b) Experimental systems

p,p′-DDT, *o,p′*-DDT, and their metabolites DDE, *p,p′*-DDD, and *o,p′*-DDD are readily absorbed by all experimental animal species tested after dermal application or ingestion. There are many more toxicokinetic data on *p,p′*-DDT than *o,p′*-DDT. No studies were identified in which *p,p′*-DDT, *o,p′*-DDT, or their metabolites were administered via inhalation. Several radiolabel studies with *p,p′*-DDT in rats or in vitro have demonstrated dermal absorption of < 5% after up to 5 days (Shah & Guthrie, 1983; Reifenrath et al., 1991; Toś-Luty et al., 2002). In rhesus monkeys, dermal absorption of *p,p′*-DDT was measured to be 9–31% in an acetone vehicle and 3–4% in soil (Wester et al., 1990). Absorption after ingestion was much greater, with uptake of > 70% measured in rats given *p,p′*-DDT in vegetable oil (Rothe et al., 1957; Keller & Yeary, 1980). Because of its lipophilicity, *p,p′*-DDT is more poorly absorbed if a non-absorbable vehicle such as mineral oil or paraffin is used (Keller & Yeary, 1980; Palin et al., 1982). Most of this *p,p′*-DDT absorption occurs by way of the intestinal lymphatic system, with a smaller amount through portal blood (Rothe et al., 1957; Jandacek et al., 2009). The carrier for *p,p′*-DDT in lymph is predominatly the lipid core of chylomicrons (Pocock & Vost, 1974).

After absorption, *p,p′*-DDT and its metabolites DDE and *p,p′*-DDD are readily distributed to tissues via lymph and blood circulation. In plasma, *p,p′*-DDT is carried by both lipoproteins and albumin (Mohammed et al., 1990). The highest concentrations of *p,p′*-DDT are generally in fat, liver, and brain, consistent with their lipophilicity, based on experiments in mice, rats, and dogs (Finnegan et al., 1949; Woolley & Talens, 1971; Mühlebach et al., 1991; Tomiyama et al., 2003, 2004; Tebourbi et al., 2006). In a study in pregnant rabbits, concentrations of *p,p′*-DDT and metabolites *p,p′*-DDD and DDE were higher in the fetus, placenta, uterus, and ovaries than in maternal plasma, indicating accumulation in fetal and reproductive tissues (Hart et al., 1972). Placental and/or lactational transfer to offspring after maternal exposure to *p,p′*-DDT has also been demonstrated in other species, including rats, dogs, and cows, with milk being a major source of neonatal exposure due to its lipid content (Woodard et al., 1945; Carter & Mann, 1949; Finnegan et al., 1949; Woolley & Talens, 1971).

Excretion of *p,p′*-DDT and *o,p′*-DDT occurs mainly through the urine, and to a lesser extent, milk (discussed previously) and faeces. *p,p′*-DDA is the predominant urinary metabolite after exposure to *p,p′*-DDT or *p,p′*-DDD, and is reported to account for 85–99% of urinary metabolites in hamsters (Gold & Brunk, 1983). *p,p′*-DDT in faeces after oral exposure may represent unabsorbed compound, while *p,p′*-DDT metabolites in faeces are likely due to biliary excretion (Jensen et al., 1957). Moreover, there are data indicating enterohepatic recirculation of *p,p′*-DDA in the rat (Gingell, 1975). Elimination in experimental animals is slow, although not as slow as estimated in humans, with most studies expected to recover only a fraction of the administered dose. In one radiolabel study in rats, excretion half-lives (the time estimated to excrete 50% of the administered dose) were estimated to be 12 days for *p,p′*-DDT, 3 days for *p,p′*-DDD, and 24 days for DDE (Fawcett et al., 1987). In another study in rats treated with DDE, the total body-burden half-life was estimated to be 120 days (Mühlebach et al., 1991). Urinary excretion of metabolites is also the main pathway of excretion of *o,p′*-DDT, based on experiments in rats,

but occurs at a faster rate than for *p,p′*-DDT (Feil et al., 1973; Reif & Sinsheimer, 1975).

4.1.2 Metabolism

(a) Humans

Based on experiments in humans given *p,p′*-DDT, DDE, or *p,p′*-DDD via ingestion, *p,p′*-DDT conversion is primarily to *p,p′*-DDD, with a smaller amount being dehydrochlorinated to DDE (Hayes et al., 1956, 1971; Morgan & Roan, 1971; Roan et al., 1971). *p,p′*-DDD readily degrades through several intermediates to form *p,p′*-DDA, which is readily excreted in the urine, while DDE is poorly eliminated and accumulates in lipid-rich tissues (Morgan & Roan, 1971). Only small amounts (near the limit of detection) of DDE have been detected in the urine of individuals given *p,p′*-DDT or DDE by ingestion (concentrations orders of magnitude lower than the urinary concentrations of *p,p′*-DDA) (Roan et al., 1971).

Studies in humans fed *o,p′*-DDT showed rapid metabolism and excretion (Morgan & Roan, 1974). Humans fed *o,p′*-DDD excreted more than half of the daily dose via the urine each day (Reif et al., 1974).

(b) Experimental systems

p,p′-DDT is metabolized to multiple intermediates and metabolites generated through complex reaction pathways. Although the same basic pathways are thought to exist in various species, including humans, there may be quantitative differences across species and tissues that have not yet been fully elucidated. The postulated metabolism scheme for *p,p′*-DDT is shown in Fig. 4.1 (based on a review by Smith, 2010).

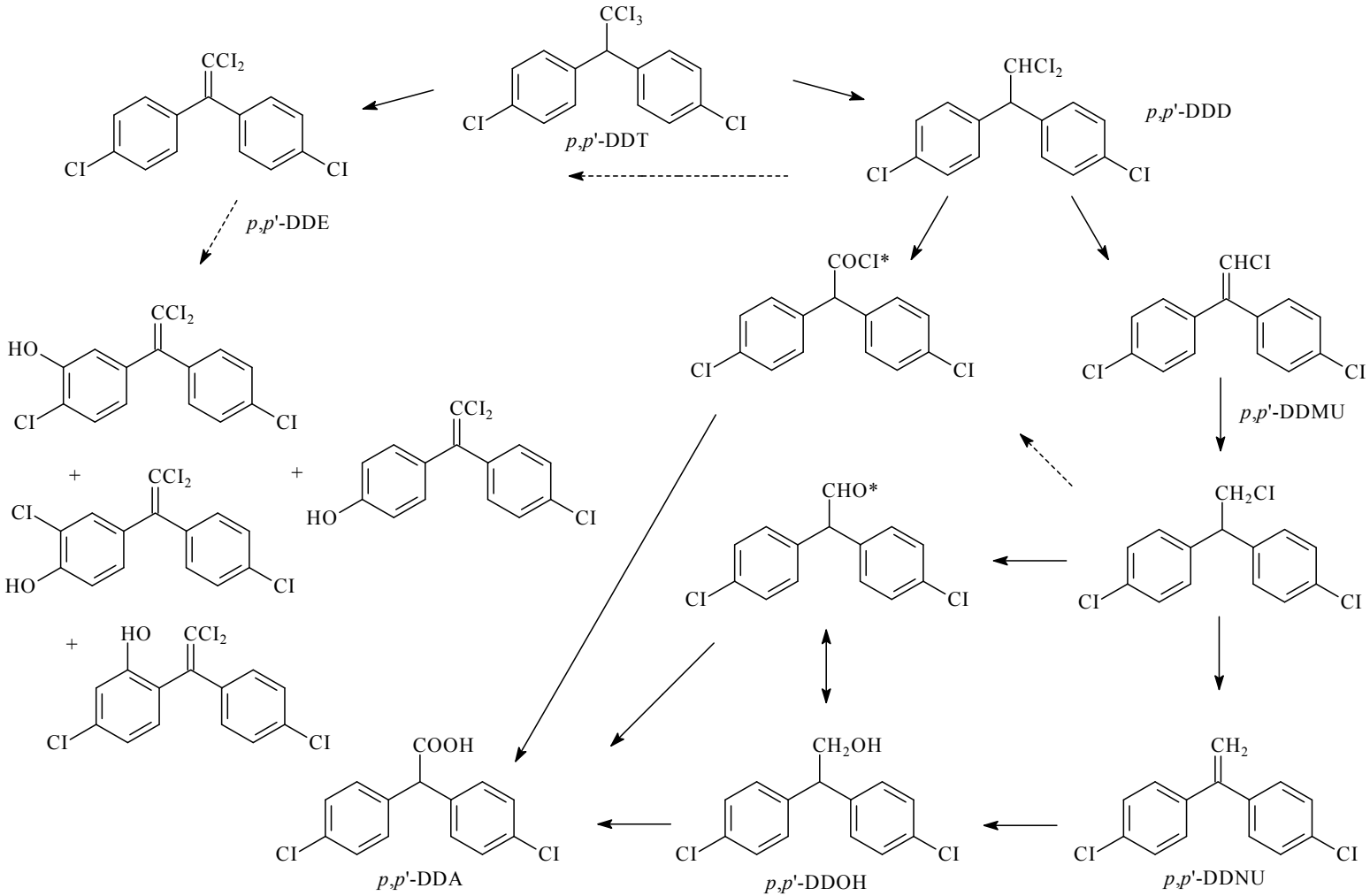
Reductive dechlorination of *p,p′*-DDT to *p,p′*-DDD in experimental animals appears to be primarily catalysed by microsomal cytochrome P450s (CYPs), and has been measured directly in vitro as well as inferred indirectly by the ability of phenobarbital and diphenylhydantoin to induce excretion (Alary et al., 1971; Fries et al., 1971; Kitamura et al., 2002). This reaction may also proceed non-enzymatically, but at a much slower rate based on experiments in rat liver microsomes and rat blood (Kitamura et al., 2002). The other fate of *p,p′*-DDT is dehydrochlorination to DDE, but the catalysis of this reaction is unclear. While earlier studies suggested that formation of DDE and *p,p′*-DDD are completely separate pathways (Peterson & Robison, 1964), later studies suggested that *p,p′*-DDD can also be converted to DDE (Gold & Brunk, 1982; Kitamura et al., 2002). However, based on the much smaller amount of urinary DDE produced after administration of *p,p′*-DDD when compared with *p,p′*-DDT, most DDE produced after exposure to *p,p′*-DDT is likely to be direct conversion from *p,p′*-DDT, at least at lower exposures (Gold & Brunk, 1982; Fox et al., 1998).

1-Chloro-2,2-bis(*p*-chlorophenyl)ethylene (*p,p′*-DDMU) is thought to be derived from *p,p′*-DDD, but not DDE (Kitamura et al., 2002). *p,p′*-DDMU and another downstream intermediate, 1-chloro-4-[1-(4-chlorophenyl)ethenyl] benzene (*p,p′*-DDNU), may form reactive epoxide intermediates (Planche et al., 1979; Gold et al., 1981).

The major urinary metabolite after administration of *p,p′*-DDT is *p,p′*-DDA. *p,p′*-DDA is produced from *p,p′*-DDD through multiple potential pathways, principally an acyl chloride intermediate (Cl^- *p,p′*-DDA) (Peterson & Robison, 1964; Gold & Brunk, 1982; Fawcett et al., 1987). Cl^- *p,p′*-DDA may can then either undergo hydrolysis to form *p,p′*-DDA or acylate cellular nucleophiles (Gold & Brunk, 1982).

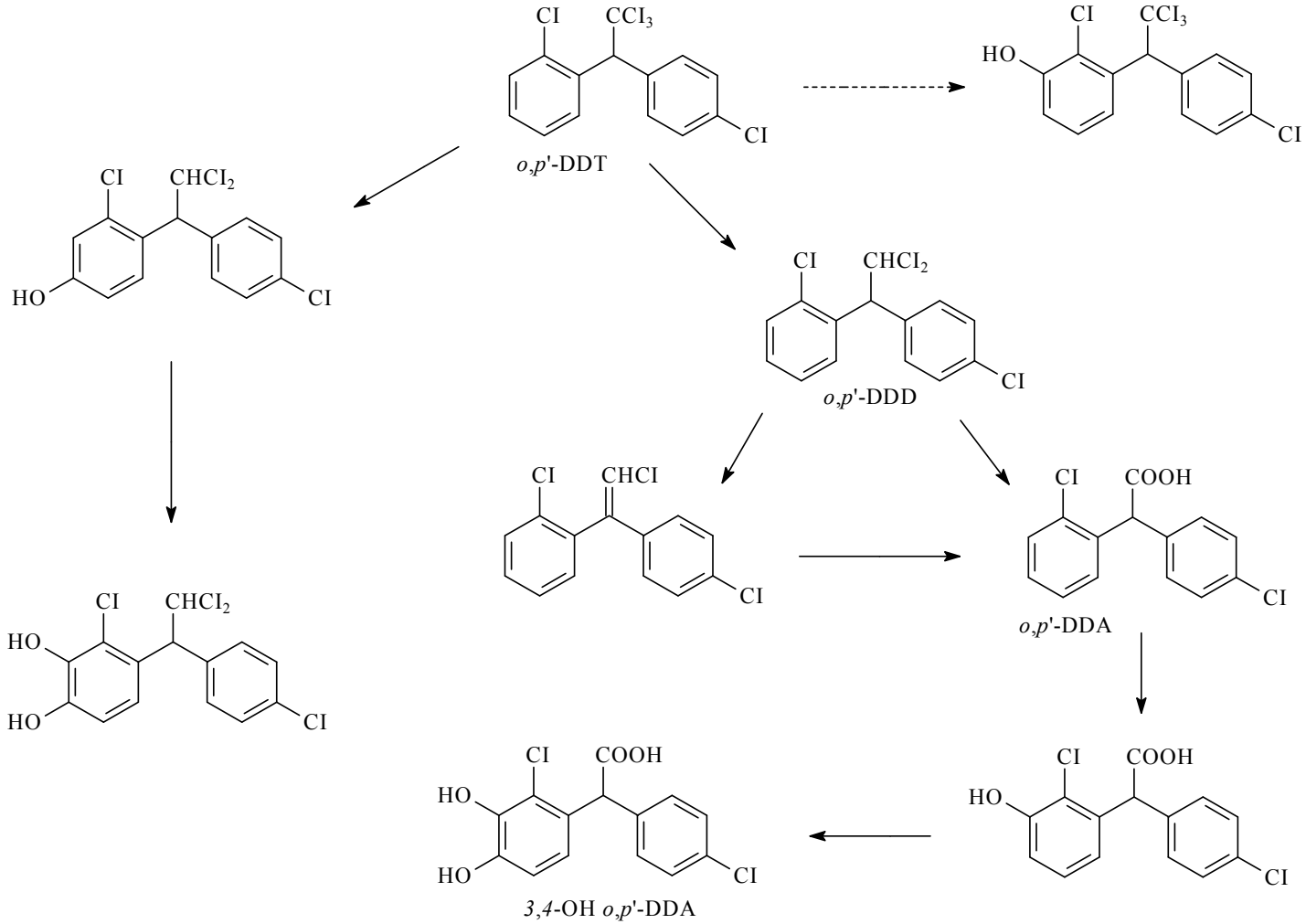
o,p′-DDT metabolism has been less extensively studied. Based on studies in rats, the primary metabolic pathway appears to be through *o,p′*-DDD to *o,p′*-DDA, with no formation of DDE (Feil et al., 1973; Reif & Sinsheimer, 1975). A postulated metabolism scheme for *o,p′*-DDT is shown in Fig. 4.2, based on a review (Smith, 2010).

Fig. 4.1 Postulated metabolism scheme of *p,p′*-DDT in rats



Reprinted from Smith (2010). In: Hayes' Handbook of Pesticide Toxicology, third edition, Robert Krieger, Chapter 93: Toxicology of DDT and some analogues, Pages No. 1975–2032, Copyright (2010), with permission from Elsevier.
The metabolites indicated by an asterisk are likely to be reactive with cellular constituents

Fig. 4.2 Postulated metabolism scheme of *o,p'*-DDT in rats



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4.1.3 Modulation of xenobiotic metabolism enzymes

No studies in exposed humans were available to the Working Group.

p,p′-DDT transactivated the pregnane X receptor (PXR) and induced the PXR-mediated expression of CYP3A4 and CYP2B6 in a hepatoma cell line (Lemaire et al., 2004).

In male Sprague-Dawley rats exposed to *p,p′*-DDE (100 mg/kg for 7 days by oral gavage), liver CYP2B1 and CYP3A1 were induced and were correlated with CAR and PXR activity in a receptor transactivation assays (Wyde et al., 2003; see Section 4.2.1(c)). *p,p′*-DDE (intraperitoneal dose of 0, 20, 60, or 100 mg/kg bw every other day for 10 days) significantly upregulated rat hepatic enzymes CYP1A1, CYP2B1, and uridine diphosphate-glucuronosyltransferase (UDPGTs), although CYP1A2 did not change significantly (Liu et al., 2011, 2014).

4.2 Mechanisms of carcinogenesis

This section summarizes evidence for the six of ten key characteristics of carcinogens (Smith et al., 2016) that had adequate data for evaluation, concerning whether DDT modulates receptor-mediated effects; is immunosuppressive; induces oxidative stress; alters cell proliferation and death; is genotoxic; and induces chronic inflammation.

4.2.1 Receptor-mediated effects

(a) Exposed humans

(i) Serum hormone levels

In studies of occupationally exposed men, there were conflicting results regarding associations between *p,p′*-DDT or *p,p′*-DDE and serum levels of testosterone, sex hormone-binding globulin (SHBG), and estradiol, while there was no association between *p,p′*-DDT or *p,p′*-DDE and luteinizing hormone (LH) or follicle-stimulating hormone (FSH). For instance, in a cross-sectional study of 59 men employed for 15.8 ± 7.8 (mean ± standard deviation, SD) years (range, 4–34 years) as DDT sprayers or working with DDT sprayers in malaria vector control in South Africa, significant positive associations were found by linear regression analysis between serum testosterone and *p,p′*-DDT ($P = 0.014$) and *p,p′*-DDD ($P = 0.050$), and between 17β-estradiol (E_2) and *p,p′*-DDT ($P = 0.001$) and *p,p′*-DDD ($P = 0.003$) after adjustment for age and SHBG (Dalvie et al., 2004b). There were no such significant associations for SHBG, and associations between any of the hormones measured and *o,p′*-DDT or *o,p′*-DDD, *o,p′*-DDE and *p,p′*-DDD were also not significant.

In a study of 107 men in Italy who had been exposed to DDT because of antimalaria spraying when they were young, *p,p′*-DDT and *p,p′*-DDE were detectable and quantifiable in 14 men and 106 men, respectively. There were no significant associations between levels of *p,p′*-DDT and *p,p′*-DDE and serum levels of any of the hormones (LH, FSH, SHBG, E_2, and testosterone) assessed approximately 50 years after exposure (Cocco et al., 2004). *o,p′*-DDT and *o,p′*-DDE were undetectable.

In a group of 137 African-American farmers (aged 33–88 years; mean, 62 years) from North Carolina, USA, who reported using DDT in their work, serum levels of DDE (presumably *p,p′*-DDE) were not correlated with serum levels of testosterone, 5α-dihydrotestosterone (DHT), SHBG, or free testosterone (Martin et al., 2002).

In men and women exposed through habitual consumption of fish, there were no associations between *p,p′*-DDT and/or *p,p′*-DDE and sex steroids, LH and FSH, and thyroid hormones triiodothyronine, thyroxine, and thyroid-stimulating hormone (T3, T4, and TSH, respectively). For example, in a study of 110 men (age range, 23–79 years) from Latvia ($n = 67$; mean age, 48 years) and Sweden ($n = 43$; mean age, 42 years) who regularly consumed fish, there were no

significant associations between plasma levels of *p,p′*-DDT or *p,p′*-DDE and plasma levels of free testosterone, LH, FSH, prolactin, TSH, and total and free T3 and T4 (Hagmar et al., 2001). Similarly, in 150 regular consumers of fish from the United States Great Lakes region, DDE was not significantly correlated with testosterone, SHBG, free testosterone, SHBG-bound testosterone, dehydroepiandrosterone, estrone sulfate, LH, and FSH, or the thyroid hormones T3, T4, and T3 uptake and free T4 index (Persky et al., 2001). In 51 women (42 were regular consumers of fish), no significant correlations between DDE and thyroid hormones were reported. A significant inverse correlation was found between DDE and estrone sulfate in the serum in a subset of 56 men from this study, but there was again no correlation between DDE and the other hormones (Turyk et al., 2006).

In men and women generally exposed through the environment, there were conflicting outcomes (both changes in hormone levels and negative results). In a study of 304 men and 300 women from an area in Brazil heavily polluted with OCPs, linear regression analysis found a significant inverse association ($P < 0.05$) between testosterone and *o,p′*-DDT, and a borderline significant inverse association ($P < 0.05$) between testosterone and *p,p′*-DDE in the serum of the men; there was no such association for *p,p′*-DDT or *p,p′*-DDD (Freire et al., 2014). When *p,p′*-DDE levels were divided into quartiles, a significant inverse association with testosterone levels was found (*P* for trend, 0.02). In a study of 257 men (age range, 18–82 years; mean, 42 years) and 436 women (age range, 18–95 years; mean, 42 years) from the native American Mohawk nation in the USA, serum levels of DDE [presumably *p,p′*-DDE] and serum testosterone levels were not significantly associated (Goncharov et al., 2009).

In peri- or postmenopausal women ($n = 77$), there was a significant inverse association between LH and serum levels of *p,p′*-DDT or *p,p′*-DDD, and between FSH and serum levels of *p,p′*-DDD (Freire et al., 2014). There was a significant inverse association between LH and *p,p′*-DDE levels across *p,p′*-DDE quartiles ($P < 0.001$), but no significant associations between serum organochlorine levels and other hormones (E_2, progesterone, and prolactin) in peri- or postmenopausal women.

Several studies of populations exposed through the environment found a positive association between *p,p′*-DDT and/or *p,p′*-DDE and T3 and/or T4, and in some there was an inverse association with TSH. However, there were also several studies that did not find such associations. In a study in Brazil, a significant inverse association was seen in men between *p,p′*-DDT and free T4 levels, but not total T3 or TSH (Freire et al., 2013). In women, in contrast, there was a positive association between *p,p′*-DDT and free T4 levels and total T3, while serum *o,p′*-DDT was also positively associated with free T4 levels.

