CHLORDANE AND HEPTACHLOR

Chlordane and heptachlor were considered together because of their close structural similarity and because technical-grade products each contain approximately 20% of the other compound.

These substances were considered by a previous Working Group, in 1978 (IARC, 1979). 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*

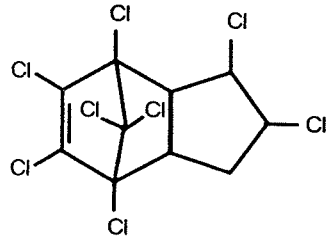
Table 1. Chemical Abstract Services Registry numbers, names and synonyms

Name	CAS Reg. Nos[a]	Chem. Abstr. names[b] and synonyms
Chlordane	57-74-9 (39400-80-1; 53637-13-1)	ENT 9932; **1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1*H*-indene**; 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7, 7a-hexahydro-4,7-methanoindene (IUPAC); octachloro-4,7-methanotetrahydroindane; 1,2,4,5,6,7,8,8-octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindan; OMS 1437
Technical-grade chlordane	12789-03-6	
cis-Chlordane	5103-71-9 (22212-52-8; 26703-86-6; 28140-46-7)	α-Chlordan; α-chlordane; *cis*-chlordan; **(1α,2α,3aα,4β,-7β,7aα)-1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene**; 1α,2α,4β,5,6,7β,8,8-octachloro-3aα,4,7,7aα-tetrahydro-4,7-methanoindan
trans-Chlordane	5103-74-2 (17436-70-3; 28181-89-7)	β-Chlordan; β-chlordane; *trans*-chlordan; **(1α,2β,3aα,4β,7β,-7aα)-1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1*H*-indene**; 1β,2α,4α,5,6,7α,8,8-octachloro-3aβ,4,7,7aβ,4,7,7aβ-tetrahydro-4,7-methanoindan
γ-Chlordane	5566-34-7	γ-Chlordan; **2,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1*H*-indene**; 2,2,4,5,6,7,8,8-octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindan stereoisomer
Heptachlor	76-44-8 (23720-59-4; 37229-06-4)	3-Chlorochlordene; E 3314; ENT 15 152; **1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methano-1*H*-indene**; 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene (IUPAC); OMS 193

Table 1 (contd)

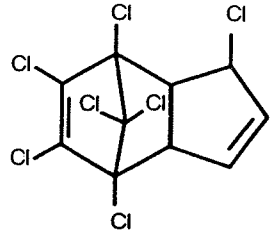
Name	CAS Reg. Nos[a]	Chem. Abstr. names[b] and synonyms
Heptachlor epoxide	1024-57-3 (4067-30-5; 24699-42-1; 24717-72-4; 28044-82-8; 66240-71-9)	ENT 25584; epoxyheptachlor; 1,4,5,6,7,8,8-heptachloro-2,3-epoxy-3a,4,7,7a-tetrahydro-4,7-methanoindan; **(1aα, 1bβ,2α,5α,5aβ,6β,6aα)-2,3,4,5,6,7,7-heptachloro-1a,1b,5,5a,6,6a-hexahydro-2,5-methano-2*H*-indeno(1,2-b)-oxirene**; heptachlor *cis*-oxide

[a]Replaced CAS Registry number(s) in parentheses
[b]In bold



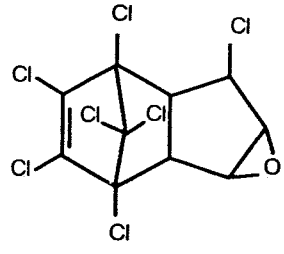
Chlordane

$C_{10}H_6Cl_8$ Mol. wt: 409.8



Heptachlor

$C_{10}H_5Cl_7$ Mol. wt: 373.5



Heptachlor epoxide

$C_{10}H_5Cl_7O$ Mol. wt: 389.4

1.1.2 *Chemical and physical properties*

Chlordane

(*a*) *Description*: Light-yellow to amber-coloured, viscous liquid (technical product) (WHO, 1988a)

(*b*) *Boiling-point*: 175°C at 1 mm Hg [0.13 kPa] (pure material) (Royal Society of Chemistry, 1989)

(*c*) *Melting-point*: 106-107°C (α-isomer); 104-105°C (γ-isomer) (WHO, 1988)
(*d*) *Spectroscopy data*: Infrared (prism [534]; grating [41094P]) spectroscopy data have been reported (Sadtler Research Laboratories, 1980).
(*e*) *Solubility*: Practically insoluble in water (0.1 mg/l at 25°C) but soluble in most organic solvents (e.g., acetone, ethanol, kerosene, trichloroethylene) (Worthing & Walker, 1987)
(*f*) *Volatility*: Vapour pressure, 1×10^{-5} mm Hg [0.13×10^{-5} kPa] at 25°C (pure); 4.6×10^{-4} mm Hg [0.61×10^{-4} kPa] at 25°C (technical product) (Royal Society of Chemistry, 1989)
(*g*) *Stability*: Decomposed by alkalis, with loss of chlorine; ultra-violet irradiation induces a change in the skeletal structure and of the chlorine content; corrosive to iron, zinc and various protective coatings (Royal Society of Chemistry, 1989)
(*h*) *Conversion factor for airborne concentrations*[1]: $mg/m^3 = 16.76 \times ppm$

Heptachlor

(*a*) *Description*: White crystalline solid with mild odour of camphor (Worthing & Walker, 1987; WHO, 1988b)
(*b*) *Boiling-point*: 135-145°C at 1-1.5 mm Hg [0.13-0.210 kPa] (US Environmental Protection Agency, 1986a)
(*c*) *Melting-point*: 95-96°C (pure compound) (Worthing & Walker, 1987)
(*d*) *Spectroscopy data*: Infrared (prism [74915]; grating [74915]) and nuclear magnetic resonance (proton [47772]) spectral data have been reported (Sadtler Research Laboratories, 1990).
(*e*) *Solubility*: Practically insoluble in water (56 µg/l at 25-29°C); fairly soluble in organic solvents: acetone (750 g/l), benzene (1060 g/l), ethanol (45 g/l) and xylene (1020 g/l) (WHO, 1988b)
(*f*) *Volatility*: Vapour pressure, 4×10^{-4} mm Hg [0.5×10^{-4} kPa] at 25°C (Worthing & Walker, 1987; WHO, 1988b)
(*g*) *Stability*: Stable in daylight, air, moisture and moderate heat (160°C); corrosive to metals; susceptible to epoxidation; slowly loses hydrogen chloride in alkaline media (WHO, 1988b; Royal Society of Chemistry, 1989)
(*h*) *Conversion factor for airborne concentrations*[1]: $mg/m^3 = 15.28 \times ppm$

Heptachlor epoxide

(*a*) *Description*: Solid (Agency for Toxic Substances and Disease Registry, 1989a)
(*b*) *Melting-point*: 160-161.5°C (US Environmental Protection Agency, 1987a)
(*c*) *Spectroscopy data*: Infrared (prism [74932]; grating [74932]) and nuclear magnetic resonance (proton [47783]) spectral data have been reported (Sadtler Research Laboratories, 1990).
(*d*) *Solubility*: Practically insoluble in water (0.35 mg/l at 25°C) (US Environmental Protection Agency, 1987a)
(*e*) *Conversion factor for airborne concentrations*[1]: $mg/m^3 = 15.93 \times ppm$

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

1.1.3 *Trade names, technical products and impurities*

Some examples of trade names are:

Chlordane: Aspon; Belt; CD 68; Chlordan; Chlorindan; Chlor Kil; Chlorotox; Corodane; Cortilan-neu; Dowchlor; Gold Crest; HCS 3260; Intox; Kypchlor; M 140; Niran[2]; Octachlor; Oktaterr; Ortho-Klor[2]; Starchlor; Sydane; Synklor; Tat Chlor 4; Termex; Topichlor; Toxichlor; Unexan-Koeder; Velsicol 1068

Heptachlor: Aahepta; Agroceres; Arbinex 30TN; Basaklor; Drinox; GPKh; Hepta; Heptachlorane; Heptagran; Heptagranox; Heptamak; Heptamul; Heptasol; Heptox; Rhodiachlor; Soleptax; Velsicol 104

Heptachlor epoxide: GPKh epoxide; HCE; Hepox; Heptepoxide; Velsicol 53-CS-17

The term chlordane commonly refers to a complex mixture of chlordane isomers, other chlorinated hydrocarbons and by-products, and at least 26 different components have been identified (WHO, 1988a). Technical-grade chlordane contains 60-75% of chlordane isomers (Royal Society of Chemistry, 1989), the major components being two stereoisomers (*cis* and *trans*, or α and γ), the nomenclature of which has been confused in the literature. The α or *cis*-isomer is described above under [5103-71-9]; the *trans*-isomer [5103-74-2], also usually known as the γ-isomer, is occasionally referred to as β-chlordane (the term γ-chlordane has been assigned by the Chemical Abstracts Service to the 2,2,4,5,6,7,8,8-octachloro-isomer [5566-34-7]). The remainder of the technical grade comprises other congeners (each $\leq$ 7%) and heptachlor. One description of the approximate composition of technical chlordane is as follows: *trans*-chlordane, 24%; *cis*-chlordane, 19%; chlordene isomers, 21.5%; heptachlor, 10%; nonachlor, 7%; octachlorocyclopentene, 1%; hexachlorocyclopentadiene, 1%; other, 16.5% (Brooks, 1974). Several reviews give details of the composition of technical-grade chlordane (Cochrane & Greenhalgh, 1976; Sovocool *et al.*, 1977; Miyazaki *et al.*, 1985; Buchert *et al.*, 1989).

Chlordane has been available in various formulations, including 5-30% granules, oil solutions containing 2-300 g/litre chlordane and emulsifiable concentrates containing 400-900 g/litre (Worthing & Walker, 1987; WHO, 1988a; Royal Society of Chemistry, 1986).

Technical-grade heptachlor contains about 72% heptachlor and 28% related compounds (20-22% γ-chlordane and 4-8% γ-nonachlor). Formulations have included emulsifiable concentrates, wettable powders, dusts and granules containing various concentrations of active material (Izmerov, 1982; Worthing & Walker, 1987; WHO, 1988b). In the USSR, the hexachlorocyclopentadiene content of heptachlor is limited by law to less than 2% (Izmerov, 1982). Heptachlor is registered in Czechoslovakia for formulation in combination with thiram (see IARC, 1976) (Royal Society of Chemistry, 1986).

1.1.4 *Analysis*

Determination of chlordane residues is difficult because of the complex nature of the components and the fact that each component degrades independently. Resulting residues may bear little relation to the proportions in the technical product. Extraction from crops, other plant products, dairy products, plants and oils has been achieved with an 80-100%

[2]Discontinued

efficiency using acetonitrile for extraction, petroleum ether for partitioning and clean-up on a Florisil column. Gel-permeation chromatography can also be used for clean-up, particularly of human adipose tissue. The method of choice for the qualitative and quantitative estimation of chlordane isomers and heptachlor is gas chromatography with electron-capture detection. Gas chromatographic analyses can be confirmed by gas chromatography–mass spectrometry, a method that can also provide better determination of some of the components, such as heptachlor epoxide. Analysis for total organically bound chlorine remains the preferred method for determination of technical-grade chlordane and heptachlor and of the active ingredient in formulations (WHO, 1988a,b).

Selected methods for the analysis of chlordane, heptachlor and heptachlor epoxide in various matrices are given in Table 2. Several reviews are available on the analysis of chlordane, heptachlor and heptachlor epoxide in technical products, formulations and as residues in various matrices, including titrimetric, colorimetric, spectrophotometric, infrared spectroscopic and gas chromatographic methods (Bowery, 1964; Raw, 1970; Izmerov, 1982; WHO, 1984a,b; Williams, 1984a,b; Anon., 1985; Worthing & Walker, 1987; Agency for Toxic Substances and Disease Registry, 1989a,b; Royal Society of Chemistry, 1989; Fendick *et al.*, 1990).

Table 2. Methods for the analysis of chlordane, heptachlor and heptachlor oxide

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection[b]	Reference
Air	Collect vapours on polyurethane foam; extract with 5% diethyl ether in hexane	GC/ECD	NR	US Environmental Protection Agency (1988a)
	Collect vapours on Chromosorb 102; desorb with toluene	GC/ECD	0.1 µg/ sample	Taylor (1979); Eller (1989)
Water	Extract with hexane; inject extract	GC/ECD	0.14, 0.003, 0.004 µg/l (0.006, 0.012 µg/l)[c]	US Environmental Protection Agency (1988b)
	Extract with dichloromethane; dry, concentrate (packed column)	GC/MS	NR, 1.9, 2.2 µg/l	US Environmental Protection Agency (1986b)
	Extract with dichloromethane; isolate; extract; dry; concentrate with methyl *tert*-butyl ether (capillary column)	GC/ECD	0.0015[c], 0.01, 0.015 µg/l	US Environmental Protection Agency (1988c)
	Extract by passing sample through liquid-solid extractor; elute with dichloromethane; conc. by evaporation (capillary column)	GC/MS	0.2, 0.1 µg/l[c], 0.04, 0.2 µg/l (0.3 g/l)[d]	US Environmental Protection Agency (1988d)
Waste-water	Extract with dichloromethane; dry; exchange to hexane	GC/ECD	0.014, 0.03, 0.083 µg/l	US Environmental Protection Agency (1986c, 1989a)

Table 2 (contd)

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection[b]	Reference
Waste-water (contd)	Extract with dichloromethane; dry; concentrate (packed column)	GC/MS	NR, 1.9 2.2 µg/l	US Environmental Protection Agency (1989b)
Formulations (chlordane)	Dissolve in toluene or benzene, then toluene; extract with 0.1N silver nitrate solution	TCM	NR	Williams (1984a)
Formulations (chlordane)	Dissolve in methanol/benzene or extract with pentane; dissolve; add Davidow reagent[e], boil; cool; read absorbance at 550 nm	Colorimetric	NR	Williams (1984a)
Formulations (heptachlor)	Dissolve in acetic acid; add silver nitrate or extract with pentane; dissolve	ACM	NR	Horwitz (1975)
	Dissolve in carbon disulfide or extract with pentane; dissolve	GC/FID	NR	Horwitz (1975)
Selected vegetables	Extract with pentane; clean-up on Florex column; evaporate to dryness; react with Polen-Silverman reagent[f]; read absorbance at 560 nm for heptachlor and at 410 nm for heptachlor oxide	Colorimetric	– 0.02, 0.02-0.04 ppm (mg/kg)	US Food and Drug Administration (1989)
Soil, sediment, wastes	Mix with anhydrous sodium sulfate; extract using Soxhlet or sonication process; clean-up using Florisil column or gel-permeation (packed column)	GC/MS	NR, 1.9, 2.2 µg/kg	US Environmental Protection Agency (1986b)
	Mix with anhydrous sodium sulfate; extract using Soxhlet or sonication process; clean-up using Florisil column or gel-permeation (capillary column)	GC/MS	NR	US Environmental Protection Agency (1986d)

[a]Abbreviations: ACM, active chlorine method; GC/ECD, gas chromatography/electron capture detection; GC/FID, gas chromatography/flame ionization detection; GC/MS, gas chromatography/mass spectrometry; TCM, total chlorine method

[b]The limits of detection are presented for chlordane, heptachlor and heptachlor epoxide, respectively; NR, not reported

[c]Detection limit(s) for α- and γ-chlordane

[d]*trans*-Nonachlor

[e]Diethanolamine-potassium hydroxide solution

[f]Prepared by dissolving potassium hydroxide in distilled water, cooling to room temperature, adding butyl Cellosolve and monoethanolamine and diluting to 1 litre with butyl Cellosolve. This solution, after standing several days, is decanted from any sediment and diluted with an equal volume of benzene.

1.2 Production and use

The discovery, chemistry and uses of chlordane and heptachlor and the problems associated with their technical-grade products have been reviewed (Brooks, 1974).

1.2.1 *Production*

Chlordane was first produced commercially in the USA in 1947. In 1974, production in the USA amounted to 9500 tonnes (WHO, 1988a); the US Environmental Protection Agency estimated that approximately 1600-1800 tonnes of chlordane were used in 1986. From 1 July 1983, the only use of chlordane approved in the USA was in the control of underground termites, but this use was prohibited in April 1988. The amounts of chlordane both produced and used have decreased considerably in recent years (US Environmental Protection Agency, 1987b; Agency for Toxic Substances and Disease Registry, 1989b).

