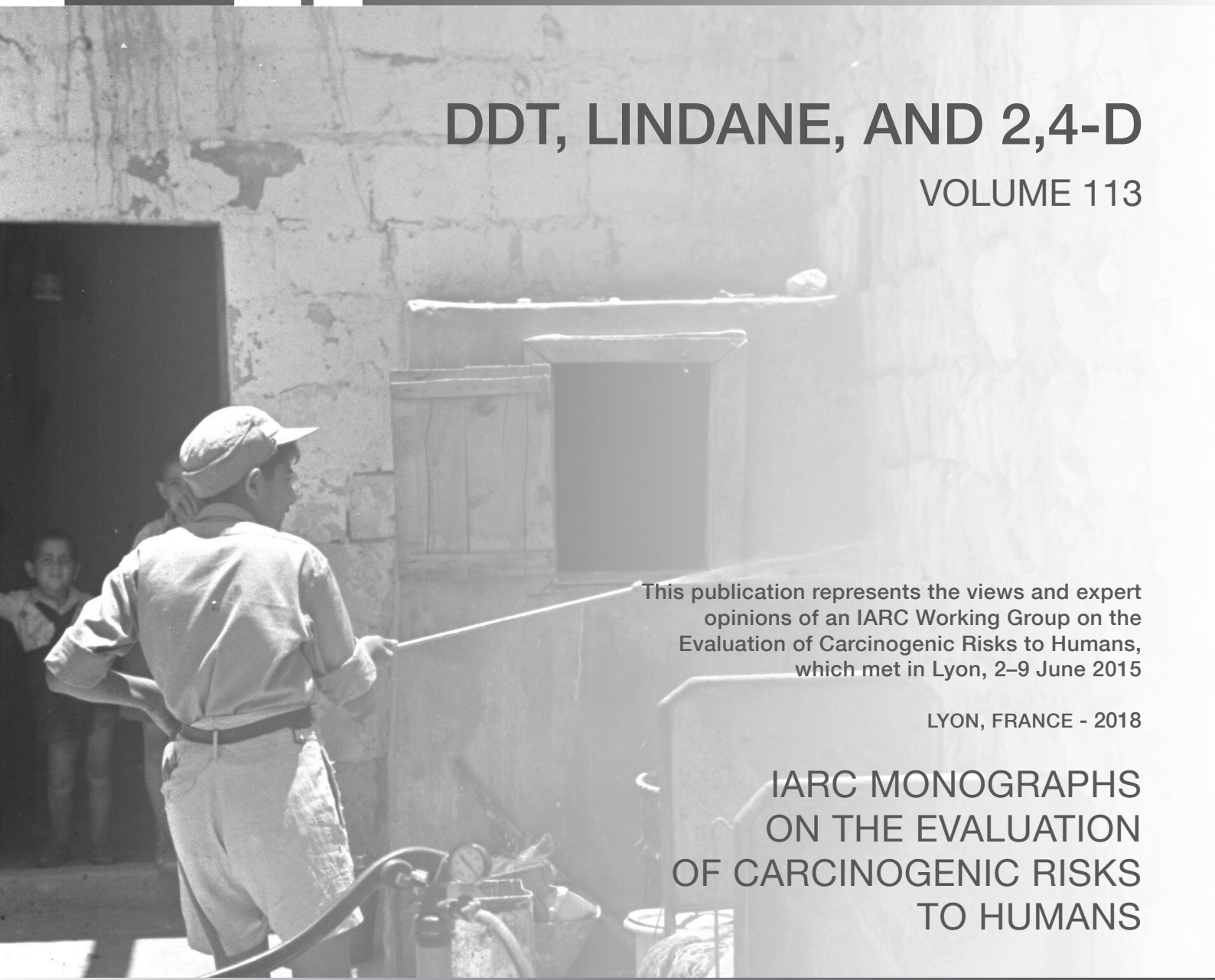
IARC MONOGRAPHS



DDT, LINDANE, AND 2,4-D

VOLUME 113

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International Agency for Research on Cancer

World Health Organization

LINDANE

1. Exposure Data

1.1 Identification of the agent

The carcinogenicity of halogenated aromatic hydrocarbon pesticides such as lindane has been evaluated previously in Volume 5, and again in Supplement 7 and Volumes 20 and 53 (IARC, 1974, 1979b, 1987, 1991). New data on lindane have since become available, and have been incorporated into the present monograph and taken into consideration in the evaluation.

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 58-89-9

Chem. Abstr. Serv. Name:
lα,2α,3β,4α,5α,6β-Hexachlorocyclohexane

Preferred IUPAC Name:
1,2,3,4,5,6-Hexachlorocyclohexane

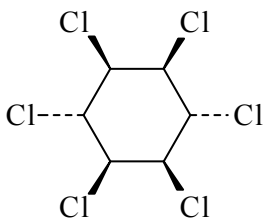
Synonyms: γ-Benzene hexachloride; γ-hexachlorocyclohexane; lindane

[The Working Group noted that the terms "γ-BHC" and "γ-lindane" have been used historically, but are incorrect.]

