DDT AND ASSOCIATED COMPOUNDS

These substances were considered by previous Working Groups, in 1973 (IARC, 1974) and 1987 (IARC, 1987a). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

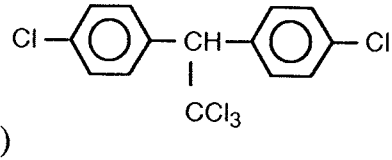
Table 1. Chemical Abstract Services Registry numbers, names and synonyms

Name	CAS Reg. Nos	Chem. Abstr. names[a] and synonyms
para,para'-DDT	50-29-3	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-trichloro-ethane; 1,1-bis(4-chlorophenyl)-2,2,2-trichloroethane; DDT; 4,4'-DDT; *para,para'*-dichlorodiphenyltrichloroethane; 4,4'-dichlorodiphenyltrichloroethane; *para,para'*-dichlorodiphenyltrichloromethylmethane; ENT 1506; OMS 0016; 1,1,1-trichloro-2,2-bis(*para*-chlorophenyl)ethane; 1,1,1-trichloro-2,2-bis(4,4'-dichlorodiphenyl)ethane; 2,2,2-trichloro-1,1-bis(4-chlorophenyl)ethane; 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (IUPAC); trichlorobis(4'-chlorophenyl)ethane; **1,1'-(2,2,2-trichloro-ethylidene)bis(4-chlorobenzene)**
ortho,para'-DDT	789-02-6	2-(2-Chlorophenyl)-2-(4-chlorophenyl)-1,1,1-trichloroethane; **1-chloro-2-(2,2,2-trichloro-1-(4-chlorophenyl)ethyl)-benzene**; 2,4'-DDT; 1,1,1-trichloro-2-(*ortho*-chlorophenyl)-2-(*para*-chlorophenyl)ethane; 1,1,1-trichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl)ethane (IUPAC)
para,para'-TDE	72-54-8	1,1-Bis(*para*-chlorophenyl)-2,2-dichloroethane; 1,1-bis(4-chlorophenyl)-2,2-dichloroethane; 2,2-bis(*para*-chlorophenyl)-1,1-dichloroethane; 2,2-bis(4-chlorophenyl)-1,1-dichloroethane; DDD; *para,para'*-DDD; 4,4'-DDD; 1,1-dichloro-2,2-bis(*para*-chlorophenyl)ethane; 1,1-dichloro-2,2-bis(4-chlorophenyl)ethane (IUPAC), dichlorodiphenyl dichloroethane; *para, para'*-dichlorodiphenyldichloroethane; *para, para'*-dichlorodiphenyl-2,2-dichloroethylene; **1,1'-(2,2-dichloroethylidene)-bis(4-chlorobenzene)**; TDE
ortho,para'-TDE	53-19-0	**1-Chloro-2-[2,2-dichloro-1-(4-chlorophenyl)ethyl]-benzene**; 2-(2-chlorophenyl)-2-(4-chlorophenyl-1,1-dichloroethane; *ortho,para'*-DDD; 1,1-dichloro-2-(*ortho*-chlorophenyl)-2-(*para*-chlorophenyl)ethane; 2,4'-dichlorodiphenyldichloroethane

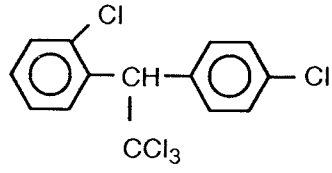
Table 1 (contd)

Name	CAS Reg. Nos	Chem. Abstr. names[a] and synonyms
para,para'-DDE	72-55-9	**2,2-Bis(4-chlorophenyl)-1,1-dichloroethene;** 1,1-bis(*para*-chlorophenyl)-2,2-dichloroethylene; 2,2-bis(4-chlorophenyl)-1,1-dichloroethylene; DDE; 4,4'-DDE; 1,1-dichloro-2,2-bis(*para*-chlorophenyl)-ethylene; *para,para'*-dichlorodiphenyldichloroethylene; 1,1-dichloro-2,2-di(4-chlorophenyl)ethylene (IUPAC); **1,1'-(dichloroethenylidene)-bis(4-chlorobenzene)**

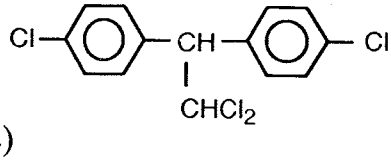
[a]In bold



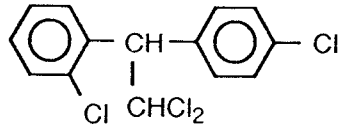
$C_{14}H_9Cl_5$ (*para,para'*-DDT) Mol. wt: 354.5



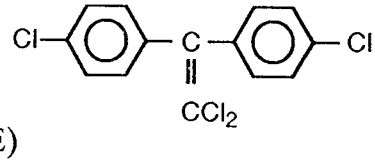
$C_{14}H_9Cl_5$ (*ortho,para'*-DDT) Mol. wt: 354.5



$C_{14}H_{10}Cl_4$ (*para,para'*-TDE) Mol. wt: 320.0



$C_{14}H_{10}Cl_4$ (*ortho,para'*-TDE) Mol. wt: 320.0



$C_{14}H_8Cl_4$ (*para,para'*-DDE) Mol. wt: 318.0

1.1.2 *Chemical and physical properties*

From Agency for Toxic Substances and Disease Registry (1989), unless otherwise noted

***para,para'*-DDT**

(*a*) *Description*: Colourless crystalline solid, odourless or with weak aromatic odour
(*b*) *Boiling-point*: 260°C
(*c*) *Melting-point*: 108-109°C

(*d*) *Spectroscopy data*: Infrared (prism [27, 127, 15542]; grating [15014, 36866]), ultraviolet [47, 4655, 36806] and nuclear magnetic resonance (proton [15, V620, 23171, 34386]; C-13 [2410, 4401]) spectral data have been reported (Sadtler Research Laboratories, 1980, 1990).

(*e*) *Solubility*: Practically insoluble in water (0.0034 mg/l at 25°C); at 27-30°C, soluble in acetone (58 g/100 ml), benzene (78 g/100 ml), cyclohexanone (116 g/100 ml), diethyl ether (28 g/100 ml) (Budavari, 1989), chloroform (96 g/100 ml) (WHO, 1989) and other organic solvents (Brooks, 1974)

(*f*) *Volatility*: Vapour pressure, 5.5×10^{-6} mm Hg [0.73×10^{-6} kPa] at 20°C

(*g*) *Stability*: Stable to oxidation; corrosive to iron; dehydrochlorinated at temperatures above its melting point to the non-insecticidal DDE, a reaction catalysed by iron (III) or aluminium chlorides, by ultraviolet light and, in solution, by alkali (Worthing & Walker, 1987)

(*h*) *Octanol/water partition coefficient (P)*: log P, 6.19

(*i*) *Conversion factor for airborne concentrations*[1]: $mg/m^3 = 14.5 \times ppm$

***ortho,para'*-DDT**

(*a*) *Description*: White, crystalline solid (WHO, 1989)

(*b*) *Melting-point*: 74-75°C

(*c*) *Spectroscopy data*: Infrared (prism [46974]; grating [31974]), ultraviolet [23375] and nuclear magnetic resonance (proton [19449]) spectral data have been reported (Sadtler Research Laboratories, 1980).

(*d*) *Solubility*: Slightly soluble in water (0.085 mg/l at 25°C); soluble in lipids and most organic solvents (IARC, 1974)

(*e*) *Volatility*: Vapour pressure, 5.5×10^{-6} mm Hg [0.73×10^{-6} kPa] at 30°C (Brooks, 1974)

(*f*) *Stability*: Stable to concentrated sulfuric acid (IARC, 1974)

(*g*) *Conversion factor for airborne concentrations*[1]: $mg/m^3 = 14.5 \times ppm$

***para,para'*-TDE**

(*a*) *Description*: Colourless, odourless crystalline solid

(*b*) *Boiling-point*: 193°C at 1 mm Hg [0.13 kPa]

(*c*) *Melting-point*: 109-110°C

(*d*) *Spectroscopy data*: Infrared (prism [18450]; grating [36636]), ultraviolet [5898] and nuclear magnetic resonance (proton [2040]; C-13 [1284]) spectral data have been reported (Sadtler Research Laboratories, 1980).

(*e*) *Solubility*: Slightly soluble in water (0.160 mg/l at 25°C)

(*f*) *Volatility*: Vapour pressure, 10.2×10^{-7} mm Hg [1.36×10^{-7} kPa] at 30°C

(*g*) *Stability*: Similar to that of *para,para'*-DDT but more slowly hydrolysed by alkalis (IARC, 1974)

(*h*) *Octanol/water partition coefficient (P)*: log P, 6.20

(*i*) *Conversion factor for airborne concentrations*[1]: $mg/m^3 = 13.09 \times ppm$

---

[1]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming standard temperature (25°C) and pressure (760 mm Hg [101.3 kPa])

***ortho,para'*-TDE**

(*a*) *Description*: Colourless crystals
(*b*) *Melting-point*: 76-78°C
(*c*) *Conversion factor for airborne concentrations*[1]: mg/m^3 = 13.09 × ppm

***para,para'*-DDE**

(*a*) *Description*: White, crystalline solid
(*b*) *Melting-point*: 88.4-90°C
(*c*) *Spectroscopy data*: Infrared (prism [27905]; grating [3631]), ultraviolet [10847] and nuclear magnetic resonance (proton [498]; C-13 [6360]) spectral data have been reported (Sadtler Research Laboratories, 1980)
(*d*) *Solubility*: Slightly soluble in water (0.12 mg/l at 25°C); soluble in lipids and most organic solvents (IARC, 1974)
(*e*) *Volatility*: Vapour pressure, 6.5 × 10^{-6} mm Hg [0.87 × 10^{-6} kPa] at 20°C
(*f*) *Stability*: Stable to concentrated sulfuric acid; may be oxidized to *para,para'*-dichlorobenzophenone, catalysed by ultraviolet radiation (IARC, 1974)
(*g*) *Octanol/water partition coefficient (P)*: log P, 7.00
(*h*) *Conversion factor for airborne concentrations*[1]: mg/m^3 = 13.01 × ppm

1.1.3 *Trade names, technical products and impurities*

Some examples of trade names are:

***para,para'*-DDT**: Aavero-extra; Agritan; Anofex; Arkotine; Azotox M 33; Benzochloryl; Bosan supra; Bovidermol; Chlorophenothane; Chlorphenotoxum; Citox; Clofenotane; Deoval; Detox; Detoxan; Dibovin; Dicophane; Dinocide; Dodat; Dykol; ENT-1506; Estonate; Genitox; Gesafid; Gesarol; Guesapon; Guesarol; Gyron; Hildit; Ivoran; Ixodex; Mutoxan; Neocid; Neocidol; Parachlorocidum; PEB1; Pentachlorin; Penticidum; Zerdane

***para,para'*-TDE**: Dilene; ME 1700; Rhothane

***ortho,para'*-TDE**: Chloditan; Mitotan; CB313; Lysodren

The WHO specification for technical DDT intended for use in public health programmes requires that the product contain 49-51% total organic chlorine, 9.5-11.5% hydrolysable chlorine and a minimum of 70% *para,para'*-DDT (WHO, 1985).

A typical sample of technical DDT had the following constituents: *para,para'*-DDT, 77.1%; *ortho,para'*-DDT, 14.9%; *para,para'*-TDE, 0.3%; *ortho,para'*-TDE, 0.1%; *para,para'*-DDE, 4%, *ortho,para'*-DDE, 0.1%; and unidentified products, 3.5% (WHO, 1989). Another analysis showed the following approximate composition (%): *para,para'*-DDT, 63-77; *ortho,para'*-DDT, 8-21; *para,para'*-TDE, 0.3-4.0; *ortho,para'*-TDE, 0.04; 1-(*ortho*-chlorophenyl)ethyl-2-trichloro-*para*-chlorobenzene sulfonate, 0.1-1.9; 2-trichloro-1-(*para*-chlorophenyl)ethanol, 0.2; bis(*para*-chlorophenyl)sulfone, 0.03-0.6; α-chloro-α-(*para*-chlorophenyl)acetamide, 0.01; α-chloro-α-(chlorophenyl) acetamide, 0.01; chlorobenzene, 0.3; *para*-dichlorobenzene (see IARC, 1987b), 0.1; 1,1,1,2-tetrachloro-2-(*para*-chlorophenyl)-ethane, trace; sodium *para*-chlorobenzenesulfonate, 0.02; ammonium *para*-chlorobenzene-

[1]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming standard temperature (25°C) and pressure (760 mm Hg [101.3 kPa])

sulfonate, 0.01; inorganics, 0.01-0.1; and unidentified components and losses, 5.1-10.6 (Bhuiya & Rothwell, 1969).

Technical DDT has been formulated in almost every conceivable form, including solutions in xylene (see IARC, 1989a) and petroleum distillates (see IARC, 1989b), emulsifiable concentrates, water-wettable powders, granules, aerosols, smoke candles, charges for vaporizers and lotions. Aerosols and other household formulations are often combined with synergized pyrethrins (WHO, 1989).

Technical TDE has been formulated as solutions in aromatic solvents, wettable powders and dusts (Brooks, 1974).

1.1.4 *Analysis*

Selected methods for the analysis of DDT and its metabolites in various media are summarized in Table 2. Reviews of analytical methods for DDT and metabolites in various media have been reported (Brooks, 1974; Horwitz, 1975a,b,c,d; WHO, 1979; Williams, 1984a; Rovinsky *et al.*, 1988; Agency for Toxic Substances and Disease Registry, 1989).

Table 2. Methods for the analysis of DDT and metabolites

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection[b]	Reference
Air	Collect vapours on glass-fibre filter with polyurethane foam; extract with 5% ether in hexane	GC/ECD	>1 ng/m^3	US Environmental Protection Agency (1988a)
	Collect vapours on polyurethane foam; extract with 5% diethyl ether in hexane	GC/ECD	NR	US Environmental Protection Agency (1988b)
	Collect vapours on glass-fibre filter; extract with isooctane	GC/ECD	NR	Taylor (1977)
Water	Extract with dichloromethane; isolate extract, dry and concentrate with methyl *tert*-butyl ether	GC/ECD	0.0025, 0.01, 0.06 µg/l	US Environmental Protection Agency (1988c)
Waste-water	Extract with dichloromethane; dry; exchange into hexane	GC/ECD	0.011, 0.004, 0.012 µg/l	US Environmental Protection Agency (1986a, 1989a)
	Extract with dichloromethane; dry and concentrate (packed column)	GC/MS	2.8, 5.6 4.7 µg/l	US Environmental Protection Agency (1989b)
Formulations	Extract with carbon disulfide and sodium sulfate; compare with reference spectrum at 9.4-10.2 µm	IR	NR	Williams (1984b)
Food (high moisture, non-fatty)	Blend with acetone; extract with petroleum ether/dichloromethane; dry; concentrate in petroleum ether and acetone	GC/HECD	NR	Williams (1985)

Table 2 (contd)

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection[b]	Reference
Soil, sediment, wastes	Mix with anhydrous sodium sulfate; extract using Soxhlet or sonication; clean-up using Florisil column or gel-permeation (packed column)	GC/MS	2.8, 5.6, 4.7 µg/l	US Environmental Protection Agency (1986b)
	Mix with anhydrous sodium sulfate; extract using Soxhlet or sonication; clean-up using Florisil column or gel-permeation (capillary column)	GC/MS	NR	US Environmental Protection Agency (1986c)

[a]Abbreviations: GC/ECD, gas chromatography/electron capture detection; GC/HECD, gas chromatography/Hall electrolytic conductivity detector; GC/MS, gas chromatography/mass spectrometry; IR, infrared spectroscopy

[b]The limits of detection are presented for 4,4′-TDE, 4,4′-DDE and 4,4′-DDT, respectively; NR, not reported

1.2 Production and use

The discovery, chemistry and uses of DDT and problems associated with its use have been reviewed (Brooks, 1974; Mellanby, 1989).

1.2.1 *Production*

Technical-grade DDT is made by condensing chloral hydrate with chlorobenzene in the presence of sulfuric acid. To prepare *ortho,para′*-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).

DDT was first synthesized in 1874, but it was not until 1939 that its insecticidal properties were discovered. By 1943, low-cost production methods had been developed, and commercial production had begun. At the height of DDT production, about 400 000 tonnes were used annually worldwide, but this decreased to approximately 200 000 tonnes in 1971. Peak production in the USA occurred in 1963, when 80 000 tonnes were produced. After restrictions were introduced in the USA in 1969 (Brooks, 1974), production of DDT in 1971 in that country was estimated to be 2000 tonnes. In 1985, approximately 300 tonnes of DDT were exported. In 1989, there were three producers, but no data were available on the current production of DDT in the USA (Agency for Toxic Substances and Disease Registry, 1989). DDT is produced currently by one company each in Italy, India and Indonesia (Meister, 1990) and in China.

TDE was introduced commercially in Germany in 1945 under the trade name Rhothane. The commercial preparation of TDE from the ethyl acetal of dichloroacetaldehyde and chlorobenzene usually gives a technical product consisting mainly of the *para,para′*-isomer, with 7-8% of the *ortho,para′*-isomer (Brooks, 1974; IARC, 1974).

1.2.2 *Use*

DDT is a nonsystemic contact and stomach insecticide with a broad spectrum of insecticidal activity (Worthing & Walker, 1987). DDT has been used primarily in the

prevention of malaria, yellow fever and sleeping sickness. In 1971, approximately 50% of production was used for these purposes (IARC, 1974).

DDT was used extensively for the control of malaria, typhus and other insect-transmitted disease during the Second World War. It has been used worldwide in agriculture in the control of insects. In 1972, 4500-6400 tonnes of DDT were used in the USA; use on cotton crops was estimated to account for 67-90% of the total use, with the remainder primarily on peanut and soya bean crops. Since 1973, use of DDT in the USA has been limited to the control of public health problems. It was estimated in 1973 that more than 2 million tonnes of DDT had been used for insect control since 1940, about 80% of that in agriculture. DDT was once registered for use on 334 commodities in the USA (Agency for Toxic Substances and Disease Registry, 1989).

Even before 1963, some restrictions had been placed on the use of DDT, mainly to minimize residues in food and in the feed of animals that produce milk and meat. Another important reason for reducing the use of DDT was the increasing resistance of pests. Although many pests of public health importance became resistant to DDT in some or all of their range, resistance among vectors of malaria was less marked. Because malaria control constitutes such a large segment of vector control, the use of DDT for vector control has tended to remain stable, while its use in agriculture has continued to decline, especially in temperate climates (WHO, 1979).