Heptachlor was isolated from technical-grade chlordane in 1946. Production of heptachlor in the USA was 2700 tonnes in 1971, 900 tonnes in 1974, 590 tonnes in 1978, 180 tonnes in 1980 and 45 tonnes in 1982. Sales of heptachlor in the USA were voluntarily stopped by the sole US producer in August 1987, and since April 1988, heptachlor can no longer be used for the underground control of termites in the USA (WHO, 1988a; Agency for Toxic Substances and Disease Registry, 1989b). Chlordane and heptachlor are currently produced by one company in the USA; heptachlor epoxide is not produced commercially in the USA.

Chlordene, the starting material for the synthesis of both chlordane and heptachlor, is prepared by the Diels-Alder condensation of hexachlorocyclopentadiene with cyclopentadiene (Agency for Toxic Substances and Disease Registry, 1989b). Chlordane is prepared by the Lewis-acid catalysed addition of chlorine to chlordene (WHO, 1984a), whereas heptachlor is prepared by the free-radical chlorination of chlordene (Sittig, 1980).

Heptachlor epoxide can be prepared from heptachlor in a one-step oxidation. It is a metabolite as well as an environmental oxidation product of heptachlor (Anon., 1985).

1.2.2 *Use*

Chlordane has been used as an insecticide since the 1950s. It is a versatile, broad-spectrum, contact insecticide and has been used mainly for nonagricultural purposes (primarily for the protection of structures, but also on lawn and turf, ornamental trees and drainage ditches). It has also been used on maize, potatoes and livestock (WHO, 1984a). The use pattern for chlordane in the USA in the mid 1970s was as follows: 35% used by pest control operators, mostly on termites; 28% on agricultural crops, including maize and citrus; 30% for home lawn and garden use; and 7% on turf and ornamental plants (Agency for Toxic Substances and Disease Registry, 1989b). Since the mid-1970s, the use of chlordane has been increasingly restricted in many countries (WHO, 1988a). By 1980, less than 4500 tonnes of chlordane were being used yearly in the USA, mostly for termite control (Esworthy, 1985). By 1986, use had been reduced to 1800 tonnes (US Environmental Protection Agency, 1987b). In Japan, where chlordane was used exclusively for termite control, it was prohibited in 1986 (Takamiya, 1990).

Heptachlor was first introduced as a contact insecticide in the USA in 1952 for foliar, soil and structural application. It has also been used in the control of malaria. It is a nonsystemic

internal and contact insecticide (WHO, 1988b). The use pattern for heptachlor in the USA in the mid-1970s was as follows: 58% on maize, 27% by pest control operators, 13% as seed treatment and 2% for miscellaneous uses, including fire ant control, use on pineapples and possibly on citrus (IARC, 1979). In 1970, the use of heptachlor throughout the world was as follows: Africa, 5%; Asia, 15%; Canada and the USA, 5%; Europe, 60%; and South America, 15% (WHO, 1988b). For example, in the Republic of Korea, average use of heptachlor was about 33 tonnes per year over the period 1962-79 (Lee, 1982). The use of heptachlor has been increasingly restricted in many countries; it is now confined almost exclusively to the control of soil insects and termites (WHO, 1988b). By 1986, less than 340 tonnes of heptachlor were used in the USA, mainly for termite control (US Environmental Protection Agency, 1987a).

1.3 Occurrence

The environmental occurrence and fate of chlordane and heptachlor have been reviewed (WHO, 1984a,b; Fendick *et al.*, 1990).

1.3.1 *Air*

Treatment for termite control in the USA in 1978, by subslab injection of 2% chlordane or exterior ditching of apartment blocks, produced high indoor air concentrations (0.4-263.5 $\mu g/m^3$) within one year; the levels after two years were 0-37.9 $\mu g/m^3$. Termite treatments in the USA in 1970 produced air concentrations within houses of 14.5-37.8 $\mu g/m^3$ (Livingston & Jones, 1981). Other US houses treated for termites with an emulsion containing 0.54% chlordane, 0.76 ppm diazinon and 0.93 ppm malathion resulted in airborne household dust containing 30 ppm (503 mg/m^3) chlordane and traces of the other pesticides (Vinopal & Olds, 1977).

1.3.2 *Water*

An episode of chlordane contamination of a segment of a municipal water system occurred in 1976 in Chattanooga, TN (USA), resulting in a concentration of chlordane in the water of up to 1200 mg/l (0.12%) (*sic*). The contamination probably occurred through careless handling of a concentrated chlordane solution, and a period of negative water pressure during dilution of the concentrate may have caused back-siphonage into the water system (Harrington *et al.*, 1978). Another public water supply was contaminated in Pittsburgh, PA: Levels of up to 6600 ppb (µg/l) chlordane were found in tap-water; six months later, the level was < 1 ppb (< 1 µg/l) (Anon., 1981).

After chlordane was applied to the surface of a lake, the concentration in the water was 4-5.5 µg/l after seven days and 0.008-0.011 µg/l after 421 days. The concentration in the lake sediments reached 20-30 µg/kg during the first 279 days and 10 µg/kg 421 days after application. Chlordane is not expected to leach since it is insoluble in water and should be adsorbed on the soil surface (US Environmental Protection Agency, 1986e).

1.3.3 *Soil*

Application of chlordane at 9 kg/ha (active ingredient) to turf over a sandy loam soil resulted in residues of 1.6-2.1 mg/kg in the root zone (0-1 cm depth) and < 0.3 mg/kg in the soil zone (1-3.5 cm depth). Total residues after 56 days had declined to 69% of the dose

originally applied. In studies in Maryland, USA, where chlordane was applied to sandy loam soil at rates of 56, 112 and 224 kg/ha, 83% of that applied was still present after one year and 45% remained after 15 years (US Environmental Protection Agency, 1986e).

Heptachlor is stable to light and moisture, and volatilization is the major mechanism of transport of topically applied material. Its half-time in soil in temperate regions ranges between 0.75 and 2 years, depending on soil type and may be less in tropical regions. Residues have been detected in soil 14 years after initial use (WHO, 1984b).

A survey on cropland soils in 37 states of the USA in 1971 revealed heptachlor residues in 4.9% of samples at a maximum of 1.37 mg/kg; heptachlor epoxide was detected in 6.9% of the samples at a maximum level of 0.43 mg/kg (Carey *et al.*, 1978).

1.3.4 *Food*

Many studies were carried out during the 1970s in Canada, the United Kingdom, the USA and other countries on the occurrence of pesticide residues in foods. Generally, residues of chlordane were seldom found. For example, in a market basket survey in the USA from 1963 to 1969, chlordane residues were found in less than 1% of samples at levels of 1-5 μg/kg (WHO, 1984a).

Significant levels were found in meat, milk and eggs, as a result of residues in feed crops or direct applications to cattle and poultry (as reported by the WHO, 1984a). In a study on eggs in Canada, *trans*-chlordane was found in 78% of samples, at a mean level of 2 μg/kg fresh weight, and *cis*-chlordane in 81% of the eggs, at a mean level of 1 μg/kg (Mes *et al.*, 1974). In another study (Herrick *et al.*, 1969), no residue was found in the eggs of chickens fed chlordane in the diet at 0.08 mg/kg for one week.

In analyses of cows' milk in the USA, 87% of samples contained chlordane, at levels ranging from 0.02 to 0.06 mg/l (IARC, 1979). In another study, the milk of cows grazing on pastures to which chlordane had been applied at 0.55 kg/ha contained an average chlordane concentration of 0.03 mg/litre; no residue was found at lower treatment levels (WHO, 1984a). Chlordane was also found in Canadian meat samples at levels ranging from 0 to 106 μg/kg in beef, 0 to 32 μg/kg in pork and 0 to 70 μg/kg in fowl (Saschenbrecker, 1976).

Of 1171 samples of fruits, meats, dairy products, grains and wine analysed for chlordane as part of the Canadian national surveillance programme (1984-89), none contained residues. Of 1227 samples of fruits, vegetables, meats, dairy products and wine analysed for heptachlor and its epoxide, four contained residues (2/21 carrots and 2/100 cucumbers), at levels of 0.01-0.02 mg/kg (Government of Canada, 1990).

In Brazil, 1998 samples of cattle meat, 102 samples of horse meat and 158 samples of corned beef and roast beef were analysed for heptachlor/heptachlor epoxide and oxychlordane/transnonaclor in 1984 and 1985; no residue was reported (limit of detection, 0.02 mg/kg) (Codex Committee on Pesticide Residues, 1989).

The daily human intake of heptachlor epoxide in the USA was calculated to be 0.29-0.64 μg/day during 1971-74 (as reported by the WHO, 1984b). The daily intake of heptachlor epoxide from food in 1965 in the USA was estimated as 2 μg/day; in 1970, this figure was 1 μg/day (Duggan & Corneliussen, 1972).

Market basket surveys carried out in 1972-73 in the USA showed maximum values for heptachlor epoxide ranging from trace to 2 μg/kg (Johnson & Manske, 1976). In a study done

in 1966-67 in the United Kingdom, the heptachlor epoxide content in the total diet was, in general, less than 0.5 μg/kg; heptachlor was not detected (Abbott *et al.*, 1969). In a series of studies of total diets in the USA, heptachlor epoxide was found in small amounts in fish, poultry, meat and dairy products, and in trace amounts in fruits, vegetables, oils and cereals. The maximum values in poultry, meat and fish ranged from trace to 2 μg/kg (Johnson & Manske, 1976).

Heptachlor was not found in foods examined between August 1972 and July 1973 in a total-diet study conducted by the US Food and Drug Administration (Johnson & Manske, 1976). In a study (reported by WHO, 1984b) conducted in 20 cities in the USA in 1974-75, only 3 of 12 food classes contained detectable residues of heptachlor epoxide. Levels ranged from 0.6-3 μg/kg. A study (reported by WHO, 1984b) that started in 1974 in the USA revealed residues of heptachlor and heptachlor epoxide at the mean levels shown in Table 3.

Table 3. Heptachlor and heptachlor epoxide levels in food[a]

Residue	Level (μg/kg wet weight)				
	Pork	Horse meat	Chicken	Beef	Turkey
Heptachlor	1.25	1.06	3.27	0.10	0.65
Heptachlor epoxide	1.95	5.28	9.58	0.50	6.66

[a]As reported by WHO (1984b)

Within the framework of the Joint FAO/WHO Food Contamination Monitoring Programme, the levels of heptachlor and heptachlor epoxide residues in various food samples in 1980-82 were reported from Austria, Canada, Denmark, Guatemala, Japan, the Netherlands and the USA. On a fat basis, the median levels ranged from 0 (not detected) in butter and cattle fat in Denmark to 13 μg/l in cows' milk in Japan. Median levels in the products ranged from 0 (not detected) in hens' eggs in Denmark to 4 μg/kg in fresh onions in Guatemala. The median levels of heptachlor epoxide on a fat basis ranged from 0 (not detected) in butter and pasteurized cows' milk to 0.30 μg/l in raw cows' milk in Germany (WHO, 1983).

Heptachlor and/or heptachlor epoxide was present in 32% of 590 fish samples in the USA in 1967-68, at levels of 0.01-8.46 mg/kg (Henderson *et al.*, 1969). Fish have been shown to accumulate heptachlor and heptachlor epoxide: 0.008 mg/kg was found after exposure to a concentration of 0.06 μg/l water. Residues of heptachlor plus heptachlor epoxide were found at 0.001-0.026 mg/kg (on a fibre basis) and < 0.01-0.8 (on a tissue basis) (Hannon *et al.*, 1970). The average concentration of heptachlor and heptachlor epoxide in oysters in the USA was < 0.01 mg/kg (Bugg *et al.*, 1967).

In a German study reported by WHO (1984b), heptachlor and heptachlor epoxide residues were determined in cheese, butter, pasteurized milk and human milk. The average total residue in milk and milk products was less than 0.05 mg/kg, but the levels in human milk were about 10 times higher, with heptachlor at 0.1 mg/kg and heptachlor epoxide at 0.34 mg/kg in milk fat.

1.3.5 *Other*

The occurrence of chlordane and heptachlor and their metabolites in human tissues and biological fluids is reviewed in section 4.1.1.

Members of families living on dairy farms who consumed milk and milk products contaminated with heptachlor were compared with a group of unexposed people. The cows' milk contained levels of heptachlor epoxide ranging up to 89.2 ppm (mg/l; lipid basis). After 33 farms in Arkansas and five in Missouri and Oklahoma had been placed in quarantine, the level of heptachlor epoxide in milk was 12.6 ppm (mg/l; lipid basis). Heptachlor epoxide and oxychlordane were detected in the serum of 23.1% of the exposed persons and *trans*-nonachlor in 30.8%, *versus* 3.7, 4.0 and 6.5%, respectively, in the control group. The mean levels (0.81, 0.70 and 0.79 µg/l) of heptachlor epoxide, oxychlordane and *trans*-nonachlor were significantly different from those found in the control group (Stehr-Green *et al.*, 1986).

1.4 Regulations and guidelines

The FAO/WHO Joint Meeting on Pesticide Residues evaluated chlordane at its meetings in 1965, 1967, 1969, 1970, 1972, 1974, 1977, 1982, 1984 and 1986 (FAO/WHO, 1965, 1968, 1970, 1971, 1973, 1975, 1978, 1983, 1985, 1987). In 1970, it re-established residue tolerances for food at 0.02-0.5 mg/kg for the sum of *cis*- and *trans*-isomers of chlordane and oxychlordane. In 1986, an acceptable daily intake in food of 0.0005 mg/kg bw was established (FAO/WHO, 1987).

The FAO/WHO Joint Meeting on Pesticide Residues evaluated heptachlor at its meetings in 1965, 1966, 1967, 1968, 1969, 1970, 1974, 1975, 1977 and 1987 (FAO/WHO, 1965, 1967, 1968, 1969, 1970, 1971, 1975, 1976, 1978, 1988). In 1970, an acceptable daily intake in food of 0.0005 mg/kg bw was established (Codex Committee on Pesticide Residues, 1990).

European Community legislation prohibits the marketing and use of plant protection products containing chlordane. The use of chlordane in agriculture is prohibited in several countries, including those of the Community, Argentina, Chile, Ecuador, Japan, Singapore, Switzerland, Sweden, the USA and Yugoslavia (WHO, 1988a) as well as Finland and the USSR. The use of chlordane is restricted in Cyprus and Venezuela. It must be registered for import, export or manufacture in India (WHO, 1988a). In Canada, since 1985, the registration of chlordane limits it to use as a restricted class termiticide. Chlordane has not been used in Norway since 1968.

European Community legislation prohibits the marketing and use of plant protection products containing heptachlor. The use of heptachlor in agriculture is prohibited in several countries, including those of the Community, Argentina, Cyprus, Ecuador, Singapore, the USA (with some exceptions, e.g., fire ants; US Environmental Protection Agency, 1987b) and Yugoslavia. Chile and Venezuela restricted its use in agriculture; its use is permitted in agriculture but prohibited in domestic sanitation in Brazil (WHO, 1988b). It has never been registered for use in Norway. The only accepted uses of heptachlor in Finland are as a termiticide in particle-board and in the plywood industry (for exported materials) and as a laboratory chemical. The registration of heptachlor in Canada was discontinued in 1985.

Maximum residue levels have been established by the Codex Alimentarius Commission for chlordane (sum of *cis*- and *trans*-chlordane or, in the case of animal products, sum of *cis*- and *trans*-chlordane and 'oxychlordane' (fat-soluble residue)) in or on the following commodities (in mg/kg): 0.05 for cottonseed oil (crude), linseed oil (crude), meat (fat), poultry meat (fat), soya bean oil (crude); and 0.02 for almonds, cottonseed oil (edible), eggs, fruit, hazelnuts, maize, oats, pecans, rice (polished), rye, sorghum, soya bean oil (refined), vegetables, walnuts, wheat (Codex Committee on Pesticide Residues, 1990).