A large study among participants of the National Health and Nutrition Examination Survey (NHANES) in the USA in 1999–2000 ($n = 986$) and 2001–2002 ($n = 1443$) reported an inverse association between serum *p,p′*-DDE and TSH, but only in women aged 66 years and older in the 1999–2000 period (Turyk et al., 2007).

When serum levels of *p,p′*-DDE and sex steroid hormones were compared in a group of 341 men (age range, 18–51 years) from an infertility clinic in Boston, USA, no significant associations were found for testosterone, SHBG, free testosterone, and E_2 (Ferguson et al., 2012). However, when serum levels of *p,p′*-DDE and thyroid hormones were compared using multivariate linear regression analysis, there were significant positive associations for total T3 and free T4, and a significant inverse association for TSH (Meeker et al., 2007).

In 48 men and 66 women (age range, 55–74 years) from a polluted area in the upper Hudson River area in New York State, USA, there was a significant ($P < 0.05$) association between the sum of *p,p′*-DDT and *p,p′*-DDE and total T4 and total T3 in women, but not in men, after adjustment

for several covariates, including other organochlorine exposures (Bloom et al., 2014). TSH and free T4 levels were not significantly associated with the sum of *p,p′*-DDT and *p,p′*-DDE in either sex.

In 834 men and 1212 women (age range, 20–75 years) in a polluted area in east Slovakia, *p,p′*-DDE levels were positively associated with those of T3 ($r = 0.072$; $P < 0.01$), but not associated with free T4 or TSH (Langer et al., 2007). No results were presented for *p,p′*-DDT.

There was no association between prenatal DDT exposure (measured in cord blood) and thyroid hormone status in newborns. In blood samples collected during pregnancy from 147 Canadian women, a significant association between *p,p′*-DDE and total T3 was found, but not for free T4 or TSH, while there were no significant associations for *p,p′*-DDT and thyroid hormones (Takser et al., 2005). In another study of cord blood, significant inverse associations with total T4 were found for *p,p′*-DDT, *p,p′*-DDE, and *o,p′*-DDE, but not for *o,p′*-DDT and *p,p′*-DDD in samples collected from 39 women in Thailand (Asawasinsopon et al., 2006). No associations were found for free T4 or TSH. In a similar study of 247 women in China, no significant associations found between *p,p′*-DDE and free T3, free T4, and TSH (Li et al., 2014b). In 259 children (age, 4 years) in Spain, blood levels of *p,p′*-DDT and *p,p′*-DDE were not associated with serum levels of T3, T4, or TSH (Alvarez-Pedrerol et al., 2008b). No significant correlations have been reported between cord blood levels of *p,p′*-DDT and *p,p′*-DDE and TSH levels in 27 newborns (age, 3 days) from the same area in Spain (Álvarez-Pedrerol et al., 2008a). In a cohort of 453 newborns in the Valencia region of Spain, cord blood levels of *p,p′*-DDT and *p,p′*-DDE were not associated with TSH serum levels. In a study of newborns in another Spanish population, *p,p′*-DDT and *p,p′*-DDE and TSH levels in the cord blood of 453 babies were not significantly associated (Lopez-Espinosa et al., 2010). An earlier report from the same group of 70 newborns also indicated the absence of a significant association between *p,p′*-DDT and *p,p′*-DDE and TSH levels in cord blood (Ribas-Fitó et al., 2003).

(ii) Other endocrine-related effects

In a nested case–control study in Spain, newborns with cryptorchidism and/or hypospadias were compared with boys without malformations and placental levels of DDT were measured (Fernandez et al., 2007). The odds ratio for cryptorchidism and/or hypospadias was 2.17 (95% CI, 0.96–5.00) for *o,p′*-DDT concentration of ≥ LOD, and 2.17 (95% CI, 0.95–5.00) for *p,p′*-DDT concentration of ≥ LOD, but no odds ratios specifically for cryptorchidism were presented. In three nested case–control studies, no such effect was found: *p,p*-DDT, *p,p′*-DDE, *p,p′*-DDD, and *o,p′*-DDT in breast milk was not correlated with cryptorchidism (Damgaard et al., 2006). Further, there was no correlation between cryptorchidism and maternal serum levels of *p,p′*-DDT and *p,p′*-DDE (Bhatia et al., 2005) and DDE (Longnecker et al., 2002). [Overall, there appeared to be no association in humans between maternal DDT exposure and cryptorchidism in male offspring.]

One study found no association between DDT exposure and anogenital distance (Longnecker et al., 2007). Another study reported an effect on anogenital distance with maternal serum DDE levels, but not with DDT levels (Torres-Sanchez et al., 2008).

In a cross-sectional study of young women in China, age at menarche was 1.11 years less ($P < 0.001$) in women in the fourth quartile of total serum DDT concentration compared with the lowest quartile, and a 10 ng/g increase in serum DDT concentrations was significantly ($P < 0.001$) associated with a 0.2 year reduction in age at menarche (Ouyang et al., 2005). In contrast, there was no association between the presence and level of *p,p′*-DDE in serum and adipose tissues and precocious puberty in a study

in Turkey of girls with premature breast development (Ozen et al., 2012). [The data indicating an association between DDT and early menarche in these and other studies were thus mixed and potentially confounded by body weight and growth, which can affect DDT congener levels in growing girls, and time between menarche and blood sampling (Wolff et al., 2007).]

Studies on diabetes and obesity are presented in Section 4.5.

(iii) Tumour receptor expression

[The Working Group noted the paucity of data evaluating DDT and receptors in tumours in humans. Available data concerning an association between *o,p′*-DDT and human epidermal growth factor receptor 2 (HER2)-positive breast cancer are presented in Section 4.4.]

(b) Human cells in vitro

(i) Estrogen receptor-mediated effects

[The Working Group noted that *o,p′*-DDT binds to and activates ER in a variety of human cell types, effects of which are blocked by an ER antagonist. *o,p′*-DDT is 100–1000 times less potent in ER binding than estradiol, and *p,p′*-DDT and DDT metabolites bind ER less potently than *o,p′*-DDT. Notably, DDT and DDT metabolite levels in human adipose tissue are 100s to 1000 times higher than in serum (Kanja et al., 1992; Toppari et al., 1996), while nipple aspirate estradiol is only 4–45 times higher than in serum (Petrakis et al., 1987).]

o,p′-DDT binds the human ER less potently than estradiol in a variety of assays: (i) cytosolic binding assays (Klotz et al., 1996; Scippo et al., 2004), binding to both ERα and ERβ (Kuiper et al., 1998), *o,p′*-DDT having greater affinity for human ERα than for human ERβ (Legler et al., 2002); (ii) assays with cells transfected with reporter vectors for ERα and ERβ (Shelby et al., 1996; Lemaire et al., 2006); (iii) yeast-based assays in which 4-hydroxy-tamoxifen abrogated the effect (Klotz et al., 1996; Dhooge et al., 2006); and (iv) assays of binding to recombinant ERα and ERβ (Scippo et al., 2004). In MCF-7 cells, nuclear redistribution of ER was induced by *o,p′*-DDT at 1 μM (Steinmetz et al., 1996). Some studies observed relatively strong ER binding (Andersen et al., 1999) and physiologically relevant ERα and ERβ transactivation, such as via CAT (chloramphenicol acetyltransferase) reporter gene transcription, in MCF-10 and MCF-7 cells (Shekhar et al., 1997; Lemaire et al., 2006). While *o,p′*-DDT and *p,p′*-DDT were not inhibitory to E_2-induced ER transactivation in the chemically activated luciferase expression (CALUX) system using human osteosarcoma cells (Sonneveld et al., 2005), *o,p′*-DDT and *p,p′*-DDT stimulated MCF-7 cells to enter and progress through the cell cycle in an ER-dependent manner that was ablated by ER antagonist ICI182,780 (Dees et al., 1997a; Shekhar et al., 1997).

The human ER, but not the rat ER, also binds *o,p′*-DDD, *o,p′*-DDE and *p,p′*-DDT (Kelce et al., 1995; Li et al., 2008). [The Working Group noted that these data suggest that the human ER is more permissive of binding by DDT-related compounds than the ER of other species.] *p,p′*-DDT is less estrogenic in vitro than *o,p′*-DDT, showing little if any binding to the human ER (Danzo, 1997; Kuiper et al., 1998; Scippo et al., 2004), weak to very weak ER transactivation, and sometimes no effect (Chen et al., 1997; Li et al., 2008;). *p,p′*-DDT also stimulated estrogenic proliferation in these systems (see Section 4.2.6).

o,p′-DDE is also less estrogenic than *o,p′*-DDT, showing weak to very weak binding to the ER (Zava et al., 1997; Scippo et al., 2004), weak ER transactivation in MCF-7 and HeLa cells and yeast systems (Balaguer et al., 1999), and weak stimulation of MCF-7 cell proliferation (Soto et al., 1995); lack of ER binding and transactivation have also been reported in Sf9 and human embryonal kidney 293 cells (Kuiper et al., 1998; Sheeler et al., 2000). *p,p′*-DDE has even less estrogenic effects, showing weak to no ER binding, and mostly no ER transactivation in

MCF-7 cells (Soto et al., 1995; Aubé et al., 2011). *o,p′*-DDD is also estrogenic, but weaker than *o,p′*-DDT showing weak to very weak ER binding, weak ER transactivation, and very weak stimulation of MCF-7 cell proliferation (Klotz et al., 1996; Aubé et al., 2011). *p,p′*-DDD had hardly any estrogenic effect, showing weak ER binding, but no ER transactivation and very weak stimulation of MCF-7 cell proliferation (Tully et al., 2000; Lee et al., 2002; Scippo et al., 2004), although ER transactivation in MCF-7 cells stronger than *o,p′*-DDT has also been reported, which effect was abrogated by 4-hydroxy-tamoxifen (Klotz et al., 1996).

ER antagonist ICI 182,780 blocked the effects of *o,p′*-DDT and *p,p′*-DDE on induction of PR and downregulation of ER; these effects were stronger than interference of Erk activation with an inhibitor of MEK1 (Silva et al., 2010).

There are data, mostly from studies with MCF-7 cells in vitro, that DDT and DDE can also act via non-genomic mechanisms involving plasma membrane-located ERs that can activate signalling pathways resulting in rapid responses (Bratton et al., 2012). In human breast-cancer cells, *o,p′*-DDE has binding affinity for GPR30 (Thomas et al., 2005). Both *o,p′*-DDE and *p,p′*-DDT also bind GPR30 in a transformed human embryonic kidney cell line (Thomas & Dong, 2006).

(ii) Effects on aromatase and steroid-hormone production

Estrogens in humans and other mammals are formed from precursor androgens by the enzyme aromatase. *p,p′*-DDE at concentrations of 50–100 ng/mL caused significant 130–135% induction of aromatase enzyme activity in primary human endometrial stromal cells (Holloway et al., 2005). In contrast, *p,p′*-DDE inhibited aromatase activity in HEK 239 human embryonic kidney cells at a concentration of 20 µM (Benachour et al., 2007). No effect of *p,p′*-DDE was found on aromatase activity in H295R human adrenocortical cancer cells at concentrations of 1–10 µM, while *o,p′*-DDT, *p,p′*-DDT, and *o,p′*-DDE were inhibitory but only at a cytotoxic concentration of 10 µM (Sanderson et al., 2002).

In human JEG-3 choriocarcinoma cells, *o,p′-DDT, p,p′-DDT, p,p′-DDE,* and *o,p′-DDE* at concentrations as low as 1 ng/mL all increased progesterone secretion as well as secretion of human chorionic gonadotropin at concentrations of 10 ng/mL and higher (Wójtowicz et al., 2007b). In human placental explant cultures, *o,p′*-DDT, *p,p′*-DDE, and *o,p′*-DDE, but not *p,p′*-DDT, increased progesterone secretion at concentrations of 100 ng/mL and higher, while conversion of dehydroepiandrosterone to E_2 was decreased by all four compounds at concentrations of 1 ng/mL and higher (10 ng/mL and higher for *o,p′*-DDE) (Wójtowicz et al., 2007c). Effects on aromatase activity were inconsistent, although the DDT and DDE isomers tended to decrease it, and aromatase protein expression [not quantified] was decreased by all four, with *o,p′-DDT, o,p′-DDE* being the most active inhibitors.

(iii) Androgen receptor-mediated effects

[The Working Group noted that DDT and its metabolites antagonize the AR, with *p,p′*-DDE being the most potent, in cells from humans and other species and in non-human experimental systems in vivo.]

In HepG2 cells stably transfected with human AR reporter constructs, transactivation by DHT was most strongly inhibited by *p,p′*-DDE (at concentrations of one to two orders of magnitude above the maximum activating DHT concentration), followed by *p,p′*-DDT, and least strongly by *o,p′*-DDT (Kelce et al., 1995; Maness et al., 1998). Inhibitory activity of *p,p′*-DDE was also observed in AR-negative human PC-3 prostate-cancer cells transfected with human AR and a reporter construct (Schrader & Cooke, 2000). *p,p′*-DDE inhibited androgen-induced human AR transactivation in yeast systems (Gaido et al., 1997; Li et al., 2008) and bound to recombinant human

AR (Scippo et al., 2004). *o,p′*-DDD and *p,p′*-DDD more strongly bound to recombinant human AR, while *o,p′*-DDT and *p,p′*-DDT showed binding comparable to that of *p,p′*-DDE (Scippo et al., 2004; Sonneveld et al., 2005). *o,p′*-DDT also binds and inhibits transactivation of the human AR in recombinant yeast (Chen et al., 1997; Gaido et al., 1997). Inhibitory activity of *p,p′*-DDE was also observed in AR-negative human PC-3 prostate-cancer cells transfected with AR and a reporter construct (Schrader & Cooke, 2000). *o,p′*-DDT and *p,p′*-DDT were equally inhibitory in the CALUX system using human osteosarcoma cells (Sonneveld et al., 2005).

p,p′-DDE induced concentration dependent proliferation of human breast-cancer cell lines expressing AR (e.g. CAMA-1) and MCF-7 cells transfected with AR (Aubé et al., 2008).

Analysis in silico indicated human AR binding of *p,p′*-DDT, but other isoforms and related congeners were not evaluated (Wang et al., 2010). A similar analysis showed that additional AR binding sites, other than that used by DHT, were subject to binding by *p,p′*-DDE (Xu et al., 2013).

(iv) Progesterone receptor-mediated effects

o,p′-DDT induced PR in MCF-7 cells in a dose-dependent manner reaching the same level as induced by 10 nM estradiol at a concentration of 1 μM; *p,p′*-DDT, *o,p′*-DDE, and *o,p′*-DDD had the same effect but to a lesser extent (Chen et al., 1997). Binding to the human PR has been reported in a competitive binding assay in T47D human breast-cancer cells with 1 nM radiolabeled R5020, a synthetic PR agonist, for *o,p′*-DDT, *o,p′*-DDD, *p,p′*-DDD, and *o,p′*-DDE at concentrations of 150 nM and higher, but not for *p,p′*-DDT, *p,p′*-DDE, and *p,p′*-DDA (Klotz et al., 1997). In a yeast system and in T47D cells containing PR reporter constructs, PR was not significantly transactivated by any of these compounds, but all inhibited PR transactivation by progesterone, mostly at concentrations of 100 nM and higher (in cells) or 1 μM and higher (in yeast) (Klotz et al., 1997). Binding to recombinant human PR was also found for *p,p′*-DDT, but not *p,p′*-DDD, while *o,p′*-DDT, *p,p′*-DDE, and *o,p′*-DDE had lower affinity (Scippo et al., 2004).

(v) Effects on HER2 receptors

At a low dose, *o,p′*-DDT (1 nM) enhanced the tyrosine kinase activity of HER2 in human MCF-7 breast-cancer cells irrespective of tamoxifen exposure or estrogen depletion of culture media (Enan & Matsumura, 1998; Hatakeyama & Matsumura, 1999). *o,p′*-DDT also gave rise to increased MCF-7 foci (abnormal concentric piling up of cells in post confluent cultures) (Hatakeyama & Matsumura, 1999). The effects of *o,p′*-DDT on tyrosine kinase activity of HER2 and MCF-7 foci formation were blocked by a mononuclear antibody specific to HER2.

(vi) Other receptor-mediated effects

Induction of cAMP production by TSH in Chinese hamster ovarian cells transfected with recombinant human TSH receptor was slightly inhibited by *p,p′*-DDT at 1 μM and significantly at 10 μM and higher; *p,p′*-DDT interfered with internalization of the TSH receptor induced by TSH, possibly by direct interaction with the receptor (Santini et al., 2003; Picchietti et al., 2009).

There are conflicting reports on whether DDT compounds can interact with the aryl hydrocarbon receptor (AhR). In human placental tissue, *o,p′*-DDT, *p,p′*-DDT, *o,p′*-DDE, and *p,p′*-DDE (100 ng/mL) all decreased the expression of AhR protein (Wójtowicz et al., 2011). In human MCF-7 and LNCaP cells *o,p′*-DDT reduced the mRNA and protein expression of Arnt2, but at a high dose of 10 μM (Qin et al., 2011).

(c) Experimental systems in vivo

(i) Estrogen receptor-mediated effects

[The Working Group noted that estrogenic effects of *o,p′*-DDT were consistently shown across numerous experimental non-human systems.]

Results from *o,p′*-DDT administration in vivo extensively supported the notion that ER activation leads to physiological consequences, e.g. increased lordosis in rats (Brown & Blaustein, 1984) and increased uterine wet weight in birds, mink, rats, and mice (Bitman et al., 1968; Duby et al., 1971; Al-Jamal & Dubin, 2000).

The first reports of estrogenic activity of DDT were published in 1968 and 1969, showing increased oviduct weights in fowl by *o,p′*-DDT, but not *p,p′*-DDT, and high tissue concentrations of both (Bitman et al., 1968). Increased uterine weights occurred in immature rats after administration of *o,p′*-DDT, technical DDT and, to a lesser extent, *p,p′*-DDT and the DDT metabolite *o,p′*-DDD, but not *p,p′*-DDD (1 or 5 mg/kg) (Welch et al., 1969). *o,p′*-DDT, technical DDT, and *p,p′*-DDT, and *o,p′*-DDD also inhibited uterine uptake of radiolabeled E_2 (Welch et al., 1969).

ER transcription-inducing effects of single intraperitoneal injections of *p,p′*-DDT (5–500 µg/kg) have been observed in liver, brain, thymus, and prostate of immature male transgenic mice with estrogen-reporter constructs in all estrogen-responsive tissues (Di Lorenzo et al., 2002). Effects were synergized by co-treatment with E_2 (50 µg/kg), and abolished by intraperitoneal injections with ICI 182,780, once before and once after the DDT injection. However, similar treatment with *o,p′*-DDT had the opposite effects in the liver by itself and antagonized the effects of co-administered E_2.

In ovariectomized DA/Han rats, three daily oral treatments of *o,p′*-DDT (500 mg/kg bw per day) markedly reduced mRNA expression of ER in the uterus (Diel et al., 2000). In prepubertal Sprague-Dawley rats given seven daily intraperitoneal injections of *p,p′*-DDT or *p,p′*-DDE (25 mg/kg), the uterine-weight response to estrone treatment was decreased and uptake of radiolabeled estrone was reduced (Welch et al., 1971). The uterine-weight response to *o,p′*-DDT and *p,p′*-DDT has been reproduced (Bitman & Cecil, 1970; Kanno et al., 2003), as has the lack of this in response to *p,p′*-DDD, *p,p′*-DDE, and *p,p′*-DDA (Bitman & Cecil, 1970). These findings were consistent with increases in uterine and vaginal epithelial thickness caused by a treatment for 7 days with *o,p′*-DDD delivered via silastic implants to ovariectomized young adult CD-1 mice at doses resulting in serum *o,p′*-DDD levels of 18 ng/mL and higher (Ulrich et al., 2000). Of note, the estrogenicity of the active DDT compounds was weak, about three to four orders of magnitude less than that of E_2. The uterotropic effect of *o,p′*-DDT was blocked by co-administration of the antiestrogen raloxifene, which does not have estrogenic effects on the uterus as does tamoxifen, demonstrating that this is an ER-mediated effect (Al-Jamal & Dubin, 2000).

(ii) Androgen receptor-mediated effects

Experimental data in vivo are consistent with *p,p′*-DDE antagonism of AR. Mice exposed to DDT had decreased AR mRNA and protein in their testes (Chaturvedi et al., 2010). Rat puberty is delayed and seminal vesicle and ventral prostate weights are reduced in adult rats exposed to DDT (Kelce et al., 1995). Three daily oral doses (12.5–50 mg/kg bw per day) of technical-grade DDT inhibited uptake of radiolabeled testosterone in the prostate of Swiss-Webster mice and reduced formation of testosterone metabolites in the mouse prostate and liver (Smith et al., 1972; Lloyd et al., 1974), and reduced formation of testosterone metabolites in the rat liver (Sierra-Santoyo et al., 2005). In one study, serum testosterone was decreased in CD rats, but increased in Long Evans rats; in both strains, E_2 levels increased,

while DHT was increased only in Long Evans rats and FSH decreased only in CD rats (LH and prolactin were not affected) (O'Connor et al., 1999). In ovariectomized DA/Han rats, three daily oral treatments of *o,p′*-DDT (500 mg/kg bw per day) markedly reduced mRNA expression of AR in the uterus (Diel et al., 2000). The anti-androgenic activity of *p,p′*-DDE in vitro is consistent with delayed preputial separation in pubertal rats and reduced accessory sex gland weights in castrated, testosterone-supplemented adult rats treated with an oral dose of 200 mg/kg bw per day for 4 days (Kelce et al., 1995) or 100 mg/kg bw per day for 7 days (O'Connor et al., 1999), although a lack of such effects has also been reported from a study in intact rats (Krause, 1977).

(iii) Other receptor-mediated effects

Regarding effects on aromatase and steroid-hormone production, oral treatment of adult male Sprague Dawley rats with *p,p′*-DDE (100 mg/kg bw per day) for 7 days caused significant induction of aromatase protein expression and aromatase activity in the liver, and elevation of circulating E_2 levels (You et al., 2001).