DDT was introduced in India for use in public health and agriculture in 1948. Since then, nearly 250 000 tonnes have been used, of which only 50 000 tonnes were in agriculture. The use of DDT in India over a 20-year period is given in Table 3 (Mehrotra, 1985). India banned the use of DDT for agricultural purposes in 1989 (County NatWest WoodMac, 1990).

Table 3. Total use of DDT (in thousands of tonnes) in India during 1960-84[a]

Type of use	1960	1966	1970	1975	1976	1977	1978	1979	1980	1984
Public health	21.0	2.7	6.2	7.3	7.3	9.0	6.8	6.5	8.5	12.0
Agriculture	0.6	2.4	2.4	2.5	1.3	2.5	4.7	4.2	4.0	2.0

[a]From Mehrotra (1985)

About 12 000 tonnes of DDT were used in Iraq by the agricultural authorities between 1960 and 1978 (Al-Omar *et al.*, 1985). In Pakistan, the yearly agricultural use of DDT (active ingredient) during the period 1977-81 ranged from 40 to 100 tonnes (Baloch, 1985). In one province in Indonesia, a large-scale malaria control programme was begun in 1952. Between 1952 and 1980, yearly usage of DDT (active ingredient) was as high as [1400 tonnes] [calculated by the Working Group from a graph] (Bang *et al.*, 1982).

TDE is a nonsystemic contact and stomach insecticide, which does not have the broad-spectrum insecticidal activity of DDT but has equal or greater potency against the larvae of some mosquitoes and lepidoptera (Brooks, 1974). It has had limited use as a pesticide (Agency for Toxic Substances and Disease Registry, 1989). In 1971, 110 tonnes of TDE were used by farmers in the USA, 67% of which was on tobacco (US National Cancer Institute, 1978).

The pure *ortho,para'*-TDE isomer, which must be specially synthesized, has been used in the treatment of adrenocortical carcinoma (Bergenstal *et al.*, 1960) and of the overproduction of adrenal cortical steroids (Wallace *et al.*, 1961; Bledsoe *et al.*, 1964; Southern *et al.*, 1966).

1.3 Occurrence

The physiochemical properties of DDT and its metabolites enable organisms to take them up readily. As these compounds are resistant to breakdown, they are readily adsorbed by sediments and soils, which can act as both sinks and long-term sources of exposure. Organisms can accumulate these chemicals from the surrounding medium and from food. Uptake from water is generally more important for aquatic organisms, whereas food provides the major source in terrestrial fauna.

Earlier data on occurrence were summarized in the previous monograph on DDT (IARC, 1974). Environmental aspects of DDT and its derivatives were reviewed (WHO, 1989). The occurrence of DDT and its metabolites in human tissues and fluids is discussed in section 4.1.1.

1.3.1 *Soil*

The absorption of DDT was greatest in muck soil and least in sandy loam soil and was closely related to the organic matter content of the soil, the major fraction identified with absorption being the humic material. The degree of sorption is strongly associated with the degree of humidification (WHO, 1989).

After application to the soil surface, 50% of DDT was lost within 16-20 days, with an estimated time for 90% loss of 1.5-2 years. When it was mixed into the soil, the half-time of DDT was 5-8 years, and it was estimated that 90% would be lost in 25-40 years (Wheatley, 1965).

In a study to determine the ability of river sediments to degrade DDT, labelled material was added to sediments in the laboratory or on mud flats in the United Kingdom. Incubation *in situ* over 46 days led to very little metabolism of DDT; some *para,para'*-TDE was produced, but metabolism did not proceed further. In the laboratory, however, a greater amount of degradation occurred over 21 days. Investigations of the microbial population of the sediment showed that some organisms were capable of degrading DDT (Albone *et al.*, 1972).

When cotton plants in Kenya were sprayed at 1.05 or 2.52 kg active ingredient/ha, and soil and leaf samples were taken, the half-times for *para,para'*-DDT in soil for the two rates were 18.5 and 2.2 days, respectively. The low persistence of surface-applied DDT in tropical climates represents a totally different situation from that reported for temperate climates. With a soil temperature of over 65°C by mid-afternoon, the loss was attributed to volatilization. Residues on cotton foliage had a similarly short half-time of 4.8 days. The metabolite *para,para'*-DDE was slightly more persistent, with a half-time of 8.8 days (Foxall & Maroko, 1984). In a review of DDT residues in Indian soils in cotton-growing areas, the half-time of DDT was about three months, as compared to 4-30 years in temperate regions (Mehrotra, 1985).

1.3.2 *Plants*

^{14}C-Labelled DDT was applied to loam and sandy soils at 4 and 2 mg/kg and oats were grown in the treated soils for 13 days. Of the total DDT applied, 95% was recovered from the loam and 84% from the sandy soil, showing that little metabolism had taken place. DDE was detected in both soils, together with very small amounts of other metabolites. Very little DDT was detected in oat roots grown on loam (0.2%); uptake was greater (4.6%) in the roots of oats grown on sand. No label was detected in the plant tops (Fuhremann & Lichtenstein, 1980).

DDT was not translocated into foliage of alfalfa after application to soil (Ware *et al.*, 1970), or into soya beans (Eden & Arthur, 1965). Only trace amounts of DDT or its metabolites were found in stored carrots, radishes and turnips which had been grown in soils containing up to 15 mg/kg DDT (Harris & Sans, 1967).

1.3.3 *Food*

Residues were found in 36 of 1535 samples analysed for DDT as part of a Canadian national surveillance programme in 1984-89. The highest levels were found in carrots (12/75 samples), cheese (10/94) and grapes (7/129). The levels ranged from 0.01 to a maximum of 0.6 mg/kg (Government of Canada, 1990).

In Brazil, the average levels of DDT in 1998 samples of cattle meat were 0.04-0.13 mg/kg, those in 102 samples of horse meat, 0.01-0.02 mg/kg and those in corned beef and roast beef, 0.03-0.04 mg/kg (Codex Committee on Pesticide Residues, 1989).

para,para'-DDE was detected in 408 of 19 851 food and animal feed samples analysed in the USA during the period 1982-86; 288 samples contained less than 0.05 mg/kg (maximum, 2.0 mg/kg) (Luke *et al.*, 1988).

1.3.4 *Fish*

Small fish take up more DDT from water than larger fish of the same species: a range in weight of mosquito fish between 70 and 1000 mg led to a four-fold difference in DDT uptake over 48 h (Murphy, 1971).

Rainbow trout were exposed to concentrations of DDT in water of 176, 137 and 133 ng/l at 5, 10 and 15 °C, respectively. Whole-body residues of DDT after 12 weeks of exposure were 3.8, 5.9 and 6.8 mg/kg for the three temperatures, indicating increased uptake by fish with temperature (WHO, 1989).

Fish accumulate DDT from food in a dose-dependent manner. Rainbow trout fed diets containing 0.2 or 1.0 mg/kg DDT retained more than 90% of the dietary intake over a 90-day exposure. The time for 50% elimination was estimated at 160 days. There was a straight-line relationship between exposure time and body burden of total DDT, with no tendency for residues to reach a plateau within 45 days of feeding. The fish had accumulated 1.1 µg/kg from food containing 0.58 µg/kg DDT, 11 µg/kg from food containing 9.0 µg/kg and 110 µg/kg from food containing 93 µg/kg at the end of the experiment (WHO, 1989).

1.4 Regulations and guidelines

Sweden was the first country to ban the use of DDT, in 1970 (WHO, 1979). Many other countries subsequently restricted its use, although DDT continues to be used in some circumstances, for the control of vector-borne diseases.

DDT and its metabolites were included in the 1987 Canadian guidelines for drinking-water quality for re-evaluation; the 1978 maximum acceptable concentration was 30 μg/l (Ritter & Wood, 1989).

The FAO/WHO Joint Meeting on Pesticide Residues evaluated DDT at its meetings in 1963, 1965, 1966, 1967, 1968, 1969, 1977, 1979, 1980, 1983 and 1984 (FAO/WHO, 1964, 1965, 1967a,b, 1968a,b, 1969, 1970a,b, 1978, 1980a,b, 1981, 1984, 1985). In 1963, an acceptable daily intake in food of 0.005 mg/kg bw was established (FAO/WHO, 1964); this was raised to 0.01 mg/kg bw in 1965. In 1967, the level was extended to metabolites. The acceptable daily intake was lowered to 0.005 mg/kg bw in 1969 and was raised to 0.02 mg/kg bw in 1984 (FAO/WHO, 1985).

Maximum residue levels were established by the Codex Alimentarius Commission for DDT (as the sum of *para,para'*-DDT, *ortho,para'*-DDT, *para,para'*-DDE and *para,para'*-TDE (fat-soluble residue)) in or on the following (in mg/kg): meat (fat), 5; fruit and vegetables, 1; eggs, 0.5; cereal grains, 0.1; milks, 0.05 (Codex Committee on Pesticide Residues, 1990).

National and regional pesticide residue limits for DDT and its metabolites in foods are presented in Table 4. Table 5 presents occupational exposure limits and guidelines for DDT in some countries. The maximum allowable concentrations in the USSR are 0.001 mg/m^3 for average daily exposure to DDT in the atmospheric air of populated areas, 0.005 mg/m^3 for a single exposure in the same areas, 0.1 mg/l for DDT in water for drinking and domestic purposes and 1 mg/kg for DDT in soil (Izmerov, 1983).

Table 4. National and regional pesticide residue limits for DDT in foods[a]

Country or region	Residue limits (mg/kg)	Commodities
Australia	5	Fat (meat, poultry)
	1.25	Goat milk (fat basis), milk (fat basis), milk products (fat basis)
	1	Edible oils, fish, fruit, margarine, vegetables
	0.5	Eggs
	0.1	Cereal grains
Austria	3[b]	Fish
	1.0[b]	Cocoa nibs, spices, tea, tea-like products, unroasted coffee
	0.5[b]	Eggs (without shell), other foodstuffs of animal origin
	0.1[b]	Oilseeds
Belgium	1[c]	Meat, poultry, hare, fowl, game, meat products, animal fats
	0.1[c]	Eggs, fruit, vegetables
	0.04[c]	Milk and milk products
	0 (0.05)[c,d]	Other foodstuffs of animal and vegetable origin
Canada	5[e]	Fish
	1.0	Butter, cheese, milk and other dairy products, meat, fat and meat by-products (cattle, hogs, poultry, sheep)
	0.5	Eggs, fresh vegetables

Table 4 (contd)

Country or region	Residue limits (mg/kg)	Commodities
Chile	7[c]	Apples, carcasses (fat), garden vegetables, peaches, pears, poultry (fat)
	3.5	Cherries, citrus fruit, plums
	1.25	Milk and dairy products (fat)
	1.0	Vegetables (root, tuber)
	0.5	Eggs
China	$\leq$ 1.0	Fish (including other seafood products)
	$\leq$ 0.2	Processed foodstuffs
	$\leq$ 0.1	Fruit, vegetables
Czechoslovakia	2[e]	Animal fats (fat basis), fish, meat
	1.25	Milk and milk products (fat basis) (imported)
	0.5	Eggs (without shell) (imported and domestic)
	0.4	Milk and milk products (fat basis)
	0.1	Fruit, potatoes, vegetables
Denmark	5[c]	Fish liver
	2	Fish and fish products
	1	Fat from meat
	0.5	Eggs
	0.2	Berries and small fruit, carrots, fruit (citrus, pome, stone, other), onions, potatoes, vegetables (leafy, other root)
	0.05	Cereals
	0.04	Milk, milk products, dairy products
European Community	1.0[b]	Fat contained in meat, preparations of meat, offal and animal fats
	0.1	Other crop and food products
	0.05	Barley, buckwheat, grain sorghum, maize, millet, oats, paddy rice, rye, triticale, wheat, other cereals
	0.04	Raw cows' milk and whole-cream cows' milk
Finland	3[c]	Codliver oil
	0.5	Crustaceans, fish, shellfish and their products (excluding codliver oil), other crops and food products
	0.1	Cereal grains
France	0.1[c]	Fruit, vegetables
	0.05[c]	Cereal grains
Germany	10[b]	Tobacco products
	5[f]	Fish liver and roe products
	3.5	Eel, salmon and sturgeon, as well as products thereof (except roe)
	2[g]	Other fish and other cold-blooded animals, seafood as well as products thereof (except liver and roe)
	1.0	Meat, meat products, edible animal fats (fat basis)
	1.0[b]	Spices, raw coffee, tea, tea-like products
	1.0[f]	Milk, dairy products
	0.5[f]	Eggs (without shell), egg products
	0.1[f]	Citrus juice, fruit, oilseed, vegetables
	0.05[g]	Other foodstuffs of plant origin
Hungary	0.1[c]	Crops, food

Table 4 (contd)

Country or region	Residue limits (mg/kg)	Commodities
India	7[h]	Fish, meat, poultry (whole product)
	3.5[h]	Fruit, vegetables (including potatoes)
	1.25[h]	Milk, milk products (fat basis)
	0.5[h]	Eggs (without shell)
Ireland	0.1[c]	All crop and food products
Israel	3	Apples, apricots, carcass meat (in fat), cherries, fruit (citrus, tropical), peaches, pears, plums, other small fruit not mentioned in list (except strawberries), poultry (in fat), vegetables
	0.25	Milk products (fat basis)
	1.0	Cottonseed, nuts (shelled), strawberries
	0.5	Eggs (without shell)
	0.05	Milk (fat basis)
Italy	1.0[c,i]	Aromatic and medicinal herbs, tea
	0.1	Coffee, fruit, garden vegetables
Japan	0.2	Apples, asparagus, baby kidney beans, baby peas, burdock, cabbage, cauliflower, celery, cherries, Chinese white cabbage, cucumbers, eggplant, garden radish, garden radish leaves, grapes, Irish potatoes, lettuce, loquats, mandarins, oranges, peaches, pears (Bartlett, Japanese), persimmon, pumpkin, soft greens, Spanish paprika, spinach, strawberries, summer oranges (peel, pulp), sweet potatoes, taro, tea, tomatoes, trefoil, turnip, turnip leaves, watermelons, white muskmelons
Kenya	7	Apples, apricots, meat (fat basis), peaches, pears, poultry (fat basis), small fruit (except strawberries), vegetables (except root)
	3.5	Cherries, fruit (citrus, tropical), plums
	1.25	Milk products (fat basis)
	1.0	Maize, millet, nuts (shelled), root vegetables, sorghum, strawberries, sunflower seeds (entire), wheat grain
	0.5	Eggs (without shell), whole milk
Luxembourg	5[j]	Fish eggs, liver products
	3.5[j]	Eel, salmon and sturgeon and derived products (except fish eggs)
	3[j]	Animal fats (except butyric fats), meat and meat products, poultry and poultry products
	2[j]	Other fish, crustaceans, molluscs and derived products (except fish eggs and liver)
	1.25[j]	Milk and milk products
	0.5[j]	Eggs (without shell), animal fats and fish meal (used as animal feed)
	0.2[j]	Other foodstuffs (used as animal feed)
	0.1[j]	Vegetable fats (used as animal feed), supplementary feed for lactating animals
	0.05	Natural foods (used as animal feed)
	0.03	Cereals (used as animal feed)

Table 4 (contd)

Country or region	Residue limits (mg/kg)	Commodities
Mexico	7	Beans, chili peppers, grapes, lettuce, pineapples, tomatoes
	6	Soya bean oil (processed)
	4	Cottonseed
	3.5	Avocado, carrots, citrus fruit, maize, papayas
	1.5	Soya beans
	1.0	Artichokes, asparagus, broccoli, cabbage, celery, okra, onions, potatoes, radishes, spinach, sweet potatoes
	0.5	Apples, cucumbers, eggplant, guavas, mangoes, melons, peaches, peanuts, pears, peas, squash, strawberries
Netherlands	5[c]	Eggs (fat basis)
	1[c]	Meat, poultry meat, other animal products (fat basis), tea
	0.5[c]	Cocoa butter (wring/refined)
	0.1[c]	Fruit, plant oil and fat, vegetables, tropical seed (fat basis)
	0.05[c]	Other foodstuffs
	0.04[c]	Milk
	0.02[c]	Other cocoa (fat basis)
New Zealand	5[e]	Meat fat in any foodstuff
	2[e]	Fruit, vegetables
	1.25[e]	Milk fat in any foodstuff
	0.5[e]	Eggs
Peru	7[h]	Fruit (drupe, pome), meat (fat basis), poultry (fat basis)
	3.5[h]	Fruit (citrus, tropical)
	1.25[h]	Milk and milk products (fat basis)
	1.0[h]	Walnuts (shelled)
	0.5[h]	Eggs (without shell)
Romania	5	Meat (cattle, goats, sheep)
	3	Meat (pigs, poultry)
	1.25	Milk and milk products
Singapore	0.2	Fat (cattle, hogs, sheep), other foodstuffs
	0.005	Milk
South Africa	3[c]	Carcass meat (fat basis)
	0.5[c]	Eggs (without shell)
	0.05[c]	Milk (fat basis)
Spain	1.0[c]	Coffee, spices, tea and similar products
	0.1[c]	Fruit, vegetables (except potatoes)
	0.05[c]	Potatoes, other plant products
Sweden	5[c]	Fishery products
	1.0[c]	Butter, cheese, fruit, vegetables
	0.5[c]	Eggs, raw meat
	0.05[c]	Cereals and hulled grain, flakes and flour made from cereals, milk, potatoes

Table 4 (contd)