Maximum residue limits have been established by the Codex Alimentarius Commission for heptachlor (sum of heptachlor and heptachlor epoxide (fat-soluble residue)) in or on the following commodities (in mg/kg): 0.5 for soya bean oil (crude); 0.2 for carrots, meat (fat), poultry meat (fat); 0.05 for eggs, vegetables (except carrots, soya beans, sugar beets and tomatoes); 0.02 for cereal grains, cottonseed, soya beans (immature seeds), soya bean oil (refined), tomatoes; 0.01 for citrus fruit, pineapples; and 0.006 for milk (Codex Committee on Pesticide Residues, 1990).

WHO (1988c) recommended guideline limit values of 0.3 µg/l for chlordane (total of isomers) and 0.1 µg/l for heptachlor and heptachlor epoxide in drinking-water. In Mexico, maximum permissible concentrations of chlordane in ambient water are 0.002 mg/l for coastal and estuarine waters and 0.003 mg/l for water treated for drinking; those of heptachlor in ambient water are 0.2 µg/l for coastal waters, 0.002 mg/l for estuarine waters and 0.018 mg/l for water treated for drinking (WHO, 1988a,b). The US Environmental Protection Agency has established a National Ambient Water Quality Criterion for heptachlor of 0.28 µg/l (Agency for Toxic Substances and Disease Registry, 1989a).

Chlordane and heptachlor epoxide were included in the 1987 Canadian guidelines for drinking-water quality for re-evaluation; the maximum acceptable concentrations in 1978 were 0.007 mg/l and 0.003 mg/l, respectively. Heptachlor was also included in the 1987 Canadian guidelines for drinking-water quality, with an interim maximum acceptable concentration of 0.28 mg/l (Ritter & Wood, 1989).

Treatment of root crops and soil with heptachlor is prohibited in the USSR, and it cannot be applied in water-catchment areas with a large number of open water reservoirs. The maximum allowable concentration of heptachlor in water used for drinking and domestic water supplies is 0.05 mg/l; that in the atmosphere of populated areas is 0.001 mg/m^3 for a maximum single concentration and 0.0002 mg/m^3 for a daily average concentration (Izmerov, 1982).

National and regional pesticide residue limits for chlordane, heptachlor and heptachlor epoxide in foods are presented in Tables 4 and 5. Tables 6 and 7 present occupational exposure limits and guidelines for chlordane and heptachlor in several countries. Because of potentially continuous household exposure, the Committee on Toxicology of the US National Academy of Sciences (1979) recommended a maximum acceptable level of 5 µg/m^3 chlordane in residences.

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

Country or region	Residue limits (mg/kg)	Commodities
Australia	0.2	Mammalian meat (fat basis)
	0.1	Sugar beets
	0.05	Cottonseed oil (crude), cucurbits, fish, linseed oil (crude), milk (fat basis), milk products (fat basis), soya bean oil (crude)
	0.02	Cereal grains, citrus, cottonseed oil (edible), eggs, fruit (pome, stone), pineapples, soya bean oil (edible), vegetables (except cucurbits)
Austria	0.05[b]	Meat, animal fats (edible), milk
	0.02	Eggs (without shell)
Belgium	0.05[c]	Meat, poultry, hare, fowl, game, meat products, animal fats
	0.005	Eggs
	0.002	Milk and milk products
	0 (0.05)[d,e]	All foodstuffs of vegetable origin
	0 (0.02)[c,e]	All other foodstuffs of animal origin
Canada	0.1[f]	Butter, cheese, milk and other dairy products, meat and meat by-products (cattle, goats, hogs, poultry sheep)
Chile	0.5[d]	Soya bean oil (unrefined)
	0.3[d]	Potatoes, sugar beets
	0.2[d]	Lettuce
	0.05[c,d]	Maize, milk and dairy products (fat basis), carcasses (fat basis), poultry (fat basis), rice (polished), wheat
	0.02	Citrus fruit, eggs, tomatoes
Czechoslovakia	0.3[d]	Sugar beets
	0.2[d]	Pineapples
	0.1[c,d]	All spices, cereals (raw), maize (roasted, sweet), cucumbers, egg-plant, green peppers, leaf vegetables, pumpkin, squash, tomatoes, watermelons
Denmark	0.05[c]	Fat from meat
	0.02[c,d]	Berries and small fruit, carrots, cereals, eggs, fruit (citrus, pome, stone, other), other root vegetables and onions
	0.01[d]	Potatoes
	0.002[c]	Milk, milk products and dairy products
European Community	0.05[g]	Fat contained in meat, preparations of meat, offal and animal fats
	0.02[g]	Barley, buckwheat, grain sorghum, maize, millet, oats, paddy rice, rye, triticale, wheat, other cereals
	0.002[g]	Raw cows' milk and whole-cream cows' milk
Finland	0.1[h]	Fish, crustaceans, shellfish and their products
France	0.05[g]	Fruit, vegetables
	0.02	Cereal grains
Germany	0.2	Tobacco products
	0.05[i]	Meat, meat products, edible animal fats, milk, dairy products (all on fat basis), spices, tea, tea-like products
	0.02[i]	Cereals, eggs (without shell), egg products
	0.01[i]	Other foodstuffs of animal and plant origin
Hungary	0.02	Imported products

Table 4 (contd)

Country or region	Residue limits (mg/kg)	Commodities
India	0.3[d]	Sugar beets
	0.2[d]	Vegetables
	0.1[d]	Fruit
	0.05[d]	Foodgrains, milk and milk products (fat basis)
Israel	0.5	Linseed oil (crude), soya bean oil (crude)
	0.3	Potatoes, radishes, sugar beets, sweet potatoes, turnips
	0.2	Asparagus, broccoli, Brussels' sprouts, cabbage, cauliflower, celery, lettuce, mustard greens, spinach
	0.1	Almonds, bananas, cottonseed oil (crude), cucumbers, figs, filberts, guavas, mangoes, melons, olives, papayas, passion fruit, peanuts, pecans, pineapples, pomegranates, pumpkins, squash, strawberries, walnuts, watermelons
	0.05	Carcass meat (fat basis), maize, milk and milk products (fat basis), oats, poultry (fat basis), rice (polished), rye, wheat, sorghum
	0.02	Beans, cottonseed oil (edible), eggplant, eggs (without shell), fruit (citrus, pome, stone), peas, peppers, pimentos, soya bean oil (edible), tomatoes, other foodstuffs
Italy	0.2[j]	Tobacco (dried)
	0.05[j]	Aromatic and medicinal herbs, teas
	0.02[j]	Coffee
Kenya	0.5	Linseed oil (crude), soya bean oil (crude)
	0.3	Parsnips, potatoes, radishes, rutabagas, sugar beets, sweet potatoes, turnips
	0.2	Asparagus, broccoli, Brussels' sprouts, cabbage, cauliflower, celery, lettuce, mustard greens, spinach, Swiss chard
	0.1	Almonds, bananas, cantaloupes, cottonseed oil (crude), cucumbers, figs, filberts, guavas, mangoes, olives, papayas, passion fruit, pecans, pineapples, pomegranates, pumpkin, squash, strawberries, walnuts, watermelons
	0.05	Milk and milk products (fat basis), meat and poultry (fat basis), sorghum
	0.02	Beans, collards, cottonseed oil (edible), eggplant, eggs (without shell), fruit (citrus, pome, stone), maize, oats, peas, popcorn, rice (polished), rye, soya bean oil (edible), tomatoes, wheat
Luxembourg	0.05[k]	Animal fats (except butyric fats), meat and meat products (fat basis), milk and milk products (fat basis), poultry and poultry products (fat basis)
	0.02[k]	Eggs (without shell)
Netherlands	0.1[g]	Cucumbers, melons, pineapples
	0.05[g]	Potatoes, other dairy products (fat basis)
	0.02[g]	Other fruit, other vegetables, pulses, plant oil
	0.002[g]	Milk
	0 (0.02)[l]	Other plant products
Romania	0.05	Meat, milk and milk products
Spain	0.05[g]	Spices, tea and similar products
	0.02[g]	Cereal grains
	0.01[g]	Other plant products

Table 4 (contd)

Country or region	Residue limits (mg/kg)	Commodities
Sweden	0.1[d]	Fruits, vegetables
	0.02	Cereals, hulled grain, flakes and flour made from cereals
	0.01	Potatoes
United Kingdom	0.05[c,d]	Meat, fat and preparations of meats (fat basis), dairy produce (> 2% fat)
	0.02	Apples, bananas, barley, blackcurrants, beans, Brussels' sprouts, cabbage, carrots, celery, cauliflower, cucumbers, eggs (birds' eggs in shell (other than eggs for hatching) and whole egg products and egg yolk products (whether fresh, dried or otherwise prepared)), grapes, leeks, lettuce, maize, mushrooms, nectarines, oats, onions, oranges, paddy rice, peaches, pears, peas, plums, potatoes, raspberries, rye, strawberries, swedes, tomatoes, turnips, wheat, other cereals, other citrus
	0.002	Milk (fresh raw cows' milk and fresh whole cream cows' milk expressed as whole milk)
USA	0.3[m]	Animal fat (rendered), fish (edible portion)
	0.1[m]	Animal feed (processed), asparagus, bananas, beans, beetroot (with or without tops), beetroot greens, berries (except cranberries, currants, elderberries, gooseberries, and olallie berries), *Brassica* (cole) leafy vegetables (except broccoli raab, Chinese mustard cabbage, and rape greens), carrots, celery, citrus fruit, maize, cucumbers, eggplant, lettuce, melons, okra, onions, papayas, parsnips, peanuts, peas, peppers, pineapples, pome fruit (except crabapples and loquats), potatoes, radishes (with or without tops), radish tops, rutabagas (with or without tops), rutabaga tops, small fruit, spinach, squash, stone fruit (except chickasaw, damson and Japanese plums), sweet potatoes, Swiss chard, tomatoes, turnips (with or without tops), turnip greens
Yugoslavia	0.05	Meat and meat products (fat basis), vegetables
	0.02	Fruit, grain

[a]From Health and Welfare Canada (1990); US Food and Drug Administration (1990)
[b]Chlordane and oxychlordane (total calculated as chlordane)
[c]Sum of *cis*- and *trans*-chlordane and oxychlordane (usually for animal products)
[d]Sum of *cis*- and *trans*-chlordane (usually for plant products)
[e]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.
[f]Calculated on the fat content; including the metabolite oxychlordane
[g]Sum of *cis*- and *trans*-isomers and oxychlordane expressed as chlordane
[h]Sum of *cis*- and *trans*-chlordane, oxychlordane and *trans*-nonachlor
[i]Chlordane and oxychlordane (calculated as chlordane) for animal products; chlordane for plant products
[j]Includes isomers and/or metabolites; active substance revoked
[k]Singly or combined, including oxychlordane, expressed as chlordane
[l]Residues shall be absent, while the value in parentheses is the highest concentration at which this requirement is still deemed to have been met.
[m]Recommended action levels

Table 5. National and regional pesticide residue limits for heptachlor in foods[a]

Country or region	Residue limits (mg/kg)	Commodities
Argentina	0[b]	Cereals, fruit, garden vegetables, oilseeds
Australia	0.5[c]	Soya bean oil (crude)
	0.2[c]	Carrots, meat fat
	0.15[c]	Milk and milk products (fat basis)
	0.05[c]	Eggs, fish, vegetables (except carrots, tomatoes)
	0.02[c]	Cereal grains, cottonseed, soya bean oil (edible), soya beans, sugar-cane, tomatoes
	0.01[c]	Citrus fruit, pineapples
Austria	0.01[c]	All foodstuffs of animal origin
Belgium	0.2[c]	Meat, poultry, hare, fowl, game, meat products, animal fats
	0.1	Herbal teas, spices and dried herbs, teas
	0.02[c]	Eggs
	0.01	Grains
	0.004[c]	Milk and milk products
	0 (0.01)[d]	Other foodstuffs of animal and vegetable origin
Brazil	0.2	Carrots, tomatoes
	0.01	Milk and milk products (fat basis)
	0.05	Eggs (without shell), vegetables
	0.02	Maize, meat (fat basis), rice
	0.01	Bananas, sugar-cane
Canada	0.2[e]	Meat, meat by-products, fat (cattle, goats, hog, poultry, sheep)
	0.1[e]	Butter, cheese, milk, other dairy products
Chile	0.2[c]	Carcasses (fat), carrots, poultry (fat)
	0.15	Milk and milk products (fat)
	0.05	Eggs, garden vegetables, sugar beets
	0.02	Cereals (raw), tomatoes
	0.01	Citrus fruit
Czechoslovakia	0.5[c]	Soya bean oil (crude)
	0.2[c]	Meat (fat basis)
	0.15[c]	Milk and milk products (fat basis)
	0.05[c]	Eggs (egg white, yolk, without shell), vegetables
	0.02[c]	Cereals (raw), cottonseed, soya bean oil (edible), soya beans, tomatoes
	0.01[c]	Citrus fruit, pineapples
Denmark	0.2[c]	Meat fat
	0.05	Carrots, eggs
	0.01	Cereals, onions, potatoes, other vegetables
	0.004	Milk, milk products, dairy products
European Community	0.2[c]	Meat fat, preparations of meat, offal and animal fats
	0.01	Barley, buckwheat, grain sorghum, maize, millet, oats, paddy rice, rye, triticale, wheat, other cereals
	0.004	Raw cows' milk, whole-cream cows' milk

Table 5 (contd)

Country or region	Residue limits (mg/kg)	Commodities
Finland	0.1[c]	Fish, crustaceans, shellfish and their products
	0.05[c]	Other crops and foodstuffs
France	0.01[c]	Cereal grains, fruit, vegetables
Germany	0.2[c]	Meat, meat products, edible animal fats (all on fat basis), tobacco products
	0.1[c]	Milk, dairy products, spices, tea, tea-like products
	0.05[c]	Eggs (without shell), egg products
	0.01[c]	Other foodstuffs of animal and plant origin
Hungary	0.05[f]	Brussels' sprouts, beetroot, cabbage, carrots, cauliflower, celery, celery leaf, celery leaf (dried), garlic, horseradish, kohlrabi, lettuce, onion (red), parsley, parsley root, radishes, savoy, sorrel, spinach
	0.02[f]	Grains (barley, oats, rye, wheat), maize, rice (brown, polished), sorghum, soya bean oil, soya beans, tomatoes, triticale
	0.01[f]	Lemons, oranges, pineapples
India	0.15[c]	Milk and milk products (fat basis)
	0.05	Vegetables
	0.01	Food grains
	0.002	Milled food grains
Ireland	0.2[c]	Carrots
	0.05	Other vegetables
	0.02	Tomatoes
	0.01	Other food products
Israel	0.5	Soya bean oil (crude)
	0.2	Carcass meat (cattle, goats, pigs, poultry, sheep) (fat basis), carrots
	0.15	Milk and milk products (fat basis)
	0.05	Eggs (without shell), sugar beets, vegetables (except where otherwise specified)
	0.02	Cottonseed, raw cereals (barley, corn, oats, rice, wheat), soya bean oil (edible), soya beans, tomatoes
	0.01	Citrus fruit, pineapples
Italy	0.01[c]	Fruit, garden vegetables
Kenya	0.5	Soya bean oil (crude)
	0.2	Carrots, fat or meat and poultry
	0.15	Milk and milk products (fat basis)
	0.05	Eggs (without shell), vegetables (except where otherwise specified)
	0.02	Cereals (raw), cottonseed, soya bean oil (edible), soya beans, tomatoes
	0.01	Citrus fruit

Table 5 (contd)