The progestin-binding site of the PR can also be bound by *o,p′*-DDT in rats (Brown & Blaustein, 1984). The PR is bound by *o,p′*-DDE, and to a lesser extent by *p,p′*-DDT and *p,p′*-DDE in birds (Lundholm, 1991). The PR is also bound by *o,p′*-DDT in fish (Das & Thomas, 1999; Berg et al., 2005).

When exposure to *p,p′*-DDE was initiated at weaning, the latency of HER2-positive mouse mammary tumours was shortened (Johnson et al., 2012).

Oral treatment of adult SD rats and Long Evans rats with *p,p′*-DDE for 15 days at 100–300 mg/kg bw per day decreased serum T4, but not T3, and increased serum levels of TSH (O'Connor et al., 1999). Treatment of adult Wistar rats with intraperitoneal injections of *p,p′*-DDT for 10 days at 50–100 mg/kg bw per day increased thyroid relative weights, decreased activity of type I, but not type II, 5′-deiodinase in liver, kidney, and in a biphasic manner thyroid, decreased serum T4 and, to a lesser extent,T3 and increased serum levels of TSH (Tebourbi et al., 2010). [The Working Group noted that it was not clear whether these DDT effects involved TSH receptor mediation or other mechanisms.]

o,p′-DDD caused a glucocorticoid deficiency in dogs, decreasing circulating 17-OH-corticosteroids and ablating adrenocorticotropic hormone (ACTH) action (Cueto & Moran, 1968). The attenuation of these effects by glucocorticoid receptor (GCR) agonist prednisolone was suggestive of GR antagonism by *o,p′*-DDD (Cueto & Moran, 1968). The eosinophilic response to ACTH was impaired in beagles after a high exposure to *o,p′*-DDT (50 mg/kg bw per day for 32 days), consistent with adrenocortical inhibitory effects of *o,p′*-DDT (Copeland & Cranmer, 1974). These effects could be secondary to liver toxicity, as elevated microsomal enzymes could have stimulated extra-adrenal metabolism of cortisol. Technical-grade DDT (mostly *p,p′*-DDT) altered the adrenal weight of rats (Foster, 1968), and *p,p′*-DDT exposure elevated corticosterone in sparrows (Scollon et al., 2004).

Several reports indicate effects of *o,p′*-DDT on expression of P450 isoforms and other genes mediated by the constitutive androstane receptor (CAR) and/or the pregnane X receptor (PXR) in rats and mice (Wyde et al., 2003; Medina-Díaz et al., 2007; Kiyosawa et al., 2008).

(d) Experimental systems in vitro

(i) Estrogen receptor-mediated effects

The agonism of ER by *o,p′*-DDT in cells from animals and other experimental systems in vitro has been well characterized (Nelson, 1974). *o,p′*-DDT has been shown to bind ER from rats (Nelson, 1974), rabbits (Andersen et al., 1999), cattle (Tiemann et al., 1996), vultures (ERα) (Naidoo et al., 2008), zebrafish (ERα and ERβ) (Legler et al., 2002), yeast (Chen et al., 1997),

as well as humans (Chen et al., 1997), albeit at differing potencies. [The Working Group noted that in most of these studies, it was not specified whether ERα or ERβ was investigated.] In primary porcine ovarian cells (granulosa and theca cells together) *p,p′*-DDE and, to a lesser extent, *o,p′*-DDT and *o,p′*-DDE, stimulated E_2 secretion at concentrations of 0.4 and 4 μg/mL, while progesterone secretion was suppressed by *o,p′*-DDT, *p,p′*-DDT, and *p,p′*-DDE, but not by *o,p′*-DDE (Wójtowicz et al., 2007a). *o,p′*-DDT, *p,p′*-DDT, *p,p′*-DDE, and *o,p′*-DDE all increased the conversion of testosterone to E_2 due to increased aromatase activity, *p,p′*-DDE being most active.

(ii) Androgen receptor-mediated effects

In monkey CV-1 cells, *o,p′*-DDT, *p,p′*-DDT, *o,p′*-DDE, and *p,p′*-DDE all potently inhibited AR transcriptional activity (Chaturvedi et al., 2010). *p,p′*-DDE strongly inhibited binding and transactivation of radiolabeled DHT to the rat prostate androgen receptor (Wakeling & Visek, 1973; Kelce et al., 1995; Danzo, 1997), while *o,p′*-DDT and *p,p′*-DDT and *p,p′*-DDD had a weak inhibitory effect (Kelce et al., 1995; Danzo, 1997). *o,p′*-DDT, *p,p′*-DDT, *p,p′*-DDD also antagonized the rat and bird AR with lower affinity than *p,p′*-DDE (Lundholm, 1991; Kelce et al., 1995). In Chinese hamster ovarian cells, *p,p′*-DDE was also the strongest inhibitor of androgen (R1881) activation of the AR, while *o,p′*-DDT and *o,p′*-DDE were also inhibitory and *o,p′*-DDD and *p,p′*-DDD were inactive (Roy et al., 2004).

(iii) Other receptor-mediated effects

In monkey cells exposed in vitro, there was no change in transcriptional activity or nuclear translocation of the GCR by o,p′-DDT, p,p′-DDT, o,p′-DDE, or p,p′-DDE (Chaturvedi et al., 2010). p,p′-DDE displaces dexamethasone from the GCR of birds (Lundholm, 1991). At higher concentrations, o,p′-DDT, p,p′-DDT and o,p′-DDE also bind the GCR in birds (Lundholm, 1991).

4.2.2 Immunosuppression

[The Working Group noted that there were consistent findings that DDT suppresses the humoral immune response across multiple species.]

(a) Humans

(i) Exposed humans

In a study of 49 patients who worked as farmers or farmhands and had been occupationally exposed to multiple insecticides for at least 6 months, detection of DDT and DDE in blood was associated with elevated levels of interleukin-4 (IL-4), a Th2 cytokine, in plasma. DDE and DDD suppressed the Th1 cytokines IL-2 and interferon-gamma (IFN-γ) (Daniel et al., 2002).

Significantly higher levels of *p,p′*-DDE were detected in the blood of patients with systemic lupus erythematosus than in healthy controls (Dar et al., 2012).

In a study of environmental exposure to DDT in 302 residents living near a Superfund site in Aberdeen, North Carolina, USA or in neighboring communities, few differences in immune markers were associated with residential location. In residents who lived closer to the site, mitogen-induced lymphoproliferative activity was statistically significantly lower than that in residents who lived farther away ($P < 0.05$) (Vine et al., 2000).

(ii) Human cells in vitro

In highly purified natural killer (NK) cells exposed to to 4,4′-DDT (5 μM) for 24 hours, ability to destroy K562 tumour cells was inhibited by 61 ± 13%. The loss of cytotoxic function seen with 4,4′ -DDT increased when exposure was increased to 6 days (Reed et al., 2004). [The Working Group noted that this study shows that DDT decreases the tumour-cell killing (lytic) function of human NK cells.]

In a follow-up study, exposure to DDT (2.5 μM) for 24 hours (which caused > 55% loss of

lytic function) decreased NK binding function by about 22%, and decreased CD16 cell-surface protein by 20% (Hurd-Brown et al., 2013). In another study, DDT substantially and persistently decreased NK cell lytic function (by 55% at 2.5 µM) within 24 hours (Udoji et al., 2010). [The Working Group noted that three independent studies showed that DDT impairs human NK cell function.]

Ndebele et al. (2004) showed that DDT significantly suppressed IL-2 production in activated CD4+ Jurkat T-cells, at the transcriptional and translational levels. Comitogenic and immunosuppressant effects of *p,p′*-DDT and its derivatives on phytohaemagglutinin-stimulated human lymphocytes have also been reported (Nikolaeva et al., 1980).

(b) Experimental systems in vivo

(i) Mice

Banerjee and colleagues showed a depression in the primary and secondary humoral immune response in mice after subchronic exposure to DDT (Banerjee et al., 1986), and also demonstrated suppression of the humoral immune response to a T-independent antigen (Banerjee, 1987a). In a subsequent study, restraint and other forms of stress potentiated DDT-induced suppression of the humoral immune response in mice (Banerjee et al., 1997).

DDT injections (once every 4 days) markedly increased the incidence of albuminuria and reduced uterine weight, but were without effect on immunity or mortality in the New Zealand Black/New Zealand White F1 hybrid (B/W) mouse model of systemic lupus erythematosus (Li & McMurray, 2009). A separate study showed that DDT accelerated the natural course of systemic lupus erythematosus in this mouse model of the disease (Sobel et al., 2005). *o,p*-DDT significantly reduced the time to development of renal impairment, the primary clinical indication of lupus in the model system (Sobel et al., 2005). There was no clear correlation between autoimmune effects and estrogenicity, as assessed via measurement of uterine hypertrophy (Sobel et al., 2005).

(ii) Rats

Banerjee (1987b) reported suppression of humoral and cell-mediated immune responses in albino rats after short-term exposure to DDT. This suppression increased in a dose- and time-dependent manner (Banerjee, 1987b). Sensitivity to these effects was increased by protein deficiency. Humoral and cellular immune suppression were induced by DDT (50 and 100 ppm) only in rats fed a diet containing 3% protein. In rats immunized with tetanus toxoid, inhibition of leukocyte and macrophage migration was also diminished (Banerjee et al., 1995). A later study demonstrated that DDT, DDE, and DDD, but not DDA, induced different degrees of humoral and cellular immune suppression, with the potency of effects in the order of DDE > DDD > DDT (Banerjee et al., 1996). In rats given DDT (100 and 200 ppm) by oral administration, the humoral immune response was markedly suppressed as assessed by anti-sheep erythrocyte antibody titres via a mechanism that may involve free radicals (Koner et al., 1998).

(iii) Rabbits

In rabbits, DDT (20 mg/kg) significantly reduced organ weights (of the lung, liver, and spleen), antiovalbumin synthesis in the lung and spleen, and maximum serum antibody titre. Serum protein levels decreased as a result of a reduction in levels of albumin and γ- and β-globulin (Chung et al., 1989).

(v) Marine mammals

A higher incidence of bacterial infections were seen in harbour porpoises from the North and Baltic seas of Germany, in comparison to whales from less polluted Arctic waters (Beineke et al., 2005). In free-ranging bottlenose dolphins (Lahvis et al., 1995), the immune response decreased with increasing concentrations of

several contaminants, including DDT, in whole blood; inverse correlations were found between concanavalin A-induced lymphocyte proliferation and concentrations of *p,p′*-DDT (Lahvis et al., 1995).

(iv) Birds

The primary humoral immune response in Japanese quail was not affected by in ovo exposure to either isomer of DDT (Bryan et al., 1989). Total circulating erythrocyte numbers were reduced in females after injection in ovo with *o,p′*-DDT but not *p,p′*-DDT. Exposure in ovo to *o,p′*-DDT, but not to *p,p′*-DDT, had long-term and estrogen-like effects on behaviour and haematology. Reproductive behaviours were attenuated with *o,p′*-DDT, which also increased the total number of eggshell malformations (Bryan et al., 1989).

Antibody-mediated immunity was not affected in chickens treated with DDT (Glick, 1974).

An antagonistic action rather than a synergistic or additive effect on blood parameters was observed when DDT and PCB (Aroclor 1254) were co-administered in White Leghorn cockerels (*Gallus domesticus*) (Iturri et al., 1982).

(vi) Frogs

In northern leopard frogs (*Rana pipiens*), sublethal doses of DDT (923 ng/g wet weightt) markedly suppressed antibody response, whereas DTH reactions were enhanced, and respiratory burst was lower (Gilbertson et al., 2003). No differences in the response were seen when pathogens were administered before DDT. A companion field study found significant differences in immune function with pesticide exposure in frogs from Ontario, Canada (Gilbertson et al., 2003).

(c) Experimental systems in vitro

In mouse J774A.1 macrophages, DDT inhibited functional activation, and reduced the capacity to limit intracellular growth of intracellular pathogens, using *Mycobacterium microti* as a model (Nuñez et al., 2002). Technical-grade DDT (a mixture of *p,p′*-DDT (85%), *o,p′*-DDT (15%), and trace amounts of *o,o′*-DDT) and *p,p′*-DDE were more potent than *p,p′*-DDT (Nuñez et al., 2002).

In a study in rat peritoneal exudate cell suspensions, macrophages treated for 4.5 hours in vitro with lipoprotein-sequestered DDT (2.5 µM) showed significant inhibition of their ability to phagocytize yeast particles (Kaminski et al., 1986). An earlier study reported no statistical difference in phagocytic activity was observed in either in vitro or in vivo in rat leukocytes (Kaliser, 1968).

Kannan and Sharma described defective lymphocyte transformation by DDT and responsiveness of rabbit peripheral blood lymphocytes to phytohaemagglutinin in vitro (Kannan & Sharma, 1979).

In beluga whale peripheral blood leukocytes and splenocytes exposed in vitro, *p,p′*-DDT and *p,p′*-DDE had no marked effect on phagocytosis (De Guise et al., 1998). However, *p,p′*-DDT, but not *p,p′*-DDE, significantly reduced the proliferative response of the splenocytes cultured either with or without phytohaemagglutinin (De Guise et al., 1998).

4.2.3 Oxidative stress

(a) Humans

In a study of 44 breast tumours and 21 benign breast biopsies, there was no correlation between *p,p′*-DDT or *p,p′*-DDE and levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG; a biomarker of oxidative DNA damage) (Charles et al., 2001). [The Working Group noted that post-diagnostic measurements in breast tumours and biopsies are of questionable relevance to the potential for DDT to induce oxidative stress.]

In in vitro studies, *p,p′*-DDT or *p,p′*-DDE increased the production of intracellular ROS and inhibited superoxide dismutase (SOD) activity in

human colorectal adenocarcinoma DLD1 cells or SW620 cells (Song et al., 2014a, b); see also xenograft experiments in nude mice, described below. *p,p′*-DDE also activated NADPH oxidase, and reduced catalase activity and glutathione content. NAC, a ROS inhibitor, suppressed the induction of Wnt/β-catenin signalling and cell proliferation by *p,p′*-DDT in DLD1 cells and by *p,p′*-DDE in both cell lines. *p,p′*-DDT also significantly elevated ROS levels in HepG2 human liver-cancer cells (Jin et al., 2014). Gamma-glutamylcysteine synthetase (γ-GCS) and SOD activity were inhibited. Beta-catenin and its downstream target genes c-Myc and cyclin D1 were significantly upregulated; co-treatment of DDT with NAC inhibited this overexpression. Moreover, *p,p′*-DDT-induced proliferation of HepG2 cells was inhibited by co-treatment with NAC or β-catenin siRNA (Jin et al., 2014).

In human peripheral blood mononuclear cells in vitro (Pérez-Maldonado et al., 2005), DDT and DDD increased oxidative stress levels by 19-fold compared with controls; for DDE, the increase was 25-fold. These increases in reactive oxygen species (ROS) preceded induction of apoptosis, which was significantly inhibited by *N*-acetyl-*L*-cysteine (NAC) for all three compounds (Pérez-Maldonado et al., 2005).

(b) Experimental systems in vivo

In xenograft experiments in nude mice, *p,p′*-DDT (5 nmol/kg, ip) increased tumour size, oxidative stress and activation of Wnt/β-catenin signalling in human DLD1 tumours (Song et al., 2014b) or HepG2 tumours (see also Section 4.2.4b). These studies were consistent with the in vitro findings in human colorectal (Song et al., 2014a, b) or HepG2 cells (Jin et al. 2014) by the same research group.

In male and female rats exposed to *p,p′*-DDT (5, 50, or 500 ppm) for 2 years, hepatic levels of 8-OH-dG were elevated throughout the study at 500 ppm in males and females, whereas hepatic lipid peroxidation was increased at 50 and 500 ppm but in males only (Harada et al., 2003; see also Section 3).

In rats exposed orally for 8 weeks, *p,p′*-DDT dose-dependently increased levels of thiobarbituric acid reactive substance (TBARS) in serum and SOD activity in erythrocytes, and suppressed the humoral immune response. Ascorbic acid attenuated the effects of *p,p′*-DDT on lipid peroxidation, SOD activity, and humoral immune suppression (Koner et al., 1998). *p,p′*-DDT (40 mg/kg) caused a time-dependent increase in hepatic mitochondrial and microsomal lipid peroxidation and DNA single-strand breaks in rats (Hassoun et al., 1993). In male F344 rats, a 16-week exposure to *p,p′*-DDT at dietary concentrations of 20 ppm or more increased glutathione *S*-transferase placental form (GST-P)-positive foci (putative preneoplastic lesions) in the liver. At concentrations of DDT of 0.5 ppm or less, oxidative stress in the liver, assessed by measuring 8-OH-dG as a marker of oxidative DNA damage, was decreased; this was associated with a decreased number of GST-P-positive foci (Sukata et al., 2002). [The Working Group noted that oxidative stress levels were not determined at the higher doses, although other studies confirm that oxidative stress is induced at these doses of *p,p′*-DDT.]

4.2.4 Altered cell proliferation or death

(a) Humans

(i) Exposed humans

Blood levels of DDT and DDE were associated with a higher frequency of apoptotic cells in exposed children (the specific isomer responsible was not identified) (Pérez-Maldonado et al., 2004).

Elevated levels of apoptosis have been noted in blood mononuclear cells isolated from children and exposed ex vivo to *p,p′*-DDT or *p,p′*-DDE (Pérez-Maldonado et al., 2005). Simultaneous elevation of ROS was also noted (see Section 4.2.3).

(ii) Human cells in vitro

o,p′-DDT induces proliferation of ER-responsive cells such as MCF-7 cells (Soto et al., 1995; Payne et al., 2000b), acting both singly and synergistically in mixtures (Payne et al., 2001) (see also Section 4.2.1). This isomer can also upregulate genes such as vascular endothelial growth factor A (VEGFA) in estrogen-responsive MCF-7 breast cancer cells in an ER-independent fashion through crosstalk between MAPK signalling pathways and transcriptional coactivators (Bratton et al., 2012). *p,p′*-DDE also stimulates proliferation of ER-positive breast-cancer cells and this induction primarily occurred after exposures at lower concentrations (Aubé et al., 2011). However, *p,p′*-DDE suppressed proliferation of androgen-dependent LNCaP cells, while *o,p′*-DDT induced MAPK phosphorylation and slightly increased proliferation of these cells, but not of androgen-independent PC-3 cells; these effects did not appear to occur via direct interaction with the AR (Tessier & Matsumura, 2001) (see also Section 4.2.1). Consistent with these observations, *o,p′*-DDT exhibited weak cell proliferation stimulatory effects, compared with estradiol, in ER-positive human MCF-7, T-47D, and MVLN breast-cancer cells (Dees et al., 1997a; Silva et al., 2007). In parallel with stimulation of MCF-7 cell proliferation, *o,p′*-DDT suppressed apoptosis at concentrations of 100 nM and higher (Diel et al., 2002).

o,p′-DDT induced the expression of the cell-death ligand TNF-α, and elevated apoptosis via a p38 MAPK-dependent mechanism in endometrial Ishikawa and human embryonic kidney (HEK) 293 cells; the apoptotic pathway involves mitochondrial release of cytochrome c with subsequent effector caspase-3/7 activation (Frigo et al., 2005). DDT exposure in vitro modulates the proliferation and viability of human endometrial endothelial cells (Welch et al., 1969; Bredhult et al., 2007, 2008). Environmental concentrations (range, 0.1–10 nM) of *p,p′*-DDT stimulated the proliferation of human colorectal adenocarcinoma DLD1 cells via a Wnt/β-catenin pathway mediated by oxidative stress (Song et al., 2014b).

Induction of cytotoxicity (e.g. in HepG2, HaCaT and primary hepatocytes) has been reported, albeit at ≈100 μM (Delescluse et al., 1998; Gerić et al., 2012; Jin et al., 2014).

(b) Experimental systems

(i) In vivo

In contrast to in vivo (using nude mice) and in vitro (in HepG2 cells) studies of low -doses of *p,p′*-DDT studies indicating a role of β-catenin (e.g., Jin et al., 2014; see Section 4.2.3b) in anti-apoptotic effects and stimulation of cell-cycle progression in liver, other studies in male C57BL mice have instead pointed to constitutive hepatic CAR- and ERα-mediated gene activation (e.g. Kazantseva et al., 2013; this study used a technical mixture containing 85% *p,p′*-DDT and 15% *o,p′*-DDT).

In rats, sublethal DDT concentrations can uncouple oxidative phosphorylation (Byczkowski, 1976). In combination with a carcinogen, *o,p′*-DDT elevated mammary-gland cell proliferation and chromosomal alterations in a rat cancer model (Uppala et al., 2005). It stimulated AP-1 activity via p38 MAPK (Bratton et al., 2009).

(ii) In vitro

In murine embryos, *o,p′*-DDT significantly reduced development to blastocyst and cell number while increasing apoptosis levels (Greenlee et al., 1999). Bredhult et al. (2007, 2008) showed dose (1–100 μM)-related decreases in *o,p′*-DDT-induced cell proliferation and cell viability (increasing proportions of apoptotic and necrotic cells).

DDT was slightly anti-apoptotic in transforming TGF-β-induced apoptosis in rat hepatoma FTO-2B cells as determined by reductions in DNA fragmentation and CPP32 (caspase-3)-like

caspase activity (Buchmann et al., 1999). At nanomolar concentrations, *o,p′*-DDE transiently elevated extracellular-regulated kinase (ERK) phosphorylation in rat pituitary GH_3/B6/F10 cells, which express ERα (Bulayeva & Watson, 2004). In primary rat Sertoli cells, DDT exposure (isomer not specified) decreases the level of follicle stimulating hormone (FSH) binding sites; FSH stimulates Sertoli proliferation perinatally, which conditions spermatogenesis (Bernard et al., 2007).

o,p′-DDT may inhibit the ER-mediated effects of other environmental contaminants, such as PCB-126, on proliferation in co-cultured porcine ovarian theca and granulosa cells (Gregoraszczuk et al., 2008).