Country or region	Residue limits (mg/kg)	Commodities
Switzerland	1.0[c]	Meat and meat products (except fish and fish-based products (fat basis)), tea and tea plants
	0.5[c]	Eggs
	0.25[c]	Cocoa butter and bulk cocoa (fat basis)
	0.125[c]	Milk and milk products (fat basis)
	0.1[c]	Cereal, fruit, vegetables
	0.01[c]	Cereal products
	0.02[c]	Infant and baby foods (as consumed); other products [limit value, 0.06]
	0.005[c]	Infant and baby foods (as consumed); milk products [limit value, 0.015]
Thailand	7	Fruit
	6	Fat and oil from animals and vegetables
	5	Aquatic animal products, meat
	2	Vegetables
	1.5	Eggs, pulses
	1.0	Milks
	0.5	Cereals
United Kingdom	1[b]	Bananas, oranges, other citrus, meat, fat and preparations of meats (fat basis), dairy produce (> 2% fat)
	0.5	Eggs (birds' eggs in shell (other than eggs for hatching) and whole egg products and egg yolk products (whether fresh, dried or otherwise prepared))
	0.1	Apples, blackcurrants, beans, Brussels' sprouts, cabbage, carrots, celery, cauliflower, cucumbers, grapes, leeks, lettuce, mushrooms, nectarines, onions, peaches, pears, peas, plums, potatoes, raspberries, strawberries, swedes, tomatoes, turnips
	0.05	Barley, maize, oats, paddy rice, rye, wheat, other cereals
	0.04	Milk (fresh raw cows' milk and fresh whole-cream cows' milk expressed as whole milk)
USA[k]	5	Fat of meat (cattle, goats, hogs, horses, sheep), fish
	3	Carrots
	1.25	Manufactured dairy products
	1.0	Beans (cocoa, whole raw), peppermint oil, potatoes, soya bean oil (crude), spearmint oil, sweet potatoes
	0.5	Artichokes, asparagus, barley grain (food, feed), broccoli, Brussels' sprouts, cabbage, cauliflower, celery, collards, eggs, endives (escarole), hay, kale, kohlrabi, lettuce, maize grain (food, feed), milo sorghum grain (food, feed), mushrooms, mustard greens, oat grain (food, feed), peppermint hay, rice grain (food, feed), rye grain (food, feed), spearmint hay, spinach, Swiss chard, tomato pomace (dried, for use in dog and cat food), wheat grain (food, feed)
	0.2	Apricots, avocadoes, beans, beans (dried), beets (roots, tops), cherries, guavas, mangoes, nectarines, okra, onions (dry bulb), papayas, parsnips (roots, tops), peaches, peanuts, peas, pineapples, plums (fresh prunes), radishes (roots, tops), rutabagas (roots, tops), soya beans, (dry), turnips (roots, tops)

Table 4 (contd)

Country or region		Residue limits (mg/kg)	Commodities
USA (contd)		0.1	Apples, blackberries, blueberries (huckleberries), boysenberries, citrus fruit, maize (fresh sweet plus cob with husk removed), cottonseed, cranberries, cucumbers, currants, dewberries, eggplant, gooseberries, hops (fresh), loganberries, melons, pears, peppers, pumpkins, quinces, raspberries, squash, squash (summer), strawberries, youngberries
		0.05	Grapes, hops (dried), tomatoes, lettuces
USSR	DDT	0.7	Tobacco products
		0.5	Fruit, vegetables
		Not permitted	All other food products including milk, meat, butter, eggs, garden strawberries and raspberries
	TDE	7	Fruits, vegetables
		3.5	Grain
Yugoslavia		2.0[e]	Vegetable oil (refined, unrefined) and their products (fat basis)
		1.0[e]	Venison, fish (fat basis)
		0.5[e]	Meat and meat products (cattle, hogs, poultry, sheep (fat basis), milk and milk products (fat basis)
		0.1[e]	Eggs (without shell) and egg products, fruit, vegetables, other food commodities
		0.03[e]	Cereals
		0.01[e]	Processed cereals

[a]From Health and Welfare Canada (1990)
[b]DDT, DDE, TDE and their isomers (total calculated as DDT)
[c]Sum of *para,para'*-DDT, *ortho,para'*-DDT, *para,para'*-DDE and *para,para'*-TDE
[d]Residues should not be present; the value in parentheses indicates the lower limit for residue determination according to the standard method of analysis, this limit having being used to reach the no-residue conclusion
[e]Including TDE and DDE
[f]TDE and isomers
[g]DDE (total calculated as DDT)
[h]Limits apply to DDT, TDE and DDE singly or in any combination
[i]Active substance revoked; EEC value for fruit and garden vegetables
[j]DDT, TDE, DDE (singly or combined, expressed as DDT)
[k]Recommended action levels, tolerances revoked (US Food and Drug Administration, 1990)

WHO (1984) recommended a guideline value of 1 µg/l for DDT (total isomers) in drinking-water, and the US Environmental Protection Agency (1980) established an ambient water quality criteria for DDT of 2.85 µg/l.

Table 5. Occupational exposure limits for DDT[a]

Country	Year	Concentration (mg/m^3)	Interpretation[b]
Austria	1987	1 (s)[c]	TWA
Belgium	1987	1	TWA
Bulgaria	1987	0.1	TWA
China	1987	0.3	TWA
Denmark	1988	1	TWA
Finland	1987	1 (s)	TWA
		3 (s)	STEL
Germany	1989	1 (s)	TWA
Hungary	1987	0.1 (s)	TWA
		0.5 (s)	STEL
India	1987	1	TWA
		3	STEL
Indonesia	1987	1 (s)	TWA
Italy	1987	1	TWA
Mexico	1987	1	TWA
Netherlands	1986	1	TWA
Poland	1987	0.1	TWA
Romania	1987	0.7 (s)	Average
		1 (s)	Maximum
Switzerland		1 (s)	TWA
United Kingdom	1987	1	TWA
		3	STEL (10 min)
USA			
ACGIH	1989	1	TWA
OSHA	1989	1 (s)	TWA
USSR	1987	0.1 (s)	MAC
Venezuela	1987	1	TWA
		3	Ceiling
Yugoslavia	1987	0.1 (s)	TWA

[a]From Arbeidsinspectie (1986); Cook (1987); Health and Safety Executive (1987); Työsuojeluhallitus (1987); Arbejdstilsynet (1988); American Conference of Governmental Industrial Hygienists (ACGIH) (1989); Deutsche Forschungsgemeinschaft (1989); US Occupational Safety and Health Administration (OSHA) (1989)

[b]MAC, maximum allowable concentration; TWA, time-weighted average; STEL, short-term exposure level

[c]Skin irritant notation

2. Studies of Cancer in Humans

2.1 Cohort studies

Venous blood samples were sought from 1708 adults in Charleston, SC, USA, enrolled in a prospective cohort study (Boyle, 1970; Keil *et al.*, 1984) in 1974-75 (468 white men, 602 white women, 310 black men and 328 black women) and were obtained for 919 subjects (304 white men, 327 white women, 204 black men and 84 black women) (Austin *et al.*, 1989).

para,para'-DDT and *para,para'*-DDE levels in the blood specimens were analysed, and total serum DDT was estimated; the mean serum DDT level was 48 ppb (μg/l) with a standard deviation of 36 ppb (μg/l). When the 919 subjects were traced through 1984, 209 were found to be deceased and 700 still alive; 10 were lost to follow-up. National and state age-, sex- and race-specific mortality rates for 1980 were used for external comparisons. In internal comparisons, the rates for persons in the upper (> 52 ppb) and middle (31-52 ppb) terciles of serum DDT levels were compared to those in the lowest tercile (0-31 ppb). These relative mortality rates were adjusted for differences in age, race, sex, years of schooling and smoking using a proportional hazards model. Mean levels were slightly higher among men than women (by 6%), among blacks than whites (by 14%) and among nonsmokers than smokers [% not given]. Compared to the general population, mortality from respiratory cancer was slightly higher among the cohort than expected (standardized mortality ratio (SMR), 1.2; 21 deaths; 95% confidence interval (CI), 0.76-1.9). Relative rates for total mortality by serum DDT levels were 1.2 (72 deaths; 0.8-1.7) for the middle tercile and 1.2 (80 deaths; 0.9-1.8) for the upper tercile (57 deaths for the lowest tercile). The trend was not significant. Relative mortality rates for respiratory cancer by tercile were 1.5 (7 deaths; 95% CI, 0.5-4.9) and 1.8 (7 deaths; 95% CI, 0.5-6.2) (5 deaths for the lowest tercile) with a non-significant trend.

Mortality was evaluated among workers employed at three manufacturing plants in Michigan and Arkansas, USA, and one research establishment in Michigan, where potential exposure to brominated chemicals existed (Wong *et al.*, 1984). Workers employed in the plants between 1935 and 1976 were identified from personnel records. Of the 3612 male workers identified, 33 were excluded because their dates of birth were not available, leaving 3579 for analysis (2806 alive as of 31 December 1976), 578 deceased (541 with death certificates) and 195 with unknown vital status. SMRs for the cohort were calculated using US white male rates to generate expected numbers. Race was not available on all employment records, but, according to the company, few blacks had worked at the plants. DDT had been produced at one time in one of the plants, and 740 workers were identified as having worked in DDT production departments. Mortality from all causes combined among these workers was about the same as expected (SMR, 0.99; 112 deaths; 95% CI, 0.82-1.2), as was mortality from all cancers (SMR, 0.95; 19 deaths; 95% CI, 0.57-1.5). Cancers for which the rates were slightly elevated, with more than one death, included leukaemia (SMR, 2.1; 2 deaths; 95% CI, 0.24-7.6) and lung (1.5; 9 deaths; 0.68-2.8). Many of the workers with potential exposure to DDT also had potential exposure to other chemicals, including inorganic brominated compounds. Information on smoking was not available for the entire cohort (see General Remarks for a discussion). In a nested case-control study of respiratory cancer, the 46 workers from the entire cohort who had died from respiratory cancer were each matched to two workers who had died from other causes (except cancer, nonmalignant respiratory disease or unknown causes) on plant, age at death and time of hiring. Information was sought on detailed work history and smoking history from employment records and other sources; information obtained on smoking was incomplete (20% were ascertained to be smokers, but no information was available on the remainder) and was not considered further. On the basis of detailed work histories, 10 cases and 25 controls were judged to have been exposed to DDT (odds ratio, 0.74 [95% CI, 0.3-1.7]).

Ditraglia *et al.* (1981) studied 354 workers at a plant in California, USA, that had produced DDT exclusively since 1947. (Three plants that produced other organochlorine pesticides were also studied, but the results presented here are restricted to the DDT plant.) All workers employed for at least six months prior to 31 December 1964 were included. Vital status as of 31 December 1976 was ascertained for 90% of the cohort: 278 were alive and 42 were dead; those whose vital status was unknown were assumed to be alive as of the closing date of the study. Mortality among the cohort was compared to that of US white males, adjusted for age and calendar time. Fewer cancers occurred than expected (SMR, 0.68; 6 deaths; 95% CI, 0.25-2.5). For respiratory cancer, an SMR of 1.3 was obtained (4 deaths, 95% CI, 0.34-3.2). Observed SMRs for all cancers combined by years since first employment at the plant were none for < 10 years, one (3.7 expected) for 10-19 years and five (3.8 expected) for 20 or more years.

Subjects enrolled in 1971-73 in a national programme to monitor the health effects of exposures to pesticides were followed to 1977 to ascertain mortality and morbidity (details of the design of this study are presented in the monograph on occupational exposures in spraying and application of insecticides, p. 62) (Morgan *et al.*, 1980). Blood samples were obtained from each of the 3669 volunteers on their entry into the study and analysed for serum DDT and DDE levels. The geometric mean for volunteers who developed cancer was similar to that of those who did not (43 ppb and 45 ppb, respectively). [Relative risks for cancer were not presented by serum DDT and DDE level.]

Cohort studies on DDT are summarized in Table 6.

Table 6. Cohort studies of populations exposed to DDT

Reference	Cancer site	No. of cases	Relative risk	95% CI	Comments
Austin *et al.* (1989)	Respiratory cancer	5 (low DDT) 7 (medium) 7 (high)	1.0 1.5 1.8	 0.5-4.9 0.5-6.2	Exposure levels based on serum levels of DDT (p for trend = 0.34) Respiratory cancer in total cohort: SMR, 1.2
Wong *et al.* (1984)	Lung Leukaemia [Lymphomas	9 2 1	1.5 2.1 0.7	0.68-2.8 0.24-7.6 0.0-5.8]	Workers at a DDT manufacturing plant; also exposed to other pesticides Nested case-control analysis gave odds ratio = 0.74 for DDT exposure
Ditraglia *et al.* (1981)	Respiratory system Lymphatic and haematopoietic system	4 0	1.3 –	0.34-3.2 –	Workers at a DDT manufacturing plant; no death from skin, brain, bladder cancer or leukaemia

2.2 Case-control studies

2.2.1 *Based on measured levels in tissues*

Caldwell *et al.* (1981) compared serum levels of DDT in 10 children with colorectal cancer diagnosed between 1974 and 1976 and 24 controls without a malignancy who had visited a health clinic. The cases were aged 14-19 years and the controls, 5-18 years. One case was deleted because no information on exposure could be found. The mean serum level of DDT was 65.6 ppb (μg/l) for the remaining cases and 28.3 ppb for the 24 controls. When two cases with very high levels (in excess of 200 ppb) were excluded, the mean level was 22.9 ppb.

Unger and Olsen (1980) analysed the levels of polychlorinated biphenyls and DDE in adipose tissue from people in Denmark who had died of cancer. In an extension of this study (Unger *et al.*, 1982), adipose tissue was obtained *post mortem* from 51 cancer cases and 63 noncancer cases between 1978 and 1980. Ten of the patients had died from cancer of the gut, 13 from lung cancer and the remainder from various other types. The controls had died of apoplexy (11), coronary or vascular disease (28) and various other diseases. Mean levels of DDE were higher (5.5 ppm) among the cancer cases than among the controls (3.4 ppm). Mean levels of polychlorinated biphenyls were also higher among the cancer cases than among the noncancer cases (10.2 ppm and 6.1 ppm, respectively). [The Working Group noted that it was difficult to separate the effects of the two compounds in the published reports.]

Breast fat tissue was obtained from 14 patients with breast cancer and 21 patients with other breast disorders who were undergoing breast surgery. Mean DDE levels were similar in the cancer cases (1.23 ppm) and the controls (1.25 ppm) (Unger *et al.*, 1984).

[Measurement of tissue levels of DDT provides information on individual exposure to DDT, but the Working Group was concerned that levels determined after diagnosis of cancer, particularly in serum, may be affected by the disease process.]

2.2.2 *Lymphatic and haematopoietic tissues*

The risk for non-Hodgkin's lymphoma from exposure to DDT was evaluated in a population-based case-control study in Washington State, USA (Woods *et al.*, 1987). The design of this investigation is given in detail in the monograph on occupational exposures in spraying and application of insecticides (p. 67). A total of 576 patients with non-Hodgkin's lymphoma and 694 controls were interviewed to obtain information on pesticide use. The odds ratio for non-Hodgkin's lymphoma was 1.8 (95% CI, 1.0-3.2) among those reporting use of DDT. Adjustment for other agricultural exposures did not substantially change this estimate. When the analysis was restricted to farmers (Woods & Polissar, 1989), the odds ratio for exposure to DDT was 1.7 (95% CI, 0.9-3.3).

In the case-control study on leukaemia in Iowa and Minnesota, USA, described in detail in the monograph on occupational exposures in spraying and application of insecticides (p. 68), the odds ratio for leukaemia was 1.2 (95% CI, 0.7-1.8) for use of DDT on crops and 1.3 (1.0-1.8) for use on animals. The odds ratio for leukaemia rose with frequency of reported use of DDT on animals from 0.6 (95% CI, 0.3-1.4; 7 cases) for fewer than five days of use per year, 1.1 (0.4-2.7; 7 cases) for 5-9 days, to 2.1 (1.1-3.9; 21 cases) for 10 or more days. No such pattern was evident for use of DDT on crops. Elevated risks for both chronic lymphatic and

chronic myeloid leukaemia were found among farmers who used DDT: the odds ratios were 1.5 (0.9-2.3; based on 36 cases) and 1.9 (0.9-4.2; 10 cases), respectively (Brown *et al.*, 1990).

Cases of chronic lymphatic leukaemia diagnosed in five hospitals in Sweden between 1964 and 1984 in patients who survived after 1981 were compared with population controls living in the catchment areas of the hospitals. The study design is described in the monograph on occupational exposures in spraying and application of insecticides (p. 68). Results of a stratified analysis based on a confounder score including age, sex, exposure to fresh wood, solvents, exhausts, DDT, horses and employment as farmer were presented. Exposure to DDT was reported by six cases and four controls; the odds ratio was 6.0 (95% CI, 1.5-23) (Flodin *et al.*, 1988). [The Working Group noted the limitation of inclusion of prevalent cases because of the potential influence on recall of exposure.]

A study on Hodgkin's disease and B-cell non-Hodgkin's lymphomas was conducted in one of the areas included in the study summarized above (Persson *et al.*, 1989) and described in the monograph on occupational exposures in spraying and application of insecticides (p. 69). The same criteria were applied for selection of cases, and the same series of controls was used. Logistic regression analysis was carried out including sex, age, occupation in farming, exposure to fresh wood and all exposures resulting in a crude odds ratio greater than 2.0. Exposure to DDT was reported by three patients with Hodgkin's disease, none with non-Hodgkin's lymphoma and three controls. The odds ratio for Hodgkin's disease was 7.5 (90% CI, 0.8-70) [The limitation of the study by Flodin *et al.* (1988) noted above also applies to this study.]

In the case-control study of malignant lymphomas in northern Sweden described in the monograph on occupational exposures in spraying and application of insecticides (p. 69) (Hardell *et al.*, 1981), 22 cases and 26 controls reported exposure to DDT [odds ratio, 1.8; 95% CI, 1.0-3.2]. Seven cases and 11 controls reported exposure to DDT and not to phenoxyacetic acid herbicides [odds ratio, 1.6; 95% CI, 0.6-4.1]. Information was not presented separately for Hodgkin's disease and non-Hodgkin's lymphoma.

Case-control studies on cancers of lymphatic and haematopoietic tissues and exposure to DDT are summarized in Table 7.