Country or region	Residue limits (mg/kg)	Commodities
Luxembourg	0.2[g]	Meat and meat products (fat basis), poultry and poultry products (fat basis), animal fats (except butyric fats)
	0.15[g]	Milk and milk products (fat basis)
	0.05[g]	Eggs (without shell), nursing foods used in feeds
	0.03[g]	Other foods used in feeds
	0.02[g]	Natural foods used in feeds (except animal fats)
Netherlands	0.5[c]	Eggs (fat basis)
	0.2[c]	Game and fowl, meat, poultry meat (all on fat basis)
	0.1[c]	Tea
	0.05[c]	Potatoes, other vegetables
	0.02[c]	Cottonseed, soya beans, tomatoes, plant oil and fat
	0.01[h]	Citrus fruit, pineapples
	0.004[c]	Milk
	0 (0.01)[i]	Other crops or foodstuffs
Peru	0.5	Soya bean oil (raw)
	0.2	Carrots, meat (fat basis), poultry (fat basis)
	0.15	Milk and milk products (fat basis)
	0.05	Eggs (without shell)
	0.02	Cereals (raw), cottonseed, soya bean oil (edible), soya beans, tomatoes
	0.01	Beets, citrus fruit, pineapples
Romania	0.20	Meat
	0.10	Milk and milk products
	0.05	Eggs (without shell)
Spain	0.10[c]	Spices, tea and similar products
	0.01[c]	Other plant products
Sweden	0.1[c]	Butter, cheese
	0.05[c]	Eggs, fruit, vegetables
	0.02[c]	Meat raw material
	0.01[c]	Cereal and hulled grain, flakes and flour made from cereals, potatoes
	0.005	Milk
Switzerland	0.2[c]	Meat and meat products (except fish and fish based products) (fat basis)
	0.125[c]	Milk and milk products (fat basis)
	0.05[c]	Cocoa butter and bulk cocoa (fat basis)
	0.02[c]	Cereals
	0.01[c]	Eggs, vegetables
	0.002[c]	Cereal products, infant and baby foods (expressed as food as consumed: milk products and other products [limit value: 0.006 mg/kg]

Table 5 (contd)

Country or region	Residue limits (mg/kg)	Commodities
Thailand	0.3[c]	Aquatic animal products, meat, milk
	0.1[c]	Vegetables
	0.05[c]	Eggs, fruit, pulses
	0.03[c]	Cereals
	0.02[c]	Fat and oil from animals and vegetables
United Kingdom	0.2[c]	Carrots, meat, fat and preparations of meats (fat basis)
	0.1[c]	Dairy produce (> 2% fat)
	0.05[c]	Beans, Brussels' sprouts, cabbage, cauliflower, celery, cucumbers,
	0.02[c]	eggs (birds' eggs in shell (other than eggs for hatching) and whole
	0.01[c]	egg products and egg yolk products (whether fresh, dried, or otherwise prepared)), leeks, lettuce, mushrooms, onions, peas, potatoes, swedes, turnips
	0.02[c]	Tomatoes
	0.01[c]	Apples, bananas, barley, blackcurrants, grapes, maize, nectarines, oats, oranges, paddy rice, peaches, pears, plums, raspberries, rye, strawberries, wheat, other cereals, other citrus
	0.004	Milk (fresh raw cows' milk and fresh whole-cream cows' milk expressed as whole milk)
USA	0.3[j]	Fish and shellfish
	0.2[c,j] (fat basis)	Cattle, goats, horses, sheep, swine, poultry, rabbits
	0.1[c,j] (fat basis)	Milk
	0.02[c,j]	Fat, meat and meat by-products, cucurbit vegetables, quinces, cucumbers, melons, pumpkins, squash (winter or summer), pineapple
	0.01[c,j]	Artichokes, asparagus, *Brassica* (cole) leafy vegetables, bulb vegetables, cereal grains, citrus fruits, leafy vegetables (except *Brassica*), non-grass animal feeds, pome fruits, small fruits and berries, stone fruits, processed animal feed, eggs, figs, fruiting vegetables except cucurbits, grass forage, fodder and hay, legume vegetables, root and tuber vegetables, beans (except snap beans), eggplant, okra, pimentoes, leafy vegetables, salsify tops, pears, rice grain, small fruits, blackberries, blueberries, boysenberries, dewberries, peppers, raspberries, tomatoes, alfalfa, apples, barley, lima beans, snap beans, beetroot, sugar beets, blackeyed peas, Brussels' sprouts, cabbage, carrots, cauliflower, cherries, clover, sweet clover, cottonseed, cowpeas, grapes, grass (pasture), grass (range), kohlrabi, lettuce, maize, oats, onions, peaches, peanuts, peas, potatoes, radishes, rutabagas, rye, sorghum (grain milo), sugar-cane, sweet potatoes, tomatoes, turnips (including tops)

Table 5 (contd)

Country or region	Residue limits (mg/kg)	Commodities
USSR	None	All food products
Yugoslavia	0.1[c]	Meat and meat products (fat basis)
	0.05[c]	Eggs (without shell) and egg products, milk and milk products (fat basis)

[a]From Health and Welfare Canada (1990)
[b]Residue below the sensitivity limit of the test method; calculated as heptachlor and its epoxide
[c]Including heptachlor epoxide
[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]Calculated on fat content; including heptachlor epoxide
[f]Heptachlor epoxide only
[g]Singly or combined, including heptachlor epoxide, expressed as heptachlor
[h]A pesticide may be used on an eating or drinking ware or raw material without a demonstrable residue remaining behind; the value listed is considered the highest concentration at which this requirement is deemed to have been met.
[i]Residues shall be absent; the value in parentheses is the highest concentration at which this requirement is still deemed to have been met.
[j]Recommended action levels, tolerances revoked (US Food and Drug Administration, 1990)

Table 6. Occupational exposure limits for chlordane[a]

Country	Year	Concentration (mg/m^3)	Interpretation[b]
Austria	1987	0.5	TWA
Belgium	1987	0.5 (s)[c]	TWA
Denmark	1988	0.5 (s)	TWA
Germany	1989	0.5 (s)	TWA
India	1987	0.5 (s)	TWA
		2 (s)	STEL
Indonesia	1987	0.5	TWA
Italy	1985	0.5 (s)	TWA
Mexico	1987	0.5 (s)	TWA
Netherlands	1987	0.5 (s)	TWA
Romania	1975	0.3	Average
		0.6	Maximum
Switzerland	1987		TWA
United Kingdom	1987	0.5 (s)	TWA
		2 (s)	STEL (10 min)
USA			
ACGIH	1989	0.5 (s)	TWA
OSHA	1989	0.5 (s)	TWA
USSR	1987	0.01 (s)	MAC

Table 6 (contd)

Country	Year	Concentration (mg/m^3)	Interpretation[b]
Venezuela	1987	0.5	TWA
		2	Ceiling
Yugoslavia	1987	0.5	TWA

[a]From Cook (1987); Arbejdstilsynet (1988); American Conference of Governmental Industrial Hygienists (ACGIH) (1989); Deutsche Forschungsgemeinschaft (1989); US Occupational Safety and Health Administration (1989)
[b]MAC, maximum allowable concentration; TWA, time-weighted average; STEL, short-term exposure level
[c]Skin irritant notation

Table 7. Occupational exposure limits for heptachlor[a]

Country	Year	Concentration (mg/m^3)	Interpretationb
Austria	1987	0.5 (s)[c]	TWA
Belgium	1987	0.5 (s)	TWA
Bulgaria	1984	0.1 (s)	TWA
Denmark	1988	0.5 (s)	TWA
Germany	1989	0.5 (s)	TWA
Finland	1987	0.5 (s)	TWA
		1.5 (s)	STEL
Indonesia	1987	0.5 (s)	TWA
Mexico	1987	0.5 (s)	TWA
Netherlands	1987	0.5 (s)	TWA
Romania	1985	0.3	Average
		0.6	Maximum
Switzerland	1987	0.5 (s)	TWA
UK	1987	0.5 (s)	TWA
		2 (s)	STEL (10 mn)
USA			
ACGIH	1989	0.5 (s)	TWA
OSHA	1989	0.5 (s)	TWA
USSR	1987	0.01 (s)	MAC
Venezuela	1987	0.5 (s)	TWA
		1.5 (s)	Ceiling
Yugoslavia	1987	0.5	TWA

[a]From Cook (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 Case reports

Infante *et al.* (1978) reported five cases of neuroblastoma in children, which were associated with pre- and postnatal exposure to chlordane for termite control, as well as three cases of aplastic anaemia and three of acute leukaemia associated with exposure to chlordane or heptachlor. Three of the patients with blood dyscrasia had also been exposed to other pesticides.

Four cases of leukaemia were among 25 cases of blood dyscrasia associated with exposure to chlordane/heptachlor (Epstein & Ozonoff, 1987) (see also Table 19).

A two-month-old neonate with a gliosarcoma was reported to have been exposed to heptachlor during prenatal development through contamination 'at unacceptable levels' of milk drunk by her mother (Chadduck *et al.*, 1987). [Details of the contamination were not given.]

2.2 Cohort studies

Three studies analysed the mortality experience of workers at two US plants—one producing chlordane and the other producing heptachlor (Ditraglia *et al.*, 1981). Exposures to other chemicals, including chlorine and dicyclopentadiene (chlordane plant) as well as endrin, chlorine, chlorendic anhydride, hexachlorocyclopentadiene and vinyl chloride (heptachlor plant) were also reported. As the bases of these studies overlap substantially, they do not provide independent information on the carcinogenicity of chlordane/-heptachlor. Table 8 shows the population enrolled in each study and the results obtained with regard to mortality from lung cancer.

Wang and MacMahon (1979a) evaluated the mortality experience of white male workers employed for three months or more at the two plants between 1946 or 1952 and 1976. The identities of 1403 of the 1685 men were established (83%); 104 deaths were determined through social security records and nine from other sources. The chlordane plant had been the place of employment for 570 of the identified men and 76 of the deaths. Expected deaths were calculated on the basis of national rates. There were 24 observed cancer deaths, with 29.3 expected (standardized mortality ratio [SMR], 0.82; 95% confidence interval [CI], 0.54-1.2). An excess of lung cancer was observed (12 observed, 9.0 expected; SMR, 1.3; 95% CI, 0.73-2.3). Seven lung cancers were observed (6.1 expected) in the chlordane plant and five (2.9 expected) in the heptachlor/endrin plant. Risks did not increase with duration of employment at the plants, but SMRs were higher for men aged < 35 years at entry (7 observed, 2.6 expected) and aged > 35 years at death (5 observed, 6.3 expected).

Another investigation included white men employed for at least six months between 1946 or 1951 and 1964, who were followed up to 1976. In the first plant, there were 327 workers, nine (3%) of whom were lost to follow-up; in the second there were 305 men, with 16 (5%) lost to follow-up. Expected deaths were calculated according to US white male mortality rates. There were 11 (SMR, 0.69; 95% CI, 0.35-1.2) and six (0.91; 0.33-2.0) cancer deaths, respectively. Mortality from respiratory cancers was slightly elevated in each plant:

Table 8. Cohort studies on white male workers in US plants producing chlordane and heptachlor

Reference	Plant	Enrolled population	Criteria for inclusion (months of employment)	Years of recruitment	Years of follow-up	Observed no. of lung cancer deaths	SMR	95% confidence interval
Wang & MacMahon (1979a)	Chlordane	570[a]	3	1946-76	1946-76	7	1.2	0.46-2.4
	Heptachlor	835[a]	3	1952-76	1952-76	5	1.7	0.57-4.1
Ditraglia *et al.* (1981)	Chlordane	327	6	1946-64	1946-76	6	1.1	0.40-2.4
	Heptachlor	305	6	1951-64	1951-76	3	1.2	0.25-3.6
Shindell & Ulrich (1986); Shindell (1987)	Chlordane	706[b]	3	1946-85	1946-85	12	0.86	0.4-1.5

[a]Two people employed in both plants

[b]87 women and 7 nonwhite men were also studied but not included in the calculation

six cases (1.1; 0.40-2.4) and three cases (1.2; 0.25-3.6), respectively. Mortality from stomach cancer was elevated (three deaths; 3.0; 0.61-8.9) among workers in the chlordane plant (Ditraglia *et al.*, 1981).

An analysis of the mortality of workers of each sex and all races who were employed for at least three months between 1946 and 1985 in the factory producing chlordane was carried out by Shindell and Ulrich (1986). Mortality was followed up to mid-1985. This study included 706 white men (of whom three were untraced) and 94 others (7 blacks and 87 women; all traced); the results given here are for white men only. Expected numbers were based on US mortality rates. There were 37 cancer deaths (40.6 expected; SMR, 0.91 [95% CI, 0.6-1.3]). The SMR for lung cancer was 0.86. The observed and expected numbers of deaths are not given, but 12 deaths from respiratory cancer are indicated in a figure giving the numbers of lung cancer deaths by years of employment; however, denominators were not provided. This lapse was pointed out in a letter by Infante and Freeman (1987). In a reply, Shindell (1987) reported 12 respiratory cancer deaths and 14.4 expected [SMR, 0.8; 0.4-1.5] and 25 other cancer deaths with 26.2 expected [1.0; 95% CI, 0.6-1.4]. No trend with duration of employment was seen for respiratory cancer.

Cancer risks have also been evaluated among cohorts of pesticide applicators engaged in termite control, in which chlordane has been the chemical most widely used until recently. Subjects may also have had contact with other pesticides.

The study of Wang and MacMahon (1979b) of the mortality experience of a cohort of over 16 000 urban applicators, described in detail in the monograph on occupational exposures in spraying and application of insecticides (p. 60), was extended (MacMahon *et al.*, 1988), to give a maximal period of follow-up of 18 years. A significant excess of lung cancer (SMR, 1.4; 90% CI, 1.1-1.6) was observed, along with nonsignificant excesses for cancers of the skin (1.3; 0.65-2.2) and bladder (1.2; 0.50-2.5). The risk for lung cancer was lower among termite control operators (0.97 [0.7-1.3]), the group who probably had more contact with chlordane, than among other employees (1.6; 1.3-1.9). Risks for cancers of the skin and bladder were about the same for the two groups. The risk for lung cancer did not rise with increasing duration of employment.

In another investigation of commercial applicators, also described in the monograph on occupational exposures (p. 62), an overall excess of lung cancer (SMR, 1.4 [95% CI, 0.9-1.9]) occurred among licensed pesticide applicators in Florida (Blair *et al.*, 1983). The risk for lung cancer death rose to nearly three fold among those licensed for 20 years or more: the SMRs were 1.0 [95% CI, 0.6-1.7] for < 10 years, 1.6 [0.8-2.8] for 10-19 years and 2.9 [1.2-5.6] for > 20 years. Excesses, based on small numbers of deaths, were also seen for leukaemia [1.3; 0.4-3.4] and for cancers of the skin [1.3; 0.2-4.8], bladder [1.6; 0.3-4.6] and brain (2.0 [0.6-4.7]). People working for firms certified for treatment of termites had an SMR of 1.4 [0.9-2.1] for lung cancer; other pest control workers had an SMR of 1.2 [0.6-2.2].

[Although none of these cohort investigations had access to information on tobacco use, smoking is probably not the explanation for the positive results because there was no excess mortality from emphysema or nonmalignant respiratory disease and because smoking is unlikely to explain the trend with duration of employment in the study of Florida applicators.]

2.3 Case-control studies

Two population-based case-control interview studies in the USA—one of soft-tissue sarcomas and non-Hodgkin's lymphoma and one of leukaemia—provide estimates of the risks for cancer associated with exposure to chlordane/heptachlor. Both are described in detail in the monograph on occupational exposures in spraying and application of insecticides (pp. 67 and 68).

An excess of non-Hodgkin's lymphoma (odds ratio, 1.6; 95% CI, 0.7-3.8) but no excess of soft-tissue sarcoma (0.96; 0.2-4.8) was associated with possible exposure to chlordane in the study from Washington State (Woods *et al.*, 1987). Adjustment for selected chemical exposures by regression analysis did not change the risk estimates substantially. In an additional report from Washington State in which the analysis was restricted to farmers (Woods & Polissar, 1989), the odds ratio for non-Hodgkin's lymphoma in relation to exposure to chlordane was 1.6 (0.5-5.1).

In the study of leukaemia in Iowa and Minnesota (Brown *et al.*, 1990), farmers who reported use of chlordane on crops had a slight deficit (odds ratio, 0.7; 95% CI, 0.3-1.6), while those who reported use of chlordane on animals had a slight excess (1.3; 0.7-2.3). Among farmers using chlordane on animals, the risks rose inconsistently with frequency of use, from an odds ratio of 1.1 (0.4-2.8) for < 5 days per year, to no exposed case and five exposed controls for 5-9 days per year, to an odds ratio of 3.2 (0.9-11.0) for > 10 days per year. This risk estimate was not adjusted for other agricultural exposures.

Cohort and case-control studies on chlordane and heptachlor are summarized in Table 9 (see also Table 8).