4.2.5 Genetic and related effects

DDT, its isomers and its metabolites have been studied in a variety of assays for genotoxic and related potential. Table 4.1, Table 4.2, Table 4.4, and Tables 4.5 and 4.7 (available online at: http://monographs.iarc.fr/ENG/Monographs/vol113/index.php) summarize the studies carried out with DDT, including several isomeric forms in humans in vivo and in vitro, in non-human mammals in vivo, in non-human mammals in vitro, and in non-mammalian systems, respectively. Table 4.3, and Tables 4.6 and 4.8 (available online at: http://monographs.iarc.fr/ENG/Monographs/vol113/index.php) summarize the studies carried out with different metabolites of DDT in humans in vitro, in non-human mammals in vivo, in non-human mammals in vitro, and in non-mammalian systems, respectively.

(a) Exposed humans

See Table 4.1

No association was seen between DNA adducts (8-OH-dG) in primary breast adenocarcinomas and p,p′-DDT and, *p,p′*-DDE tissue levels (Charles et al., 2001).

Induction of DNA strand breaks was demonstrated by the comet assay in lymphocytes from maternal and umbilical cord blood collected from 50 mother–infant pairs exposed to different pesticides, including DDT (with a stronger response in infants than in mothers) (Alvarado-Hernandez et al., 2013); in the lymphocytes of children from different Mexican communities (Pérez-Maldonado et al., 2006; Pérez-Maldonado et al., 2011; Jasso-Pineda et al., 2015) [Causative effect of DDT alone cannot be demonstrated in the latter]; and in lymphocytes from women from Mexican communities affected by malaria and with a history of indoor DDT spraying (Yáñez et al., 2004). No association was found between DNA strand breaks assessed by the comet assay in sperm cells and *p,p′*-DDE, PCB, and hexachlorobenzene in blood samples from subfertile male donors (Hauser et al., 2003).

No association was seen between DNA strand breaks assessed by the comet assay and micronucleus formation and the blood level of *p,p′*-DDE (among other pollutants in the blood and urine) in a study of residents from areas with different types of pollution (De Coster et al., 2008). However, higher p53 protein levels in serum were associated with higher values of serum DDE, HCB and certain PCBs. Furthermore, higher levels of DDE were associated with higher levels of carcinoembryonic antigen after correction for confounding factors (De Coster et al., 2008).

A weak association was found between DNA damage in sperm chromatid and DDT/DDE plasma levels in donors from malaria-endemic areas living in houses sprayed annually with DDT (de Jager et al., 2009). No association was found between DNA damage by the sperm chromatid structure assay in fishermen with low and high consumption of fatty fish (an important source of exposure to persistent organochlorine pollutants) and serum levels of 2,2′,4,4′,5,5′-hexachlorobiphenyl and *p,p′*-DDE (Rignell-Hydbom et al., 2005).

Table 4.1 Genetic and related effects of DDT in exposed humans

Tissue	Cell type (if specified)	End-point	Test	Description of exposed and controls	Response, significance	Comments	Reference
Breast	Tumour cells (carcinoma)	DNA damage	Oxidative DNA damage	44 primary tumours (cancerous) and 21 benign breast biopsy (non-cancerous) tissues from USA residents	–		Charles et al. (2001)
Blood	Lymphocytes	DNA damage	Comet assay	Maternal and umbilical cord blood was collected from 50 mother–infant pairs living in a rural area from Mexico where agriculture is the main economic activity. Determinations of *p,p′*-DDT, *p,p′*-DDE, aldrin, heptachlor epoxide, oxichlordane, chlordane, nonachlor, mirex, endosulfan, α-, β-, and γ-HCH were performed	+	Positive response higher in infants than in mothers [Causative effect of DDT alone cannot be demonstrated]	Alvarado-Hernandez et al. (2013)
Blood	Lymphocytes	DNA damage	Comet assay	276 children from 11 communities in four states of Mexico exposed to a chemical mixture including agrochemicals, i.e. high levels of DDT, polycyclic aromatic hydrocarbons, arsenic, among others. Levels of arsenic and 1-hydroxypyrene in urine and lead and total DDT (*p,p′*-DDE and *p,p′*-DDT) in blood were quantified	+	[Causative effect of DDT alone cannot be demonstrated]	Jasso-Pineda et al. (2015)
Blood	Lymphocytes isolated	DNA damage	Comet assay	61 healthy children in 2003 and during the y 2004, 57 children from the same communities in southern Mexico were assessed. Level of *p,p′*-DDT, *p,p′*-DDD and *p,p′*-DDE was determined	+	Association between DNA damage and *p,p′*-DDT and *p,p′*-DDE levels was found, but not for *p,p′*-DDD	Pérez-Maldonado et al. (2006)
Blood	Lymphocytes isolated	DNA damage	Comet assay	73 children from 4 different Mexican communities. Level of *p,p′*-DDT, *p,p′*-DDD and *p,p′*-DDE was determined	+	Association between DNA damage and *p,p′*-DDT and *p,p′*-DDE levels was found but not for *p,p′*-DDD	Pérez-Maldonado et al. (2011)

Table 4.1 (continued)

Tissue	Cell type (if specified)	End-point	Test	Description of exposed and controls	Response, significance	Comments	Reference
Blood	Lymphocytes isolated	DNA damage	Comet assay	54 healthy women residents of the state of San Luis Potosi, Mexico. One group of women had a history of indoor DDT spraying, and another group had no history of DDT spraying. All women had a similar ethnic and socioeconomic background (low-income Mexican indigenous), and had lived in their community for at least 5 yr before the study. DDT, DDE and DDD level were determined in blood samples	+	Number of donors from each studied group not mentioned. Blood levels of DDT, DDD, and DDE were significantly correlated with DNA damage. This association remained significant after controlling for nutritional status, smoking habits and alcohol ingestion	Yáñez et al. (2004)
Sperm	Sperm cells	DNA damage	Comet assay	212 male partners of a studied subfertile couple and 142 non-study subjects fitting the same inclusion criteria as the men recruited in the study from Massachusetts (USA). PCB, HCB and *p,p′*-DDE levels were determined in blood samples from the donors	(+)	No statistically significant consistent associations between the comet assay parameters and any of the individual PCB congeners, sum of PCB, or *p,p′*-DDE [Causative effect of DDT alone cannot be demonstrated]	Hauser et al. (2003)
Blood	Blood cells	DNA damage	Comet assay	1583 residents aged 50–65 from 9 areas with different types of pollution in Flanders (Belgium). *p,p′*-DDE was found in donors together with several other pollutants compounds including cadmium, lead, HCB, PCBs and dioxins measured in blood and urine	–	No association between *p,p′*-DDE and DNA damage was found	De Coster et al. (2008)

Table 4.1 (continued)

Tissue	Cell type (if specified)	End-point	Test	Description of exposed and controls	Response, significance	Comments	Reference
Sperm	Spermatocytes	DNA damage	Sperm chromatin structure assay	311 male donors from a malaria endemic area (Limpopo Province, South Africa). The housing in these communities consists of traditional mud dwellings with thatched (grass) roofs or brick and cement houses. DDT is sprayed inside onto unpainted brick, cement and mud walls annually, but not on the painted walls. Levels of *p,p′*-DDT and *p,p′*-DDE were determined in blood donor samples	+	Weak association between DDT/DDE plasma levels and chromatin integrity of sperm	de Jager et al. (2009)
Sperm	Spermatocytes	DNA damage	Sperm chromatin structure assay	176 Swedish fishermen (with low and high consumption of fatty fish, a very important exposure source of persistent organochlorine pollutants). Serum levels of 2,2',4,4',5,5'-hexachlorobiphenyl (PCB-153) and *p,p′*-DDE were determined	–	Results indicate a trend to an association DNA fragmentation and *p,p′*-DDE levels	Rignell-Hydbom et al. (2005)
Paraffin-embedded tumour tissue	Pancreatic tumour cells	Mutation	*KRAS* mutation	103 pancreatic ductal adenocarcinoma Spanish patients in whom *KRAS* mutation was determined	+	Cases whose tumours harboured a *KRAS* mutation had higher concentrations of *p,p′*-DDT, *p,p′*- DDE and polychlorinated biphenyls. *p,p′*-DDT, *p,p′*-DDE and PCB were significantly associated with the two most prevalent *KRAS* mutations (Val and Asp) [Causative effect of DDT alone cannot be demonstrated]	Porta et al. (2009)

Table 4.1 (continued)

Tissue	Cell type (if specified)	End-point	Test	Description of exposed and controls	Response, significance	Comments	Reference
Paraffin-embedded tumour tissue	Pancreatic tumour cells	Mutation	*KRAS* mutation	51 patients with pancreatic ductal carcinoma from eastern Spain. Cases of pancreatic cancer with wildtype *KRAS* (n = 17) were frequency matched for age and sex to cases of pancreatic cancer with a *KRAS* mutation (n = 34, case–case study) with positive levels in serum of *p,p′*-DDE, *p,p′*-DDT and PCB congeners	+	Serum concentrations of *p,p′*-DDT and *p,p′*-DDE were significantly higher in pancreatic cancer cases with a *KRAS* mutation than in cases without a mutation. A specific association was observed between a glycine to valine substitution at codon 12 and both *p,p′*-DDT and *p,p′*-DDE concentrations [Causative effect of DDT alone cannot be demonstrated]	Porta et al. (1999)
Paraffin-embedded tumour tissue	Pancreatic tumour cells	Mutation	*KRAS* mutation	61 diagnosed patients identified with pancreatic cancer in the San Francisco Bay area (USA) with positive levels in serum of *p,p′*-DDE, *p,p′*-DDT and 11 PCB congeners	-		Slebos et al. (2000)
Blood	Lymphocytes	Chromosomal damage	Chromosomal aberrations	Exp 1: 50 workers from insecticide plants S. Paulo (Brazil), 25 of them directly exposed to DDT from 2 mo to 10 yr (average weekly exposure of 48 h) DDT levels were determined in plasma donor samples	+		Rabello et al. (1975)

Table 4.1 (continued)

Tissue	Cell type (if specified)	End-point	Test	Description of exposed and controls	Response, significance	Comments	Reference
Blood (cont.)				Exp 2: 8 subjects directly exposed to DDT (São Paulo, Brazil) for at least 20 days up to 2 yr (mean 2 mo; 48 h/wk) and 10 labourers with no history of occupational exposure to DDT. DDT levels were determined in plasma donor samples Exp 3: 15 workers at a pesticide plant in the city of São Paulo, S. Paulo (Brazil). Exposure (including to methylparathion and DDT) varied from 1 wk up to 7 yr, with intermittent periods of non-exposure. 13 unexposed controls			Rabello et al. (1975) (cont.)
Blood	Lymphocytes	Chromosomal damage	Chromosomal aberrations	42 male workers (Idaho) occupationally exposed to DDT, 2,4-D, malathion, ethyl parathion, endosulfan, atrazine, dicamba, among other pesticides; 16 normal healthy donors from the same age group	+	[Causative effect of DDT alone cannot be demonstrated]	Yoder et al. (1973)
Blood	Lymphocytes	Chromosomal damage	Chromosomal aberrations	25 male workers (India) occupationally exposed to DDT, BHC, malathion, parathion, dimethoate, fenitrothion, urea and gromor. 30 normal healthy males from the same age group and socioeconomic class for the control	+	[Causative effect of DDT alone cannot be demonstrated]	Rupa et al. (1988)
Blood	Lymphocytes	Chromosomal damage	Micronucleus formation	Maternal and umbilical cord blood was collected from 50 mother–infant pairs from living in a rural area from Mexico where agriculture is the main economic activity. Determinations of aldrin, heptachlor epoxide, oxichlordane, chlordane, nonachlor, mirex, endosulfan, α,α-,β-,γ-HCH, *p′p′*-DDT,and *p′p′*-DDE were performed	–	No variation between infants and mothers	Alvarado-Hernandez et al. (2013)

Table 4.1 (continued)

Tissue	Cell type (if specified)	End-point	Test	Description of exposed and controls	Response, significance	Comments	Reference
Blood	Lymphocytes	Chromosomal damage	Micronucleus formation	151 residents near a pesticide dump site, 151 controls comparison area residents from Aberdeen, North Carolina, USA; Exposure to complex pesticide mixture (DDT, aldrin, dieldrin, endosulfan, among others), organic solvents and heavy metals. Of 20 organochlorines tested in exposed residents, only DDE was detected in the blood of participants (except for one individual)	–		Vine et al. (2000)
Blood	Lymphocytes	Chromosomal damage	Sister chromatid exchanges	25 male workers (India) occupationally exposed to DDT, BHC, malathion, parathion, dimethoate, fenitrothion, urea and gromor were selected. 30 normal healthy males from the same age group and socioeconomic class for the control	+	[Causative effect of DDT alone cannot be demonstrated]	Rupa et al. (1988)
Blood	Lymphocytes	Chromosomal damage	Sister-chromatid exchanges	61 male pesticide applicators who worked in cotton fields (India) and regularly sprayed pesticides such as DDT, BHC, endosulfan, malathion, methyl parathion, phosphamidon, dimethoate, monocrotophos, quinalphos fenvelrate, and cypermethrin. Median use of pesticides 8 h/day and 9 mo/yr; 45 unexposed men were used as matched control group	+	[Causative effect of DDT alone cannot be demonstrated]	Rupa et al. (1991)
Blood	Lymphocytes	Chromosomal damage	Micronucleus formation	1583 residents aged 50–65 yrs from 9 areas with different types of pollution in Antwerp and Ghent (Belgium). *p,p′*-DDE was found in donors together with several other pollutants compounds including cadmium, lead, HCB, PCBs, and dioxins measured in blood and urine	–	No association between *p,p′*-DDE and chromosomal damage was found	De Coster et al. (2008)

+, positive; –, negative; BHC, β-hexachlorocyclohexane; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; mo, month; PCB, polychlorinated biphenyl; wk, week; yr, year

Regarding mutations, results were inconclusive for associations between *KRAS* mutation in cancer patients and serum levels of DDT or PCB congeners. A positive association was reported in patients with pancreatic ductal adenocarcinoma and higher serum levels of *p,p′*-DDT, *p,p′*-DDE, and PCBs. Specifically, an association was observed between a glycine-to-valine substitution at codon 12 of *KRAS* and concentrations of both *p,p′*-DDT and *p,p′*-DDE (Porta et al., 1999, 2009) [A causative effect of DDT alone could not be demonstrated]. The absence of *KRAS* mutation in pancreatic cancer was associated with higher serum levels of *p,p′*-DDE, but the association lacked statistical significance, and no association with absence or presence of the mutation was found for 11 PCB congeners (Slebos et al., 2000).

Chromosomal aberrations were induced in lymphocytes from insecticide-plant workers directly and continuously exposed to DDT; DDT induced mostly chromatid-type aberrations (Rabello et al., 1975). No induction was seen when workers were chronically but intermittently exposed to low doses of pesticides; thus a long-term exposure to small doses of pesticides in the workplace did not seem to increase the basal level of chromosomal damage (Rabello et al., 1975).

Induction of chromosomal aberrations in lymphocytes was reported in workers occupationally exposed to DDT, among other pesticides (Yoder et al., 1973; Rupa et al., 1988). [A causative effect of DDT alone could not be demonstrated]

No induction of micronucleus formation was seen in lymphocytes from individuals living near a pesticide dump site and exposed to a complex pesticide mixture, including DDT (Vine et al., 2000). No induction of micronucleus formation was reported in circulating lymphocytes from maternal and umbilical cord blood collected from 50 mother–infant pairs exposed to different pesticides including DDT (Alvarado-Hernandez et al., 2013).

Sister-chromatid exchanges were observed in lymphocytes from workers occupationally exposed to DDT, among other pesticides (Rupa et al., 1988, 1991).

(b) Human cells in vitro

See Table 4.2 and Table 4.3

DNA adducts were induced by *p,p′*-DDT in L-02 embryo hepatocyte cells (Shi et al., 2010). DNA strand breaks, assessed by the comet assay, were induced by *p,p′*-DDT in L-02 embryo hepatocyte cells (Shi et al., 2010), and by *p,p′*-DDT, *p,p′*-DDE and *p,p′*-DDD in lymphocytes (Yáñez et al., 2004; Gajski et al., 2007; Gerić et al., 2012). *p,p′*-DDT, *p,p′*-DDE and *p,p′*-DDD did not induce DNA strand breaks by the Fpg-modified comet methodology in lymphocytes (Gerić et al., 2012). DDT was negative in the assay for unscheduled DNA synthesis in lymphocytes (Rocchi et al., 1980), in VA-4 (Ahmed et al., 1977), or in HeLa (Brandt et al., 1972) cells. A positive result for inhibition of the metabolic cooperation was reported in ASS skin fibroblast cells exposed to DDT (Davidson et al., 1985).

Chromosomal aberrations were not induced in lymphocytes by *p,p′*-DDT (Hart et al., 1972), or by a non-specified formulation (*p,p′*-DDT, 63–77%; *o,p′*-DDT, 8–20%; *p,p′*-DDE, 3–5%; and *o,p′*-DDD, 0.2–4%) (Lessa et al., 1976).

Micronuclei were induced in L-02 embryo hepatocyte cells by *p,p′*-DDT (Shi et al., 2010), and in lymphocytes by *p,p′*-DDT, *p,p′*-DDE, and *p,p′*-DDD (Gajski et al., 2007; Garaj-Vrhovac et al., 2008; Gerić et al., 2012). Other nuclear abnormalities (nuclear buds and nucleoplasmic bridges) were induced in lymphocytes by *p,p′*-DDT (Garaj-Vrhovac et al., 2008). Micronuclei were not induced in HepG2 cells by DDT (Wu et al., 2003).

(c) Non-human mammals

See Table 4.4 (and Tables 4.5 and 4.6 online http://monographs.iarc.fr/ENG/Monographs/vol113/index.php).

Table 4.2 Genetic and related effects of DDT in human cells in vitro

Tissue, cell line	End-point	Test	Results		Dose (LED or HID)	Comments	Reference
			Without metabolic activation	With metabolic activation			
L-02 embryo hepatocyte cell line	DNA oxidative damage	DNA adducts (8-OHdG) formation	+	NT	0.001 µmol/L	*p,p′*-DDT	Shi et al. (2010)
L-02 embryo hepatocyte cell line	DNA damage	Comet assay	+	NT	0.01 µmol/L	*p,p′*-DDT	Shi et al. (2010)
Lymphocytes	DNA damage	Comet assay	+	NT	250 µg/mL	*p,p′*-DDT	Gajski et al. (2007)
Lymphocytes	DNA damage	Comet assay	+	NT	0.1 µg/mL	*p,p′*-DDT	Gerić et al. (2012)
Lymphocytes	DNA damage	Comet assay	+	NT	40 µg/mL	*p,p′*-DDT	Yáñez et al. (2004)
Lymphocytes	DNA damage	Fpg-modified comet assay	–	NT	0.1 µg/mL	*p,p′*-DDT	Gerić et al. (2012)
VA-4 cell line	DNA damage	UDS assay	–	-	1000 µM	DDT	Ahmed et al. (1977)
HeLa cell line	DNA damage	UDS assay	–	NT	18 µg/mL	DDT	Brandt et al. (1972)
Lymphocytes	DNA damage	UDS assay	–	NT	500 µg/mL	DDT	Rocchi et al. (1980)
ASS$^-$ skin fibroblast cell line	Mutation	Inhibition of metabolic cooperation assay	+	NT	5 µg/mL	DDT	Davidson et al. (1985)
Lymphocytes	Chromosomal damage	Chromosomal aberrations	–	NT	100 µg/mL	*p,p′*-DDT	Hart et al. (1972)
Lymphocytes	Chromosomal damage	Chromosomal aberrations	–	NT	40 µg/mL	Formulated product DDT (63–77% of *p,p′*-DDT; 8–20% of *o,p′*-DDT; 3–5% of *p,p′*-DDE and 0.2–4% of *o,p′*-DDD).	Lessa et al. (1976)
L-02 embryo hepatocyte cell line	Chromosomal damage	Micronucleus formation	+	NT	0.01 µmol/L	*p,p′*-DDT	Shi et al. (2010)
Lymphocytes	Chromosomal damage	Micronucleus formation	+	NT	0.1 µg/mL	*p,p′*-DDT	Gerić et al. (2012)

Table 4.2 (continued)

Tissue, cell line	End-point	Test	Results		Dose (LED or HID)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Lymphocytes	Chromosomal damage	Micronucleus formation	+	NT	250 µg/mL	*p,p′*-DDT	Gajski et al. (2007)
Lymphocytes	Chromosomal damage	Micronucleus formation/Other nuclear abnormalities	+	NT	0.025 µg/mL	*p,p′*-DDT	Garaj-Vrhovac et al. (2008)
HepG2 cell line	Chromosomal damage	Micronucleus formation	–	NT	60 µM	DDT	Wu et al. (2003)

+, positive; –, negative; DDD, dichlorodiphenyldychloroethane; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; HCB, hexachlorobenzene; HID, highest ineffective dose; LED, lowest effective dose; NT, not tested; 8-OH-dG, 8-oxo-2′-deoxyguanosine; PAHs, polycyclic aromatic hydrocarbons; PCBs, polychlorinated biphenyls; SEQ, sediment equivalent; UDS, unscheduled DNA synthesis

Table 4.3 Genetic and related effects of metabolites of DDT in human cells in vitro

Tissue, cell line	End-point	Test	Results		Dose (LED or HID)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Lymphocytes	DNA damage	Comet assay	+	NT	4.1 µg/mL	*p,p′*-DDE	Gerić et al. (2012)
Lymphocytes	DNA damage	Comet assay	+	NT	40 µg/mL	*p,p′*-DDE	Yáñez et al. (2004)
Lymphocytes	DNA damage	Comet assay	+	NT	3.9 µg/mL	*p,p′*-DDD	Gerić et al. (2012)
Lymphocytes	DNA damage	Comet assay	+	NT	40 µg/mL	*p,p′*-DDD	Yáñez et al. (2004)
Lymphocytes	DNA damage	Fpg-modified comet assay	–	NT	4.1 µg/mL	*p,p′*-DDE	Gerić et al. (2012)
Lymphocytes	DNA damage	Fpg-modified comet assay	–	NT	3.9 µg/mL	*p,p′*-DDD	Gerić et al. (2012)
Lymphocytes	Chromosomal damage	Micronucleus formation	+	NT	4.1 µg/mL	*p,p′*-DDE	Gerić et al. (2012)
Lymphocytes	Chromosomal damage	Micronucleus formation	+	NT	3.9 µg/mL	*p,p′*-DDD	Gerić et al. (2012)