2.2.3 *Soft-tissue sarcoma*

Four population-based case-control studies in Sweden assessed the risk of soft-tissue sarcoma, primarily in association with exposure to phenoxyacetic acid herbicides and chlorophenols (Hardell & Sandström, 1979; Eriksson *et al.*, 1981; Hardell & Eriksson, 1988; Eriksson *et al.*, 1990a). The studies are described in detail in the monograph on occupational exposures in spraying and application of insecticides (pp. 69-70). In the first study, in northern Sweden, four cases and 14 controls reported exposure to DDT (crude odds ratio, 1.2 [95% CI, 0.4-3.7] (Hardell & Sandström, 1979). In the second study, in southern Sweden, seven cases and 11 controls reported exposure to DDT [crude odds ratio 1.3; 95% CI, 0.5-3.4] (Eriksson *et al.*, 1981). In the third study, in northern Sweden, six cases, 19 population-based controls and eight cancer controls reported exposure to DDT [crude odds ratio, 1.9; 95% CI, 0.7-5.0 (population controls); crude odds ratio, 2.7; 95% CI, 0.9-7.8 (cancer controls)]. One case, 10 population-based controls and three cancer controls

Table 7. Case-control studies of cancers of lymphatic and haematopoietic tissues containing information of exposure to DDT

Reference Location	Cancer site	No. of exposed cases/ controls	Relative risk	95% CI	Comments
Woods *et al.* (1987); Woods & Polissar (1989) Washington State, USA	Non-Hodgkin's lymphoma	Not reported	1.8	1.0-3.2	Not adjusted for other agricultural exposures
		Not reported	1.7	0.9-3.3	Farmers only
Persson *et al.* (1989) Sweden	Non-Hodgkin's lymphoma	0/3	–	–	Adjusted for some other agricultural exposures
	Hodgkin's disease	3/3	7.5	0.8-70	90% CI
Hardell *et al.* (1981) Northern Sweden	Malignant lymphoma	22/26	[1.8]	[1.0-3.2]	Crude risk calculated from data in paper. Not adjusted for other agricultural exposures.
		7/11	[1.6]	[0.6-4.1]	Crude risk for DDT, without exposure to phenoxyacetic acid herbicides
Brown *et al.* (1990) Iowa and Minnesota, USA	Leukaemia	35/75 80/149	1.2 1.3	0.7-1.8 1.0-1.8	DDT used on crops DDT used on animals Not adjusted for other agricultural exposures; risks increased with duration of use[a]
	Chronic lymphatic leukaemia	36	1.5	0.9-2.3	DDT used on crops and animals[b]
	Chronic myeloid leukaemia	10	1.9	0.9-4.2	
Flodin *et al.* (1988) Sweden	Chronic lymphatic leukaemia	6/4	6.0	1.5-23	Adjusted for other agricultural exposures

[a]Increased risks reported also in association with exposure to other insecticides
[b]No data provided for other subtypes of leukaemia

reported exposure to DDT without exposure to phenoxyacetic acid herbicides [crude odds ratio, 0.6 (95% CI, 0.1-5.0)] for population controls and [1.2 (95% CI, 0.1-12.1)] for cancer controls (Hardell & Eriksson, 1988). In the fourth study, from central Sweden, exposure to DDT was reported by 22 cases and 33 controls (odds ratio, 0.61; 95% CI, 0.34-1.1) (Eriksson *et al.*, 1990a).

In the case-control study on soft-tissue sarcomas in Kansas, USA, also described in the monograph on occupational exposures (p. 66), an odds ratio of 2.3 (95% CI, 0.9-5.6, based on 10 exposed cases and 28 exposed controls) was reported for use of DDT on animals (Hoar Zahm *et al.*, 1988). In the population-based case-control study of soft-tissue sarcoma in

Washington State, USA (Woods *et al.*, 1987) (see p. 67), the odds ratio for soft-tissue sarcoma was 1.1 (0.4-3.2).

Case-control studies on soft-tissue sarcoma and exposure to DDT are summarized in Table 8.

Table 8. Case-control studies of soft-tissue sarcoma containing information on exposure to DDT

Reference Location	No. of exposed cases/ controls	Relative risk	95% CI	Comments
Hardell & Sandström (1979) Sweden	4/14	1.2	[0.4-3.7]	Not adjusted for other agricultural exposures
Eriksson *et al.* (1981) Sweden	7/11	[1.3]	[0.5-3.4]	Crude risk calculated from data in paper; not adjusted for other agricultural exposures
Hardell & Eriksson (1988) Sweden	6/19 6/8	[1.9][a] [2.7][b]	[0.7-5.0] [0.9-7.8]	Crude risk calculated from data in paper; not adjusted for other agricultural exposures
	1/10 1/3	[0.6][a] [1.2][b]	[0.1-5.0] [0.1-12.1]	Crude risk for exposure to DDT and not phenoxyacetic acids
Eriksson *et al.* (1990a) Sweden	22/33	0.61	0.34-1.1	Not adjusted for other agricultural exposures
Hoar Zahm *et al.* (1988) Kansas, USA	10/28	2.3	0.9-5.6	DDT on animals[c]; not adjusted for other agricultural exposures
Woods *et al.* (1987) Washington, USA	Not reported	1.1	0.4-3.2	Not adjusted for other agricultural exposures

[a]Population controls
[b]Cancer controls
[c]No data provided for DDT use on crops

2.2.4 *Other cancers*

A proportionate analysis of occupational mortality in Washington State, USA, identified a 30% increased risk for respiratory cancer among orchardists (Milham, 1983), and a case-control study was thus undertaken in Washington State in 1968-80 (Wicklund *et al.*, 1988). The design of the study is described in the monograph on occupational exposures in spraying and application of insecticides (p. 70). A total of 89 cases and 89 controls were assumed to have had exposure to DDT. When men exposed to DDT but not to lead arsenate were considered, there were 33 cases and 29 controls, and the odds ratio (adjusted for smoking) was 0.91 (95% CI, 0.40-2.1). [The Working Group noted that the unexposed group included men for whom details on exposure to DDT were not available, which may have biased the odds ratio towards the null.]

Two case-control studies in Sweden examined the risks for colon cancer (Hardell, 1981) and nasal and nasopharyngeal cancer (Hardell *et al.*, 1982), primarily in relation to exposure

to phenoxyacetic acid herbicides and chlorophenols. These studies are described in the monograph on occupational exposures (p. 71). Odds ratios for exposure to DDT, without controlling for other agricultural exposures, were [0.8; 0.4-1.7] for colon cancer and [1.2; 95% CI, 0.5-2.9] for nasal and nasopharyngeal cancer. In the study of colon cancer, exposure to DDT was also analysed after excluding subjects who had been exposed to phenoxyacetic acids and chlorophenols; the odds ratio was [0.5; 0.2-1.6].

Men aged 25-80 who had been diagnosed with liver cancer between 1974 and 1981 and reported to the Department of Oncology, Umeå, Sweden, were included in another case-control study (Hardell *et al.*, 1984), described in the monograph on occupational exposures (p. 71). Odds ratios for exposure to DDT, without controlling for other agricultural exposures, were [0.4; 95% CI, 0.1-1.1] for exposure to DDT in farming and [1.3; 0.4-4.0] for exposure to DDT in forestry.

These studies are summarized in Table 9.

Table 9. Case-control studies of other cancers containing information of DDT exposure

Reference Location	Cancer	No. of exposed cases/ controls	Relative risk	95% CI	Comments
Hardell (1981) Sweden	Colon	9/40	[0.8]	[0.4-1.7]	Crude risk calculated from data in paper; not adjusted for other agricultural exposures
	Colon	3/21	[0.5]	[0.2-1.6]	Crude risk calculated from data in paper; for exposure to DDT and not phenoxyacetic acids or chlorophenols
Hardell *et al.* (1982) Sweden	Nose, naso-pharynx	6/40	[1.2]	[0.5-2.9]	Crude risk calculated from data in paper; not adjusted for other agricultural exposures
Hardell *et al.* (1984) Sweden	Primary liver	4/20	[0.4]	[0.1-1.1]	Crude risk calculated from data in paper; not adjusted for other agricultural exposures; farmers
	Primary liver	5/8	[1.3]	[0.4-4.0]	Crude risk calculated from data in paper; not adjusted for other agricultural exposures; foresters
Wicklund *et al.* (1988) USA	Respiratory	33/29	0.9	0.40-2.1	Both cases and controls were orchard workers

3. Studies of Cancer in Experimental Animals

The carcinogenicity of DDT in experimental animals has been reviewed (Cabral, 1985).

The Working Group was aware of studies of *para,para'*-DDT by oral and subcutaneous administration and by skin application in mice, rats, hamsters and trout by Bennison and Mostofi (1950; mice, skin), Halver (1967; trout), Weisburger and Weisburger (1968; rat, oral), Gargus *et al.* (1969; mice, subcutaneous), the US National Technical Information Service (1968) and Innes *et al.* (1969; mice; *para,para'*-TDE, oral and subcutaneous; DDT, subcutaneous), Agthe *et al.* (1970; hamster, oral), Shabad *et al.* (1973; mice, oral) and Lacassagne and Hurst (1965; rat; *ortho,para'*-TDE, oral). These were considered in the previous IARC monograph (IARC, 1974). Studies of oral administration of DDT to mice (Del Pup *et al.*, 1978; Reuber, 1979; Lipsky *et al.*, 1989) and rats (Shivapurkar *et al.*, 1986) were considered but are not summarized here since they do not contribute to an evaluation of carcinogenicity.

Because of the large number of studies, histopathological findings are summarized for some studies in Table 10 at the end of this section (p. 209).

3.1 Oral administration

3.1.1 *Mouse*

In 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, seven days old, were given daily single doses of 46.4 mg/kg bw (maximum tolerated dose) *para,para'*-DDT [purity unspecified] by stomach tube, followed by daily administration of the same absolute amount until 28 days of age, at which time the mice were transferred to a diet containing 140 mg/kg *para,para'*-DDT. Animals were killed at 81 weeks of age. About 30% of females of both strains died during the treatment. Hepatomas were found in male and female mice of each strain, and malignant lymphomas were found in (C57Bl/6 × AKR)F_1 females (see Table 10) (US National Technical Information Service, 1968; Innes *et al.*, 1969).

In a five-generation study, originally designed to investigate the effects of DDT on behaviour, one treated and one control group of BALB/c mice were taken from each of the five generations and studied for tumour incidence. A total of 683 mice received a diet containing 2.8-3 mg/kg *para,para'*-DDT ([purity unspecified] melting-point, 108-109°C), and 406 received a control diet. Lung carcinomas were observed in 116 of the treated mice and in five controls [$p < 0.001$]. [The incidence of lung adenomas was not reported, although the authors noted an average incidence of 5% in their colony of mice.] The incidence of leukaemias was 85/683 in treated mice (64 in females) and 10/406 in controls [$p < 0.001$] (see Table 10) (Tarján & Kemény, 1969).

In a two-generation dose-response study, 939 treated and 242 control CF-1 mice were fed dietary concentrations of 0 or 2, 10, 50 or 250 mg/kg technical-grade DDT (73-78% *para,para'*-DDT, 20% *ortho,para'*-DDT, 1% *meta,para'*-DDT, 0.5-1.5% *para,para'*-TDE and 0.5% *para,para'*-DDE), starting at 6-7 weeks of age for the parent (P) generation and continuing in the P and offspring (F_1) for life. There was excess mortality from week 60 onwards among mice of the P and F_1 generations that had received 250 mg/kg of diet DDT.

Only the incidence of liver-cell tumours was increased by exposure to DDT: males, 25/113 (controls), 57/124, 52/104, 67/127, 82/103 in treated groups; females, 4/111 (controls), 4/105, 11/124, 13/104, 60/90 in treated groups. The excess of liver-cell tumours over that in controls in mice of each sex fed 250 mg/kg of diet DDT was significant ($p < 0.01$). The excess over that in controls of liver-cell tumours in males fed 2, 10 or 50 mg/kg of diet was significant ($p < 0.01$) in animals surviving more than 70 weeks. In females, all liver-cell tumours were found after 100 weeks of age, and the excess over that controls was significant ($p < 0.05$) in the group fed 50 mg/kg diet DDT and ($p < 0.01$) in the group fed 250 mg/kg of diet DDT. Four liver-cell tumours, all occurring in DDT-treated mice, gave metastases. No remarkable difference was observed between P and F_1 mice in this study (Tomatis *et al.*, 1972).

In a continuation of this study (Turusov *et al.*, 1973), the effects of the same doses of DDT were studied in six consecutive generations of CF-1 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 DDT significantly increased the incidence of liver-cell tumours (hepatomas) in males; in females, hepatoma incidence increased considerably after exposure to 250 mg/kg (see Table 10). No progressive increase in hepatoma incidence from generation to generation was noted in treated mice. Malignant hepatoblastomas were observed at a slightly increased incidence in DDT-treated male mice: 3/328 in control males, 5/354, 14/362, 12/383 and 25/350 in 2, 10, 50 and 250 ppm DDT-treated males, respectively [positive trend, $p < 0.001$]. Ten of 56 hepatoblastomas found in DDT-treated mice metastasized to the lungs. DDT did not alter significantly the tumour incidence at sites other than the liver.

In a two-generation study, 515 female and 430 male BALB/c mice were administered dietary concentrations of 0, 2, 20 or 250 mg/kg technical-grade DDT (70-75% *para,para'*-DDT, 20% *ortho,para'*-DDT and 0.2-4% *para,para'*-TDE) 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 (at the high dose) because of toxicity. In animals that survived more than 60 weeks, only liver-cell tumours were found in excess, and only at 250 mg/kg of diet was the increase significant (see Table 10) (Terracini *et al.*, 1973a). Confirmatory results were obtained in two subsequent generations of BALB/c mice fed DDT, although F_1, F_2 and F_3 mice, which were exposed to DDT both *in utero* and after birth for life, developed more liver tumours than did P mice, which were exposed to DDT only after weaning (Terracini *et al.*, 1973b).

Groups of 30-32 CF-1 mice of each sex were fed diets containing 50 or 100 mg/kg *para,para'*-DDT (purity, > 99.5%) for two years. A control group of 47 mice of each sex was available. A significant increase in the incidence of liver-cell tumours was observed in treated males and females (see Table 10) (Walker *et al.*, 1973).

In a subsequent study, 30 male and 30 female CF-1 mice were fed 100 mg/kg of diet *para,para'*-DDT (> 99.5% pure) for 110 weeks. The animals were not sent for autopsy until the intra-abdominal masses reached a size that caused the animals to become anorexic or clinically affected. A significant increase ($p < 0.01$) in the incidence of liver tumours (23/30 males and 26/30 females compared with 11/45 and 10/44 controls, respectively) was observed within 26 months (see Table 10) (Thorpe & Walker, 1973).

Groups of 30 male and 30 female Swiss inbred mice, six weeks of age, were held as untreated controls or were given technical-grade DDT (70.5% *para,para'*-DDT, 21.3% *ortho,para'*-DDT) orally as 100 mg/kg of diet DDT or by daily gavage of 0.25 mg DDT in olive oil for 80 weeks. Survival (37-54%) and weight gains were not affected by treatment. The incidence of lymphomas was significantly increased ($p < 0.05$) in treated males and females (see Table 10) (Kashyap *et al.*, 1977). [The Working Group noted the small number of animals used.]

Groups of 50 male and 50 female $B6C3F_1$ mice, six weeks old, were fed diets containing technical-grade DDT (principal component, about 70%, assumed to be *para,para'*-DDT) for 78 weeks and were then held for 14 or 15 additional weeks before terminal sacrifice. Groups of 20 mice were fed a control diet for 91 or 92 weeks. Initially, males received diets containing 10 or 20 mg/kg and females received diets containing 50 or 100 mg/kg DDT; after nine weeks, these concentrations were gradually increased up to 25 and 50 mg/kg of diet for males and 100 and 200 mg/kg of diet for females because of the absence of toxicity. The time-weighted average dietary concentrations were 22 and 44 mg/kg of diet 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 control, 20/50 low-dose and 37/50 high-dose animals; terminal survival of female mice was 20/20 control, 45/50 low-dose and 36/50 high-dose animals. There was no difference in body weight gain between treated and control mice. The incidence of malignant lymphoma was increased in females (control, 0/20; low-dose, 3/49; high-dose, 7/46 [$p < 0.05$, trend test]) (see Table 10) (US National Cancer Institute, 1978). [The Working Group noted that females received four times higher doses than males.]

3.1.2 *Rat*

In two two-year experiments started at an interval of one year, 228 Osborne-Mendel rats, three weeks of age, received diets containing technical-grade DDT (81.8% *para,para'*-DDT, 18.2% *ortho,para'*-DDT) as a powder or as a solution in corn oil at concentrations of 0 (24 males and 12 females), 100 (12 males), 200 (24 males and 12 females), 400 (24 males and 12 females), 600 (24 males and 24 females) or 800 (36 males and 24 females) mg/kg of diet. Of the 192 rats exposed to DDT, 111 died before 18 months of treatment; only 14 rats given 800, 23 rats given 600, 14 given 400, 24 given 200, six given 100 mg/kg of diet and 20 controls were alive at this time. Tumour incidences were not given for each dose level. Among the 81 rats that survived at least 18 months, four had 'low-grade' hepatic-cell carcinomas (measuring 0.5-1.2 cm), and 11 showed nodular adenomatous hyperplasia (nodules measuring up to 0.3 cm). No liver lesion was found in control rats. Hepatic-cell tumours were reported to occur spontaneously in 1% of the rats of this colony and nodular adenomatous hyperplasia was reported to be rare (Fitzhugh & Nelson, 1947). [The Working Group noted the inadequate reporting.] An unspecified amount of histopathological material from this study was reviewed by Reuber (1978), who confirmed the presence of neoplastic liver lesions in treated animals.

In two experiments reported from the same institution, groups of 30 male and 30 female Osborne-Mendel rats were exposed from weaning for at least two years to either 80 or 200 mg/kg of diet DDT [purity unspecified] and were compared to two control groups of 30

animals of each sex. Undifferentiated bronchogenic carcinomas were seen in 2/120 controls (two experiments combined), in 8/60 rats (males and females combined) fed 80 mg/kg of diet DDT, and in none of the animals receiving 200 mg/kg of diet DDT. One hepatoma occurred in a control female in one experiment and another in a female given 200 mg/kg of diet DDT. Incidences of other tumours were similar in control and treated rats (see Table 10) (Radomski *et al.*, 1965; Deichmann *et al.*, 1967).

Groups of 36 or 37 male and 35 female outbred Wistar rats, seven weeks of age, were fed a control diet or a diet containing 500 mg/kg of diet technical-grade DDT (70-75% *para,para'*-DDT, 20% *ortho,para'*-DDT, 0.2-4% *para,para'*-TDE) until 152 weeks of age. Survival was not affected by the treatment and was greater than 50% at 100 weeks in all groups. Body weight gains were decreased by 10-20% in the treated groups as compared to 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 (neoplastic nodules) was increased in treated males (9/37; controls, 0/36) [$p = 0.001$] and females (15/35; controls, 0/35) [$p < 0.001$] (see Table 10) (Rossi *et al.*, 1977).