Table 9. Studies of populations exposed to chlordane/heptachlor

Reference and design	Cancer	No. of cases	Relative risk	95% CI	Comments
MacMahon *et al.* (1988) Cohort	*Entire cohort of applicators*				
	Lung	108	1.4	1.1-1.6	Pesticide applicators; chlordane use for termites a component; 90% CI
	Skin	9	1.3	0.65-2.2	
	Bladder	5	1.2	0.50-2.5	
	Lymphatic and haematopoietic	25	1.0	0.67-1.4	
	Termite control operators only				
	Lung	30	0.97	[0.7-1.3]	90% CI
	Skin	3	1.2	[0.4-2.9]	
	Bladder	2	1.3	[0.3-3.9]	
Blair *et al.* (1983) Cohort	Lung	34	1.4	[0.9-1.9]	Pesticide applicators; chlordane use for termites a component; lung cancer risk among employees of firms licensed to treat termites was 1.4
	Skin	2	[1.3]	[0.2-4.8]	
	Bladder	3	[1.6]	[0.3-4.6]	
	Brain	5	2.0	[0.6-4.7]	
	Leukaemia	4	[1.3]	[0.3-3.4]	
Woods *et al.* (1987) Case-control	Soft-tissue sarcoma	Not reported	0.96	0.2-4.8	Author indicates that 1.6% of study population was possibly exposed to chlordane
	Non-Hodgkin's lymphoma	Not reported	1.6	0.7-3.8	

Table 9 (contd)

Reference and design	Cancer	No. of cases	Relative risk	95% CI	Comments
Woods & Polissar (1989) Case-control	Non-Hodgkin's lymphoma	Not reported	1.6	0.5-5.1	Farmers only
Brown *et al.* (1990) Case-control	Leukaemia Leukaemia	7 19	0.7 1.3	0.3-1.6 0.7-2.3	Used on plants Used on animals

3. Studies of Cancer in Experimental Animals

The carcinogenicity of chlordane and heptachlor/heptachlor epoxide in experimental animals has been reviewed (US Environmental Protection Agency, 1986a).

Selected histopathological materials from several of the carcinogenicity studies on chlordane/heptachlor and/or heptachlor epoxide which were reviewed in a previous monograph (IARC, 1979) were re-evaluated by a panel of pathologists (Pesticide Information Review and Evaluation Committee) convened by the US National Academy of Sciences (1977) at the request of the US Environmental Protection Agency. The intent was to provide uniform diagnosis of hepatocellular neoplasms which had been diagnosed under several different classification systems for liver neoplasia by the original investigators or, in some cases, a second review panel of pathologists. The review panel diagnosed hepatocellular tumour and hepatocellular carcinoma and nodule change or nodule according to the definitions given in Annex 1 to this monograph (p. 177).

3.1 Oral administration

3.1.1 *Mouse*

Epstein (1976) and the US Environmental Protection Agency (1986a) reported a previously unpublished study by the Food and Drug Administration, carried out in 1965, in which three groups of 100 male and 100 female C3H mice [age unspecified] were fed 0 or 10 mg/kg of diet *heptachlor* or *heptachlor epoxide* [purity unspecified] for 24 months. A review of the histopathology of liver samples from this study by the panel of the US National Academy of Sciences (1977) indicated a significant increase in the incidence of hepatocellular carcinomas in females but not in males given heptachlor, and in both males and females given heptachlor epoxide (Table 10).

In an unpublished study conducted by the International Research and Development Corporation in 1973 and reported by Epstein (1976), groups of 100 male and 100 female Charles River CD-1 mice, seven weeks of age, were fed *a mixture of 75% heptachlor epoxide and 25% heptachlor* [purity unspecified] at levels of 0, 1, 5 or 10 mg/kg of diet for 18 months. Excluding 10 animals sacrificed from each group for interim study at six months, mortality at 18 months was 34-49%, with the exception of males and females receiving the 10 mg/kg diet level, which had mortalities of approximately 70%; in addition, comparatively large numbers

Table 10. Tumour incidence in C3H mice treated with heptachlor and heptachlor epoxide[a]

Treatment	Males		Females	
	Hepatocellular carcinomas	Hepatocellular carcinomas and nodules	Hepatocellular carcinomas	Hepatocellular carcinomas and nodules
Controls	29/77	48/77	5/53	11/53
Heptachlor (10 mg/kg diet)	35/85	72/85 ($p = 0.001$)	18/80 ($p = 0.04$)	61/80 ($p < 0.001$)
Heptachlor epoxide (10 mg/kg diet)	42/78 ($p = 0.031$)	71/78 ($p < 0.001$)	34/83 ($p < 0.001$)	75/83 ($p < 0.001$)

[a]From National Academy of Sciences (1977)

of animals from all groups were lost to histology by autolysis. A review of the histopathology of liver samples from this study by the panel of the US National Academy of Sciences (1977) indicated a significant increase in the combined incidence of hepatocellular carcinomas and nodules in the high-dose groups (Table 11).

Table 11. Tumour incidence in CD-1 mice treated with a mixture of heptachlor and heptachlor epoxide[a]

Concentration (mg/kg diet)	Males		Females	
	Hepatocellular carcinomas	Hepatocellular carcinomas and nodules	Hepatocellular carcinomas	Hepatocellular carcinomas and nodules
Controls	1/59	2/59	1/74	1/74
1	1/58	1/58	0/71	0/71
5	2/66	4/66	1/65	3/65
10	1/73	27/73 ($p < 0.001$)	4/52	16/52 ($p < 0.001$)

[a]From National Academy of Sciences (1977)

In an unpublished study conducted by the International Research and Development Corporation in 1973 and reported by Epstein (1976), groups of 100 male and 100 female Charles River CD-1 mice, six weeks of age, were fed 0, 5, 25 or 50 mg/kg of diet *technical-grade chlordane* [purity unspecified] for 18 months. Excluding 10 animals sacrificed from each group for interim study at six months, mortality at 18 months was 27-49%, with the exception of males and females receiving the 50 mg/kg diet level, in which mortalities of 86 and 76%, respectively, were seen; in addition, a relatively large number of animals were lost by autolysis. A review of of the histopathology of liver samples from this study by the panel of the US National Academy of Sciences (1977) indicated a significant increase in the incidence

of hepatocellular carcinomas in mid-dose males and in mid-dose and high-dose females (Table 12).

Table 12. Tumour incidence in CD-1 mice treated with chlordane[a]

Concentration (mg/kg diet)	Males		Females	
	Hepatocellular carcinomas	Hepatocellular carcinomas and nodules	Hepatocellular carcinomas	Hepatocellular carcinomas and nodules
Control	1/33	4/33	0/44	1/44
5	1/55	11/55	0/61	0/61
25	11/51 ($p = 0.015$)	30/51 ($p < 0.001$)	11/51 ($p < 0.001$)	23/51 ($p < 0.001$)
50	7/44	25/44 ($p < 0.001$)	6/40 (($p = 0.009$)	22/40 ($p < 0.001$)

[a]From National Academy of Sciences (1977)

Groups of 50 male and 50 female B6C3F$_1$ hybrid mice, five weeks of age, were fed *analytical-grade chlordane* (consisting of 94.8% chlordane (71.7% *cis*-chlordane and 23.1% *trans*-chlordane), 0.3% heptachlor, 0.6% nonachlor, 1.1% hexachlorocyclopentadiene, 0.25% chlordene isomers and other chlorinated compounds) for 80 weeks. Males received initial levels of 20 and 40 mg/kg of diet and females 40 and 80 mg/kg of diet; time-weighted average dietary concentrations were 30 and 56 mg/kg of diet for males and 30 and 64 mg/kg of diet for females. There were 20 male and 20 female matched controls and 100 male and 80 female pooled controls. Survivors were killed at 90 weeks. Survival in all groups was relatively high: over 60% in treated males, over 80% in treated females and over 90% in male and female controls (US National Cancer Institute, 1977a). A review of the histopathology of liver samples from this study by the panel of the US National Academy of Sciences (1977) indicated a significant increase in the incidence of hepatocellular carcinomas by linear trend analysis in males and females given diets containing chlordane, and a significant increase in the combined incidence of hepatocellular carcinomas and 'nodular changes' in high-dose males and females (Table 13).

Table 13. Tumour incidence in B6C3F$_1$ mice treated with chlordane or heptachlor[a]

Treatment	Males		Females	
	Hepatocellular carcinomas	Hepatocellular carcinomas and nodules	Hepatocellular carcinomas	Hepatocellular carcinomas and nodules
Controls	2/20	5/20	1/19	1/19
Chlordane (low)	4/45	16/45	0/46	2/46
Chlordane (high)	12/46 ($p = 0.031$) (trend)	30/46 ($p = 0.003$)	7/47 ($p = 0.018$) (trend)	20/47 ($p = 0.002$)
Controls	2/19	5/19	0/10	1/10
Heptachlor (low)	3/45	14/45	0/44	3/44
Heptachlor (high)	2/45	24/45 ($p = 0.042$)	2/42	21/42 (($p = 0.022$)

[a]From National Academy of Sciences (1977)

Groups of 50 male and 50 female B6C3F$_1$ hybrid mice, five weeks of age, were fed *technical-grade heptachlor* (72% heptachlor, 18% *trans*-chlordane, 2% *cis*-chlordane, 2% nonachlor, 1% chlordene, 0.2% hexachlorobutadiene) in the diet for 80 weeks. Males received initial dietary concentrations of 10 and 20 mg/kg of diet and time-weighted average concentrations of 6 and 14 mg/kg of diet; females received initial concentrations of 20 and 40 mg/kg of diet and time-weighted average concentrations of 9 and 18 mg/kg of diet. Initial dose levels were reduced during the experiment due to adverse toxic effects. Matched controls consisted of 20 males and 20 females; and pooled controls consisted of 100 males and 80 females. Survival in all groups was relatively high: over 70% of treated and control males and 60% of treated and control females were still alive at 90 weeks. Survival of female mice showed a significant trend to lower survival in treated groups compared to that of controls (US National Cancer Institute, 1977b). A review of the histopathology of liver samples from this study by the panel of the US National Academy of Sciences (1977) indicated a significant increase in the combined incidence of hepatocellular carcinomas and 'nodular changes' ($p < 0.05$) in males and females receiving the high dose (Table 13).

Groups of 80 male and 80 female Charles River (ICR) (SPF) mice, five weeks of age, were fed diets containing 0, 1, 5 or 12.5 mg/kg of diet *'technical chlordane'* (containing unspecified amounts of *cis*- and *trans*-chlordane, isomers of chlordene, heptachlor and nonachlor) for 104 weeks. Eight males and eight females from each group were killed for evaluation at 52 weeks. Survival of treated groups did not differ from that of controls: at 104 weeks, males: 28 controls, 21 low-dose, 32 mid-dose and 29 high-dose; females: 30 controls, 35 low-dose, 38 mid-dose and 37 high-dose. The incidence of hepatocellular adenomas was significantly increased in male mice receiving the high dose (control, 12/79; low-dose, 14/79; mid-dose, 14/80; high-dose, 27/80; $p < 0.01$). The number of high-dose male mice with haemangiomas of the liver was also significantly increased (control, 4/79; low-dose, 1/79; mid-dose, 8/80; high-dose, 14/80; $p < 0.05$) [The authors described haemangiomas as 'benign tumors of vascular cells associated with the liver adenomas'.] (Khasawinah & Grutsch, 1989a). [The Working Group noted that hepatocellular adenocarcinomas were apparently also diagnosed in all groups of treated and control male mice, but the incidences of these tumours were not reported specifically. The combined incidences of hepatocellular adenomas and adenocarcinomas in male mice could not be determined from the report, and the incidences of hepatocellular neoplasms were not given for female mice.]

3.1.2 *Rat*

Epstein (1976) reported on an unpublished study, carried out in 1955, in which groups of 20 male and 20 female CF rats, 10 weeks of age, were administered 0, 1.5, 3, 5, 7 or 10 mg/kg of diet *heptachlor* [purity unspecified] by spraying alcoholic solutions onto Purina Chow pellets, for 110 weeks. Mortality in all test groups was stated to be random. No increase in the incidence of liver tumours was found in treated animals. [The Working Group noted the small number of animals and the uncertain concentrations of heptachlor in the feed.]

Epstein (1976) reported on another unpublished study by the same laboratory, carried out in 1959, in which groups of 25 male and 25 female CFN rats, seven weeks of age, were fed 0.5, 2.5, 5.0, 7.5 or 10.0 mg/kg of diet *heptachlor epoxide* [purity unspecified] by spraying alcoholic solutions on Purina Chow pellets, for 108 weeks. Survival at that time was over 45%

in treated and control groups. A review of the histopathology of liver samples from this study by the panel of the US National Academy of Sciences (1977) found no increase in the incidence of liver tumours in treated animals. [The Working Group noted the small number of animals and the uncertain concentrations of heptachlor epoxide in the feed.]

A group of 95 male and female suckling Wistar rats were administered 10 mg/kg bw *heptachlor* (97% pure) in corn oil by gavage on five successive occasions at two-day intervals starting at 10 days of age; 19 male and 27 female controls received corn oil alone. Excluding nine male and 20 female treated animals that were sacrificed for interim histology at 60 weeks, survival in treated and control groups was high and comparable. The numbers of tumours in treated and control groups were comparable; 'lipomatous' renal tumours were noted in two females treated with heptachlor (Cabral *et al.*, 1972). [The Working Group noted the small number of doses administered and the short duration of treatment.]

Groups of 50 male and 50 female Osborne-Mendel rats, five weeks of age, were administered *analytical-grade chlordane* (see p. 142) in the diet for 80 weeks at initial dose levels of 400 and 800 mg/kg of diet for males and 200 and 400 mg/kg of diet for females. These were reduced during the experiment due to adverse toxic effects, and the time-weighted average dietary concentrations were 204 and 407 mg/kg of diet for males and 121 and 242 mg/kg of diet for females. There were 10 male and 10 female matched controls and 60 male and 60 female pooled controls. Survivors were killed at 109 weeks, at which time approximately 50% of treated and control males and 60% of treated females and 90% of control females were still alive. In treated females, there was an increase in the incidence of follicular-cell thyroid neoplasms (6/32 high-dose, $p < 0.05$; 4/43 low-dose, 3/58 pooled controls; $p = 0.03$, trend test). There was also an increase in the incidence of malignant fibrous histiocytomas [site unspecified] in treated males: 7/44 in high-dose animals ($p < 0.05$), 1/44 in low-dose animals and 2/58 in pooled controls (US National Cancer Institute, 1977a). [The Working Group noted the short duration of treatment.]

Groups of 50 male and 50 female Osborne-Mendel rats, five weeks of age, were fed *technical-grade heptachlor* (see p. 143) in the diet for 80 weeks. Males received initial dietary concentrations of 80 and 160 mg/kg of diet and time-weighted average concentrations of 39 and 78 mg/kg of diet; females received initial concentrations of 40 and 80 mg/kg of diet and time-weighted average concentrations of 26 and 51 mg/kg of diet. Matched controls consisted of 10 males and 10 females; and pooled controls consisted of 60 males and 60 females. At 110 weeks, 60-75% of all treated and control groups were still alive. Thyroid follicular-cell neoplasms occurred in 14/38 high-dose females and 3/58 controls ($p < 0.01$) and in 9/38 low-dose males and 4/51 controls ($p < 0.05$); the incidence in high-dose males was 3/38 (US National Cancer Institute, 1977b). [The Working Group noted the short duration of treatment.]

Groups of 80 male and 80 female Fischer 344 (SPF) rats, five weeks of age, were fed diets containing 0, 1, 5 or 25 mg/kg of diet *technical-grade chlordane* (containing unspecified amounts of *cis*- and *trans*-chlordane, isomers of chlordene, heptachlor and nonachlor) for 130 weeks. Eight males and nine females in each group were killed for evaluation at 26 and 52 weeks. Survival at 130 weeks was: males—13 controls, 20 low-dose, 11 mid-dose and nine high-dose; females—23 controls, 24 low-dose, 28 mid-dose and 24 high-dose. Survival in all groups was greater than 65% at 104 weeks. The incidence of hepatocellular nodules as

diagnosed by the original pathologist was increased in treated male rats, with an incidence of 1/80 controls, 2/80 low-dose, 3/80 mid-dose and 9/80 high-dose males, the latter being significantly different from that in controls ($p < 0.05$). A group of seven other pathologists re-evaluated selected liver sections and observed increased incidences of hepatocellular adenomas: in 2/64 controls, 4/64 low-dose, 2/64 mid-dose and 7/64 high-dose males ($p = 0.018$ trend test) (Khasawinah & Grutsch, 1989b).