+, positive; –, negative; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; HID, highest ineffective dose; LED, lowest effective dose; NT, not tested

Table 4.4 Genetic and related effects of DDT in non-human mammals in vivo

Species, strain, sex	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mammals								
Rat, Sprague-Dawley, female	Hepatic cells	DNA damage	Alkaline elution	+	40 mg/kg	p.o. × 1, sampled after 6, 12, and 24 h	DDT	Hassoun et al. (1993)
Rat, Wistar, female	Hepatic cells	DNA damage	Primary DNA-lesions	+	500 mg/kg	p.o. × 1 by gavage	DDT	Hilpert et al. (1983)
Rat, Wistar, female	Lymphocytes isolated	DNA damage	Comet assay	+	7 mg/m^3	Inh. 8 h/d, 6 d/wk for 5 mo	DDT	Canales-Aguirre et al. (2011)
Rat, Wistar, male	Epithelial mammary cells	DNA damage	Comet assay	+	7 mg/m^3	Inh. 8 h/d, 6 d/wk for 5 mo	DDT	Canales-Aguirre et al. (2011)
Rat, Wistar, male	Stomach, colon, liver, kidney, bladder, lung,	DNA damage	Comet assay	+	75 mg/kg	p.o. × 1, sampled after 3, 8 and 24 h	*p,p′*-DDT	Sekihashi et al. (2002)
Rat, Wistar, male	Brain, bone marrow	DNA damage	Comet assay	–	75 mg/kg	p.o. × 1, sampled after 3, 8 and 24 h	*p,p′*-DDT	Sekihashi et al. (2002)
Mouse, ddY, male	Stomach, colon, liver, kidney, bladder, lung, brain, bone marrow	DNA damage	Comet assay	–	75 mg/kg	p.o. × 1 killed after 3, 8, and 24 h	*p,p′*-DDT	Sekihashi et al. (2002)
Rat, albino, male	Germ cells	Mutation	Dominant lethal assay	+	50 mg/kg	p.o. 1 × /d for 5 days then mated with females immediately after the last injection. Females killed 13 days after the mid-week of mating	*p,p′*-DDT	Palmer et al. (1973)
Rat, albino, male	Germ cells	Mutation	Dominant lethal assay	–	80 mg/kg	p.o. 1 × /d for 5 days then mated with females immediately after the last injection. Females killed 13 days after the mid-week of mating	*p,p′*-DDT	Palmer et al. (1973)

Table 4.4 (continued)

Species, strain, sex	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mouse, Swiss ICR/Ha, male	Germ cells	Mutation	Dominant lethal (acute) assay	–	130 mg/kg	i.p. × 1	DDT	Epstein et al. (1972)
Mouse, NMRI, male	Germ cells	Mutation	Dominant lethal (acute) assay	–	1200 mg/kg	i.p. x 1	DDT	Buselmaier et al. (1972)
Mouse, Swiss CD-1, male	Germ cells	Mutation	Dominant lethal (acute) assay	–	105 mg/kg	i.p. x 1	DDT	Epstein & Shafner (1968)
Mouse, CF/1, aabbcc, male	Germ cells	Mutation	Spot test	–	25 mg/kg	p.o. in diet for life span over 5 generations	DDT	Wallace et al. (1976)
Mouse, Swiss albino, male	Germ cells	Mutation	Dominant lethal (acute) assay	+	150 mg/kg	p.o. 1 × /day for 2 days	Formulation (*p,p′*-DDT, 80%; *o,p′*-DDT, 18%; *p,p′*-DDE, 2%)	Clark (1974)
			Dominant lethal (chronic) assay	+	100 mg/kg	p.o. 2 × /wk for 10 wk	Formulation (*p,p′*-DDT, 80%; *o,p′*-DDT, 18%; *p,p′*-DDE, 2%)	
Rat, Sprague-Dawley, female	Mammary gland tissue sections	Chromosomal damage	Chromosomal aberrations	+	50 mg/kg	s.c. on d 21, 23, 25, 27, 29, 31, 32, and 34 postpartum, sampled on day 35	*o,p′*-DDT	Uppala et al. (2005)
Rat, Osborne-Mendel, male	Bone marrow cells	Chromosomal damage	Chromosomal aberrations	–	200 mg/kg	i.p × 1, sampled after 18, 24, and 48 h	DDT	Legator et al. (1973)
				–	200 mg/kg	i.p 1 × /d for 5 days, sampled 6 h after the last injection	DDT	
				–	100 mg/kg	p.o. × 1. sampled after 18, 24, and 48 h	DDT	
				–	100 mg/kg	p.o. 1 × /day for 5 days, sampled 6 h after the last injection	DDT	
Rat, Wistar, female	Oral mucosa cells	Chromosomal damage	Micronucleus induction	+	7 mg/m^3	Inh. 8 h/day, 6 d/wk for 5 mo	DDT	Canales-Aguirre et al. (2011)
Rat, Sprague-Dawley, female	Mammary gland tissue sections	Chromosomal damage	Micronucleus formation	–	50 mg/kg	s.c. on day 21, 23, 25, 27, 29, 31, 32 and 34 postpartum, sampled on day 35	*o,p′*-DDT	Uppala et al. (2005)

Table 4.4 (continued)

Species, strain, sex	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mouse, BALB/c, sex NR	Bone marrow cells	Chromosomal damage	Chromosomal aberrations	+	100 mg/kg	i.p. × 1	DDT	Johnson & Jalal (1973)
Mouse, BALB/c, sex NR	Bone marrow cells	Chromosomal damage	Chromosomal aberrations	+	50 mg/kg	i.p. × 1, killed 48 h after treatment	DDT	Larsen & Jalal (1974)
Mouse, sex NR	Spleen cells	Chromosomal damage	Chromosomal aberrations	+	5.5 mg/kg	i.p. × 1, killed 6, 24, and 48 h after treatment	DDT	Amer et al. (1996)
Mouse, Swiss albino, male	Spermatocytes	Chromosomal damage	Chromosomal aberrations	+	250 mg/kg	p.o. × 1 × /day for 2 d	Formulation (*p,p′*-DDT, 80%; *o,p′*-DDT, 18%; *p,p′*-DDE, 2%)	Clark (1974)
Rabbit, New Zealand White, female	Lymphocytes	Chromosomal damage	Chromosomal aberrations	–	50 mg/kg	p.o. × 1 at day 7, 8, 9, and 28 of gestation	*p,p′*-DDT	Hart et al. (1972)
Mouse, BALB/c, sex NR	Bone marrow cells	Chromosomal damage	Chromosomal stickiness	+	100 mg/kg	i.p. × 1	DDT	Johnson & Jalal (1973)
Mouse, BALB/c, sex NR	Bone marrow cells	Chromosomal damage	Chromosomal stickiness	–	250 mg/kg	i.p. × 1	DDT	Larsen & Jalal (1974)
Mouse, CD1, male	Hair follicle	Chromosomal damage	Nuclear aberration assay	+	1/4 dermal LD50	Topically × 1, 24 h before analysis	DDT	Schop et al. (1990)
Mouse, CD1, male	Bone marrow cells	Chromosomal damage	Micronucleus formation	–	1/4 dermal LD50	Topically × 1, 24 h before analysis	DDT	Schop et al. (1990)
Mouse hybrid C57BL/6 × C3H/He	Bone marrow cells	Chromosomal damage	Micronucleus formation	–	1/2 LC50	i.p 1 × /day for 5 d, killed 4 h after the last injection	DDT	Bruce & Heddle (1979)

+, positive; –, negative; ± , equivocal (variable response in several experiments within an adequate study); DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; HID, highest ineffective dose; inh., inhalation; i.p., intraperitoneal; LC, lethal concentration; LD, lethal dose; LED, lowest effective dose (units as reported); mo, month; NR, not reported; NT, not tested; NA, not applicable; p.o., oral; s.c., subcutaneous; wk, week

(i) In vivo

The comet assay for DNA strand breaks gave negative results in mouse stomach, colon, liver, kidney, lung, brain, and bone marrow cells after oral exposure to *p,p′*-DDT (Sekihashi et al., 2002). In rats, oral exposure to *p,p′*-DDT induced DNA strand breaks assessed by the comet assay in stomach, colon, liver, kidney, bladder, and lung, but not in brain and bone marrow cells (Sekihashi et al., 2002). DNA strand breaks by alkaline elution were seen in rat hepatocytes after oral exposure to DDT (Hassoun et al., 1993). Inhalation exposure to DDT induced DNA strand breaks in the comet assay in rat lymphocytes and epithelial mammary cells (Canales-Aguirre et al., 2011).

In mice, there was no mutagenic effect of DDT as seen by the dominant lethal assay after intraperitoneal exposure (Epstein & Shafner, 1968; Buselmaier et al., 1972; Epstein et al., 1972), or by the spot test after oral exposure to DDT (Wallace et al., 1976). A positve mutagenic effect was seen in the dominant lethal assay in mice following 2-day or 10-week oral exposure to a non-specified DDT formulation (*p,p′*-DDT, 80%; *o,p′*-DDT, 18%; and *p,p′*-DDE, 2%) (Clark, 1974). In rats, there are inconsistent results for mutagenic effects. Positive results were also seen for the dominant lethal assay after oral exposure to *p,p′*-DDT, but negative results were seen after intraperitoneal exposure (Palmer et al., 1973). Positive results were reported for inhibition of metabolic cooperation in hepatocytes of rats exposed orally to *p,p′*-DDT (Sugie et al., 1987).

Induction of chromosomal aberrations in mouse bone marrow and spleen cells was observed after intraperitoneal exposure to DDT (Johnson & Jalal, 1973; Larsen & Jalal, 1974; Amer et al., 1996), and in spermatocytes after oral exposure to a non-specified DDT formulation (*p,p′*-DDT, 80%; *o,p′*-DDT, 18%; and *p,p′*-DDE, 2%) (Clark, 1974). Induction of chromosomal damage by chromosomal stickiness analysis gave both positive (Johnson & Jalal, 1973) and negative (Larsen & Jalal, 1974) results in mouse bone marrow cells after intraperitoneal exposure to DDT. Chromosomal damage by the hair follicle assay was induced in mice after topical exposure to DDT (Schop et al., 1990). No induction of micronuclei was seen in mouse bone marrow cells after topical exposure to DDT (Schop et al., 1990), or in hybrid C57BL/6 × C3H/He mice after intraperitoneal treatment (Bruce & Heddle, 1979).

Inconclusive results were reported for the induction of chrosomal aberrations by DDT in the rat. Positve results were seen after subcutaneous treatment of rats with *o,p′*-DDT (Uppala et al., 2005). No induction of chromosomal aberrations was reported in rat bone marrow cells after intraperitoneal and oral exposure to DDT (Legator et al., 1973). Positive results for micronucleus formation were found in rat oral mucosa after oral exposure to DDT (Canales-Aguirre et al., 2011), but not in rat mammary gland cells after subcutaneous exposure to *o,p′*-DDT (Uppala et al., 2005). In rabbits, no induction of chromosomal aberrations in lymphocytes was seen in pregnant females treated orally with *p,p′*-DDT on days 7, 8, 9, and 28 of gestation (Hart et al., 1972).

(ii) In vitro

DNA strand breaks were induced by *p,p′*-DDE, but not DDT, in the alkaline elution assay in rat primary hepatocytes (Sina et al., 1983).

Results were negative with DDT, DDE, or *p,p′*-DDE in the assay for unscheduled DNA synthesis in primary hepatocytes of mice, rats, and Chinese hamsters (Klaunig et al., 1984; Maslansky & Williams, 1981; Probst et al., 1981; Williams et al., 1982). No induction of DNA damage was found with *p,p′*-DDT in the alkaline elution assay with and without S9 in Chinese hamster V79 cells (Swenberg et al., 1976; Swenberg, 1981).

In the cell transformation assay, DDT was positive in mouse Balb/c 3T3 fibroblasts with or without S9 (Fitzgerald et al., 1989), but *p,p′*-DDT and *p,p′*-DDE gave negative results in mouse embryo cells (Langenbach & Gingell, 1975). *p,p′*-DDE gave positive results in assays for TK (Clive et al., 1979; McGregor et al., 1988) and *Hprt* mutation (Amacher & Zelljadt, 1984) in L5178Y mouse lymphoma cells. DDT was not mutagenic in the ARL/HGPRT assay in rat liver cells (Telang et al., 1981). *p,p′*-DDT was negative in *Hprt*, 6-thioguanine (6-TO) resistance, and diphtheria toxin *(DT)* resistance assays in Chinese hamster V79 cells (Kelly-Garvert & Legator, 1973; Tsushimoto et al., 1983).

p,p′-DDE, but not *p,p′*-DDT, induced chromosomal aberrations in Chinese hamster V79 cells (Kelly-Garvert & Legator, 1973). In Chinese hamster B14 F28 cells, chromosomal aberrations were induced by *p,p′*-DDT, *p,p′*-DDE, and *p,p′*-DDA, but not by *p,p′*-DDD (Mahr & Miltenburger, 1976). In Chinese hamster ovary cells, DDE did not induce chromosomal aberrations, regardless of the presence or absence of S9 microsomal fraction, but induced a borderline increase in the frequency of sister-chromatid exchange when S9 was present (Galloway et al., 1987).

In rat kangaroo cells, chromosomal aberrations were induced after exposure to *p,p′*-DDT, *o,p′*-DDT, *p,p′*-DDE, *o,p′*-DDE, *p,p′*-DDD, and *o,p′*-DDD, but not after exposure to *p,p′*-DDA (Palmer et al., 1972). In rabbit lymphocytes, *p,p′*-DDT did not induce chromosomal aberrations (Hart et al., 1972). In whale skin fibroblasts, micronucleus formation was induced by *p,p′*-DDT when S9 was present (Gauthier et al., 1999).

(e) Non-mammalian systems

See Tables 4.7 and 4.8 (available online at http://monographs.iarc.fr/ENG/Monographs/vol113/index.php).

(i) Insects

In *Drosophila melanogaster*, positive findings were reported in *Accord* insertion assays for DDT (Catania et al., 2004), as well as in the dominant lethal assay for a non-specified DDT formulation (*p,p′*-DDT, 80%; *o,p′*-DDT, 18%; and *p,p′*-DDE, 2%) (Clark, 1974). Mutagenic effects in the sex-linked recessive lethal assay were inconsistent. A positive mutagenic effect was reported for *p,p′*-DDE (in feeding media but not when injected) (Valencia et al., 1985) and 2,2-bis(*p*-chlorophenyl) acetic acid (DDA) (Vogel, 1972). Negative results were reported in the sex-linked recessive lethal test with *p,p′*-DDT, DDE, DDD, DDOM and a non-specified DDT formulation (*p,p′*-DDT, 80%; *o,p′*-DDT, 18%; and *p,p′*-DDE, 2%) (Pielou, 1952; Vogel, 1972; Clark, 1974). The formulation was positive in the dominant lethal test and induced chromosomal aberrations (Clark, 1974). Chromosomal aberrations were not induced by an unspecified formulation (Woodruff et al., 1983) or by *p,p′*-DDE in the heritable translocation assay (Valencia et al., 1985). In other insects, chromosomal damage was induced in *Anopheles arabiensis* and *Anopheles gambie* survivors of DDT exposure (Nigatu et al., 1995; Brooke et al., 2002).

(ii) Lower eukaryotes

In *Saccharomyces cerevisiae*, results were negative in assays for mitotic gene conversion and colony formation with DDT, DDE, DDD, or DDA (Fahrig, 1974), and in the assay for mitotic chromosomal loss with *p,p′*-DDT (Albertini et al., 1988). Chromosomal damage was induced in the intrachromosomal recombination assay by *p,p′*-DDE in the absence but not in the presence of S9 (Schiestl, 1989; Schiestl et al., 1989).

In *Aspergillus nidulans*, *p,p′*-DDT was negative in assays for forward mutation and for chromosomal aberrations (Crebelli et al., 1986).

In *Neurospora crassa*, a formulation of DDT (*p,p′*-DDT, 80%; *o,p′*-DDT, 18%; *p,p′*-DDE; 2%)

gave negative (in vivo) or equivocal (in vitro) results in the host-mediated assay (Clark, 1974).

(iii) Prokaryotes

In *Salmonella typhimurium*, DDT was negative in the assay for reverse mutation, regardless of the presence or absence of S9, in strains TA92, TA98, TA100, TA1535, TA1536, TA1537, TA1538, TA1978, C3076, D3052, and G46 (Byeon et al., 1976; Marshall et al., 1976; Van Dijck & Van de Voorde, 1976; Probst et al., 1981; Glatt & Oesch, 1987). No mutagenic effects were reported with *p,p′*-DDT or DDE, regardless of the presence or absence of S9, in numerous strains (TA92, TA98, TA100, TA1535, TA1536, TA1537, TA1538, TA1950, and TA1978) (Marshall et al., 1976; Van Dijck & Van de Voorde, 1976; Moriya et al., 1983; Glatt & Oesch, 1987).

A positive result was reported in the assay for reverse mutation with the DDT metabolite l-chloro-2,2-bis(*p*-chlorophenyl)ethene (DDMU)-epoxide in strain TA100 in the absence of S9 (Gold et al., 1981). No mutagenic effect of the DDT metabolite 2,2-bis(*p*-chlorophenyl)-2-chloroacetaldehyde (αC1-DDCHO) was reported in strain TA100 (Gold et al., 1981), or with DDT metabolite 1,1-bis(*p*-chlorophenyl)-2,2-dichloroethane in strain TA98 (Glatt & Oesch, 1987). However, mutagenic activity was observed for the latter when norharman was added to the S9 (Glatt & Oesch, 1987).

In *Escherichia coli* Q-13 exposed to DDT in the presence of S9, no DNA damage was seen in the DNA-cell-binding assay (Kubinski et al., 1981). In *E. coli*, DDT was not mutagenic in the SOS chromotest assay, with or without S9, in strain PQ37 (Dayan et al., 1987). No mutagenic effects were seen with DDT, DDE, or *p,p′*-DDE, with or without S9, in strain WP2 *uvrA*, or in strain WP2 *hcr* with *p,p′*-DDT or *p,p′*-DDE (Probst et al., 1981; Moriya et al., 1983; Mamber et al., 1984; Glatt & Oesch, 1987). *p,p′*-DDT, *p,p′*-DDE, and *p,p′*-DDD were not mutagenic in the assay for reverse mutation, with or without S9, in strain Pol-A (Fluck et al., 1976). In *Bacillus subtilis*, a negative result in the Rec assay was reported with DDT (Shirasu et al., 1976).

In *Serratia marcescens*, DDD gave positive results in the assay for reverse mutation (Buselmaier et al., 1973). Negative results were reported with DDT, DDE, and DDA in the host-mediated assay (in vivo) (Buselmaier et al., 1973).

4.2.6 Inflammation

(a) Humans

No studies in exposed humans were available to the Working Group.

DDT and its metabolites induced a pro-inflammatory state, with production of pro-inflammatory cytokines and prostaglandins, in multiple types of human cells in vitro. In peripheral blood mononuclear cells isolated from healthy individuals (not exposed to DDE), a proinflammatory state was induced at a low concentration of p,p′-DDE (10 μg/mL), while apoptosis was triggered at the higher concentration of p,p′-DDE (80 μg/mL) (Alegría-Torres et al., 2009; Cárdenas-González et al., 2013). p,p′-DDE enhanced the expression of proinflammatory cytokines (TNF-α, IL-1beta, IL-6) and COX-2 induction at the protein level (Cárdenas-González et al., 2013). In a human trophoblast-derived cell line, exposure to DDE and DDD induced the expression of COX-2 protein, leading to increased production of prostaglandin E(2) (PGE2) (Dominguez-Lopez et al., 2012). In the U937 human macrophage cell line, *p,p′*-DDT upregulated mRNA expression of the pro-inflammatory genes COX-2 and VEGF (Sciullo et al., 2010). Studies by Dutta et al. (2008) showed that DDT significantly enhanced production of tumour necrosis factor-α (TNF-α) and nitric oxide (NO) in macrophages. In human MCF-7 and MDA-MB-231 breast-cancer cell lines, *o,p′*-DDT markedly increased COX-2 protein levels, COX-2 mRNA expression and promoter

activity, and production of PGE(2), activating the cyclic-AMP response element (CRE), and raising levels of cAMP and binding of cyclic-AMP response element binding protein (CREB). *o,p′*-DDT induced the activity of aromatase, and was correlated with upregulation of COX-2, and mediated via CRE activation and PKA and PI3-kinase/Akt signalling pathways in breast-cancer cells (Han et al., 2010).

(b) Experimental systems

(i) In vivo

In the intestine of CYP3A4-transgenic mice, *o,p′*-DDT (1 mg/kg) induced increases in CYP3A4 and mouse Cyp3a11 mRNA (Medina-Díaz et al., 2007). The inducibility of CYP3A4 was attenuated at higher doses of *o,p′*-DDT, accompanied by moderate increases in the mRNA of interleukin-6 (a repressor of CYP3A4 transcription) (Medina-Díaz et al., 2007). [The Working Group notes the relevance of this finding to the induction of lymphomas in the gastrointestinal tract and liver tumours.]

In rats exposed to *p,p′*-DDT (0, 5, 50, or 500 ppm) for up to 2 years, microcystic anaemia was induced in a dose-dependent manner (Tomita et al., 2013). In ovarectomized rats, *p,p′*-DDT significantly increased (by threefold) the number of blood eosinophils, and increased their degranulation (Bustos et al., 1995).

(ii) In vitro

Similar to findings in human macrophages, *o,p′*-DDT increased the production of NO and proinflammatory cytokines (IL-1beta, IL-6, TNF-α) in a dose-dependent manner in murine macrophages (Kim et al., 2004). In murine RAW 264.7 macrophages, exposure to *o,p′*-DDT caused a marked increase in the production of PGE2 (a COX-2 metabolite), and a dose-dependent increase in levels of COX-2 protein and mRNA Han et al. (2008).

In bovine epithelial cells and muscle strips of bovine oviducts, DDT and DDE significantly enhanced prostaglandin secretion at concentrations that did not affect cell viability (Wrobel et al., 2012), consistent with findings in cells from humans and other mammalian species.