Groups of 50 male and 50 female Osborne-Mendel rats, seven weeks of age, were fed diets containing technical-grade DDT (principal component, 70%, assumed to be *para,para'*-DDT) for 78 weeks and killed at 111 weeks. The initial concentrations of DDT were 420 or 840 mg/kg of diet for males and 315 or 630 mg/kg of diet for females; these concentrations were subsequently increased to 500 and 1000 and then decreased to 250 and 500 mg/kg of diet for males and were decreased to 158 and 315 mg/kg of diet for females when signs of toxicity (tremors) appeared. The time-weighted average concentrations were 321 and 642 mg/kg of diet for males and 210 and 420 mg/kg of diet for females. Groups of 20 males and 20 females received a control diet. Body weights of high-dose rats were lower than those of controls by as much as 15% during the study. Survival was not affected by the treatment. There was no increase in the incidence of tumours that could be attributed to treatment with DDT (US National Cancer Institute, 1978). [The Working Group noted the short duration of treatment.]

Groups of 38 male and 38 female MRC Porton rats, six to seven weeks of age, were fed control diet or a diet containing 500 mg/kg technical-grade DDT (78.9% *para,para'*-DDT, 16.7% *ortho,para'*-DDT, 1.6% *para,para'*-DDE, 0.6% *para,para'*-TDE, 0.2% *ortho,para'*-DDE, 0.1% *ortho,para'*-TDE and 1.9% unknown) for 144 weeks. Groups of 30 male and 30 female rats received diets containing 125 or 250 mg/kg of diet DDT. Survival and body weight gains were not significantly different between treated and control groups; survival at 80 weeks was greater than 70% in all groups except that of high-dose males (61%). The incidence of liver-cell tumours was significantly increased in female rats (0/38 control, 2/30 low-dose, 4/30 mid-dose, 7/38 high-dose; $p < 0.001$, trend test). Liver-cell nodules [hyperplastic] or foci of cellular alteration occurred significantly more frequently ($p < 0.05$) in low- and mid-dose females than in controls. Residues of DDT, TDE and DDE in liver, determined in three male and three female high-dose rats killed at 52 weeks, were on average 2.5 times higher in females than males (Cabral *et al.*, 1982a).

3.1.3 *Hamster*

Groups of 30-40 male and 29-40 female outbred Syrian golden hamsters, five weeks old, were fed for life on diets containing 0, 125, 250 or 500 mg/kg of diet technical-grade DDT (78.9% *para,para'*-DDT, 16.7% *ortho,para'*-DDT, 1.6% *para,para'*-DDE, 0.6% *para,para'*-TDE, 0.2% *ortho,para'*-DDE, 0.1% *ortho,para'*-TDE and 1.9% unknown). Survival and body weight gains were comparable between treated and control animals. The experiment was terminated at 120 weeks when the last survivor was killed. There was no significant difference in tumour incidence in the various groups; however, a significant trend was observed for tumours of the adrenal cortex (mostly adenomas) in males: 3/40 control, 4/30 low-dose, 6/31 mid-dose and 8/39 high-dose [$p = 0.04$] (Cabral *et al.*, 1982b).

Groups of 45 or 48 male and 46 or 48 female Syrian golden hamsters, eight weeks old, were fed diet containing 0 or 1000 mg/kg DDT (70-75% *para,para'*-DDT, 20% *ortho,para'*-DDT, 0.2-4% *para,para'*-TDE) until 128 weeks of age. Survival was 60% or greater in all groups at 80 weeks. Adrenal gland tumours ('mainly cortical adenomas') occurred in 14/35 treated males compared to 8/31 male controls [$p > 0.05$] and in 10/36 treated females compared to 2/42 female controls [$p < 0.01$] (see Table 10) (Rossi *et al.*, 1983).

Groups of 30 male and 30 female hamsters [strain unspecified] were given diets containing 0, 250, 500 or 1000 mg/kg technical-grade DDT for 18 months. No difference in body weight gains between groups was observed. Mean survival time ranged from 13 to 14.9 months in male and female control groups, to 17.3 and 17.1 months in high-dose male and female groups. The incidence of lymphosarcomas was reduced from 50% in male controls and 41% in female controls to 0 in the high-dose groups of each sex (Graillot *et al.*, 1975). [The Working Group noted the short duration of treatment.]

3.2 Skin application

Mouse: Groups of 30 male and 30 female Swiss inbred mice, six weeks of age, were held as untreated controls or were administered 0.25 mg/animal technical-grade DDT (70.5% *para,para'*-DDT, 21.3% *ortho,para'*-DDT) in 0.1 ml olive oil twice weekly by skin application for 80 weeks. Survival (40-57%) and weight gains were not affected by treatment, and no increase in tumour incidence was observed (Kashyap *et al.*, 1977). [The Working Group noted the short duration of treatment.]

3.3 Subcutaneous and/or intramuscular injection

Mouse: Groups of 30 male and 30 female Swiss inbred mice, six weeks of age, were held as untreated controls or received twice-monthly subcutaneous injections of 0.25 mg/animal technical-grade DDT (70.5% *para,para'*-DDT, 21.3% *ortho,para'*-DDT) in 0.1 ml olive oil for 80 weeks. Survival (40-57%) and weight gain were not affected by treatment. The incidence of liver-cell carcinomas was 7/26 in treated females and 0/20 in control females [$p = 0.01$] (see Table 10) (Kashyap *et al.*, 1977).

3.4 Studies with known carcinogens

Rat: Dietary intake of DDT was found to promote 2-acetylaminofluorene-induced tumorigenesis in rat liver, in a way similar to that of phenobarbital (Peraino *et al.*, 1975). It also significantly shortened the latent period for the appearance of mammary tumours in rats treated with 2-acetamidophenanthrene (Scribner & Mottet, 1981).

3.5 Carcinogenicity of metabolites

TDE

Mouse: A group of 60 male and 60 female CF-1 mice, 6-7 weeks old, was fed a diet containing 250 mg/kg *para,para'*-TDE (99% pure) until 130 weeks of age; 100 males and 90 females served as controls. The incidence of hepatomas was significantly increased in treated males, and the incidences of lung tumours were significantly increased in males and females compared with controls (see Table 10) (Tomatis *et al.*, 1974).

Groups of 50 male and 50 female $B6C3F_1$ mice, six weeks of age, were fed diets initially containing 315 or 630 mg/kg technical-grade TDE (principal component, 60%, assumed to be *para,para'*-TDE, 19 unidentified impurities) for 78 weeks and were killed at 90 weeks. The dietary concentrations were increased to 425 and 850 mg/kg due to lack of toxicity. The time-weighted average dietary concentrations were 411 and 822 mg/kg of diet. Further groups of 20 males and 20 females were fed control diets. Body weight gain of high-dose females was somewhat reduced late in the study. Survival was not affected by treatment; terminal survival was 13/20 control, 30/50 low-dose and 27/50 high-dose males and 18/20 control, 41/50 low-dose and 44/50 high-dose females. There was no significant increase in the incidence of hepatocellular carcinomas (see Table 10) (US National Cancer Institute, 1978). [The Working Group noted the short duration of treatment.]

Rat: Groups of 50 male and 50 female Osborne-Mendel rats, seven weeks of age, were fed diets containing technical-grade TDE (principal component, 60%, assumed to be *para,para'*-TDE, 19 unidentified impurities) for 78 weeks and were killed at 111 weeks. The initial dietary concentrations for male rats of 1400 or 2800 mg/kg were increased to 1750 and 3500 mg/kg due to lack of toxicity. Females received diets containing 850 or 1700 mg/kg of diet throughout the study. The time-weighted average concentrations given to males were 1647 and 3294 mg/kg of diet. Further groups of 20 males and 20 females were fed control diets. Body weight gains were substantially reduced in high-dose rats and somewhat reduced in low-dose rats compared to controls. Survival was not affected by treatment. Increased incidences of tumours of the thyroid gland were seen in animals of each sex, but significance was reached only for follicular-cell adenomas and carcinomas combined in low-dose males ($p < 0.05$) (see also Table 10) (US National Cancer Institute, 1978).

DDE

Mouse: A group of 60 male and 60 female CF-1 mice, 6-7 weeks old, was fed a diet containing 250 mg/kg *para,para'*-DDE (99% pure) until 130 weeks of age. A group of 100 males and 90 females was used as controls. An increased incidence of hepatomas was found in treated males and treated females compared with controls (see Table 10) (Tomatis *et al.*, 1974).

Groups of 50 male and 50 female $B6C3F_1$ mice, six weeks of age, were fed diets containing *para,para'*-DDE (> 95% pure) for 78 weeks and were killed at 92 weeks. The initial dietary concentrations of 125 and 250 mg/kg of diet were increased during the study to 150 and 300 mg/kg due to lack of toxicity. When toxicity became apparent, the concentrations in the diet were held constant, but the high-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 males and females,

respectively. Further groups of 20 males and 20 females were fed control diets. Body weight gain was reduced somewhat in treated females compared to controls. At 70 weeks survival was 5/20 control, 35/50 low-dose and 31/50 high-dose males; at 75 weeks, survival in females was 19/20 control, 47/50 low-dose and 28/50 high-dose animals. The incidences of hepatocellular carcinoma were 0/19 control, 7/41 low-dose and 17/47 high-dose males and 0/19 control, 19/47 low-dose and 34/48 high-dose females ($p < 0.001$ for both low- and high-dose female mice and $p = 0.001$ for high-dose males) (see Table 10) (US National Cancer Institute, 1978). [The Working Group noted the low survival and the frequent changes in dietary concentrations of DDE.]

Rat: Groups of 50 male and 50 female Osborne-Mendel rats, seven weeks of age, were fed diets containing *para,para'*-DDE (> 95% pure) for 78 weeks and were killed at 111 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 and 675 mg/kg of diet for males and 187 and 375 for females due to the onset of toxic signs. Additionally, the high-dose diets were replaced by control diet every fifth week during the latter part of the study. 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. Further groups of 20 males and 20 females were fed control diets. Body weight gains were somewhat reduced in treated male and high-dose female rats compared to controls. Survival at 92 weeks was 16/20 control, 34/50 low-dose and 26/50 high-dose males and 20/20 control, 42/50 low-dose and 36/50 high-dose females. No increase in tumour incidence was observed (US National Cancer Institute, 1978). [The Working Group noted the short duration of treatment.]

Hamster: Groups of 40-47 male and 43-46 female Syrian golden hamsters, eight weeks old, were fed a control diet or a diet containing 500 or 1000 mg/kg *para,para'*-DDE (purity, 99%) until 128 weeks of age. Survival was 50% or greater in all groups at 80 weeks. There were significantly ($p < 0.05$) increased incidences of liver-cell tumours (neoplastic nodules) in both groups of treated males and females: males—control, 0/10; low-dose, 7/15; and high-dose, 8/24; females—control, 0/31; low-dose, 4/26; and high-dose, 5/24 (Rossi *et al.*, 1983).

4. Other Relevant Data

The toxicokinetics of DDT has been reviewed (WHO, 1979; FAO/WHO, 1964, 1965, 1967b, 1968b, 1970b, 1980a; Hayes, 1982; FAO/WHO, 1985; Agency for Toxic Substances and Diseases Registry, 1989).

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

DDT is absorbed by all routes; its fate and its metabolism in man was studied in volunteers receiving known quantities of technical-grade DDT (77% *para,para'*, 23% *ortho,para'*), *para,para'*-2,2-bis(*para*-chlorophenyl)acetic acid (DDA), *para,para'*-TDE or *para,para'*-DDE (Roan, 1970; Morgan & Roan, 1971; Roan *et al.*, 1971). DDT, TDE or DDA ingested at 5, 10 or 20 mg per day for 21-183 days was partly excreted as DDA in urine—most

Table 10. Summary of selected experimental carcinogenicity studies

Reference	Species/ strain	Sex	Dose schedule	Experimental parameter/ observation	Group					Statistical trend
					0	1	2	3	4	
DDT										
Innes *et al.* (1969)	Mouse (C57Bl/6 × C3H/ Anf)F_1	M	Gavage/day 28 days; in diet to 81 weeks of age	Dose (gavage; mg/kg bw)	0	46.4				
				Dose (mg/kg of diet)	0	140				
				Hepatoma	8/79	11/18**				NA
		F	Gavage/day 28 days; in diet to 81 weeks of age	Dose (gavage; mg/kg bw)	0	46.4				
				Dose (mg/kg of diet)	0	140				
				Hepatoma	0/87	4/18**				NA
	Mouse (C57Bl/6 × AKR)F_1	M	Gavage/day 28 days; in diet to 81 weeks of age	Dose (gavage; mg/kg bw)	0	46.4				
				Dose (mg/kg of diet)	0	140				
				Hepatoma	5/90	7/18**				NA
		F	Gavage/day 28 days; in diet to 81 weeks of age	Dose (gavage; mg/kg bw)	0	46.4				
				Dose (mg/kg of diet)	0	140				
				Hepatoma	1/82	1/18				
				Lymphoma	4/82	6/18**				NA
Tarján & Kemény (1969)		M & F	Diet 5-generation	Dose (mg/kg diet)	0	2.8-3				
				Lung carcinomas	5/406	116/683***				
				Leukaemia	10/406	85/683				
				Lymphosarcomas	1/406	15/683				NA
Turusov *et al.* (1973)	Mouse CF-1	M	Diet multi-generation	Dose (mg/kg diet)	0	2	10	50	250	
				Liver-cell tumours	97/328	179/354**	181/362**	214/383**	301/350**	
				Hepatoblastomas	3/328	5/354	14/362*	12/383*	25/350**	[$p < 0.001$]
		F	Diet multi-generation	Liver-cell tumours	16/340	12/339	32/355*	43/328**	192/293**	[$p < 0.001$]
Terracini *et al.* (1973a)	Mouse BALB/c	M	Diet for lifespan 2-generation	Dose (mg/kg of diet)	0	2	20	250		
				Liver-cell tumours[a]	1/62	3/48	0/48	14/31**		[$p < 0.001$]
				Malignant lymphoma	6/107	5/112	4/106	1/106		[$p = 0.04$]
		F	Diet for lifespan 2-generation	Dose (mg/kg of diet)	0	2	20	250		
				Liver-cell tumours[a]	0/124	0/130	1/126	71/115**		[$p < 0.001$]

Table 10 (contd)

Reference	Species/ strain	Sex	Dose schedule	Experimental parameter/ observation	Group					Statistical trend
					0	1	2	3	4	
Walker *et al.* (1973)	Mouse CF-1	M	Diet for 2 years	Dose (mg/kg of diet)	0	50	100			
				Liver-cell tumours	6/47	12/32*	17/32**			[$p < 0.001$]
		F	Diet for 2 years	Dose (mg/kg of diet)	0	50	100			
				Liver-cell tumours	8/47	15/30**	24/32**			[$p < 0.001$]
Thorpe & Walker (1973)	Mouse CF-1	M	Diet for 110 weeks	Dose (mg/kg of diet)	0	100				
				Liver-cell tumours	11/45	23/30**				NA
				Malignant lymphoma	16/45	4/30				[$p < 0.05$]
		F	Diet for 110 weeks	Dose (mg/kg of diet)	0	100				
				Liver-cell tumours	10/44	26/30**				NA
				Malignant lymphoma	16/44	6/30				
Kashyap *et al.* (1977)	Mouse Swiss	M	Diet or gavage for 80 weeks		Untreated	Diet	Gavage			
				Dose (mg/kg of diet) (mg/animal)	0	100	0.25			NS
				Lymphoma	2/26	8/27*	6/24			
				Lung adenoma	4/26	8/27	7/24			
		F	Diet or gavage for 80 weeks	Dose (mg/kg of diet) (mg/animal)	0	100	0.25			
				Lymphoma	2/20	8/22*	8/24			
				Lung adenoma	1/20	3/22	5/24			NS
US National Cancer Institute (1978)	Mouse $B6C3F_1$	F	Diet for 78-92 weeks	Dose (mg/kg of diet)	0	87	175			
				Survival (70 weeks)	20/20	45/50	36/50			
				Lymphoma	0/20	3/49	7/46			$p < 0.05$
Radomski *et al.* (1965); Deichmann *et al.* (1967)	Rat Osborne-Mendel	M & F	Diet for 2 years	Dose (mg/kg of diet)	0	80	200			
				Lung carcinoma	2/120	8/60*	0/60	NS		
		F	Diet for 2 years	Dose (mg/kg of diet)	0	80	200			
				Hepatoma	1/30	0/30	1/30			
Rossi *et al.* (1977)	Rat Wistar	M	Diet until 152 weeks of age	Dose (mg/kg of diet)	0	500				
				Liver-cell tumours	0/36	9/37**		NA		
		F	Diet until 152 weeks of age	Dose (mg/kg of diet)	0	500				
				Liver-cell tumours	0/35	15/35***		NA		

Table 10 (contd)

Reference	Species/ strain	Sex	Dose schedule	Experimental parameter/ observation	Group					Statistical trend
					0	1	2	3	4	
Cabral *et al.* (1982a)	Rat MRC Porton	F	Diet for 144 weeks	Dose (mg/kg of diet) Liver-cell tumours	0 0/38	125 2/30	250 4/30	500 7/38		$p < 0.001$
Cabral *et al.* (1982b)	Hamster Syrian golden	M	Diet for 120 weeks	Dose (mg/kg of diet) Adrenal cortex tumour (mostly adenomas)	0 3/40	125 4/30	250 6/31	500 8/39		[$p = 0.04$]
		F		Adrenal cortex tumour	0/39	0/28	1/28	3/40		NS
Rossi *et al.* (1983)	Hamster Syrian golden	M	Diet until 128 weeks of age	Dose (mg/kg of diet) Adrenal cortex tumour (mostly adenomas)	0 8/31	1000 14/35				NA
		F		Adrenal cortex tumour	2/42	10/36**				NA
Kashyap *et al.* (1977)	Mouse Swiss	F	Subcutaneous	Dose (mg/animal) Liver-cell carcinomas	0 0/20	0.25 7/26				[$p = 0.01$]
TDE										
Tomatis *et al.* (1974)	Mouse CF-1	M	Diet until 130 weeks of age	Dose (mg/kg of diet) Liver-cell tumours Lung tumours	0 33/98 53/98	250 31/59** 51/59**				NA
		F	Diet until 130 weeks of age	Dose (mg/kg of diet) Liver-cell tumours Lung tumours	0 1/90 37/90	250 1/59 43/59**				NA
US National Cancer Institute (1978)	Mouse $B6C3F_1$	M	Diet for 78 weeks	Dose (mg/kg of diet) Hepatocellular carcinoma	0 2/18	411 12/44	822 14/50			NS
		F	Diet for 78 weeks	Dose (mg/kg of diet) Hepatocellular carcinoma	0 0/20	411 2/48	822 3/47			NS
National Cancer Institute (1978)	Rat Osborne-Mendel	M	Diet for 78 weeks	Dose (mg/kg of diet) Follicular-cell adenoma and carcinoma	0 1/19	1647 16/49*	3294 11/49			$p = 0.03$
		F	Diet for 78 weeks	Dose (mg/kg of diet) Follicular-cell adenoma and carcinoma	0 2/19	850 11/48	1700 6/50			NS