3.2 Administration with known carcinogens

Chlordane (25 and 50 mg/kg diet) or heptachlor (5 and 10 mg/kg diet) was fed in the diet for 25 weeks at concentrations of 5-50 mg/kg to groups of 40 male B6C3F$_1$ mice previously treated with *N*-nitrosodiethylamine at 20 mg/l in drinking-water for 14 weeks. An increase in the incidence and multiplicity of liver adenomas and carcinomas was seen over that observed in untreated mice or mice receiving treatment with *N*-nitrosodiethylamine only (Williams & Numoto, 1984).

4. Other Relevant Data

The toxicology of chlordane and heptachlor has been reviewed (FAO/WHO, 1964, 1965, 1967, 1968, 1971, 1978, 1983; WHO, 1984a,b; FAO/WHO, 1987; US Public Health Service, 1989a,b).

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

The main components of technical-grade chlordane—chlordane, heptachlor and *trans*-nonachlor—have all been identified in human tissues following a variety of exposures, indicating that all are absorbed (see Tables 14-16). *trans*- and *cis*-Chlordane are metabolized to oxychlordane, and heptachlor is metabolized to heptachlor epoxide; a minor component of technical-grade chlordane, *trans*-nonachlor, has been found in human plasma and milk as a major residue of technical-grade chlordane. Being lipophilic, these compounds are stored mainly in the adipose tissue. Elimination takes place *via* both urine (Curley & Garrettson, 1969) and faeces (Garrettson *et al.*, 1985). Breast milk is a supplementary excretory route in lactating women (WHO, 1984a,b).

A positive relationship was found in pest control operators between blood levels of total chlordane (*trans*-nonachlor, oxychlordane and heptachlor epoxide) and the conditions of spraying technical-grade chlordane: total amount of chlordane sprayed ($r = 0.68$), number of spraying days in the last year ($r = 0.78$) and particularly in the last three months ($r = 0.81$). Blood levels are reported in Table 14 (Saito *et al.*, 1986).

Levels of chlordane residue determined after accidental ingestion of chlordane preparations are summarized in Table 15.

Table 14. Compounds derived from technical-grade chlordane in the blood of 51 pest control operators[a]

Compound	Positive samples (%)	Level (μg/l)	
		Mean	Range
Total chlordane	37	0.89	ND-5.6
Oxychlordane	22	0.29	ND-1.5
Heptachlor epoxide	20	0.29	ND-1.6
trans-Nonachlor	37	0.55	ND-2.9

[a]From Saito *et al.* (1986)

Table 15. Total chlordane levels in human tissue after accidental ingestion of technical-grade chlordane

Time after event	Chlordane (μg/g)			Estimated half-time (days)	Reference
	Adipose tissue	Serum	Tissues: serum		
> 3 h	3.12	2.71	[1.15:1]	21	Curley & Garrettson (1969)
8 days	–	–	147:1		
3 months	25.53	0.017	1470:1		
First day	–	3.4	–	88	Aldrich & Holmes (1969)
3 days	–	0.138	–		
130 days	–	0.03	–		
Third day	–	[0.103]	–	–	Olanoff *et al.* (1983)
After 49 days	–	0.039	–		
After 58 days			–		
oxychlordane	0.51				
trans-nonachlor	1.88				
heptachlor epoxide	2.62				

–, not reported

Heptachlor epoxide was the first among the materials derived from technical chlordane to be analysed routinely in human adipose tissue. Residues in humans originate from the use of technical-grade chlordane in agriculture and households. Studies on the storage of heptachlor epoxide and oxychlordane in the adipose tissue of the general population in different countries are summarized in Table 16. *trans*-Nonachlor has also been identified in the adipose tissue of people representative of the general population of the USA (Sovocool & Lewis, 1975).

The presence of heptachlor epoxide in the adipose tissue of stillborns (Wassermann *et al.*, 1974) and in the blood of newborns (cord blood) (D'Ercole *et al.*, 1976) demonstrates placental transfer of heptachlor and/or heptachlor epoxide.

Table 16. Storage of heptachlor epoxide and oxychlordane in the adipose tissue of the general population

Country	No. of samples	Heptachlor epoxide (μg/g)		Oxychlordane (μg/g)		Reference
		Mean	Range	Mean	Range	
USA	25	0.24	0.03–1.45			Hayes *et al.* (1965)
Italy	18	0.46	0.01–1.50			Paccagnella *et al.* (1967)
United Kingdom	248	0.04	0.0–0.40			Abbott *et al.* (1968)
Netherlands	11	0.01	0.004–0.03			de Vlieger *et al.* (1968)
USA	64	0.10[a]	0.03–0.61			Zavon *et al.* (1969)
France	98	0.28 0.36	[ND - ~ 1.6 men]; ([ND - ~ 0.65 women)			Fournier *et al.* (1972)
United Kingdom	201	0.03	0.0–0.14			Abbott *et al.* (1972)
Japan	241	0.02	< 0.01–0.2			Curley *et al.* (1973)
USA	27			0.14 77.8% positive	0.03–0.40	Biros & Enos (1973)
Israel	53[b]	0.015	0.0001–0.132			Wassermann *et al.* (1974)

[a]On lipid basis

[b]Results cited for age group 25-44 years; total number of samples, 307; age range, stillborn—≥ 70 years

Components of technical-grade chlordane and their metabolites are excreted in human milk in quantities that vary with agricultural and household use, dietary habits, individual phenotype and time of milk sampling. In Israel, the mean levels of heptachlor epoxide in the milk of 29 women 2-4 days after delivery were 9.1 μg/litre in whole milk and 720 μg/kg fat. The values were 9.8 μg/litre in women aged 20-29 and 7.2 μg/litre in those aged 30-39 (Polishuk *et al.*, 1977). [The number of positive samples was not given, and the means are presumed to be for all samples tested.] The levels of heptachlor epoxide in the breast milk in 50 women in Switzerland were < 10-110 μg/kg fat with a mean value of 30 μg/kg fat (Schuepbach & Egli, 1979). A total of 1436 samples of breast milk were analysed in a study in the USA; the mean level of oxychlordane was 96 μg/kg fat in 1061 positive samples, and the mean level of heptachlor epoxide was 91 μg/kg fat in 906 positive samples. In a subset of 288 samples from southeastern USA, oxychlordane was found at 116 μg/kg fat in 239 samples and heptachlor epoxide at 128 μg/kg fat in 221 samples (Savage *et al.*, 1981). In 29 positive samples analysed in Japan, *cis*-chlordane was found at geometric mean levels of 3.08 μg/kg fat and 0.09 μg/litre whole milk; *trans*-chlordane at 1.20 μg/kg fat and 0.04 μg/litre whole milk; oxychlordane at 11.5 μg/kg fat and 0.39 μg/litre whole milk; heptachlor epoxide at 20 μg/kg fat and 0.66 μg/litre whole milk; *trans*-nonachlor at 15.7 μg/kg fat and 0.55 μg/litre whole milk; and *cis*-nonachlor at 4.0 μg/kg fat and 0.14 μg/litre whole milk (Tojo *et al.*, 1986). Analysis of samples from 155 primipara mothers in Finland in 1984-85 showed fat contents of 410 μg/kg total chlordane (*cis*- and *trans*-chlordane, oxychlordane and *trans*-nonachlor) (20 positive samples), 100 μg/kg *cis*-chlordane (8), 200 μg/kg *trans*-chlordane (9), 70 μg/kg heptachlor (16), 230 μg/kg oxychlordane (6), 100 μg/kg heptachlor epoxide (9) and 760 μg/kg *trans*-nonachlor (7) (Mussalo-Rauhamaa *et al.*, 1988). In women who followed a strict vegetarian diet, the mean levels of heptachlor epoxide in milk were 1-2% of the average for the US general population (Hergenrather *et al.*, 1981). In a Japanese study, the level of total chlordane in milk was higher in eight women with a high frequency of fish intake than in four with a low frequency of intake (2.53 ng/ml *versus* 1.25 ng/ml) (Tojo *et al.*, 1986). Curley and Kimbrough (1969) found traces of heptachlor epoxide in milk during lactation. A downward trend in level with progression of the lactation period was reported by Mes *et al.* (1984) for oxychlordane and *trans*-nonachlor and by Klein *et al.* (1986) for heptachlor epoxide.

4.1.2 *Experimental systems*

The metabolism of chlordane (WHO, 1984a; Nomeir & Hajjar, 1987) and of heptachlor (WHO, 1984b; Fendick *et al.*, 1990) has been reviewed.

Chlordane is readily absorbed from the gastrointestinal tract in rats and mice (Barnett & Dorough, 1974; Tashiro & Matsumura, 1977; Ewing *et al.*, 1985), from the skin of rats (Ambrose *et al.*, 1953) and from the respiratory system in rats (Nye & Dorough, 1976).

Heptachlor is readily absorbed *via* most routes of exposure and is readily metabolized to heptachlor epoxide by mammals (US Public Health Service, 1989a; Fendick *et al.*, 1990). Heptachlor epoxide is stored mainly in fat but also in liver, kidney and muscle in rats and dogs. In rats fed 30 mg/kg diet heptachlor for 12 weeks, maximal heptachlor epoxide concentrations occurred in fat within two to four weeks; 12 weeks after cessation of exposure, heptachlor epoxide had completely disappeared from the adipose tissue (Radomski &

Davidow, 1953). Heptachlor is also stored in fat as heptachlor epoxide in steers (Bovard *et al.*, 1971) and laying hens (Kan & Tuinstra, 1976). Heptachlor epoxide and a hydrophilic metabolite, 1-*exo*-hydroxy-2,3-epoxychlordene, were excreted in the faeces and urine of rats and rabbits treated with heptachlor (Klein *et al.*, 1968). Another metabolite, a dehydrogenated derivative of 1-hydroxy-2,3-epoxychlordene, has been isolated from rat faeces (Matsumura & Nelson, 1971).

Following uptake of chlordane after oral administration to rats, it was rapidly distributed, with the highest levels in fat and lower levels in other organs in the following order: liver, kidney, brain and muscle. Treatment with *trans*-chlordane resulted in slightly higher tissue concentrations than that with *cis*-chlordane. Patterns of distribution were similar following single and repeated oral dosing (Barnett & Dorough, 1974).

The major route of metabolism of chlordane in treated animals is *via* oxychlordane. Heptachlor is a minor metabolite of both optical isomers of chlordane. *cis*- and *trans*-Chlordane give rise qualitatively to the same metabolites (Tashiro & Matsumura, 1977). Four metabolic pathways for the metabolism of chlordane have been proposed (Nomeir & Hajjar 1987, Fig. 1):

(i) hydroxylation to form 3-hydroxychlordane followed by dehydration to form the postulated precursor of oxychlordane, 1,2-dichlorochlordene;
(ii) dehydrochlorination to form heptachlor with the subsequent formation of heptachlor epoxide and various hydroxylation products;
(iii) dechlorination to monochlorodihydrochlordene;
(iv) replacement of chlorine atoms by hydroxyl groups with the formation of mono-, di- and trihydroxy metabolites that are excreted or conjugated with glucuronic acid.

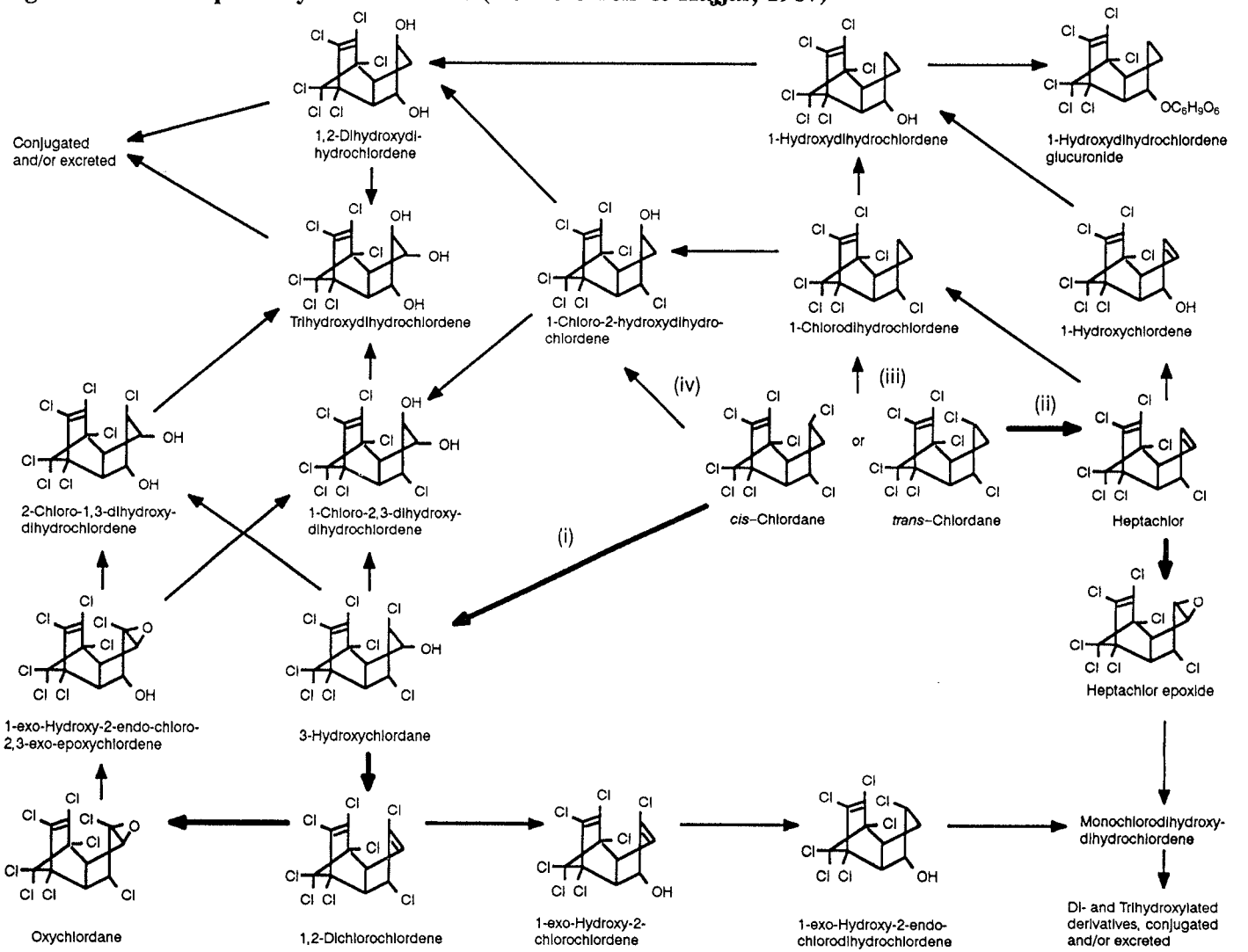
Human liver preparations have little capability to convert *trans*-nonachlor (a minor component of technical-grade chlordane) to *trans*-chlordane in comparison to rat liver prepared similarly (Tashiro & Matsumura, 1978).

Phenobarbital pretreatment significantly enhanced the metabolism of heptachlor in rats, causing a 6- to 11-fold increase in the formation of heptachlor epoxide in liver (Miranda *et al.*, 1973). In liver microsomes from rats and humans, heptachlor epoxide constituted 85.8% of the metabolized heptachlor in rats but only 20.4% in the human liver microsome system. Other metabolites identified in the human liver microsome system were 1-hydroxy-2,3-epoxychlordene (5%), 1-hydroxychlordene (4.8%) and 1,2-dihydroxydihydrochlordene (0.1%); 68.6% was unmetabolized heptachlor (Tashiro & Matsumura, 1978).

Rats and mice eliminated 80–$\geq$ 90% of single oral doses of ^{14}C-labelled chlordane within seven days (Barnett & Dorough, 1974; Tashiro & Matsumura, 1977; Ewing *et al.*, 1985). Most of the radiolabel was eliminated in faeces. C57Bl/6JX mice showed two distinct excretory patterns: the vast majority were high excretors, their elimination rate during the first day after dosing being 20 times faster than that of the low excretors (Ewing *et al.*, 1985).