4.2.7 Other mechanisms

Several studies were identified on epigenetic alterations with DDT exposure. In humans, Huen et al. (2014) reported an association between higher prenatal exposure to DDT and/or DDE and lower Alu methylation at birth, particularly after adjusting for cell type composition ($P = 0.02$ for *o,p′* -DDT) in a birth cohort of Mexican-American children in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study. In leukocyte DNA from Japanese women, the global methylation level was significantly decreased by 0.33–0.83% per quartile category for serum *o,p′*-DDT and *p,p′*-DDT, amongst other compounds (Itoh et al., 2014). Similarly, after adjusting for age and cigarette smoking, Rusiecki et al. (2008) reported statistically significant inverse linear relationships in the Alu assay with *p,p′*-DDT, *p,p′*-DDE, and the sum of all persistent organic pollutants, but no multivariate analyses were conducted and the results were not adjusted for multiple comparisons. Studies in rats also reported epigenetic effects with DDT (Shutoh et al., 2009; Skinner et al., 2013; Chanyshev et al., 2014).

Regarding immortalization, the AHS reported that the mean relative telomere length in buccal cells decreased significantly with lifetime intensity-weighted days ($P = 0.04$), but not with lifetime days of DDT use ($P = 0.08$) (Hou et al., 2013).

Regarding DNA repair, Kushida et al. (2005) reported that mRNA levels for 8-oxoguanine glycosylase 1 were inversely correlated with GST-P-positive foci in liver in studies *of N*-diethylnitrosamine initiation and DDT promotion.

4.3 Data relevant to comparisons across agents and end-points

4.3.1 General description of the database

The analysis of the in-vitro bioactivity of the agents reviewed in *IARC Monographs* Volume 113 (i.e. 2,4-D, lindane, and DDT) was informed by data from high-throughput screening assays generated by the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast™) research programmes of the government of the USA (Kavlock et al., 2012; Tice et al., 2013). At its meeting in 2014, the Advisory Group To Recommend Priorities for the *IARC Monographs* programme encouraged inclusion of analysis of high-throughput and high-content data (including from curated government databases) (Straif et al., 2014).

Lindane, DDT (*p*,*p*′-DDT, *o*,*p*′-DDT, *p*,*p*′-DDE, *p*,*p*′-DDD), and 2,4-D were among the approximately 1000 chemicals tested across the full assay battery of the Tox21 and ToxCast research programmes as of 27 April 2015. This assay battery includes 342 assays, for which data on 821 assay end-points (several assays include multiple end-point readouts) are publicly available on the website of the ToxCast research programme (EPA, 2015a). Detailed information about the chemicals tested, assays used, and associated procedures for data analysis is also publicly available (EPA, 2015b). It should be noted that the metabolic capacity of the cell-based assays is variable, and generally limited.

4.3.2 Aligning in vitro assays to 10 "key characteristics" of known human carcinogens

In order to explore the bioactivity profiles of the agents being evaluated in *IARC Monographs* Volume 113 with respect to their potential impact on mechanisms of carcinogenesis, the 821 available assay end-points in the ToxCast/Tox21 database were first mapped to the 10 key characteristics of known human carcinogens (Smith et al., 2016). Working Group members and *IARC Monographs* staff made independent assignments for each assay type to one or more "key characteristics." The assignment was based on the biological target being probed by each assay. The consensus assignments comprise 265 assay end-points that mapped to 6 of the 10 "key characteristics" as shown below. Within each key characteristic, the assays were further divided by the Working Group into subsets of similar end-points.

1. *Is electrophilic or can undergo metabolic activation (31 end-points)*: no assays directly measure electrophilicity or metabolic activation. However, assay end-points measuring CYP inhibition (29 end-points) and aromatase inhibition (2 end-points) were mapped to this characteristic.
2. *Is genotoxic (0 end-points):* no assay end-points were mapped to this characteristic.
3. *Alters DNA repair or causes genomic instability (0 end-points):* no assay end-points were mapped to this characteristic.
4. *Induces epigenetic alterations (11 end-points):* the assay end-points mapped to this characteristic measure targets associated with DNA binding (e.g. transcription factors) (4 end-points) and transformation catalysts (e.g. histone deacetylase) (7 end-points).
5. *Induces oxidative stress (18 end-points):* the assay end-points mapped to this characteristic measure oxidative stress via cell imaging (7 end-points), markers of oxidative stress (e.g. nuclear factor erythroid 2-related factor, NRF2) (6 end-points), and metalloproteinase (5 end-points).
6. *Induces chronic inflammation (45 end-points):* the assay end-points mapped to this characteristic measure cellular adhesion (14 end-points), cytokines (e.g. IL8) (29

end-points), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity (2 end-points).

7. *Is immunosuppressive (0 end-points):* no assay end-points were mapped to this characteristic.
8. *Modulates receptor-mediated effects (92 end-points):* a large and diverse collection of cell-free and cell-based assay end-points measuring nuclear and other receptor bioactivity, specifically aryl hydrocarbon receptor (AhR) (2 end-points), androgen receptor (11 end-points), ER (18 end-points), farnesoid X receptor (FXR) (7 end-points), peroxisome proliferator-activated receptor (PPAR) (12 end-points), pregnane X receptor_vitamin D receptor (PXR_VDR) (7 end-points), retinoic acid receptor (RAR) (6 end-points), and others (29 end-points), were mapped to this characteristic.
9. *Causes immortalization (0 end-points):* no assay end-points were mapped to this characteristic.
10. *Alters cell proliferation/death or nutrient supply (68 end-points):* the assay end-points mapped to this characteristic measure cytotoxicity (41 end-points), mitochondrial toxicity (7 end-points), cell cycle (16 end-points), and cell proliferation (4 end-points).

By matching assays to key characteristics, additional insights could be obtained on the bioactivity profile for each compound specifically for the purpose of evaluating their potential to interact with or affect mechanisms involved in carcinogenesis. In addition, for each chemical, the results of the in-vitro assays that represent each "key characteristic" can be compared with the results for a larger compendium of substances with similar in-vitro data, so that a particular chemical can be aligned with other chemicals with similar toxicological effects. Nonetheless, the available assays do not cover the full spectrum of targets that may be associated with these mechanisms, and metabolic capacity in many of the assays is limited, which could account for any absence of bioactivity. Conversely, the presence of bioactivity alone does not definitively imply that the agent exhibits that key characteristic, as the assay data are considered along with other information, both in vivo and in vitro.

The Working Group then extracted information from the ToxCast database concerning whether a chemical was "active" or "inactive" for each of the selected assay end-points (Sipes et al., 2013; EPA, 2015b). In the analysis by the Working Group, each "active" was given a value of 1, and each "inactive" was given a value of 0. Thus, by assigning all active compounds a value of 1, the micromolar "potency" estimates from the concentration–response data were not explicitly modelled.

Next, to integrate the data across individual assay end-points into the cumulative score for each "key characteristic," the toxicological prioritization index (ToxPi) approach (Reif et al., 2010) and associated software (Reif et al., 2013; Filer et al., 2014) were used. In the Working Group's analyses, the ToxPi score provides a visual measure of the potential for a chemical to be associated with a "key characteristic" relative to 181 chemicals that have been previously evaluated by the *IARC Monographs* and that have been screened by ToxCast. Assay end-point data were available in ToxCast for these 181 chemicals, and not for other chemicals previously evaluated by IARC. ToxPi is a dimensionless index score that integrates multiple, different, assay results and displays them visually. Within each subset of end-points ("slice"), data are translated into ToxPi slice-wise scores for all compounds as detailed below and in the publications describing the approach and the associated software package (Reif et al., 2013). Within each individual slice for a given chemical, the distance from the origin represents the relative chemical-elicited activity of the component assays (i.e. slices extending farther from the origin were associated with

"active" calls on more assays). The overall score for a chemical, visualized as a radial ToxPi profile, is the aggregation of all slice-wise scores.

The list of ToxCast/Tox21 assay end-points included in the analysis by the Working Group, description of the target and/or model system for each end-point (e.g. cell type, species, detection technology, etc.), their mapping to 6 of the 10 "key characteristics" of known human carcinogens, and the decision as to whether each chemical was "active" or "inactive" are available as supplemental material to *Monographs* Volume 113 (IARC, 2017b). The output files generated for each "key characteristic" are also provided in the supplemental material, and can be opened using ToxPi software that is freely available for download without a licence (Reif et al., 2013).

4.3.3 Specific effects across 6 of the 10 "key characteristics" based on data from high-throughput screening data in vitro

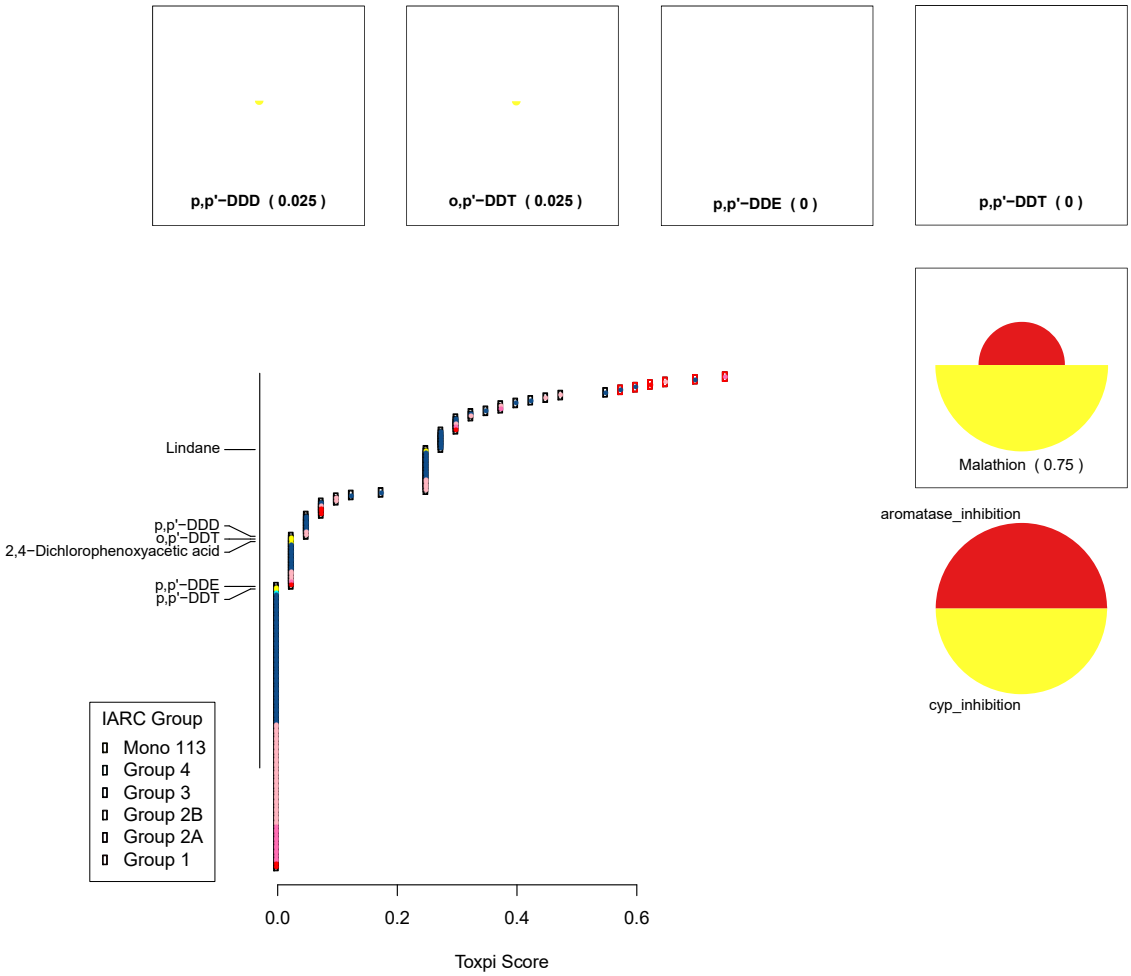
The relative effects of DDT were compared with those of 181 chemicals selected from the more than 800 chemicals previously evaluated by the *IARC Monographs* and also screened by the Tox21/ToxCast programmes, and with those of the other compounds evaluated in the present volume of the *IARC Monographs* (Volume 113) and with their metabolites. Of these 181 chemicals previously evaluated by the *IARC Monographs* and screened in the ToxCast/Tox21 programmes, 8 are classified in Group 1 (*carcinogenic to humans*), 18 are in Group 2A (*probably carcinogenic to humans*), 59 are in Group 2B (*possibly carcinogenic to humans)*, 95 are in Group 3 (*not classifiable as to its carcinogenicity to humans*), and 1 is in Group 4 (*probably not carcinogenic to humans).* The results are presented in a dot plot as a rank order of all compounds in the analysis arranged in the order of their relative activity*).* The results are presented in a dot plot as a rank order of all compounds in the analysis arranged in the order of their relative activity. The relative positions of lindane, DDT (*p,p′*-DDT, *o,p′*-DDT, *p,p′*-DDE, *p,p′*-DDD), and 2,4-D in the ranked list are also shown on the *y*-axis. The colour scheme legend (lower left in each plot) annotates each compound according to its previous *IARC Monographs* group classification. The legend key (lower right graphic in each plot) lists components of the ToxPi chart as subcategories that comprise assay end-points in each characteristic, as well as their respective colour-coding (see Section 4.3.2; IARC, 2017b). The ToxPi profile and numeric score are shown for the highest-ranked chemical in each analysis (directly above the legend key) to represent the maximum ToxPi score and and for DDT (upper frames).

Characteristic (1) *Is electrophilic or can undergo metabolic activation*: *p,p′*-DDT was not active for any of the assay end-points tested. *o,p′*-DDT was active for 1 of the assay end-points tested. *p,p′*-DDE was not active for any of the assay end-points tested. *p,p′*-DDD was active for 1 of the assay end-points tested. In comparison, the highest-ranked chemical, malathion (IARC Group 2A; IARC, 2017a), was active for 20 out of 29 assay end-points related to CYP inhibition and in 1 out of 2 related to aromatase inhibition (Fig. 4.3).

Characteristic (4) *Induces epigenetic alterations: p,p′*-DDT was active for two of the assay end-points tested. *o,p′*-DDT was active for 2 of the assay end-points tested. *p,p′*-DDE was active for 2 of the assay end-points tested. *p,p′*-DDD was active for 4 of the assay end-points tested. In comparison, the highest-ranked chemical, captan (IARC Group 3; IARC, 1983) was active for 0 out of 4 DNA binding assay end-points and 5 out of 7 transformation catalyst (e.g. histone modification) assay end-points (Fig. 4.4).

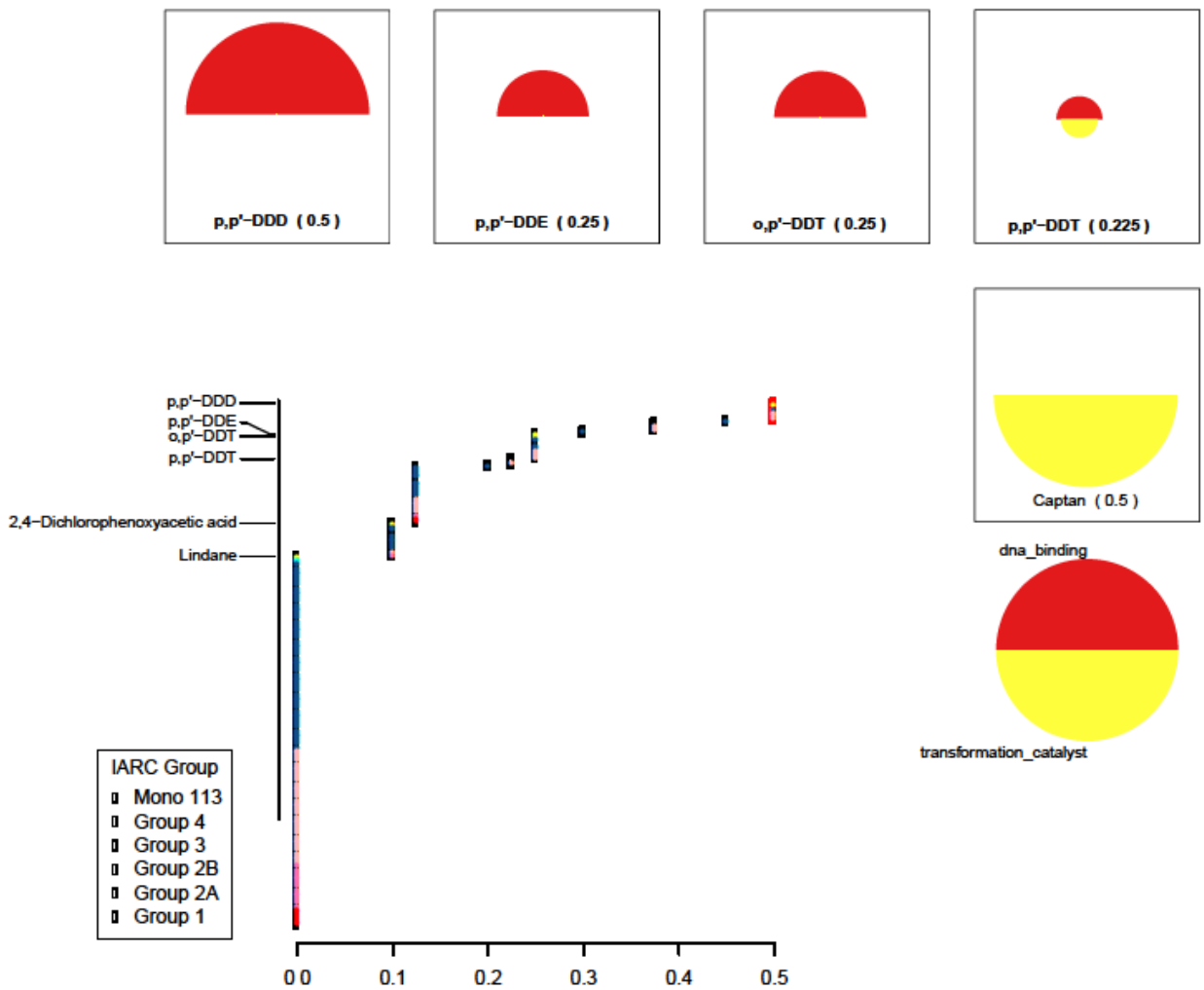
Characteristic (5) *Induces oxidative stress*: *p,p′*-DDT was active for 9 of the assay end-points tested. *o,p′*-DDT was active for 4 of the assay end-points tested. *p,p′*-DDE was active for 5 of the assay end-points tested. *p,p′*-DDD was active

Fig. 4.3 ToxPi ranking for DDT and its metabolites using ToxCast assay end-points mapped to metabolic activation



On the left-hand side, the relative rank of DDT, and its metabolites, is shown (*y*-axis) with respect to their ToxPi score (*x*-axis) as compared with the other chemicals evaluated in the present volume (IARC Monograph 113) and the 181chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the top-ranked chemical (in this case, DDT) and the target chemical(s) (DDT and its metabolites) are shown with their respective ToxPi score in parentheses.

Fig. 4.4 ToxPi ranking for DDT and its metabolites using ToxCast assay end-points mapped to epigenetic alterations



On the left-hand side, the relative rank of DDT, and its metabolites, is shown (*y*-axis) with respect to their ToxPi score (*x*-axis) as compared with the other chemicals evaluated in the present volume (IARC Monograph 113) and the 181 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the top-ranked chemical (in this case, captan) and the target chemical(s) (DDT and its metabolites) are shown with their respective ToxPi score in parentheses.

for 8 of the assay end-points tested. In comparison, the highest-ranked chemical, carbaryl (IARC Group 3; IARC, 1983) was active for 2 out of 5 metalloproteinase assay end-points, 3 out of 7 oxidative stress assay end-points, and 3 out of 6 oxidative-stress marker assay end-points (Fig. 4.5).

Characteristic (6) *Induces chronic inflammation*: *p,p′*-DDT was active for 1 of the assay end-points tested. *o,p′*-DDT was not active in any of the assay end-points tested. *p,p′*-DDE was not active in any of the assay end-points tested. *p,p′*-DDD was active for 1 of the assay end-points tested. In comparison, the highest-ranked chemical, 4,4′-methylenedianiline (IARC Group 2B; IARC, 1986) was active for 2 out of 14 cellular adhesion assay end-points, and 2 out of 29 cytokine assay end-points (Fig. 4.6).

Characteristic (8) *Modulates receptor-mediated effects: p,p′*-DDT was active for 21 of the assay end-points tested. *o,p′*-DDT was active for 19 of the assay end-points tested. *p,p′*-DDE was active for 17 of the assay end-points tested. *p,p′*-DDD was active for 15 of the assay end-points tested. In comparison, the highest-ranked chemical, clomiphene citrate (IARC Group 3; IARC, 1979) was active for 5 out of 11 AR assay end-points, 13 out of 18 ER assay end-points, 3 out of 7 FXR assay end-points, 6 out of 29 other nuclear-receptor assay end-points, 2 out of 12 PPAR assay end-points, 5 out of 7 PXR_VDR assay end-points, and 1 out of 6 RAR assay end-points (Fig. 4.7).

Characteristic (10) *Alters cell proliferation, cell death, or nutrient supply:p,p′*-DDT was active for 29 of the assay end-points tested. *o,p′*-DDT was active for 24 of the assay end-points tested. *p,p′*-DDE was active for 18 of the assay end-points tested. *p,p′*-DDD was active for 27 of the assay end-points tested. In comparison, the highest-ranked chemical, ziram (IARC Group 3; Monograph volume 53) was active in 2 out of 16 cell-cycle assay end-points, 33 out of 41 cytotoxicity end-points, and 2 out of 7 mitochondrial-toxicity assay end-points (Fig. 4.8).

4.3.4 Summary of all effects across the "key characteristics" based on data from high-throughput screening in vitro

As a high-level summary of activity, data were recombined into six ToxPi slices, where each slice represents activity across all component assays mapped to a given characteristic. In the figure (Fig. 4.9), slices are labelled "metabolism" (*Is electrophilic or can undergo metabolic activation*), "epigenetic" (*Induces epigenetic alterations*), "stress" (*Induces oxidative stress*), "inflammation" (*Induces chronic inflammation*), "receptor" (*Modulates receptor-mediated effects*), and "cellular" (*Alters cell proliferation, cell death, or nutrient supply*). Overall, *p,p′*-DDT was active for 62 of the assay end-points tested. *o,p′*-DDT was active for 50 of the assay end-points tested. *p,p′*-DDE was active for 42 of the assay end-points tested. *p,p′*-DDD was active for 56 of the assay end-points tested. In comparison, the highest-ranked chemical, clomiphene citrate (IARC Group 3; IARC, 1979) was active for 97 assay end-points.