Table 10 (contd)

Reference	Species/ strain	Sex	Dose schedule	Experimental parameter/ observation	Group					Statistical trend
					0	1	2	3	4	
DDE										
Tomatis *et al.* (1974)	Mouse CF-1	M	Diet until 110 weeks of age	Dose (mg/kg of diet)	0	250				
				Liver-cell tumours	33/98	39/53**				NA
		F	Diet until 110 weeks of age	Dose (mg/kg of diet)	0	250				
				Liver-cell tumours	1/90	54/55***				NA
US National Cancer Institute (1978)	Mouse $B6C3F_1$	M	Diet for 78 weeks	Dose (mg/kg of diet)	0	148	261			
				Survival at 70 weeks	5/20	35/50	31/50			
				Hepatocellular carcinoma	0/19	7/41	17/47*			$p < 0.001$
		F	Diet for 78 weeks	Dose (mg/kg of diet)	0	148	261			
				Survival at 75 weeks	19/20	47/50	28/50			
				Hepatocellular carcinoma	0/19	19/47***	34/48***			$p < 0.001$
Rossi *et al.* (1983)	Hamster Syrian golden	M	Diet until 128 weeks of age	Dose (mg/kg of diet)	0	500	1000			
				Liver-cell tumours	0/10	7/15*	8/24*			NA
		F	Diet until 128 weeks of age	Dose (mg/kg of diet)	0	050	1000			
				Liver-cell tumours	0/31	4/26*	5/24*			NA

NA, not applicable; NS, not statistically significant

*$p < 0.05$

**$p < 0.01$

***$p < 0.001$

[a]In mice that died after 60 weeks

rapidly following DDA ingestion and least following DDT. Urinary excretion of DDA began within 24 h of ingestion of DDT, TDE or DDA. Urinary DDA returned to its predose level two to three days after its administration but continued to be excreted slightly above the predose level for more than four months following termination of ingestion of TDE or DDT. DDE failed to produce any increase in DDA excretion (Roan *et al.*, 1971). Dechlorination of DDT (administered to volunteers at 5, 10 or 20 mg day for 183 days) led to conversion to TDE (measured in serum and adipose tissue) and further metabolism to the readily excreted DDA. Dehydrochlorination of DDT yielded DDE, a stable metabolite. In two subjects who ingested technical-grade DDT, the conversion of *para,para'*-DDT to *para,para'*-DDE was limited, as assessed by measuring DDE concentrations in serum and adipose tissue (Morgan & Roan, 1971). After oral administration of technical-grade DDT at 10 or 20 mg per day for six months, the level of *ortho,para'*-DDT was reported to decline more rapidly than that of *para,para'*-DDT. After the treatment period, excretion of DDA declined sharply, despite a very slow decrease in serum and adipose tissue levels of DDT (Roan, 1970).

A positive dose-related correlation between exposure to DDT and urinary excretion of DDA has been observed (Perini & Ghezzo, 1970; Wolfe & Armstrong, 1971), indicating that the urinary level of DDA could be used as a monitoring test of the extent of recent exposure to DDT.

As discussed in section 1.3, DDT and its metabolites tend to accumulate in the human body as well as in the environment (WHO, 1979, 1989), and DDT and/or its metabolites have been determined in several human organs and maternal milk. As use of DDT was either banned or restricted during the 1970s throughout the world, temporal changes occurred in some pharmacokinetic parameters of DDT in the general population. Some examples in various countries are shown in Tables 11-13.

4.1.2 *Experimental systems*

The metabolism of DDT has been reviewed (WHO, 1979; Lund, 1989; Agency for Toxic Substances and Disease Registry, 1989).

Several metabolic pathways leading from DDT to DDA have been proposed, and those suggested for the degradation of DDT, including areas at which reactive metabolites may be involved, are given in Figure 1. The biological half-time for DDT is about one month in dogs (Deichmann *et al.*, 1969), two months in hens (Lillard & Noles, 1973), three months in monkeys (Durham *et al.*, 1963) and approximately five weeks in rats (Datta & Nelson, 1968). In the latter species, the half-time was reduced to five days under conditions of starvation for three days followed by a restricted diet (Mitjavila *et al.*, 1981). Most species, including humans but with the exception of rhesus monkeys, store DDE more tenaciously than they do DDT (WHO, 1979). DDA is the major and final water-soluble metabolite in the urine of rats, mice and rabbits (Reif & Sinsheimer, 1975; Gold & Brunk, 1982; White & Sweeney, 1945).

In the main pathway from *para,para'*-DDT *via para,para'*-TDE to *para,para'*-DDA, the formation of two reactive intermediates is postulated, i.e., a free radical and an acid chloride (Baker & Van Dyke, 1984; Gold & Brunk, 1984). Both intermediates are probably capable of binding covalently to cellular macromolecules. Other reactive intermediates in the metabolism of DDT include side-chain epoxides of DDE, 1-chloro-2,2-bis(*para*-chlorophenyl)ethene and 1,1-bis(*para*-chlorophenyl)ethene (Planche *et al.*, 1979; Gold *et al.*, 1981;

Table 11. Temporal trends in total DDT levels in human adipose tissue (mg/kg) in the US population (range of reported values)[a]

Period	DDT (mg/kg)
1955-65	6.7-19.9
1965-72	5.5-23.2
1975-88	1[b]-4.3

[a]From WHO (1979); Adeshina & Todd (1990)
[b]North Texas only

Table 12. Temporal trends in total DDT levels in human blood in different populations (mean or range of means)[a]

Country	Period[b]	DDT (μg/l)[c]
Brazil	1973	45
	[late 1970s][d]	30
Canada	[early 1970s][d]	32
	[early 1980s][d]	2-3
India	1975	166-683
	1979-80	26.2

[a]From Agarwal *et al.* (1976); WHO (1979); Procianoy & Schvartsman (1981); Saxena *et al.* (1983); Mes *et al.* (1984)
[b]In square brackets, approximate date (dates not given in article)
[c]Reported as μg/l or approximated from concentrations given in paper

Table 13. Temporal trends in concentrations of DDT-derived material in human milk[a]

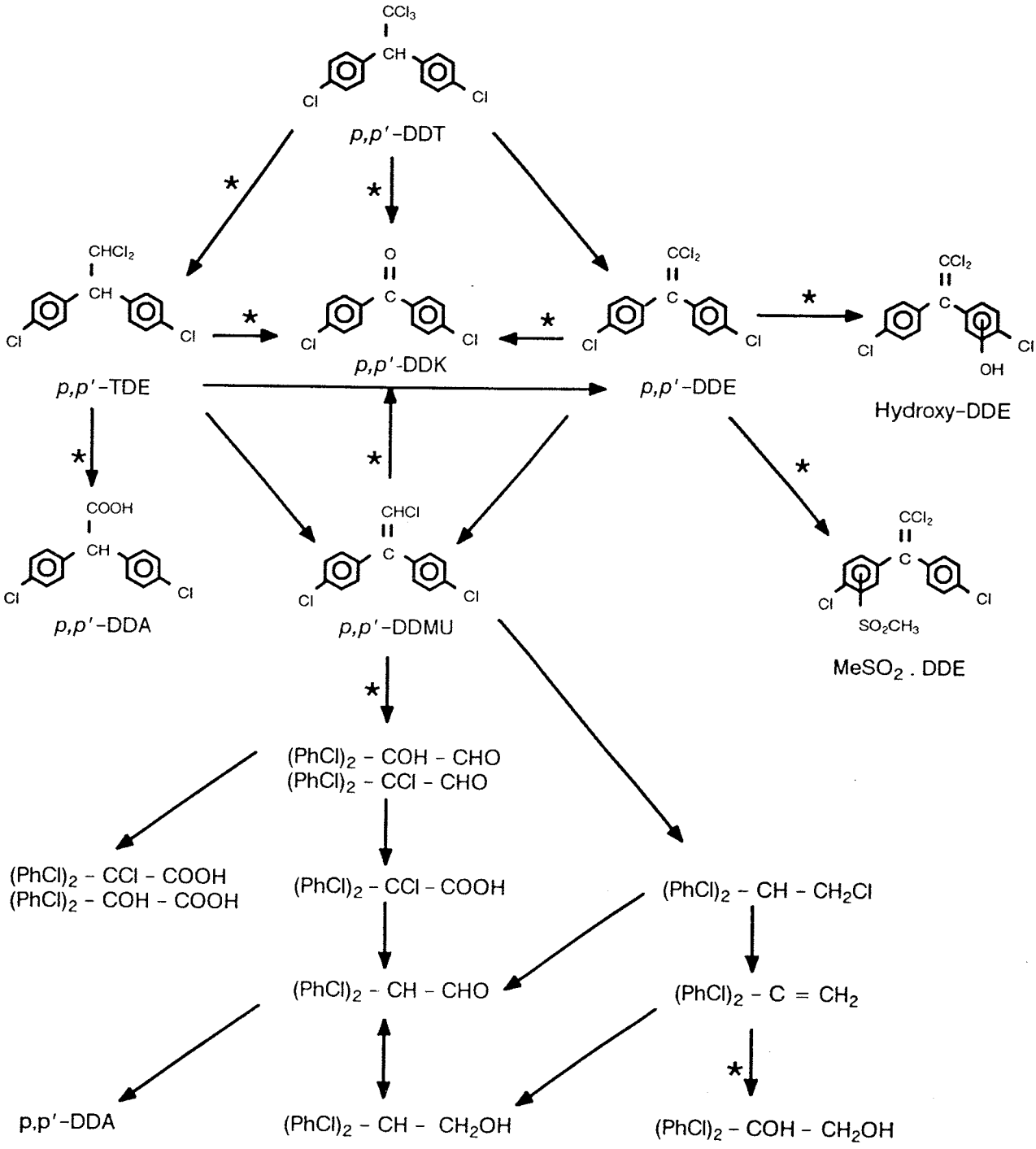
Country	Period	mg/l[b]
France	1971-73	0.11
	1979	0.001
Sweden	1967	0.1
	1978-79	0.06

[a]From Luquet *et al.* (1974); WHO (1979); Hofvander *et al.* (1981); Klein *et al.* (1986)
[b]Reported as mg/l or approximated from concentrations in paper

Fawcett *et al.*, 1987). Ring epoxides (arenoxides) may lead to the formation of the methyl sulfone of DDE (Jensen & Jansson, 1976; Lund, 1989).

In a study in mice pretreated for five months with DDE and subsequently given radiolabelled DDE, however, most of the radiolabel in urine, faeces and liver was bound to unchanged DDE and one phenolic metabolite (Gold & Brunk, 1986). The authors concluded that there was no indication for the metabolism of DDE to a reactive electrophilic species.

Fig. 1. Compilation of metabolic pathways proposed for DDT in rodents; asterisks indicate where reactive intermediates are suggested to be formed[a]



[a]From Lund (1989); *p,p'*-DDK, bis(4-chlorophenyl)ketone; DDA, *para,para'*-2,2-bis(*para*-chlorophenyl)acetic acid; DDMU, 1-chloro-2,2-bis(*para*-chlorophenyl)ethene; PhCl, 4-chlorophenyl

Several studies have indicated that the metabolic pathways are similar in various species including humans (Reif & Sinsheimer, 1975; Gingell, 1976; Fawcett *et al.*, 1987). Hamsters differ from mice, however, in that after dietary treatment with *para,para'*-DDT, they do not excrete DDE in the urine; furthermore, the relative DDE tissue levels in hamsters are much lower than those in mice (Gingell & Wallcave, 1974; Gingell, 1976). The metabolism of DDT is promoted by DDT itself in hamsters but not in mice (Gingell & Wallcave, 1974). Monkeys fed diet containing up to 5000 ppm (mg/kg) of *para,para'*-DDT stored little or no DDE in body fat, but when DDE itself was fed (at 200 ppm in the diet), DDE was readily accumulated in body fat (Durham *et al.*, 1963).

ortho,para'-TDE was bound irreversibly in the alveolar and bronchiolar areas of rabbit and mouse lung (Lund *et al.*, 1986; Lund, 1989). 3-Methylsulfonyl-DDE was bound covalently in the zona fasciculata of the mouse adrenal cortex, causing necrotic changes (Lund *et al.*, 1988).

4.2 Toxic effects

4.2.1 *Humans*

Signs and symptoms reported following acute intoxication by DDT include nausea, vomiting, paraesthesia, dizziness, ataxia, confusion, tremor and, in severe cases, convulsions (WHO, 1979; Hayes, 1982).

Increased serum levels of triglyceride, cholesterol and γ-glutamyl transpeptidase were associated with increased serum levels of DDT in a largely black, agricultural US community, where over a period of years fish had been consumed that was contaminated with DDT, as they were caught from a river in which DDT wastes from a nearby manufacturing plant had accumulated in sediments. Serum levels of DDT were several fold higher than the US average (Kreiss *et al.*, 1981).

Therapeutic use of *ortho,para'*-TDE for Cushing's syndrome and adrenocortical carcinoma at doses of 1-12 g per day for up to 34 months was associated with fatigue, nausea, anorexia, vomiting and diarrhoea (Southern *et al.*, 1966; Hoffman & Mattox, 1972; Luton *et al.*, 1979).

4.2.2 *Experimental systems*

The acute toxicity of DDT is high in insects (LD_{50}, 14 mg/kg bw) and less pronounced in mammals (oral LD_{50}, 150-400 mg/kg bw; Fahmy *et al.*, 1973; Hrdina *et al.*, 1975; Lund, 1989). The oral LD_{50}s in rats of DDE, TDE and DDA are lower (880-1240, > 4000 and 600-1900 mg/kg bw, respectively) (WHO, 1979).

Acute intoxication with DDT elicits symptoms mainly from the central nervous system, and death is usually caused by respiratory arrest. Large doses of DDT cause focal necrosis of liver cells in several species (WHO, 1979).

Long-term studies of oral administration of DDT have been performed in rats, mice, hamsters, dogs and monkeys (reviewed by the Agency for Toxic Substances and Disease Registry, 1989). The liver is one of the main target organs, and hepatic effects range from increased liver weights to cellular necrosis. As reported by the Agency for Toxic Substances and Disease Registry (1989), the no-observed-adverse-effect level for hepatic effects in a study by the US National Cancer Registry (1978) was 32 mg/kg bw per day for 78 weeks in

rats, and that in a study by Durham *et al.* (1963) was 8 mg/kg bw per day when given to rhesus monkeys for 3.5-7.5 years.

Effects on the central nervous system such as tremors and hyperactivity are also associated with chronic exposure to DDT. As reported by the Agency for Toxic Substances and Disease Registry (1989), tremors were apparent with doses of 10.5 mg/kg bw per day in the study of the US National Cancer Institute (1978) in rats; in a study by Cabral *et al.* (1982b), it was reported that hamsters showed no clinical sign of neurotoxicity at doses up to 40 mg/kg bw per day for life.

DDT and its derivatives induce a variety of microsomal enzymes in rodents and primates, mainly involving cytochrome P450-related enzymes (WHO, 1979; Campbell *et al.*, 1983). In rats, DDT increased the hepatic activity of microsomal drug hydroxylation and glucuronidation (Vainio, 1974, 1975). Species differences in isozyme-specific induction by DDT and its derivatives may contribute to species differences in the toxicology of these compounds. In the livers of partially hepatectomized rats treated *in vivo* with *N*-nitrosodiethylamine, DDT induced the metabolism of pentoxy- and benzyloxyresorufin, markers of cytochrome P450b isozymes, but not of ethoxyresorufin, a marker of the cytochrome P450c-d isozymes (Flodström *et al.*, 1990). Ioannides *et al.* (1984) also showed that DDT has no significant effect on ethoxyresorufin *O*-deethylase in rat liver or kidney [described in the paper in terms of the former terminology as cytochrome P448 activity]. Mice appear to be relatively resistant to induction of hepatic microsomal enzymes by DDT (Chhabra & Fouts, 1973).

ortho,para'-DDT has oestrogenic activity in rats, while *para,para'*-DDT has less and TDE and DDE have little or no activity (Welch *et al.*, 1969; Robison *et al.*, 1985a).

Feeding of *para,para'*-DDT to Wistar rats at 100 mg/kg of diet significantly suppressed both humoral and cell-mediated immune responses after 18-22 weeks (Banerjee, 1987).

DDT also enhanced the incidence of γ-glutamyltranspeptidase-positive enzyme-altered foci *in vivo* in partially hepatectomized, *N*-nitrosodiethylamine-initiated male Sprague-Dawley rats that received 1000 ppm (mg/kg) DDT in the diet for 11 weeks. It induced significantly more foci per cubic centimetre and a larger percentage of liver tissue occupied by focus tissue than was seen in a vehicle-treated group. The related compound, fenarimol, caused no significant change in the incidence of foci, although it induced cytochrome P450-related enzyme activities similar to those induced by DDT (Flodström *et al.*, 1990). Induction of altered foci by DDT has also been demonstrated using other protocols (Ito *et al.*, 1983).

DDT at 200 μM stimulated protein kinase C activity *in vitro* in preparations from mouse brain (Moser & Smart, 1989). In contrast, DDT (at 25 μM) did not stimulate protein kinase C activity in hamster V-79 cells (utilized for studies on cell-cell communication), nor could any binding of DDT to the phorbol ester receptor be demonstrated (Wärngård *et al.*, 1989). Furthermore, cytosolic calcium was not involved in the DDT-induced loss of gap-junctional intercellular communication in rat liver WB-F344 cells (Fransson *et al.*, 1990). Co-administration of quercetin with DDT *in vivo* did not prevent the development of preneoplastic enzyme-altered foci in the livers of rats that had undergone a partial hepatectomy and been initiated with *N*-nitrosodiethylamine (Wärngård *et al.*, 1989).