Mice were given repeated doses of technical-grade chlordane (containing 5.88% *trans*- and 1.45% *cis*-nonachlor) in olive oil by gavage at 0.48 mg/mouse every other day for 29 days. No increase in body burden of *trans*- or *cis*-chlordane was noted; rather, the levels decreased continuously, indicating that chlordane induced its own metabolism. The levels of *trans*- and

Fig. 1. Metabolic pathways of chlordane (from Nomeir & Hajjar, 1987)



cis-nonachlor and of oxychlordane, however, increased throughout the study period (Hirasawa & Takizawa, 1989).

In cows fed hay containing heptachlor over 30 days, heptachlor epoxide was present in the milk from 10 days after the start of feeding (Huber & Bishop, 1961).

4.2 Toxic effects

4.2.1 *Humans*

Case reports and epidemiological studies of poisoning with technical-grade chlordane and heptachlor following both occupational exposures and exposure of the general population are summarized in Table 17.

4.2.2 *Experimental systems*

Chlordane

The toxic effects of chlordane have been reviewed (WHO, 1984a).

The acute oral LD_{50} of chlordane in peanut oil was 335 (299-375) mg/kg bw for male and 430 (391-473) for female Sherman rats (Gaines, 1960). The LD_{50} values for *cis*- and *trans*-chlordane were reported to be similar (392 and 327 mg/kg bw, respectively). The major metabolite, oxychlordane, was reported to have an LD_{50} in rats of 19.1 mg/kg bw, and several other metabolites had LD_{50} values > 4600 mg/kg bw. The signs associated with acute chlordane poisoning include ataxia, convulsions, respiratory failure and cyanosis, followed by death (WHO, 1984a).

Oral doses of chlordane of 50 mg/kg bw per day for 15 days resulted in convulsions and death in rats, whereas doses of 25 mg/kg bw per day had no such effect (Ambrose *et al.*, 1953).

In long-term studies (see section 3), chlordane caused tremor in female rats fed the high dose during one week, decreased body weight gains in high-dose animals and increased liver weights (US National Cancer Institute, 1977; Khasawinah & Grutsch, 1989b). In mice (Khasawinah & Grutsch, 1989a), the liver was the target organ for non-neoplastic toxicity; the serum levels of aspartate transferase and alanine transferase were elevated in animals of each sex, and liver weights were increased in males fed 12.5 mg/kg of diet. Increased liver-cell volume was seen in males and females fed 5 or 12.5 mg/kg, whereas hepatocyte degeneration and necrosis were seen only in treated males. Chlordane induced hepatic drug-metabolizing enzymes in experimental animals (WHO, 1984a) and enhanced oestrone metabolism in rats and mice (Welch *et al.*, 1971).

Mice treated with chlordane at doses of 0.1-8 mg/kg bw for 14 days showed a dose-related increase in cell-mediated immunity, as evaluated *in vitro*. Expression of delayed hypersensitivity and the antibody response to sheep red blood cells *in vivo* were unaltered (Johnson *et al.*, 1986).

Wistar rats and cynomolgus monkeys were exposed to chlordane by inhalation at concentrations close to 0.1, 1 and 10 mg/m^3 for 8 h per day on five days per week for 90 days (Khasawinah *et al.*, 1989). In rats, the liver was the main target organ, and liver weights were significantly increased in animals of each sex exposed to 10 mg/m^3. Histopathological changes, such as centrilobular hepatocyte enlargement, were observed in males and females at 1 and 10 mg/m^3. In male rats, increased weight of the follicular thyroid epithelium was

Table 17. Case reports, health surveys and epidemiological studies of cases of poisoning with technical-grade chlordane and technical-grade heptachlor

Population	Clinical features	Reference
34 workers manufacturing and formulating chlordane, aldrin, dieldrin	No evidence of adverse health effects	Princi & Spurbeck (1951)
24 workers employed for 2 months to 5 years in a plant manufacturing chlordane	No evidence of adverse health effects	Alvarez & Hyman (1953)
A female worker spilled a mixture of pesticides (including chlordane) on her clothing	Confusion, generalized convulsions, death; congestion of brain, lung and stomach mucosa	Derbes *et al.* (1955)
Suicide of a 32-year-old woman who ingested a 5% chlordane talc formulation; estimated ingested dose of chlordane: 6 g (104 mg/kg bw)	Vomiting, dry cough, agitation and restlessness, haemorrhagic gastritis, bronchopneumonia, muscle twitching, convulsions, death after 9.5 days	Derbes *et al.* (1955)
15 workers exposed for 1-15 years to chlordane during manufacture	No evidence of adverse health effects	Fishbein *et al.* (1964)
A 20-month-old boy drank an unknown quantity of a 74% technical-grade chlordane formulation	Vomiting 45 min after ingestion and seizures; serum alkaline phosphatase and thymal turbidity levels slightly elevated after 3 months	Curley & Garrettson (1969)
A 4-year-old girl ingested an unknown amount of 45% chlordane	Convulsions, increased excitability, loss of coordination, dyspnoea, tachycardia	Aldrich & Holmes (1969)
A segment of a municipal water system in Chattanooga, TN (USA), 1976, was contaminated with chlordane, initially up to 1200 mg/l; 1-3 days later, 0.0001-92.5 mg/l. Of 105 residents in affected houses, 71 reported contact with contaminated water	13/71 (18%) described mild symptoms compatible with chlordane exposure (gastrointestinal and/or neurological)	Harrington *et al.* (1978)
Case reports of blood dyscrasias associated with exposure to chlordane or heptachor alone or in combination with other agents	25 previously reported and 6 new cases include 22 aplastic anaemia, 3 acute leukaemia, 2 leukopenia and 1 each hypoplastic anaemia, haemolytic anaemia, megaloblastic anaemia and thrombocytopenia	Infante *et al.* (1978)
Workers employed for more than 3 months in the manufacture of chlordane and heptachlor, 1946-76 [study population overlaps with that of Shindell & Ulrich, 1986]	17 deaths from cerebrovascular disease observed *versus* 9.3 expected	Wang & MacMahon (1979a)

Table 17 (contd)

Population	Clinical features	Reference
Cohort of 16 126 men employed as pesticide applicators for 3 months or more in 1967, 1968 and 1976, including group of 6734 termite control operators	All deaths, 311 (SMR, 84); cerebrovascular disease among termite control operators (SMR, 39)	Wang & MacMahon (1979b)
A 62-year-old man accidentally ingested ~300 ml of 75% chlordane	Unresponsive to verbal commands, generalized tonic seizures, profuse diarrhoea, transient increase in liver enzymes; recovery by 2 months	Olanoff *et al.* (1983)
A 59-year-old man with a history of Alzheimer's disease inadvertently drank from a bottle containing a chlordane formulation	Rapid occurrence of convulsions, death, despite cardiopulmonary resuscitation and treatment	Kutz *et al.* (1983)
A 30-year-old woman exposed to chlordane through excessive household use	Numbness around mouth and nose and in arm used for spraying; nausea, vomiting, persistent fatigue and anorexia, menometrorrhagia; irregular theta discharges on EEG	Garrettson *et al.* (1985)
Workers employed in the manufacture of chlordane for 3 months or more, in 1946–85 [study population overlaps with that of Wang & MacMahon, 1979a]	20 deaths from cerebrovascular disease observed *versus* 11.7 expected	Shindell & Ulrich (1986)
45 members of dairy-farm families who consumed milk and milk products contaminated with heptachlor metabolites	No heptachlor-related metabolic effect observed in routine liver function tests or specific assays for hepatic enzyme induction	Stehr-Green *et al.* (1986)
25 case reports of blood dyscrasias associated with exposure to chlordane and heptachlor; of 16 cases for which exposure data available, 75% involved home and garden applications and 25% professional applicators	Aplastic anaemia, thrombocytopenic purpura, leukaemia, pernicious anaemia, megaloblastic anaemia	Epstein & Ozonoff (1987)
261 residents of 85 households treated with chlordane for termite control	Headache in 22% of cases; sore throat and respiratory infections in 16%; fatigue, 14%; sleeping difficulties, blurred vision and fainting also frequent	Menconi *et al.* (1988)

observed in 11/35 animals at 10 mg/m^3. A dose-related increased in cytochrome P450 concentration and microsomal protein was evident in each sex throughout the dose range studied. Essentially all of the observed changes were reversed within 90 days after cessation of exposure. No significant finding was noted in male or female monkeys exposed to up to 10 mg/m^3; however, cytochrome P450 and microsomal protein were not measured.

Chlordane at 200 μM stimulated protein kinase C *in vitro* in preparations from mouse brain, liver and epidermis. The stimulation was calcium- and phospholipid-dependent and could be inhibited by quercetin, a known inhibitor of protein kinase C activity (Moser & Smart, 1989).

Heptachlor

The toxic effects of heptachlor have been reviewed (WHO, 1984b; Fendick *et al.*, 1990).

The acute oral LD_{50} of heptachlor in peanut oil was 100 (74-135) mg/kg bw for male and 162 (140-188) mg/kg bw for female Sherman rats (Gaines, 1960). The signs associated with acute heptachlor poisoning include hyperexcitability, tremors, convulsions and paralysis. Liver damage may occur as a late manifestation (WHO, 1984b).

Heptachlor epoxide has a higher acute toxicity than the parent compound, e.g., the oral LD_{50} of the epoxide in rats was 62 mg/kg bw (Sperling & Ewinike, 1969), and the intravenous lethal doses for heptachlor and heptachlor epoxide in mice were 40 and 10 mg/kg bw, respectively (WHO, 1984b).

Daily oral doses of pure heptachlor at 50 and 100 mg/kg bw were lethal to rats after 10 days. In animals given 5 mg/kg bw, hyperreflexia, dyspnoea and convulsions occurred, and pathological changes were observed in the liver, kidney and spleen (Pelikan *et al.*, 1968).

As reported in a review, rats were fed heptachlor epoxide in the diet at concentrations varying from 5 to 300 mg/kg for two years. All animals given 80 mg/kg in the diet or more were reported to have died within 20 weeks, and all female rats given 40 mg/kg in the diet died within 54 weeks, whereas male mortality was unaffected. Liver weights were increased in males at dietary levels higher than 10 mg/kg and in females from 5 mg/kg upwards (WHO, 1984b). Dogs given 5 mg/kg bw heptachlor per day orally died within 21 days (Lehman, 1952).

Heptachlor induced hepatic drug-metabolizing enzymes (for review, see Fendick *et al.*, 1990) and enhanced oestrone metabolism in rats (Welch *et al.*, 1971). Dietary levels of 2 mg/kg heptachlor given for two weeks induced aniline hydroxylase and aminopyrine demethylase in rats (Den Tonkelaar & Van Esch, 1974). It inhibited oxidative phosphorylation in rat liver mitochondria (Nelson, 1975) and (at 200 μM) stimulated protein kinase C *in vitro* in preparations from mouse brain (Moser & Smart, 1989).

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

An ecological study was done to compare the incidence rates of 37 congenital malformations in Hawaii and in the USA as a whole (Le Marchand *et al.*, 1986), following contamination of milk on Oahu Island by heptachlor. Milk contamination occurred between the autumn of 1980 and December 1982 and was traced to contaminated foliage of pineapple plants used as cattle feed. Data on birth defects were obtained from the Birth Defects

Monitoring Program, which covers 62-76% of all births in Hawaii. Temporal and geographical comparisons were made (Table 18). Increased incidence rates were reported on Oahu for cardiovascular malformations and hip dislocation: In 1978-80, the incidence rates for cardiovascular malformations were 63.2/10 000 births on Oahu Island and 24.9 on the other Hawaian islands; in 1981-83, these rates were 76.2 and 24.4, respectively. For hip dislocation, the only increase occurred in 1981-83: rates were 42.2/10 000 on Oahu and 22.4 on the other islands. All of the increased rates for Oahu were statistically significant ($p < 0.01$). The authors noted that the increase in cardiovascular malformations and hip dislocation began in 1978-80, which included only the first few months of contamination. [The Working Group noted that the incidence rates for hip dislocation were unstable.]

Table 18. Incidence rates per 10 000 births of cardiovascular malformations and hip dislocation on Oahu Island and on the other Hawaiian islands, 1970-83[a]

Defect	Oahu				Other islands			
	1970-74	1975-77	1978-80	1981-83	1970-74	1975-77	1978-80	1981-83
Cardiovascular malformations	38.3	33.6	63.2	76.2	21.3	23.4	24.9	24.4
Hip dislocation	12.6	8.8	29.3	42.2	9.9	30.8	31.1	22.4

[a]From Le Marchand *et al.* (1986)

4.3.2 *Experimental systems*

The reproductive effects of chlordane and heptachlor/heptachlor epoxide have been reviewed (WHO, 1984a,b; US Public Health Service, 1989a,b).

Smith *et al.* (1970) found little effect of heptachlor on the hatchability of hens' eggs treated at doses below 1.5 mg/egg.

Incubation of sea-urchin embryos at the two-cell stage in the presence of heptachlor at 0.02 mM/litre (~7 ppm) until controls had developed up to the pluteus stage resulted in impaired development of the fertilized eggs; no living embryo was formed. When embryos were incubated in sea-water containing heptachlor for only 2 h, no effect on embryonic development was observed. When heptachlor was added 15 min before fertilization and the eggs allowed to incubate in the medium for an additional 15 min, the effect of heptachlor on fertilization and development to the two-cell stage was delayed; 7% reached the two-cell stage (Bresch & Arendt, 1977).

Rats treated with 320 mg/kg [0.032%] chlordane in their diet had substantially impaired fertility and reduced survival of the offspring (Ambrose *et al.*, 1953).

Pregnant CD-1 mice were treated with chlordane orally at a dose of 50 mg/kg bw on gestation days 8-12. Although 3/25 animals died, no effect was observed on number of live pups or pup weight on postnatal days 1 and 3 (Chernoff & Kavlock, 1983).

Spyker Cranmer *et al.* (1978) explored the effect of chlordane on endocrine function in mice. Mice were treated orally with 0.16 or 8.0 mg/kg bw from mating to parturition on day 22 of gestation. During the first week of life, 55% of offspring born to mothers receiving 8.0 mg/kg died. At 101 days of age, there was no difference in plasma or adrenal

corticosterone levels or adrenal weight between control and treated female offspring; male offspring of dams treated at the lower dose, however, appeared to have increased levels of plasma corticosterone and increased adrenal weight.

In a continuation of this study, Cranmer *et al.* (1984) evaluated plasma corticosterone concentrations over the lifespan of mice treated prenatally throughout gestation with chlordane at 0.16 or 8.0 mg/kg bw per day. At 400 days, plasma corticosterone levels were increased among male mice treated at either level. There was no difference in the corticosterone levels at 800 days in the lower-dose group (no male offspring from the higher-dose group was available for sacrifice at 800 days). Among female mice, corticosterone levels were elevated only at 400 days among those treated at 0.16 mg/kg.

Spyker Cranmer *et al.* (1982) evaluated cell-mediated and humoral immune response in adult BALB/c mice treated *in utero* with chlordane at 0.16 or 8.0 mg/kg bw per day from mating throughout gestation. Cell-mediated immunity (measured by contact hypersensitivity) was decreased in a dose-dependent manner in offspring at 101 days; no difference in humoral immune response was seen between treated and control mice.

Menna *et al.* (1985) explored the effect of prenatal exposure to chlordane on response to influenza A virus infection. BALB/c mice were treated orally with chlordane at doses of 0.16, 2.0, 4.0 and 8.0 mg/kg from mating to day 19, and at 38 days of age the mice were inoculated with influenza type A/PR/8/34(HON1) at three different rates. Survival was enhanced following the challenge, and antiviral titres were higher in mice treated with chlordane *in utero* than in controls.

Cytotoxic T lymphocyte activity was unchanged in 100-day-old mice treated with chlordane *in utero*, but natural killer cell activity was increased, only in female offspring. By 200 days of age, natural killer cell activity had declined in treated male and female offspring (Blaylock *et al.*, 1990). Prenatal treatment with chlordane also substantially decreased the number of granulocyte/macrophage and splenic colony forming units at both 100 and 200 days of age. The number of bone-marrow cells in these mice was unchanged at 100 days of age (Barnett *et al.*, 1990).