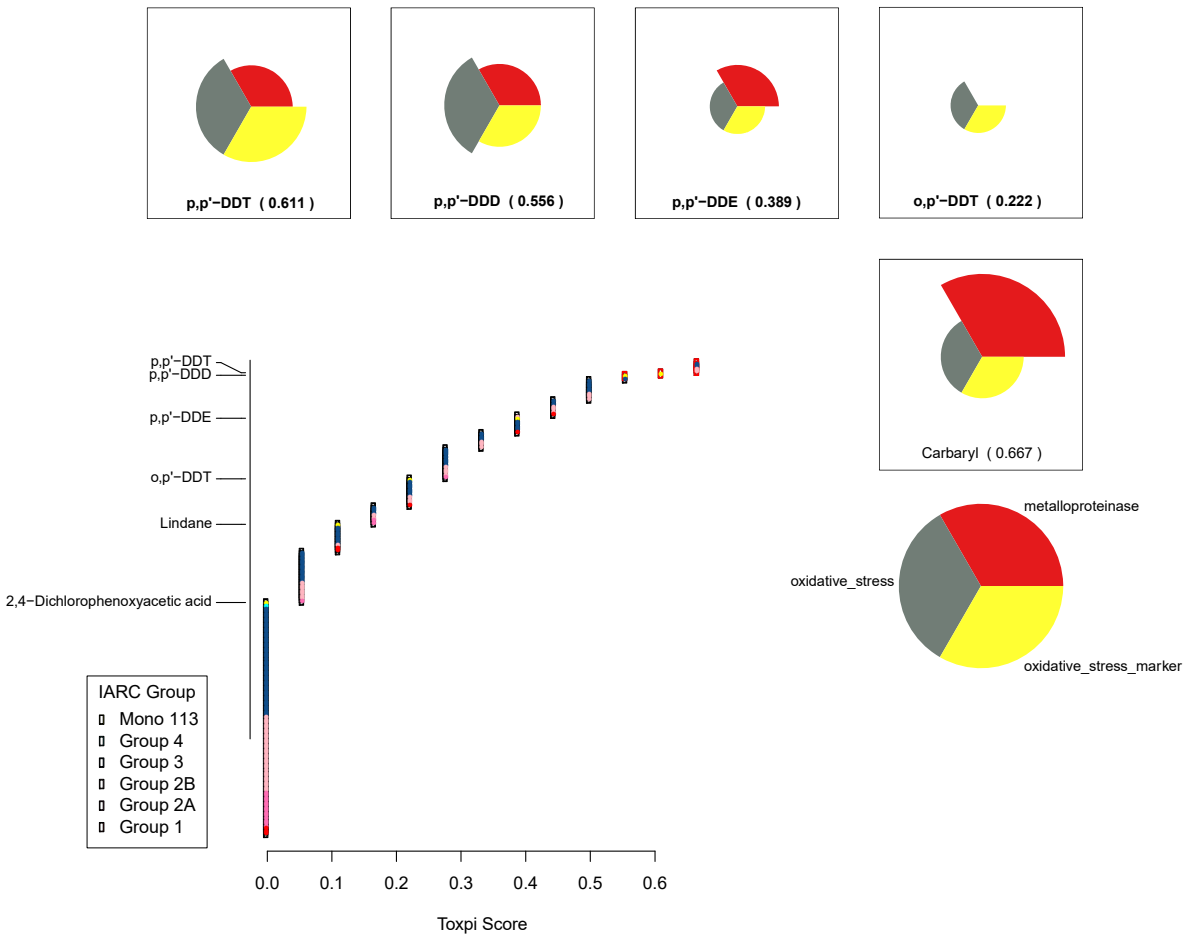
4.4 Cancer susceptibility data

4.4.1 Inter-individual variability

(a) Genetic susceptibility

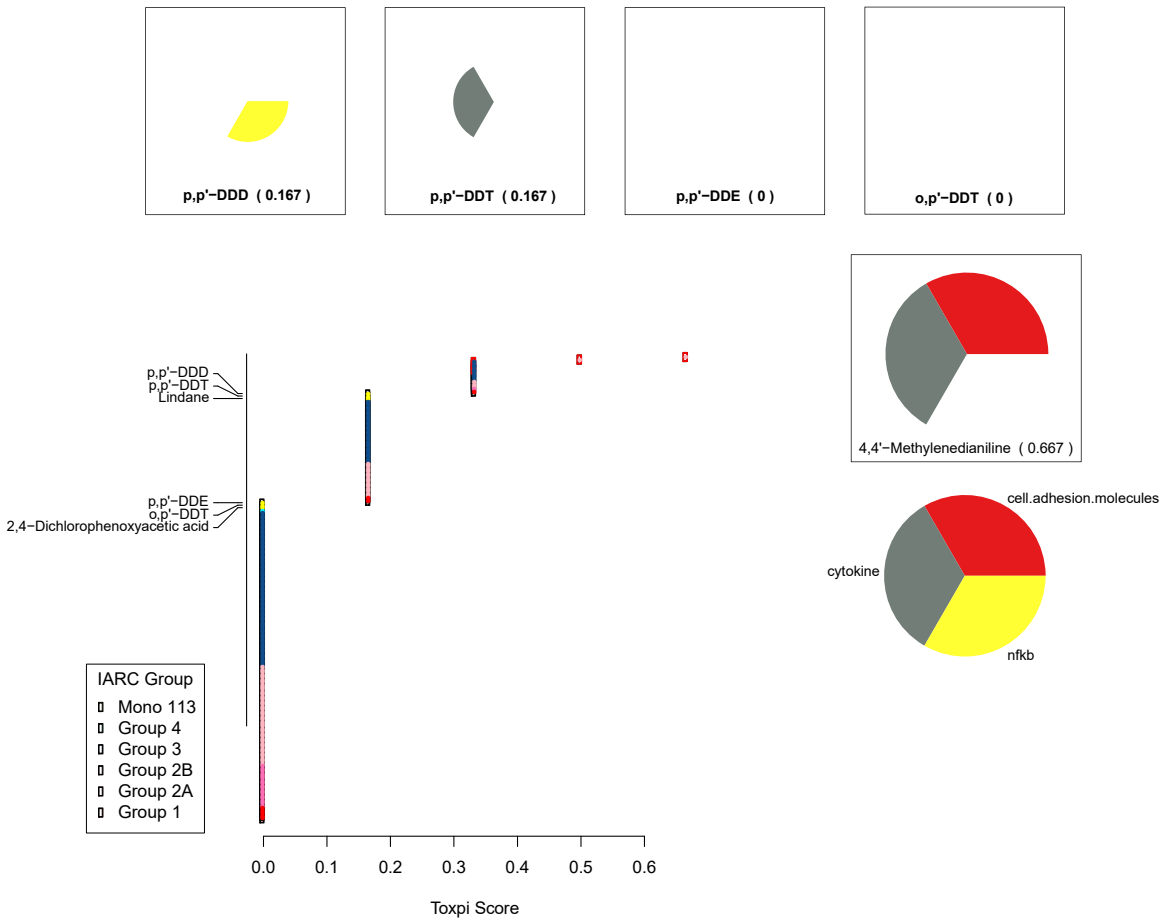
The Working Group identified a single study in humans on genetic susceptibility to cancer associated with exposure to DDT or its metabolites. Excessive nucleotide repeats in the AR did not modify the association between *p,p′*-DDE and testicular germ cell carcinoma in a case–control study in a population of men in the USA (Biggs et al., 2008).

Fig. 4.5 ToxPi ranking for DDT and its metabolites using ToxCast assay end-points mapped to oxidative stress markers



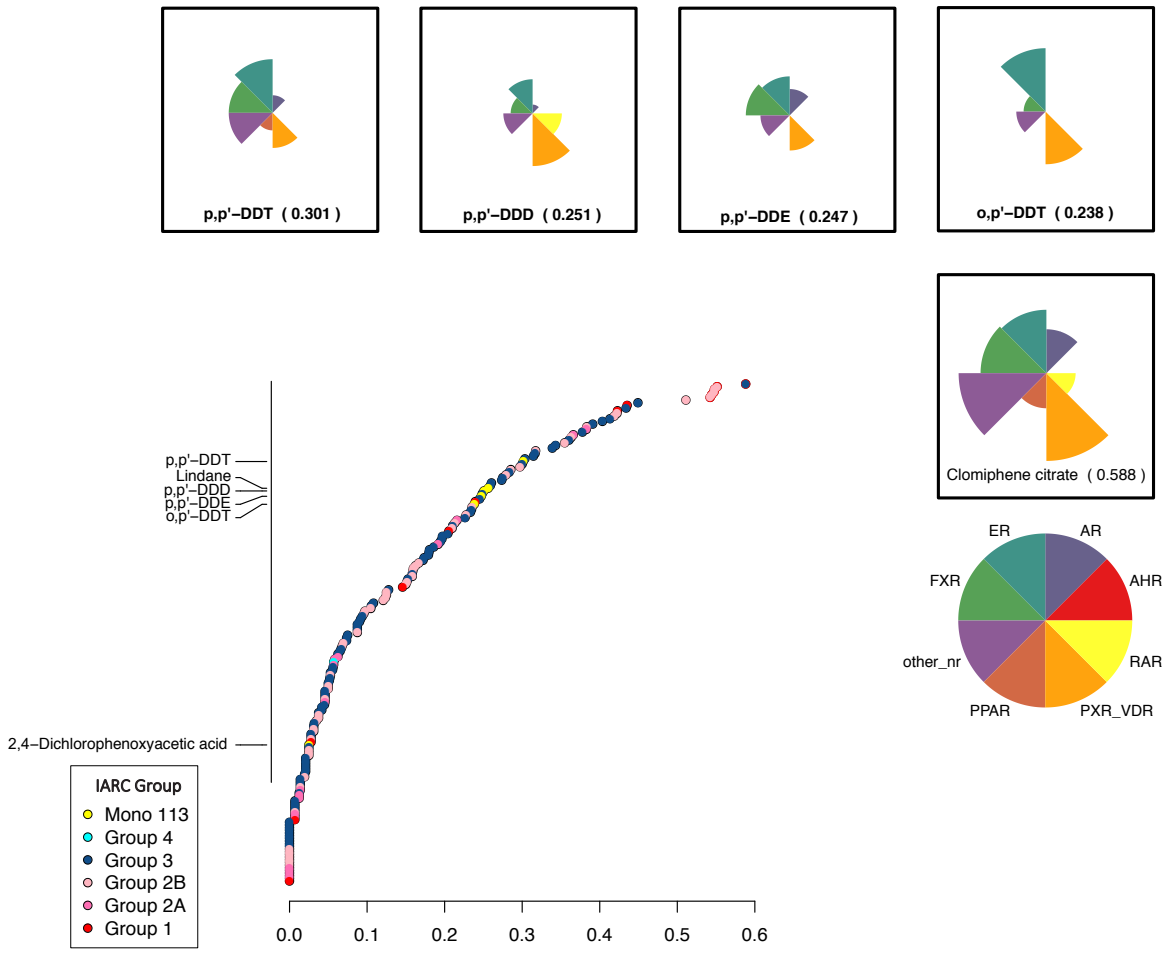
On the left-hand side, the relative rank of DDT, and its metabolites, is shown (*y*-axis) with respect to their ToxPi score (*x*-axis) as compared with the other chemicals evaluated in the present volume (IARC Monograph 113) and the 181 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the top-ranked chemical (in this case, carbaryl) and the target chemical(s) (DDT and its metabolites) are shown with their respective ToxPi score in parentheses.

Fig. 4.6 ToxPi ranking for DDT and its metabolites using ToxCast assay end-points mapped to chronic inflammation



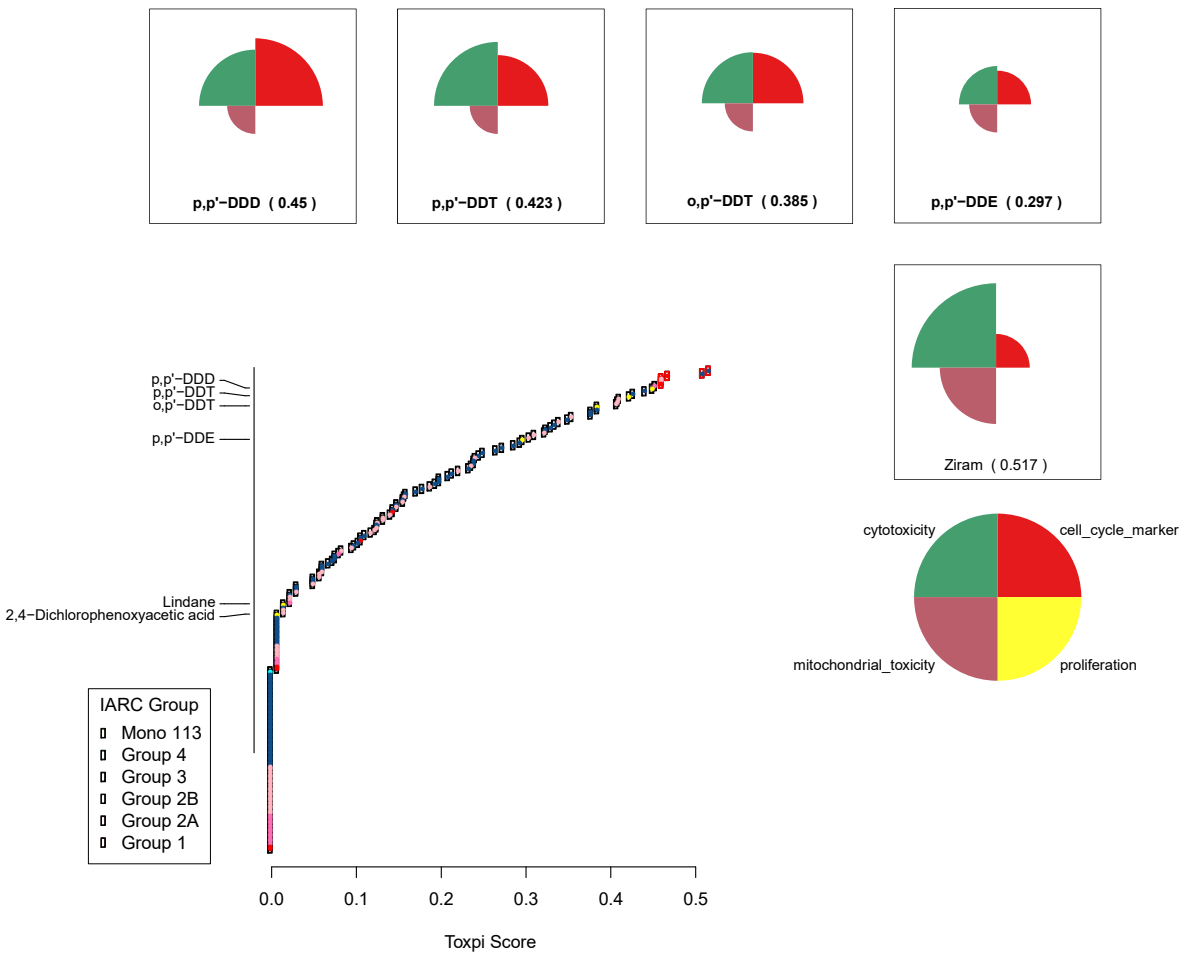
On the left-hand side, the relative rank of DDT, and its metabolites, is shown (*y*-axis) with respect to their ToxPi score (*x*-axis) as compared with the other chemicals evaluated in the present volume (IARC Monograph 113) and the 181 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the top-ranked chemical (in this case, 4,4'-methylenedianiline) and the target chemical(s) (DDT and its metabolites) are shown with their respective ToxPi score in parentheses.

Fig. 4.7 ToxPi ranking for DDT and its metabolites using ToxCast assay end-points mapped to modulation of receptor-mediated effects



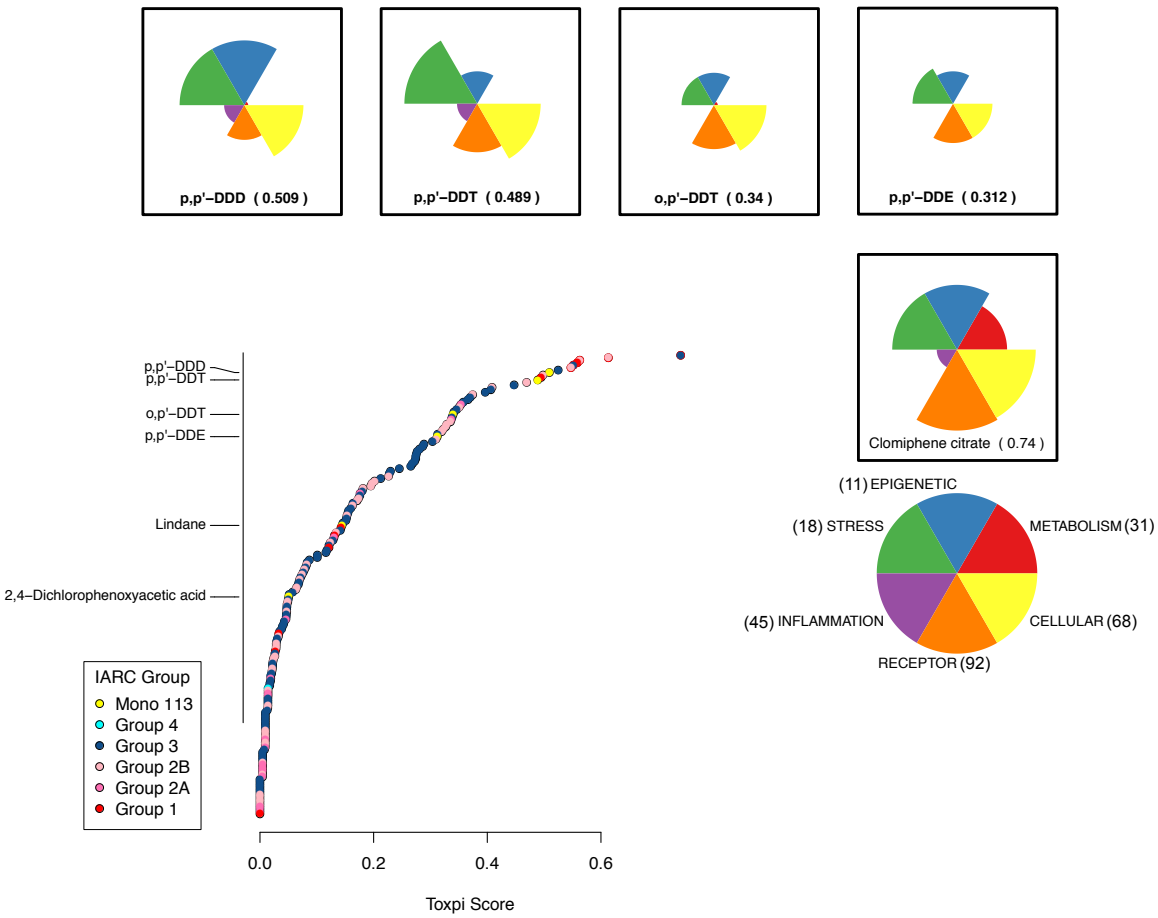
On the left-hand side, the relative rank of DDT, and its metabolites, is shown (*y*-axis) with respect to their ToxPi score (*x*-axis) as compared with the other chemicals evaluated in the present volume (IARC Monograph 113) and the 181 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the top-ranked chemical (in this case, clomiphene citrate) and the target chemical(s) (DDT and its metabolites) are shown with their respective ToxPi score in parentheses.

Fig. 4.8 ToxPi ranking for DDT and its metabolites using ToxCast assay end-points mapped to cytotoxicity and proliferation



On the left-hand side, the relative rank of DDT, and its metabolites, is shown (*y*-axis) with respect to their ToxPi score (*x*-axis) as compared with the other chemicals evaluated in the present volume (IARC Monograph 113) and the 181 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the top-ranked chemical (in this case, ziram) and the target chemical(s) (DDT and its metabolites) are shown with their respective ToxPi score in parentheses.

Fig. 4.9 ToxPi ranking for DDT and its metabolites using ToxCast assay end-points: summary of key characteristics



On the left-hand side, the relative rank of DDT, and its metabolites, is shown (*y*-axis) with respect to their ToxPi score (*x*-axis) as compared with the other chemicals evaluated in the present volume (IARC Monograph 113) and the 181 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the top-ranked chemical (in this case, clomiphene citrate) and the target chemical(s) (DDT and its metabolites) are shown with their respective ToxPi score in parentheses.

(b) Immune susceptibility

A case–control study in China, in which serum levels of both *p,p′*-DDT and *p,p′*-DDE were higher in cases of HCC than in controls demonstrated that both hepatitis B virus surface antigen and aflatoxin B1 interacted with *p,p′*-DDT ($P < 0.05$ for interaction) in association with greater odds of HCC (Zhao et al., 2012).

(c) Hormone receptor status

In a study by Cohn et al. (2007), most cases of breast cancer were ER- and PR-positive and HER2-negative. Maternal serum level of *o,p′*-DDT was positively associated with advanced stage and HER2 positivity of the breast cancers, which was independent of *p,p′*-DDE and not affected by maternal overweight and breast cancer history. Although only 22 advanced-stage tumours and 16 HER2-positive cancers were available for analyses, the results were statistically significant; for a doubling of *o,p′*-DDT at a diagnosis of advanced stage, the odds ratio was 2.2 (95% CI, 1.1–4.2; $P = 0.02$) and 2.1 (95% CI, 1.0–4.8; $P = 0.05$ at a diagnosis of HER2-positivity). *o,p′*-DDT levels for women in the fourth quartile of the study were triple those of women in the first quartile, and risk of cancer of the breast in these women was quadrupled (for advanced stage disease: OR, 4.6; 95% CI, 1.3–16.5 for 4th quartile compared with the 1st quartile; for HER2-positive cancers: OR, 4.6; 95% CI,1.1–19.7). [These observations suggested a strong effect on breast cancer stage and HER2 status at diagnosis of *o,p′*-DDT exposure in utero in these women.]