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

In one study of 101 spontaneous abortions in Florida, USA (28 in whites and 73 in blacks) and 152 normal pregnancies (45 in whites and 107 blacks), blood was collected and analysed for the concentration of DDT. The women investigated lived in an area where DDT was used extensively for industrial and residential pest control. No difference was found between the two groups. No confounding was apparently exerted by age or parity (O'Leary *et al.*, 1970). [The Working Group noted that the levels of exposure may have been low and homogeneous.]

In a study in Brazil, 54 maternal-infant pairs were divided into two groups: term deliveries (30 pairs) and pre-term deliveries (24). None of the mothers had had known occupational exposure or domiciliary use of DDT, but all lived in an area highly contaminated with DDT. Maternal blood and cord blood were collected at the time of delivery, and DDT metabolites were measured. No difference was found in the concentration of DDT metabolites between mothers in the two groups, and there was no correlation between DDT levels in the neonates and their gestational ages; however, a significant correlation was detected between low birth weight and DDT levels in neonates ($p < 0.05$). The authors interpreted those findings as indicating that the most important factor determining the cord blood level of DDT is the amount of fetal adipose tissue (Procianoy & Schvartsman, 1981).

In a study from Israel, mean serum levels of total DDT were 71.1 ppb (μg/l) in 17 women who gave birth prematurely and 26.5 ppb in a group of 10 women with term deliveries (Wassermann *et al.*, 1982).

In a study in North Carolina, USA, birthweight, head circumference, neonatal jaundice and neurological and behavioural changes were determined in 912 infants born between 1978 and 1982 and followed to 1985. Blood samples from the mothers and the babies and samples of placenta and milk or colostrum were collected and analysed for the concentration of DDE. DDE levels in milk fat at birth were presented in categories ranging from 0 to ≥ 6 ppm (μg/kg). No association was found between DDE concentrations and birthweight, head circumference and hyperbilirubinaemia; a statistically significant association was detected between the levels and hyporeflexia, measured in the babies through a reflex score (Rogan *et al.*, 1986).

4.3.2 *Experimental systems*

The effects of DDT on reproduction and development have been reviewed (Ware, 1975; Agency for Toxic Substances and Disease Registry, 1989).

Because they have weak oestrogenic effects, DDT and its metabolites have been investigated for reproductive and developmental effects (Bitman & Cecil, 1970; Bustos *et al.*, 1988; Mason & Schulte, 1981; Robison *et al.*, 1985a,b; Uphouse & Williams, 1989). Studies by Deichmann and Keplinger (1966) [abstract] and Deichmann *et al.* (1971) suggested impaired reproduction. Gellert *et al.* (1974) and Gellert and Heinrichs (1975) demonstrated altered reproductive function in rats treated perinatally with DDT or metabolites.

Treatment of 10-day old NMRI mice with DDT or its metabolite, 2,2-bis(4-chlorophenyl)ethanol-palmitic acid, at doses as low as 1.4 μmol/kg bw (0.5 mg/kg bw for DDT) resulted in changes in behaviour (such as disruption of a nonassociative learning process).

DDT treatment also resulted in changes in acetylcholine metabolism in the brain in adulthood (Eriksson *et al.*, 1990b).

Developmental effects, such as decreased survival of neonatal rats, were observed after feeding technical-grade DDT to rats at 200 ppm (mg/kg) in the diet. Premature puberty was seen in dogs fed 5 mg/kg per day (Ottoboni, 1969; Ottoboni *et al.*, 1977). Del Pup *et al.* (1978) examined the effect of technical-grade DDT (100 ppm [mg/kg] in the diet) on stable mouse populations, each containing about 400 animals. During the 70-week treatment with DDT, no alteration in viability index (survival at day 4:survival at day 1) was observed; however, a decrease in the lactation index (survival at day 30:survival at day 4) was noted. The no-observed-adverse-effect level for developmental effects was reported to be 1 mg/kg bw per day for all three studies (Agency for Toxic Substances and Disease Registry, 1989).

Tarján and Kemény (1969) conducted five-generation studies in BALB/c mice by feeding them DDT (mostly *para,para'*-) at 2.8-3.0 ppm [mg/kg] in the diet. No effect on number of pregnancies, births, litters, offspring or weanling survival was noted.

Male rats were given DDT at either 500 mg/kg bw on days 4 and 5 of life or 200 mg/kg bw per day from day 4 to day 23 of life by gavage. Testicular weight was decreased by both treatments, as was tubular diameter. Spermatogenesis and fertility were also impaired (Krause *et al.*, 1975).

Dean *et al.* (1980) examined the effect of a single injection of DDT (8% (w/v) DDT (95% *para,para'*-) [40 mg] in 0.5 ml arachis oil, intraperitoneally) on gestational day 13 on the androgen status of two-, four-, six-, eight- and ten-day-old male rats. Cross-fostering of litters from treated and control rats suggested that substantial amounts of DDT were transferred to the pups during lactation. Neonatal exposure to DDT increased hepatic metabolism of testosterone without altering circulating testosterone levels or testicular synthesis of testosterone.

Preimplantation treatment of New Zealand white rabbits with DDT decreased the size of the conceptus by approximately 60% and decreased the weight of 28-day-old fetuses, of fetal brain and of fetal kidney. It also altered the protein profile of the yolk sac fluids, as demonstrated by polyacrylamide gel electrophoresis (Fabro *et al.*, 1984).

Early studies on reproductive effects suggested that DDT affects avian eggshell thickness (Bitman *et al.*, 1969). These studies demonstrated that administration of *ortho,para'*- or *para,para'*-DDT in the diet at 100 ppm (mg/kg) decreased egg weight, eggshell thickness and the percentage of calcium in the shells. A series of studies conducted since that time further defined the effect of DDT and its metabolites on eggshell thickness (see WHO, 1979, for review).

Swartz (1984) evaluated the effect on DDT on the chick embryo, with specific attention to gonadal development. DDT at 5, 10 or 20 mg was injected into the yolk sac of eggs, which were incubated for five or 12 days before examination. After five days of incubation, no difference in the number of primordial germ cells was observed in treated or control chicks; after 12 days of incubation, however, there were differences in the morphology and histochemistry of the chick gonads.

Treatment of quail eggs with an aqueous suspension of DDT over five generations produced a progressive decrease over generations in the number of germ cells in the gonad of

the chicks (David, 1977). Shellenberger (1978) observed no effect of *para,para'*-DDT at 5 or 50 ppm (mg/kg) in the diet on quail growth or reproduction over four generations and no effect on growth, egg production, hatchability or fertility.

Bryan *et al.* (1989) examined the effect of *ortho,para'*-DDT (1-10 mg) and *para,para'*-DDT (1-10 mg) on Japanese quail following treatment *in ovo* beginning on day 1 of incubation. Neither *ortho,para'*- nor *para,para'*-DDT affected hatchability, survival to day 16 post-hatching or the numbers of malpositioned or malformed chicks at doses up to 10 mg/egg. A dose-dependent increase in the percentage of chicks with ataxia and tremor and embryos that pipped but did not emerge was observed when eggs were treated with *para,para'*-DDT. Survival to five weeks of age was decreased in chicks treated with 6.25 mg *ortho,para'*-DDT and above and with 1.75 mg *para,para'*-DDT and above. Feather morphology was altered in more than 50% of birds treated with 6.25 mg *ortho,para'*-DDT and above and 1.75 mg *para,para'*-DDT and above. Ovipositions and the percentage hatched were decreased by exposure to 5 mg *ortho,para'*- and 1.75 mg *para,para'*-DDT. Reproductive behaviour was altered by treatment with 6.25 mg *ortho,para'*- but not with 1.75 mg *para,para'*-DDT.

Jelinek *et al.* (1985) found an increased incidence of malformations in a chick embryo screening test. Fry and Toone (1981) injected DDT into gulls' eggs at concentrations comparable to those found in contaminated eggs in the 1970s (2-100 ppm [mg/kg] per whole egg). Treatment induced abnormal development of gonadal tissues, with formation of ovarian tissue and oviducts in male embryos.

4.4 Genetic and related effects (see also Tables 14-17 and Appendices 1 and 2)

4.4.1 *Humans*

Blood samples were taken from 50 workers in three pesticide plants in Brazil who were of similar socioeconomic status and were either directly or indirectly exposed to DDT. They were divided into two groups on the basis of their type of employment and DDT plasma levels: 20 people in a 'control group' had a DDT plasma level of 0.275 μg/ml (range, 0.03-1.46 μg/ml), and 30 people in an 'exposed group' had a plasma level of 0.993 μg/ml (range, 0.16-3.25 μg/ml). The frequencies of cells with chromatid aberrations was 8.8% in the control group and 12.0% in the exposed group ($p < 0.05$, analysis of variance); there was no difference in the frequency of cells with chromosome-type aberrations (Nazareth Rabello *et al.*, 1975). [The Working Group noted that smoking was not controlled for and that details of the choice of the original controls were not given. Furthermore, a 72-h culture time was used, and only 50 metaphases per individual were analysed, thus weakening the significance of the results.]

4.4.2 *Experimental systems*

DDT

DDT did not induce DNA damage in either bacteria or cultured rodent and human cells. It did not induce gene mutation in bacteria, fungi or insects, in rodent host-mediated assays or in the mouse spot test *in vivo*. Gene mutation was not induced in Chinese hamster V79 cells at the *hprt* locus. Tests for the induction of aneuploidy in insects gave conflicting results,

while one study in *Drosophila melanogaster* showed that DDT induced dominant lethality in insects.

Conflicting results were obtained in tests for chromosomal aberration in cultured rodent and human cells.

Inhibition of gap-junctional intercellular communication (as measured by inhibition of metabolic cooperation or dye transfer) was found consistently in rodent and human cells following treatment with DDT. In corroboration of these findings, exposure of rats to DDT *in vivo* reduced the number of gap junctions. Conflicting results were obtained in cell transformation assays.

In a study *in vivo*, positive results were reported for chromosomal aberrations in mouse bone-marrow cells. The Working Group noted that an additional study, reported from the same laboratory, was inadequate for evaluation because of the small number of control animals (Larsen & Jalal, 1974). Negative results were obtained in the same tests in the rat. A weak positive response was seen for induction of chromosomal aberrations in mouse spermatocytes in a single study. Dominant lethal tests in mice and rats gave equivocal results. No significant effect on sperm morphology was observed in several studies; but, in a single study in rats, significant changes were found.

para,para'-TDE

para,para'-TDE was not mutagenic to bacteria, and an unspecified isomer of TDE did not induce unscheduled DNA synthesis in primary cultures of mouse, rat or Syrian hamster hepatocytes. *para,para'*-TDE weakly induced chromosomal aberrations in rodent cells. In a single study, it inhibited gap-junctional intercellular communication in cultured rodent cells. In one study, it did not induce transformation in mouse embryo cells.

ortho,para'-TDE

ortho,para'-TDE did not induce mutation in *Salmonella typhimurium*. An unspecified isomer of TDE did not induce unscheduled DNA synthesis in primary cultures of rat, mouse or Syrian hamster hepatocytes. Equivocal results were obtained for induction of chromosomal aberrations in cultured rodent cells. In a single study, it did not induce transformation in mouse embryo cells.

para,para'-DDE

para,para'-DDE did not induce DNA damage in bacteria or mutation in bacteria or yeast. It induced intrachromosomal rearrangements in yeast. [The Working Group noted that this is a newly developed, not yet validated assay system involving DNA rearrangement in an integrated recombinant plasmid.] *para,para'*-DDE did not induce unscheduled DNA synthesis in primary cultures of rat, mouse or hamster hepatocytes. It induced gene mutation in insects and rodent cells. Weak positive results were obtained in a single study for sister chromatid exchange and in the majority of studies on chromosomal aberrations in rodent cells.

In single studies, *para,para'*-DDE inhibited gap-junctional intercellular communication between cultured rodent cells, but it did not induce transformation of mouse embryo cells.

Table 14. Genetic and related effects of DDT

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ECB, Breakage in plasmid DNA *in vitro*	–	0	100.0000	Griffin & Hill (1978)
BSD, *Bacillus subtilis rec* strains, differential toxicity	–	–	72.6000	Matsui *et al.* (1989)
ERD, *Escherichia coli*, WP2, differential toxicity	–	0	2000.0000	Rashid & Mumma (1986)
ERD, *Escherichia coli* K-12, differential toxicity	–	0	2000.0000	Rashid & Mumma (1986)
ERD, *Escherichia coli* WP2, differential toxicity	–	–	2000.0000	De Flora *et al.* (1984)
SAD, *Salmonella typhimurium* TA1538/1978, differential toxicity	–	0	2000.0000	Rashid & Mumma (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	170.0000	Bartsch *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–[c]	–	177.0000	Planche *et al.* (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	35.0000	Probst *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500.0000	Byeon *et al.* (1976)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	–	500.0000	Glatt & Oesch (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	250.0000	Bruce & Heddle (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	370.0000	Van Dijck & Van de Voorde (1976)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	177.0000	Nishimura *et al.* (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	De Flora *et al.* (1989)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1250.0000	Marshall *et al.* (1976)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	35.0000	Probst *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500.0000	Byeon *et al.* (1976)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	0	–	500.0000	Glatt & Oesch (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1250.0000	Marshall *et al.* (1976)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	35.0000	Probst *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)

Table 14 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA7, *Salmonella typhimurium* TA1537, reverse mutation	0	–	500.0000	Glatt & Oesch (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	250.0000	Bruce & Heddle (1979)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1250.0000	Marshall *et al.* (1976)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	35.0000	Probst *et al.* (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2500.0000	Byeon *et al.* (1976)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	0	–	500.0000	Glatt & Oesch (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	170.0000	Bartsch *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–[c]	–	177.0000	Planche *et al.* (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	35.0000	Probst *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500.0000	Byeon *et al.* (1976)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	–[d]	500.0000	Glatt & Oesch (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	250.0000	Bruce & Heddle (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	370.0000	Van Dijck & Van de Voorde (1976)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	177.0000	Nishimura *et al.* (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500.0000	De Flora *et al.* (1989)
SAS, *Salmonella typhimurium* TA92, reverse mutation	0	–	500.0000	Glatt & Oesch (1987)
SAS, *Salmonella typhimurium* TA1536, reverse mutation	–	–	1250.0000	Marshall *et al.* (1976)
SAS, *Salmonella typhimurium* C3076, reverse mutation	–	–	35.0000	Probst *et al.* (1981)
SAS, *Salmonella typhimurium* D3052, reverse mutation	–	–	35.0000	Probst *et al.* (1981)
SAS, *Salmonella typhimurium* G46, reverse mutation	–	–	35.0000	Probst *et al.* (1981)
SAS, *Salmonella typhimurium* TA1978, reverse mutation	–	–	370.0000	Van Dijck & Van de Voorde (1976)

Table 14 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ECW, *Escherichia coli* WP *uvrA*, reverse mutation	–	–	35.0000	Probst *et al.* (1981)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	0	–	500.0000	Glatt & Oesch (1987)
EC2, *Escherichia coli* WP2, reverse mutation	–	–	35.0000	Probst *et al.* (1981)
EC2, *Escherichia coli* WP2 *hcr*, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
ANN, *Aspergillus nidulans*, aneuploidy	–	0	990.0000	Crebelli *et al.* (1986)
ANF, *Aspergillus nidulans*, forward mutation	–	0	990.0000	Crebelli *et al.* (1986)
NCF, *Neurospora crassa*, forward mutation	–	0	7500.0000	Clark (1974)
*, Wasp, recessive/dominant lethal mutation	–	0	10.0000[e]	Grosch & Valcovic (1967)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	–	0	20.0000	Pielou (1952)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	–	0	0.0000	Clark (1974)
DML, *Drosophila melanogaster*, dominant lethal mutation	+	0	0.0000	Clark (1974)
DMN, *Drosophila melanogaster*, aneuploidy	+	0	0.0000	Clark (1974)
DMC, *Drosophila melanogaster*, chromosome loss	–	0	25.0000	Woodruff *et al.* (1983)
DIA, DNA damage, Chinese hamster V79 cells	–	–	354.0000	Swenberg *et al.* (1976)
DIA, DNA damage, Chinese hamster V79 cells	–	–	1060.0000	Swenberg (1981)
DIA, DNA damage, rat hepatocytes	–	0	106.0000	Sina *et al.* (1983)
URP, Unscheduled DNA synthesis, rat hepatocytes	–	0	35.0000	Maslansky & Williams (1981)
URP, Unscheduled DNA synthesis, rat hepatocytes	–	0	35.0000	Probst *et al.* (1981)
UIA, Unscheduled DNA synthesis, mouse hepatocytes	–	0	35.0000	Klaunig *et al.* (1984)
UIA, Unscheduled DNA synthesis, mouse hepatocytes	–	0	35.0000	Maslansky & Williams (1981)
UIA, Unscheduled DNA synthesis, hamster hepatocytes	–	0	35.0000	Maslansky & Williams (1981)
G9H, Gene mutation, Chinese V79 hamster cells, *hprt* locus	–	0	35.0000	Kelly-Garvert & Legator (1973)
G9H, Gene mutation, Chinese V79 hamster cells, *hprt* locus	–	0	14.2000	Tsushimoto *et al.* (1983)