4.4 Genetic and related effects (see Tables 19 and 20 and Appendices 1 and 2)

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

Chlordane induced neither DNA damage nor point mutation in bacteria. It caused gene conversion in *Saccharomyces cerevisiae* and mutation in plants. In cultured mammalian cells, it did not induce unscheduled DNA synthesis but did induce gene mutations at the *tk* and Na^+/K^+ ATPase loci. It inhibited gap-junctional intercellular communication in cultured mammalian cells. In cultured human cells, conflicting results were obtained for unscheduled DNA synthesis; evidence was obtained for sister chromatid exchange induction but not for the induction of gene mutation. Sister chromatid exchange was induced in intestinal cells of *Umbra limi* (mud-minnow) *in vivo*. No dominant lethal effect was found in mice.

Heptachlor did not induce DNA damage or point mutation in bacteria or gene conversion in *Saccharomyces cerevisiae*. It induced mutation and chromosomal aberrations

Table 19. Genetic and related effects of chlordane

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ECB, Chromosome breakage, plasmid DNA *in vitro*	–	0	100.0000	Griffin & Hill (1978)
SAD, *Salmonella typhimurium* TA1538/1978, differential toxicity	–	0	2000.0000	Rashid & Mumma (1986)
BSD, *Bacillus subtilis rec* strains, differential toxicity	–	–	50.0000	Matsui *et al.* (1989)
ERD, *Escherichia coli* WP2, differential toxicity	–	0	2000.0000	Rashid & Mumma (1986)
ERD, *Escherichia coli* K12, differential toxicity	–	0	2000.0000	Rashid & Mumma (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	0.0000	Probst *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	0.0000	Gentile *et al.* (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	Mortelmans *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	0.0000	Probst *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	0.0000	Gentile *et al.* (1982)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500.0000	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.0000	Probst *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.0000	Gentile *et al.* (1982)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500.0000	Mortelmans *et al.* (1986)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	0.0000	Probst *et al.* (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	0.0000	Gentile *et al.* (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	0.0000	Probst *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	0.0000	Gentile *et al.* (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500.0000	Mortelmans *et al.* (1986)
SAS, *Salmonella typhimurium* G46, reverse mutation	–	–	0.0000	Probst *et al.* (1981)
SAS, *Salmonella typhimurium* C3076, reverse mutation	–	–	0.0000	Probst *et al.* (1981)
SAS, *Salmonella typhimurium* D3052, reverse mutation	–	–	0.0000	Probst *et al.* (1981)
EC2, *Escherichia coli* WP2, reverse mutation	–	–	0.0000	Probst *et al.* (1981)

Table 19 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ECW, *Escherichia coli* WP2 *uvr*A⁻, reverse mutation	–	–	0.0000	Probst *et al.* (1981)
SCG, *Saccharomyces cerevisiae*, gene conversion	0	+	6.6000	Gentile *et al.* (1982)
PLM, *Zea mays*, forward mutation	+	0	0.0000	Gentile *et al.* (1982)
*, DNA synthesis inhibition, mouse lymphoma cells	–	0	4.0000	Brubaker *et al.* (1970)
URP, Unscheduled DNA synthesis, rat hepatocytes	–	0	4.0000	Maslansky & Williams (1981)
UIA, Unscheduled DNA synthesis, mouse hepatocytes	–	0	4.0000	Maslansky & Williams (1981)
UIA, Unscheduled DNA synthesis, hamster hepatocytes	–	0	4.0000	Maslansky & Williams (1981)
URP, Unscheduled DNA synthesis, mouse hepatocytes	–	0	41.0000	Probst *et al.* (1981)
G9O, Gene mutation, V79 Chinese hamster cells, Na^+/K^+ ATPase locus	+	0	4.0000	Ahmed *et al.* (1977a)
G9H, Gene mutation, V79 Chinese hamster cells, *hprt* locus	–	0	1.6000	Tsushimoto *et al.* (1983)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	+	0	25.0000	McGregor *et al.* (1988)
GIA, Gene mutation, rat liver epithelial cells, *hprt* locus	–	0	41.0000	Telang *et al.* (1982)
GIA, Gene mutation, V79 Chinese hamster cells, diphtheria toxin resistance	–	0	1.6000	Tsushimoto *et al.* (1983)
SVA, Sister chromatid exchange, *Umbra limi* intestinal cells *in vivo*	+	0	0.0002	Vigfusson *et al.* (1983)
UHF, Unscheduled DNA synthesis, human fibroblasts	+	–	0.4000	Ahmed *et al.* (1977b)
UHT, Unscheduled DNA synthesis, HeLa cells	–	0	16.0000	Brandt *et al.* (1972)
GIH, Gene mutation, human fibroblasts	–	–	41.0000	Tong *et al.* (1981)
SHL, Sister chromatid exchanges, human lymphoid cells *in vitro*	+	+	41.0000	Sobti *et al.* (1983)
DLM, Dominant lethal test, mice	–	0	240.0000 × 1 i.p.	Epstein *et al.* (1972)
DLM, Dominant lethal test, mice	–	0	75.0000 × 5 p.o.	Epstein *et al.* (1972)
DLM, Dominant lethal test, mice	–	0	100.0000 × 1 i.p.	Arnold *et al.* (1977)
DLM, Dominant lethal test, mice	–	0	100.0000 × 1 p.o.	Arnold *et al.* (1977)
ICR, Inhibition of metabolic cooperation, rat liver epithelial cells	+	0	0.2000	Telang *et al.* (1982)

Table 19 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ICR, Inhibition of metabolic cooperation in V79 cells	(+)	0	1.6000	Tsushimoto *et al.* (1983)
ICR, Inhibition of metabolic cooperation mouse hepatocytes	+	0	20.0000	Ruch *et al.* (1990)
ICR, Inhibition of metabolic cooperation rat hepatocytes	+	0	20.0000	Ruch *et al.* (1990)

*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

Table 20. Genetic and related effects of heptachlor

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ECB, Breakage of plasmid DNA *in vitro*	–	0	100.0000	Griffin & Hill (1978)
SAD, *Salmonella typhimurium* TA1538/1978, differential toxicity	–	0	2000.0000	Rashid & Mumma (1986)
ERD, *Escherichia coli* WP2, differential toxicity	–	0	2000.0000	Rashid & Mumma (1986)
BSD, *Bacillus subtilis rec* strains, differential toxicity	–	–	356.0000	Matsui *et al.* (1989)
ERD, *Escherichia coli* K12, differential toxicity	–	0	2000.0000	Rashid & Mumma (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	0.0000	Probst *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	(+)[c]	5.0000	Gentile *et al.* (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	167.0000	Zeiger *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	Mersch-Sundermann *et al.* (1988)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	–	500.0000	Mersch-Sundermann *et al.* (1988)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500.0000	Marshall *et al.* (1976)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	0.0000	Probst *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	(+)[c]	10.0000	Gentile *et al.* (1982)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	167.0000	Zeiger *et al.* (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500.0000	Marshall *et al.* (1976)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.0000	Probst *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	167.0000	Zeiger *et al.* (1987)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500.0000	Marshall *et al.* (1976)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	0.0000	Probst *et al.* (1981)

Table 20 (contd)

Test system	Result[a]		Dose[b] LED/HID		Reference
	Without exogenous metabolic system	With exogenous metabolic system			
SA8, *Salmonella typhimurium* TA1538, 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	–	–	0.0000		Probst *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	(+)[c]	5.0000		Gentile *et al.* (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500.0000		Moriya *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	167.0000		Zeiger *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500.0000		Mersch-Sundermann *et al.* (1988)
SAS, *Salmonella typhimurium* TA1536, reverse mutation	–	–	500.0000		Marshall *et al.* (1976)
SAS, *Salmonella typhimurium* G46, reverse mutation	–	–	0.0000		Probst *et al.* (1981)
SAS, *Salmonella typhimurium* C3076, reverse mutation	–	–	0.0000		Probst *et al.* (1981)
SAS, *Salmonella typhimurium* D3052, reverse mutation	–	–	0.0000		Probst *et al.* (1981)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	500.0000		Mersch-Sundermann *et al.* (1988)
EC2, *Escherichia coli* WP2, reverse mutation	–	–	0.0000		Probst *et al.* (1981)
EC2, *Escherichia coli* WP2 *hcr*, reverse mutation	–	–	2500.0000		Moriya *et al.* (1983)
ECW, *Escherichia coli* WP2 *uvr*A$^-$, reverse mutation	–	–	0.0000		Probst *et al.* (1981)
SCG, *Saccharomyces cerevisiae*, gene conversion	–	–	0.0000		Gentile *et al.* (1982)
PLM, *Zea mays*, forward mutation	+	0	0.0000		Gentile *et al.* (1982)
PLC, *Lens* sp, chromosomal aberrations,	+	0	1000.0000		Jain (1988)
PLC, *Pisum* sp, chromosomal aberrations,	+	0	1000.0000		Jain (1988)
PLC, *Tradescantia*, micronuclei	+	0	1.8800		Sandhu *et al.* (1989)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–	0	5.0000	(feeding solutions)	Benes & Sram (1969)
URP, Unscheduled DNA synthesis, rat hepatocytes	–	0	3.7000		Maslansky & Williams (1981)
UIA, Unscheduled DNA synthesis, mouse hepatocytes	–	0	3.7000		Maslansky & Williams (1981)

Table 20 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
UIA, Unscheduled DNA synthesis, hamster hepatocytes	-	0	3.7000	Maslansky & Williams (1981)
UIA, Unscheduled DNA synthesis, mouse hepatocytes	-	0	3.7000	Probst *et al.* (1981)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	+	0	25.0000	McGregor *et al.* (1988)
GIA, Gene mutation, rat liver epithelial cells, *hprt* locus	-	0	37.0000	Telang *et al.* (1982)
UHF, Unscheduled DNA synthesis, human fibroblasts	-	+	37.0000	Ahmed *et al.* (1977b)
*, Inhibition of DNA synthesis, testicular cells in mice	-	0	40.0000	Seiler (1977)
DLM, Dominant lethal test, mice	-	0	24.0000	Epstein *et al.* (1972)
DLM, Dominant lethal test, mice	-	0	15.0000 × 1 p.o.[d]	Arnold *et al.* (1977)
DLM, Dominant lethal test, mice	-	0	15.0000 × 1 i.p.[d]	Arnold *et al.* (1977)
ICR, Inhibition of metabolic cooperation, V79 cells	+	0	10.0000	Kurata *et al.* (1982)
ICR, Inhibition of metabolic cooperation, rat liver epithelial cells	+	0	0.0400	Telang *et al.* (1982)
ICR, Inhibition of metabolic cooperation, rat hepatocytes	+	0	20.0000	Ruch *et al.* (1990)
ICM, Inhibition of metabolic cooperation, mouse hepatocytes	+	0	20.0000	Ruch *et al.* (1990)

*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]Plant activation

[d]25:75 mixture of heptachlor:heptachlor epoxide; not displayed on profile

in plants but not in *Drosophila melanogaster*. Heptachlor did not induce unscheduled DNA synthesis in cultured rodent cells, but did so in human fibroblasts. It induced gene mutation at the *tk* but not at the *hprt* locus in rodent cells. Heptachlor inhibited gap-junctional intercellular communication in cultured mammalian cells. It did not inhibit DNA synthesis in mouse testicular cells and did not induce dominant lethal effects in mice *in vivo*.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Chlordane has been used since the 1950s as a broad-spectrum contact insecticide, mainly for nonagricultural purposes and to a lesser extent on crops and on livestock. Since the mid-1970s, its use has generally been restricted to underground control of termites.

Heptachlor has been used since the 1950s as an insecticide in agriculture and in the control of termites and soil insects. Like chlordane, its use is now largely restricted to subsoil treatment for termites.

Chlordane and heptachlor have been formulated as granules, emulsifiable concentrates and solutions.

Both compounds can persist in soil for many years. Human exposure to chlordane and heptachlor occurs mainly during their application and in the air of buildings where they have been applied for termite control. When these compounds were used on crops, exposure may have occurred at much lower levels as a result of consumption of foods containing residues.

5.2 Carcinogenicity in humans

Case reports of leukaemia and other blood dyscrasias have been associated with exposure to chlordane/heptachlor, primarily in domestic situations.

Mortality from lung cancer was slightly elevated in two cohort studies of pesticide applicators and one of chlordane/heptachlor manufacturers. Termite control operators probably have greater exposure to chlordane than other pesticide applicators; however, in one study of applicators, the excess occurred only among workers who were not engaged in termite control. In the other study of applicators, the relative risk for lung cancer among workers engaged in termite control was similar to that of workers engaged in other pest control. Inconsistencies in these findings make it difficult to ascribe the excesses to exposure to chlordane.

Small excess risks for other cancers, including leukaemia, non-Hodgkin's lymphoma and soft-tissue sarcoma and cancers of the brain, skin, bladder and stomach were observed, with little consistency among studies.

5.3 Carcinogenicity in experimental animals

Chlordane, technical-grade chlordane, heptachlor, technical-grade heptachlor, heptachlor epoxide and a mixture of heptachlor and heptachlor epoxide have been tested for carcinogenicity by oral administration in several strains of mice and rats. These studies uniformly demonstrate increases in the incidence of hepatocellular neoplasms in mice of each sex. Increases in the incidence of thyroid follicular-cell neoplasms were observed in rats

treated with chlordane and technical-grade heptachlor. An increased incidence of malignant fibrous histiocytomas was observed in one study in male rats treated with chlordane. A small increase in the incidence of liver adenomas was seen in one study in male rats treated with technical-grade chlordane.

5.4 Other relevant data

Metabolites of chlordane and heptachlor, like those of other chlorinated hydrocarbons, accumulate in human fat. Chlordane and heptachlor induce liver microsomal enzymes. The liver is the target organ for chronic toxicity.

No data were available on the genetic and related effects of chlordane or heptachlor in humans.

Chlordane and heptachlor did not cause dominant lethal effects in mice. Both compounds inhibited gap-junctional intercellular communication and induced gene mutation in rodent cells but did not induce unscheduled DNA synthesis. In plants, heptachlor induced mutation and chromosomal aberrations. Neither chlordane nor heptachlor was mutagenic to bacteria and neither damaged bacterial or plasmid DNA.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of chlordane and of heptachlor.

There is *sufficient evidence* in experimental animals for the carcinogenicity of chlordane and of heptachlor.

Overall evaluations

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

Heptachlor *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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Annex 1.

Criteria for classification of rodent hepatocellular neoplasms[a]

Hepatocellular carcinoma: focal thickening of hepatocellular plates producing trabeculae that are at least 4-5 cells thick, or the presence of papillary formations with finger-like projection of hepatocytes completely surrounded by endothelial cells. Cytological variation is frequently prominent, with a high nucleus: cytoplasm ratio; but the cells may at times resemble normal hepatocytes. Infiltration of the surrounding parenchyma is rare but indicates malignancy.

Basophilic nodules: hepatocyte plates 1-3 cells thick, characterized by intense cytoplasmic staining with haematoxylin. Most of the cells are small and rather uniform, but some show a significant degree of cytological variation. These nodules are characterized by increased cell number with compression of surrounding parenchyma.

Hyperplastic nodules: several cytological variants exist. In the mouse, these nodules frequently show considerable megalocytosis with numerous, often bizarre mitotic figures. A feature common to all of them is hyperplasia with compression of the surrounding parenchyma and 2-cell-thick hepatocyte plates. Swelling of individual hepatocytes is often prominent in these nodules. Portal triads are absent.

Nodules showing features indicative of carcinoma: histological changes may not be diagnostic of carcinoma, but the presence of a combination of several features strongly suggests transition to hepatocellular carcinoma. These features may include a suspicion of trabeculae formation, basophilic cytoplasmic changes, the formation of 'nodules within nodules' (clusters of hepatocytes within hyperplastic nodules showing different cytological features), a peculiar 'packing' phenomenon with close compression of many hepatocytes or marked cytological atypia with the presence of unusually large numbers of mitotic cells.

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[a]Elaborated by the Pesticide Information Review and Evaluation Committee convened by the US National Academy of Sciences (1977)