The possibility that PR+, HER2+, and triple-negative status modifies the association between DDT or DDE exposures and cancer was indirectly suggested by a case–control study on breast cancer in Canadia, which found a significant trend for the odds ratios associated with *p,p′*-DDE and ER negative breast cancer status, but no association with ER-positive breast cancer status (Woolcott et al., 2001).

Three case–control studies on *p,p′*-DDT and *p,p′*-DDE in the USA did not find an association between these exposures and breast cancer, irrespective of joint ER+ and PR+ status (Wolff et al., 2000a, b; Zheng et al., 2000).

4.4.2 Life-stage susceptibility

(a) Perinatal exposure

(i) Humans

While few in number, all of the studies of cancer in humans on perinatal exposure to DDT have reported positive results. A prospective nested case–control study of women in California, USA, found a positive trend between serum *p,p′*-DDT level and future risk of breast cancer (Cohn et al., 2007). A significant interaction was reported between *p,p′*-DDT and age in 1945, whereby the greatest increased risk of breast cancer was observed among women who had serum *p,p′*-DDT in the highest tertile and were younger than 4 years in 1945 (Cohn et al., 2007).

Maternal exposure to *o,p′*-DDT assessed in the perinatal period was also associated with increased risk of breast cancer among adult daughters (Cohn et al., 2015; see Section 2 for further study details).

In a multi-decade prospective study examining the association between prenatal exposure to DDT compounds detected in maternal sera in the USA, male offspring had an increased risk of testicular cancer associated with higher DDT/DDE ratio and lower *o,p′*-DDT and *p,p′*-DDE levels in their mothers' sera (Cohn et al., 2010). [The Working Group noted that this pattern of associations was consistent with a slower rate of *p,p′*-DDT metabolism in association with elevated testicular cancer risk in offspring.] However, in a case–control study in Sweden, *p,p′*-DDE level measured in maternal sera was not associated with testicular cancer status (Hardell et al., 2006b).

(ii) Experimental systems

Carcinogenesis was enhanced when DDT exposures occured before tissues were fully developed (such as cross-generational, prenatal, preweaning and prepuberty). Mice with prepubertal exposure to *p,p′*-DDE had an early onset of HER2-positive tumours (Johnson et al., 2012). In a study in which mice were exposed to technical DDT (*p,p′*-DDT, 73–78%; *o,p′*-DDT, 20%; *m,p′*-DDT, 1%; *p,p′*-DDE, 0.5% ; and *p,p′*-DDD, 0.5–1.5%) and followed to the F_3 generation (Tomatis et al., 1972), there was an increase in tumour number (see Section 4.3) that was potentiated as generations increased up to F_3 (Terracini et al., 1973b). There was also an apparent increase in body mass in F_0 females and F_1 males and females [no additional follow-up reported] (Tomatis et al., 1972). Body mass and abdominal fat was increased in F_3 rats for which F_0 females had been exposed to *p,p′*-DDT while pregnant (Skinner et al., 2013).

(b) Menopause

Data regarding an association between DDE and cancer of the breast among postmenopausal women are inconsistent. In studies demonstrating a positive association with DDE and breast cancer and that also looked for DDE interaction with menopausal status, DDE was associated with heightened risk in postmenopausal women. The positive association between serum *p,p′*-DDE level and breast cancer was heightened among postmenopausal women compared with pre- or perimenopausal women in hospital-based studies in Belgium and Mexico (Romieu et al., 2000; Charlier et al., 2004).

In case–control studies of women in Spain, Poland, and the USA, in whom *p,p′*-DDE level had no association with cancer of the breast, menopausal status did not modify the null association (Zheng et al., 2000; Ibarluzea et al., 2004; Ociepa-Zawal et al., 2010). Similarly, in a 10-year prospective follow-up of women in Japan, in whom *p,p′*-DDE level had no association with breast cancer, menopausal status did not modify the null association (Iwasaki et al., 2008).

4.5 Other adverse effects

4.5.1 Humans

Prospective studies in Spain and the USA have indicated that exposure to DDE in utero and in the early postnatal period is associated with increased risk of overweight/obesity in toddlers and adult offspring (Karmaus et al., 2009; Warner et al., 2014). A more extensive literature also demonstrates positive associations between *p,p′*-DDE and *p,p′*-DDT exposure with diabetes in humans (reviewed in Taylor et al., 2013). [DDT and metabolites are associated with type 2 diabetes and obesity in humans.] *p,p′*-DDT and *p,p′*-DDE showed a strong association with type 2 diabetes after adjusting for age, sex, BMI, alcohol consumption, and cigarette smoking (Son et al., 2010).

Studies of maternal DDT exposure and adverse birth outcomes (e.g. pre-term birth, small for gestational age, spontaneous abortion, birth weight) have reported mixed results. One large study found a statistically significant trend for pre-term birth and small-for-gestational-age babies (Longnecker et al., 2001). Another smaller study found statistically significant correlations between lower birth weight and DDE in placenta or DDT in breast milk (Dewan et al., 2013). Other, mostly smaller, studies found weak or non-statistically significant changes in outcomes such as preterm birth, small-for-gestational-age birth, birth weight, or gestational age (Gladen et al., 2003; Farhang et al., 2005; Jusko et al., 2006; Khanjani & Sim, 2006; Sagiv et al., 2007; Vafeiadi et al., 2014). One study suggested that DDT and its metabolite DDE have opposite associations with birth weight (Kezios et al., 2013).

A few studies have examined other developmental or reproductive outcomes. A study

by Korrick et al. (2001) reported an association between spontaneous abortion and maternal serum DDE levels.

Venners et al. (2005) showed a positive associations between the risk of subsequent early pregnancy loss and the preconception serum total DDT in 388 newly married, female textile workers in China between 1996 and 1998 (Venners et al., 2005). One study reported the rate of birth defects to be associated with occupational exposure to DDT (Salazar-García et al., 2004).

4.5.2 Experimental systems

Reproductive and developmental toxicity of DDT in experimental systems has been reviewed by ATSDR (2002) and Smith (2010). Decreased foetal body weights were reported in rabbits given DDT during gestation (Hart et al., 1971; Fabro et al., 1984). Male reproductive effects have been reported in several studies in rats (Kelce et al., 1995; You et al., 1998; Ben Rhouma et al., 2001). A two-generation study of reproductive toxicity in rats found no reproductive or developmental effects except for decreased pup viability at one time-point at the highest dose and, at the two higher doses, altered hormone levels and delayed male sexual maturation (Hojo et al., 2006). In a study of mouse preimplantation embryos exposed in vitro to DDT, some alterations in development in vitro were observed, but upon transfer to recipient mice, no measureable effects on implantation rates, transfer efficiencies, or multiple other pup characteristics were reported (Greenlee et al., 2005).

5. Summary of Data Reported

5.1 Exposure data

From the discovery of its insecticidal properties in 1939 until its production and use began to be phased out in the early 1970s, 1,1′-(2,2,2-trichloro-ethylidene)bis(4-chlorobenzene) – DDT – was used extensively for insect control in public health and agriculture worldwide. It has been estimated that a total of 1.8 million tonnes of DDT have been produced globally since the 1940s. Apart from its use as a pesticide, DDT is also reported to be used in some countries as an intermediate in the production of the pesticide dicofol and of antifouling paint. While its use in agriculture has been largely prohibited, DDT was, and still is is in some countries, used to control vectors for malaria and a few other diseases of public health importance (e.g. leishmaniasis).

Currently, DDT is manufactured in one country, and its use is officially limited to vector control in several countries in Africa and Asia.. Accordingly, occupational exposure to DDT can still occur among workers in manufacturing and sprayers in vector-control programs, but the number of people affected is small.The population at large is still exposed to DDT, despite the fact that it is no longer used in many countries because of earlier widespread application and the environmental and biological persistence of the compound and its metabolites, DDT and its metabolites have been detected in air, rain, soil, glaciers, water, animal and plant tissues, food, and the work environment. In most countries, exposure of the general population in most countries occurs mainly through the diet. Blood DDT and DDE levels in the general population have dropped at least two to three orders of magnitude over time in most parts of the world, but to a lesser degree where DDT continues to be used.

5.2 Human carcinogenicity data

The risk of cancer associated with exposure to DDT has been evaluated in numerous cohort and case–control studies in several countries. The largest quantity of data is available for cancer of the breast and lymphoma. Cancers of the liver, testis, prostate, endometrium, pancreas, lung, and colon have also been studied. Exposure has been assessed in these studies by biological measurement of markers of exposure to DDT, mostly *p,p*-DDE and *p,p′*-DDT, as well as with questionnaires, sometimes in combination with expert assessment. An important consideration in studies using biological markers is whether the samples were obtained before or after disease onset, when disease progression or treatment may affect the concentration of the marker.

5.2.1 Cancer of the liver

The association of liver cancer with DDT exposure was assessed in three large studies in Linxian, Haimen, and Xiamen, China. Nested case–control studies in Linxian and Haimen reported a strong association with a significant trend between hepatocellular carcinoma and concentrations of *p,p′*-DDT, but not *p,p′*-DDE, in blood samples collected before diagnosis. These studies are consistently positive for *p,p′*-DDT, and inconsistent for *p,p*-DDE; the observed associations for DDT are strong, with dose–response relationships, and the odds ratios were adjusted for important risk factors for hepatocellular carcinoma, including markers for hepatitis (HBV sAg). The population-based case–control study in Xiamen, which had higher exposure to DDT than the study in Linxian, also reported a strong association with *p,p′*-DDT concentration, with a significant dose–response trend in blood samples taken after diagnosis, as well as a weaker association with *p,p′*-DDE. Risk estimates were adjusted for hepatitis and aflatoxin exposure. However, it was unclear how the controls in the Xiamen study were selected. In contrast, no increased risk of cancer of the liver was observed in a cohort of men occupationally exposed to DDT during an antimalarial spraying campaign in Sardinia, Italy.

5.2.2 Cancer of the testis

Six studies have assessed the association between DDT or DDE measurements in blood samples and cancer of the testis. A statistically significant positive association between *p,p′*-DDE and testicular cancer was seen in a large nested case–control study using blood samples taken before diagnosis among United States servicemen. Positive but non -significant associations were found in a smaller nested case–control study in Norway using blood samples taken before diagnosis. These two studies provide the strongest evidence for an association between exposure to DDT and testicular cancer. Positive non-significant associations were found in two small case–control small studies using post-diagnostic blood samples, while no association was detected in a large population-based case–control study using post-diagnostic blood samples. Results were inconsistent in two small studies (one also evaluating levels among cases, mentioned above) that examined DDT and/or DDE levels in mothers of the cases of testicular cancer.

5.2.3 Cancer of the breast

More than 40 epidemiological studies conducted in North America, Latin America, Asia, and Europe since 1993 have assessed the relationship between exposure to DDT and risk of cancer of the breast . Almost all studies used *p,p′*-DDE measurements in blood or adipose tissue as an exposure indicator, and some reported results for *p,p′*-DDT. Biological measurements of exposure were made at diagnosis or several years before. No association overall was found

between *p,p′*-DDE or *p,p′*-DDT levels and breast cancer. Stratification by hormone-receptor status of the breast tumour, or menopausal status, did not modify the results. Several meta-analyses on *p,p′*-DDE exposure was that the available studies supported the view that DDE is not associated with an increased risk of breast cancer in humans. However, the potential influence of age at exposure to DDT in relation to risk of breast cancer remains of interest, as suggested by two studies that reported an increased risk of breast cancer in women highly exposed to DDT early in life.

5.2.4 Non-Hodgkin lymphoma

More than 30 studies have evaluated risk of lympho-haematopoietic malignancies in relation to DDT exposure using biomarkers or questionnaires, in a few instances supported by expert assessment of agricultural exposures. The large Agricultural Health Study in the USA observed significant upward trends in risk of non-Hodgkin lymphoma in relation to several indicators of DDT use while controlling for other suspected risk factors. However, a retrospective cohort mortality study of applicators involved in an antimalarial campaign in Sardinia, Italy, with almost exclusive use of DDT, did not identify any association between DDT exposure and lymphoma. Evidence from case–control studies based on self-reported or expert assessments from questionnaire was inconsistent, with no association in several large studies and positive associations in some smaller studies. Evidence was also inconsistent in studies using measurements in biological specimens as biomarkers of exposure to DDT. In studies that adjusted for exposure to other pesticides or persistent organochorines, the associations with DDT were typically weakened. Conflicting results on the association of DDT with the overall group of lymphomas might be related to heterogeneity of association by subtype, but studies of leukaemia and lymphoma subtypes were based on relatively small numbers.

5.2.5 Cancer of the prostate

Several studies have examined the association between exposure to DDT and cancer of the prostate. Positive associations with DDT were found in two population-based case–control studies, in which exposure was assessed by experts or by a job–exposure matrix from the job history. In the United States Agricultural Health Study, there was no clear relationship between lifetime cumulative exposure to DDT and the incidence of total or aggressive cancer of the prostate. The largest study using *p,p′*-DDE measurements, conducted in the French Caribbean, reported a modest but statistically-significant increased risk of prostate cancer associated with *p,*p′-DDE serum concentration measured in blood sampled after diagnosis. Conversely, no significant association with *p,p′*-DDE was observed in four other studies that used serum measurements of *p,p′*-DDE, including a large nested case–control study in Japan.

5.2.6 Other cancer sites

Exposure to DDT or DDE and risk of cancer has also been examined at other cancer sites, including the pancreas, endometrium, colon, and lung. There was no evidence for an association between these cancers and exposure to DDT.

5.3 Animal carcinogenicity data

In mice, 12 out of 13 studies of carcinogenicity with DDT (11 oral administration studies by feeding or gavage, and one subcutaneous injection study) in males and/or females gave positive results (some for multiple sites). One skin application study gave negative results.

In treated mice, DDT consistently increased the incidence of benign and/or malignant

tumours of the liver that were classified across the various studies as benign or malignant liver cell tumours, hepatomas (not further classified), benign or malignant hepatomas, or hepatocellular adenoma or carcinoma.

In nine of these positive studies (including the subcutaneous injection study), there was an increase in the incidence of liver cell tumours (benign, malignant, or combined benign or malignant): six studies were positive for males and females, two studies for males only, and one study for females only; in one of these studies there was also an increase in the incidence of hepatoblastoma.

In three of these positive studies, there was an increase in the incidence of malignant lymphoma: one study was positive for males and females, one for males, and one for females. In another of these positive studies, there was an increase in the incidences of malignant lymphoma, leukaemia and pulmonary carcinoma in males and females (combined).

In rats, six of nine carcinogenicity studies by oral administration (feeding) in males and/or females were positive. In four studies, there was an increase in the incidence of liver cell tumours (benign, malignant, or combined benign or malignant): three studies were positive for males and four for females; in one of these studies, there was also an increase in the incidence of ovary carcinoma. The incidences of thyroid follicular cell adenoma or carcinoma (combined) and of adrenal gland pheochromocytoma were also increased in females in the fifth positive study. In the sixth positive study, there was a small but significant increase in the incidence of bronchogenic carcinoma in males and females (combined). In several initiation-promotion studies, DDT promoted benign and/or malignant liver tumours.

In hamsters, two out of three carcinogenicity studies by oral administration (feeding) were positive: there was an increase in the incidence of adrenal cortex adenoma in males in one study and in females in another study.

In one study in monkeys, one prostatic adenocarcinoma and one HCC were reported in two cynomolgus monkeys out of 24 DDT-exposed cynomolgus or rhesus monkeys. No tumours were observed in 17 untreated cynomolgus or rhesus monkeys.

The DDT metabolite DDD was carcinogenic in one of two mouse oral administration (feeding) studies. In this study, DDD caused an increase in the incidence of hepatoma (benign or malignant, combined) in males, and of lung adenoma or adenocarcinoma (combined) in males and females. In one feeding study in rats, DDD caused an increase in the incidence of thyroid follicular cell adenoma or carcinoma (combined) in males.

The DDT metabolite DDE was carcinogenic in mice with an increase in the incidence of hepatocellular tumours (benign and malignant) in two oral administration (feeding) studies in males and females, but not in one study in male and female rats. One feeding study in hamsters showed an increase in the incidence of hepatocellular adenoma or carcinoma (combined) in males and females.

5.4 Mechanistic and other relevant data

p,p′-DDT and *o,p′*-DDT are highly lipophilic and readily absorbed via all routes of exposure. Both DDT isomers are distributed widely in the body by both lymphatic and blood circulation, with a preference for adipose and other lipid-rich tissues. *p,p′*-DDT and *o,p′*-DDT are metabolized to *p,p′*-DDD and *o,p′*-DDD, respectively, which readily degrade to *p,p′*-DDA and *o,p′*-DDA excreted in urine. *p,p′*-DDT is also metabolized to DDE, which is poorly eliminated and more lipophilic than the parent compound. Human half-lives of *p,p′*-DDT and DDE are long, on

the order of 5 (for *p,p′*-DDT) to 10 (for DDE) years, whereas *o,p′*-DDT is rapidly metabolized and excreted. *p,p′*-DDT has been reported to induce several P450 enzymes in rats and several PXR-mediated P450s in a human hepatoma cell line. Metabolism in humans and experimental systems are expected to be similar.

With respect to the key characteristics of human carcinogens, adequate data were available to evaluate whether DDT modulates receptor-mediated effects, is immunosuppressive, induces oxidative stress, alters cell proliferation, cell death or nutrient supply, is genotoxic, and induces chronic inflammation.

The evidence is *strong* that DDT modulates receptor-mediated effects that can operate in humans. DDT and its metabolites can modulate thyroid hormones in exposed humans. While evidence is less clear for effects on the sex steroid hormone axis in men and women, estrogenic effects of *o,p′*-DDT and *p,p′*-DDT, such as binding and activation of ER, were consistently seen across numerous experimental systems, including human cells, and were blocked by anti-estrogens in human breast cancer cells and in mice. Evidence that DDT and its metabolites antagonize the AR, with *p,p′*-DDE being the most potent, was consistent across non-human experimental systems in vivo and in cells from a variety of species including humans. DDT and its metabolites can bind and activate progesterone in cells from multiple species including humans. DDT induced PR expression in ER-positive breast cancer cells. It also activated PR in such cells and in a yeast system, and blocked transactivation of PR by progesterone. Some studies also report activation of CAR or PXR by DDT. Some studies suggest a relationship between *o,p′*-DDT or *p,p′*-DDE and breast or mammary cancer that involves HER2.

The evidence is *strong* that DDT is immunosuppressive, and this can operate in humans. In studies in exposed humans, immunological changes are reported to be correlated with *p,p′*-DDT or *p,p′*-DDE levels, though subjects in these studies were also exposed to other contaminants that may be correlated with *p,p′*-DDT or *p,p′*-DDE levels. Additionally, human natural killer cell suppression has been observed in multiple in vitro studies of *p,p′*-DDT, indicative of its potential to decrease immunosurveillance. In mice exposed in vivo to *p,p′*-DDT or *o,p′*-DDT, suppression of B-cell function indicating effects on humoral immune response have been reported, with potentiation via stress that is consistent with data showing modulation of glucocorticoids. Suppression of humoral immune response by *p,p′*-DDT, *o,p′*-DDT, or *p,p′*-DDE has also been reported in rats, rabbits, and marine mammals in vivo, as well as mice and rats in vitro.

The evidence is *strong* that DDT induces oxidative stress, and this can occur in humans. *p,p′*-DDT, *p,p′*-DDD, and/or *p,p′*-DDE activated the Wnt/β-catenin pathway via ROS and stimulated proliferation of human colorectal and liver cancer cells in vitro and in xenografted mice. *p,p′*-DDT, *p,p′*-DDD, and/or *p,p′*-DDE increased ROS levels in human peripheral blood mononuclear cells. Several of these effects were inhibited by anti-oxidant treatment. In liver of exposed rats, *p,p′*-DDT increased lipid peroxidation and levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG).

The evidence is *moderate* that DDT alters cell proliferation or cell death. There is evidence, primarily for *o,p′*-DDT, of ER-dependent induction of cell proliferation in particular cell types *in vitro*. In some cell types *in vitro*, *o,p′*-DDT induces apoptosis although in others, a suppression of this end-point has been noted.

The evidence for genotoxicity of DDT is *moderate*. There is some evidence of DNA damage, chromosome aberrations, and micronuclei in human cells exposed to DDT in vitro. Experimental mammalian in vivo and in vitro data are mixed, for some of these same end-points. Data in non-mammalian experimental systems are predominantly negative.

The evidence that DDT induces inflammation is *moderate*. While the number of studies is small, there are data in human and mammalian cells in vitro that *p,p′*-DDT, *o,p′*-DDT, *p,p′*-DDD, or *p,p′*-DDE can induce a pro-inflammatory state. However, there are no data in exposed humans and very few data in experimental systems in vivo.

In high throughput testing in the Tox21 and ToxCast research programs of the United States government, *p,p′*-DDT, *o,p′*-DDT, *p,p′*-DDE, and *p,p′*-DDD were positive in between 42 and 62 high throughput assay end-points, mostly related to receptor-mediated effects or cell proliferation/cell death/nutrient supply, among the 265 assay end-points relevant to the key characteristics of human carcinogens.

There is some evidence pertaining to cancer susceptibility factors related to infectious agents and perinatal exposures.

Overall, the mechanistic data provide strong support for the carcinogenicity findings of DDT. This includes strong evidence that DDT modulates receptor-mediated effects, is immunosuppressive, and induces oxidative stress, and that these effects can operate in humans.

6. Evaluation

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of DDT. Positive associations have been observed between DDT and cancers of the liver and testis, and non-Hodgkin lymphoma.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of DDT.

There is *sufficient evidence* in experimental animals for the carcinogenicity of DDE.

There is *sufficient evidence* in experimental animals for the carcinogenicity of DDD.

6.3 Overall evaluation

DDT is *probably carcinogenic to humans* (*Group 2A*).

6.4 Rationale

In addition to limited evidence for the carcinogenicity of DDT in humans and sufficient evidence for the carcinogenicity of DDT in experimental animals, there is strong mechanistic evidence for DDT that three key characteristics of known human carcinogens can operate in humans: receptor-mediated effects, immunosuppression, and oxidative stress.

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