Table 14 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CIC, Chromosomal aberrations, Chinese hamster V79 cells	–	0	45.0000	Kelly-Garvert & Legator (1973)
CIC, Chromosomal aberrations, Chinese hamster B14F28 cells	+	0	49.0000	Mahr & Miltenburger (1976)
TBM, Cell transformation, BALB/c 3T3 mouse fibroblast cells	+	+	10.0000	Fitzgerald *et al.* (1989)
TCL, Cell transformation, mouse embryo cells	–	0	15.0000	Langenbach & Gingell (1975)
UHT, Unscheduled DNA synthesis, HeLa cells	–	0	18.0000	Brandt *et al.* (1972)
UHT, Unscheduled DNA synthesis, human fibroblasts	–	–	354.0000	Ahmed *et al.* (1977)
UHT, Unscheduled DNA synthesis, human lymphocytes	–	0	500.0000	Rocchi *et al.* (1980)
GIH, Gene mutation, human fibroblasts	–	–	35.0000	Tong *et al.* (1981)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	0	0.2000	Lessa *et al.* (1976)
HMM, Host-mediated assay, *Neurospora crassa*	–	0	150.0000 × 2 p.o.	Clark (1974)
HMM, Host-mediated assay, *Salmonella typhimurium his* G46	–	0	500.0000	Buselmaier *et al.* (1972)
MST, Mouse spot test *in vivo*	–	0	250.0000	Wallace *et al.* (1976)
CBA, Chromosomal aberrations, mouse bone-marrow cells	+	0	100.0000 × 1 i.p.	Johnson & Jalal (1973)
CBA, Chromosomal aberrations, rat bone marrow *in vivo*	–	0	200.0000 × 1 i.p.	Legator *et al.* (1973)
CBA, Chromosomal aberrations, rat bone marrow *in vivo*	–	0	100.0000 × 5 i.p.	Legator *et al.* (1973)
CBA, Chromosomal aberrations, rat bone marrow *in vivo*	–	0	100.0000 × 1 p.o.	Legator *et al.* (1973)
CBA, Chromosomal aberrations, rat bone marrow *in vivo*	–	0	80.0000 × 5 p.o.	Legator *et al.* (1973)
CGC, Chromosomal aberrations, mouse spermatocytes *in vivo*	(+)	0	150.0000	Clark (1974)
DLM, Dominant lethal test, mice	–	0	130.0000 × 1 i.p.	Epstein *et al.* (1972)
DLM, Dominant lethal test, mice	–	0	1200.0000 × 1 i.p.	Buselmaier *et al.* (1972)
DLM, Dominant lethal test, mice	(+)	0	150.0000 × 2 p.o.	Clark (1974)
DLR, Dominant lethal test, rats	(+)	0	50.0000	Palmer *et al.* (1973)
DLM, Dominant lethal test, mice	–	0	105.0000	Epstein & Shafner (1968)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	(+)	0	1.0000	Nazareth Rabello *et al.* (1975)

Table 14 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ICR, Inhibition of metabolic cooperation, rat liver epithelial cells	+	0	0.3500	Williams *et al.* (1981)
ICR, Inhibition of metabolic cooperation, Chinese hamster V79 cells	+	0	2.0000	Kurata *et al.* (1982)
ICR, Inhibition of metabolic cooperation, Chinese hamster V79 cells	+	0	3.6000	Tsushimoto *et al.* (1983)
ICR, Inhibition of metabolic cooperation, Chinese hamster V79 cells	+	0	6.0000	Wärngård *et al.* (1985)
ICR, Inhibition of metabolic cooperation, Chinese hamster V79 cells	+	0	10.0000	Zeilmaker & Yamasaki (1986)
ICR, Inhibition of metabolic cooperation, Chinese hamster V79 cells	+	0	0.5000	Aylsworth *et al.* (1989)
ICR, Inhibition of metabolic cooperation, Chinese hamster V79 cells	+	0	7.0000	Wärngård *et al.* (1989)
ICR, Inhibition of metabolic cooperation, mouse hepatocytes	+	0	1.0000	Klaunig & Ruch (1987)
ICR, Inhibition of metabolic cooperation, mouse hepatocytes	+	0	9.0000	Klaunig *et al.* (1990)
ICR, Inhibition of metabolic cooperation, Chinese hamster V79 cells	+	0	3.5000	Flodström *et al.* (1990)
ICR, Inhibition of metabolic cooperation, rat liver WB-F344 cells	+	0	3.5000	Flodström *et al.* (1990)
ICR, Inhibition of metabolic cooperation, Djungarian hamster fibroblasts, SV40 transformed	+	0	100.0000	Budunova *et al.* (1989)
ICH, Inhibition of metabolic cooperation, human skin fibroblasts	+	0	5.0000	Davidson *et al.* (1985)
ICH, Inhibition of metabolic cooperation, teratocarcinoma cells	+	0	5.0000	Zhong-Xiang *et al.* (1986)
* Reduction of gap junctions, rat liver cells *in vivo*	+	0	500.0000	Sugie *et al.* (1987)
SPM, Sperm morphology, mice	-	0	50.0000	Wyrobek & Bruce (1975)
SPM, Sperm morphology, mice	-	0	125.0000	Bruce & Heddle (1979)
SPM, Sperm morphology, mice	-	0	100.0000	Topham (1980)
SPR, Sperm morphology, rats	+	0	200.0000	Krause *et al.* (1975)

*Not displayed on profile

[a] +, positive; (+), weakly positive; -, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)

[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

[c] With S9 but no cofactors

[d] Also tested with 1,1,1-trichloropropene-2,3-oxide (microsomal epoxide hydrolase inhibitor)

[e] 10 μg per wasp

Table 15. Genetic and related effects of *para,para'*-TDE

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	Glatt & Oesch (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500.0000	Glatt & Oesch (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500.0000	Glatt & Oesch (1987)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500.0000	Glatt & Oesch (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500.0000	Glatt & Oesch (1987)
SAS, *Salmonella typhimurium* TA92, reverse mutation	–	–	500.0000	Glatt & Oesch (1987)
ECW, *Escherichia coli* WP2, *uvrA*, reverse mutation	–	–	500.0000	Glatt & Oesch (1987)
EC2, *Escherichia coli* WP2 *hcr*, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
URP, Unscheduled DNA synthesis, rat hepatocytes	–	0	32.0000[c]	Maslansky & Williams (1981)
UIA, Unscheduled DNA synthesis, mouse hepatocytes	–	0	32.0000[c]	Maslansky & Williams (1981)
UIA, Unscheduled DNA synthesis, hamster hepatocytes	–	0	32.0000[c]	Maslansky & Williams (1981)
CIC, Chromosomal aberrations, Chinese hamster B14F28 cells	(+)	0	45.0000	Mahr & Miltenburger (1976)
CIA, Chromosomal aberrations, other animals cells *in vitro*	(+)	0	10.0000	Palmer *et al.* (1972)
TCL, Cell transformation, mouse embryo cells	–	0	15.0000[c]	Langenbach & Gingell (1975)
HMM, Host-mediated assay, *Salmonella typhimurium his* G46	–	0	500.0000[c]	Buselmaier *et al.* (1972)
ICR, Inhibition of metabolic cooperation, animal cells *in vitro*	+	0	5.0000	Kurata *et al.* (1982)

[a] +, positive; (+), weakly positive; –, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)

[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

[c] Isomer not specified

Table 16. Genetic and related effects of *ortho,para'*-TDE

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	50.0000	Mortelmans *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	50.0000	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	50.0000	Mortelmans *et al.* (1986)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	166.0000	Mortelmans *et al.* (1986)
URP, Unscheduled DNA synthesis, rat hepatocytes	–	0	32.0000[c]	Maslansky & Williams (1981)
UIA, Unscheduled DNA synthesis, mouse hepatocytes	–	0	32.0000[c]	Maslansky & Williams (1981)
UIA, Unscheduled DNA synthesis, hamster hepatocytes	–	0	32.0000[c]	Maslansky & Williams (1981)
SIC, Sister chromatid exchange, Chinese hamster cells *in vitro*	–	–	16.0000	Galloway *et al.* (1987)
CIC, Chromosomal aberrations, Chinese hamster CHO cells	–	–	50.0000	Galloway *et al.* (1987)
CIA, Chromosomal aberrations, other animals cells *in vitro*	(+)	0	10.0000	Palmer *et al.* (1972)
HMM, Host-mediated assay, *Salmonella typhimurium his* G46	–	0	500.0000[c]	Buselmaier *et al.* (1972)
TCL, Cell transformation, mouse embryo cells	–	0	15.0000[c]	Langenbach & Gingell (1975)

[a] +, positive; (+), weakly positive; –, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)

[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

[c] Isomer not specified

Table 17. Genetic and related effects of *para,para'*-DDE

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, Breakage in plasmid DNA *in vitro*	0	–	100.0000	Mamber *et al.* (1984)
PRB, Breakage in plasmid DNA *in vitro*	–	–	3180.0000	Brams *et al.* (1987)
ERD, *Escherichia coli*, WP2, differential toxicity	0	–	1000.0000	Mamber *et al.* (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	–	2500.0000	McCann *et al.* (1975)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	370.0000	Van Dijck & Van de Voorde (1976)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	Simmon & Kauhanen (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	860.0000	Bartsch *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000.0000	De Flora (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	Mortelmans *et al.* (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500.0000	Brams *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	–	500.0000	Glatt & Oesch (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	De Flora *et al.* (1989)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	0	–	2500.0000	McCann *et al.* (1975)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500.0000	Marshall *et al.* (1976)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	370.0000	Van Dijck & Van de Voorde (1976)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500.0000	Simmon & Kauhanen (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000.0000	De Flora (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500.0000	Mortelmans *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	0	–	500.0000	Glatt & Oesch (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	0	–	2500.0000	McCann *et al.* (1975)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500.0000	Marshall *et al.* (1976)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	370.0000	Van Dijck & Van de Voorde (1976)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500.0000	Simmon & Kauhanen (1978)

Table 17 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000.0000	De Flora (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500.0000	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500.0000	Brams *et al.* (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	0	–	500.0000	Glatt & Oesch (1987)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500.0000	Marshall *et al.* (1976)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	370.0000	Van Dijck & Van de Voorde (1976)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500.0000	Simmon & Kauhanen (1978)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	5000.0000	De Flora (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2500.0000	Brams *et al.* (1987)
SA8, *Salmonella typhimurium*, TA1538, reverse mutation	0	–	500.0000	Glatt & Oesch (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	–	2500.0000	McCann *et al.* (1975)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	370.0000	Van Dijck & Van de Voorde (1976)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500.0000	Simmon & Kauhanen (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	860.0000	Bartsch *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000.0000	De Flora (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500.0000	Mortelmans *et al.* (1986)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	–	500.0000	Glatt & Oesch (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500.0000	De Flora *et al.* (1989)
SAS, *Salmonella typhimurium* TA1536, reverse mutation	–	–	500.0000	Marshall *et al.* (1976)
SAS, *Salmonella typhimurium* TA1978, reverse mutation	–	–	370.0000	Van Dijck & Van de Voorde (1976)
SAS, *Salmonella typhimurium* TA1950, reverse mutation	–	–	370.0000	Van Dijck & Van de Voorde (1976)
SAS, *Salmonella typhimurium* TA92, reverse mutation	0	–	500.0000	Glatt & Oesch (1987)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	500.0000	Glatt & Oesch (1987)
EC2, *Escherichia coli* WP2 *hcr*, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
EC2, *Escherichia coli* WP2, reverse mutation	0	–	1000.0000	Mamber *et al.* (1984)

Table 17 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
*, *Saccharomyces cerevisiae*, intrachromosomal recombination	+	0	100.0000	Schiestl *et al.* (1989)
*, *Saccharomyces cerevisiae*, intrachromosomal recombination	+	0	100.0000	Schiestl (1989)
SCH, *Saccharomyces cerevisiae*, homozygosis	–	–	25000.0000	Simmon & Kauhanen (1978)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+	0	10000.0000	Valencia *et al.* (1985)
DMH, *Drosophila melanogaster*, heritable translocation test	–	0	10000.0000	Valencia *et al.* (1985)
DIA, DNA damage, rat hepatocytes [?]	+	0	95.0000	Sina *et al.* (1983)
URP, Unscheduled DNA synthesis, rat hepatocytes	–	0	31.0000	Maslansky & Williams (1981)
URP, Unscheduled DNA synthesis, rat hepatocytes	–	0	2000.0000	Williams *et al.* (1982)
UIA, Unscheduled DNA synthesis, mouse hepatocytes	–	0	31.0000	Maslansky & Williams (1981)
URP, Unscheduled DNA synthesis hamster hepatocytes	–	0	31.0000	Maslansky & Williams (1981)
GCO, Gene mutation, Chinese hamster ovary cells *in vitro*	+	0	16.0000	Amacher & Zelljadt (1984)
G5T, Gene mutation, mouse lymphoma L5178Ycells, *tk* locus	+	–	40.0000	Clive *et al.* (1979)
SIC, Sister chromatid exchange, Chinese hamster cells *in vitro*	–	(+)	5.0000	Galloway *et al.* (1987)
CIC, Chromosomal aberrations, Chinese hamster V79 cells	(+)	0	35.0000	Kelly-Garvert & Legator (1973)
CIC, Chromosomal aberrations, Chinese hamster B14F28 cells	(+)	0	44.0000	Mahr & Miltenburger (1976)
CIC, Chromosomal aberrations, Chinese hamster CHO cells	–	–	60.0000	Galloway *et al.* (1987)
CIA, Chromosomal aberrations, other animals cells *in vitro*	(+)	0	10.0000	Palmer *et al.* (1972)
HMM, Host-mediated assay, *Salmonella typhimurium his*G46	–	0	500.0000	Buselmaier *et al.* (1972)
TCL, Cell transformation, mouse embryo cells	–	0	15.0000	Langenbach & Gingell (1975)
ICR, Inhibition of metabolic cooperation, animal cells *in vitro*	+	0	10.0000	Kurata *et al.* (1982)

*Not displayed on profile

[a] +, positive; (+), weakly positive; –, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)

[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Technical-grade DDT is a complex mixture of *para,para'*-DDT, its isomers and related compounds. It has been used since 1943 as a nonsystemic insecticide with a broad spectrum of activities. DDT has been used extensively for the control of vectors of malaria, typhus, yellow fever and sleeping sickness, and also on food crops. Its use is banned in some countries and has been restricted since the 1970s in many others to the control of vector-borne diseases.

DDT has been formulated in almost every conceivable form, including granules and powders, solutions, concentrates, aerosols and others, alone and in combination with other insecticides.

DDT is ubiquitous in the environment. It is highly persistent and has been found extensively in foods, soils and sediments. Residual levels in human tissues have been declining slowly with the decreasing use of DDT worldwide.

Exposure may occur during its production and application and as a result of persistent residual levels in surface water and sediments, and in foods.

5.2 Carcinogenicity in humans

Slight excess risks for lung cancer were observed among workers at two DDT producing facilities in the USA. A nested case-control study in one of these investigations found a slight deficit of respiratory cancer. No other cancer occurred in sufficient numbers for analysis. In a prospective cohort study in which exposures were estimated on the basis of serum levels of DDT, the risk for lung cancer rose with increasing concentration but was based on small numbers.

Several investigators have compared serum or tissue levels of DDT and/or DDE among individuals with and without cancer, with inconsistent results.

Results from case-control studies of soft-tissue sarcoma do not point to an association.

An elevated risk for non-Hodgkin's lymphoma in relation to potential exposure to DDT was found in a study from Washington State in the USA, but not for other agricultural exposures. An elevated risk for malignant lymphomas was also found in a case-control study in northern Sweden, with adjustment for exposure to herbicides. The only study available found no association between exposure to DDT and primary liver cancer. In the USA, a slight increase in the risk for leukaemia occurred among farmers who reported use of DDT and many other agricultural exposures. The relative risks for leukaemia rose with frequency of use of DDT on animals.

Epidemiological data on cancer risks associated with exposure to DDT are suggestive, but limitations in the assessments of exposure in the studies and the finding of small and inconsistent excesses complicate an evaluation. The slight excesses of respiratory cancer seen among cohorts exposed to DDT are based on differences of five or fewer cases between exposed and unexposed groups. In case-control studies of lymphatic and haematopoietic cancers, exposure to agricultural pesticides other than DDT resulted in excesses as large as or larger than those associated with exposure to DDT. In most of the case-control studies, adjustment was not made for the potential influence of other exposures.

The cohort and case-control studies that have become available since the last evaluation was made in 1987 (see IARC, 1987) add to some extent to the concern about DDT. Most of these investigations were not specifically designed to evaluate the effects of DDT; consequently, the findings for DDT were not reported as fully as would have been desirable.

5.3 Carcinogenicity in experimental animals

DDT has been tested adequately for carcinogenicity by oral administration in mice, rats and hamsters, and by subcutaneous administration in mice. Following oral administration to mice, it caused liver-cell tumours, including carcinomas, in animals of each sex and hepatoblastomas in males. In one study, the incidence of lung carcinomas was increased, and in three studies the incidence of malignant lymphomas was increased; the incidence of lymphoma was decreased in two studies (see also General Remarks). The incidence of liver tumours was increased in mice following subcutaneous injection of DDT. Oral administration of DDT to rats increased the incidence of liver tumours in female rats in one study and in male rats in two studies. In two studies in which DDT was administered orally to hamsters at concentrations similar to or higher than those found to cause liver tumours in mice and rats, some increase in the incidence of adrenocortical adenomas was observed.

A metabolite of DDT, *para,para'*-DDE, has been tested for carcinogenicity by oral administration in mice and hamsters. A second metabolite, TDE, was tested by oral administration in mice and rats. TDE increased the incidence of liver tumours in male mice and of lung tumours in animals of each sex in one of the two studies in mice. An increase in the number of thyroid tumours was observed in one study in male rats. DDE produced a high incidence of liver tumours in male and female mice in two studies. An increased incidence of neoplastic liver nodules was observed in one study in male and female hamsters.

5.4 Other relevant data

The liver is the target organ for the chronic toxicity of DDT. This compound induced liver microsomal enzymes in rodents and primates and increased the frequency of enzyme-positive foci in rat liver.

DDT impaired reproduction and/or development in mice, rats, rabbits, dogs and avian species.

In one study, higher DDT levels were noted in the serum of women who had delivered prematurely than in those who had had a normal delivery. Studies of spontaneous abortion, gestational period and newborn status showed no clear association with body levels of DDT.

In one study, increased frequencies of chromatid-type but not chromosome-type aberrations were observed in peripheral lymphocytes of workers with increased plasma levels of DDT. No data were available on the genetic and related effects of metabolites of DDT in humans.

DDT reduced gap-junctional areas in rat liver cells *in vivo* and inhibited gap-junctional intercellular communication in rodent and human cell systems. Conflicting data were obtained with regard to some genetic endpoints. In most studies, DDT did not induce genotoxic effects in rodent or human cell systems nor was it mutagenic to fungi or bacteria.

para,para'-DDE weakly induced chromosomal aberrations in cultured rodent cells and caused mutation in mammalian cells and insects, but not bacteria. *para,para'*-DDE inhibited gap-junctional intercellular communication in cultured rodent cells.

In most studies, *para,para'*-TDE did not induce genetic effects in short-term tests *in vitro*. It inhibited gap-junctional intercellular communication in cultured rodent cells.

There is no evidence that *ortho,para'*-TDE induced genetic effects in short-term tests *in vitro* on the basis of the few studies available.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of DDT.

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

Overall evaluation

DDT *is possibly carcinogenic to humans (Group 2B).*

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[1]For definition of the italicized terms, see Preamble, pp. 26-28.

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