Trade Names: Lindane has been used in formulations for many commercial products. The trade names listed here are presented as examples and are not intended to represent an exhaustive list, or to focus on any particular manufacturer or user: Aalindan; Agrocide; Aparasin; Aphtiria; Ben-Hex; Bexol; Celanex; Chlorosene; Gammalin; Gamene Gammexane; Gexane; Hexide: Hortex; Lindator; Lindex; Nexit; Pflanzol; Quellada.

Additional trade names are available in the PubChem Compound Database (PubChem Compound Identifier 727; NCBI, 2015).

1.1.2 Structural and molecular formulae, and relative molecular mass



From RSC (2015)

Molecular formula: $C_6H_6Cl_6$ or $ClCH(CHCl)_4CHCl$

Isomers differ in the spatial positions of the chlorine atoms; dashed and solid bridges represent positions below and above the plane, respectively (RSC, 2015)

Relative molecular mass: 290.81

Additional chemical structure information is available in the PubChem Compound Database (NCBI, 2015) and the Merck Index Online (RSC, 2015).

1.1.3 Chemical and physical properties of the pure substance

Description: White crystalline powder (IPCS/ILO, 2009)

Solubility: Volatile in air and poorly soluble in water (g/100 mL at 20 °C, 0.0007) (IPCS, ILO-ICSC 0053). Soluble in ethyl alcohol and ethyl ether, benzene, chloroform (NCBI, 2015)

Octanol/water partition coefficient: log P_{ow}, 3.61–3.72 (IPCS, ILO/ICSC 0053; IPCS/ILO, 2009)

Conversion factor in air (at 25 °C): 1 ppm = 11.89 mg/m^3, assuming normal temperature (25 °C) and pressure (101 kPa) (EPA, 2015a).

1.2 Production and use

Hexachlorocyclohexane (HCH) was first synthesized by Michael Faraday in 1825. After the discovery in 1912 of the δ- and γ-isomers by Teunis Van der Linden, the name "lindane" was given to the γ-isomer.

Many HCH isomers exist, but only six isomers are relatively stable, including α-, β-, γ-, δ-, and ε-isomers. Only γ-HCH has insecticidal properties (Brooks, 1977). Both technical-grade lindane that contains more than 90% γ-HCH (IRPTC, 1983) and technical-grade HCH that contains approximately 60–70% α-HCH, 5–12% β-HCH, 10–40% γ-HCH, 6–10% δ-HCH, and 3–4% ε-HCH (Kutz et al., 1991), have been used worldwide for the insecticidal properties of the γ-isomer. The International Organization for Standardization (ISO) common name and the WHO specification use "lindane" to refer to material containing > 99% γ-HCH.

Table 1.1 Production of lindane

Production	Tonnes per year
World production, 1986[a]	Approx. 38 000
World production, 1988–1993[b]	4 400
World production, 1990–1995	3 222
Production in western Europe, 1990s	Approx. 2 055
Production in the European Economic Community, 1991[c]	1 000–5 000

[a] International Uniform Chemical Information Database (UCLID, 1994)
[b] Detzel et al. (1998)
[c] Rippen (1990/2000)
From UNECE (2004); data from Hazard Substances Committee (OSPAR Commission, 2002)

1.2.1 Production

Technical-grade HCH is produced as a mixture of isomers by photochlorination of benzene, a reaction that can be started by free-radical initiators such as visible or ultraviolet light, X-rays, or γ-rays (ATSDR, 2005). The active γ-HCH (lindane) can be concentrated by treatment with methanol or acetic acid, followed by fractional crystallization, to produce technical-grade lindane containing 99.9% of the γ-isomer.

Historical sites for the production of technical-grade HCH and/or lindane can be found in many countries in Europe, including Bulgaria, Czechia, France, Germany, Italy, Poland, Romania, Spain, Turkey, and the United Kingdom. Production in countries that are members of the United Nations Economic Commission for Europe (UNECE) took mainly place from 1950 or earlier until 1970, and stopped from 1970 onward. Only rough estimates on years of production and on produced volumes were available to the Working Group (Table 1.1; UNECE, 2004).

Commercial production of lindane in the United States of America (USA) began in 1945 and peaked in the 1950s, when 17.6 million pounds [7983 tonnes] was manufactured (IARC, 1974). In 1978, the United States Environmental

Protection Agency (EPA) banned production of technical HCH (UNECE, 2004).

Lindane is produced by 13 manufacturers worldwide, including 7 in India and 4 in China (SRI, 2009), and is available from 42 suppliers, including 19 suppliers in the USA (ChemSources, 2009).

1.2.2 Use

Lindane was extensively used in the past few decades. In 1992, global use of technical-grade HCH was estimated at 0.55 million tonnes, while global use of lindane was estimated at 0.72 million tonnes (Volder & Li, 1995). Technical-grade HCH and lindane were primarily used as insecticides to treat wood and wooden structures, seed, and livestock. Major uses today are as insecticide for fruit and vegetable crops, and in baits and seed treatments for rodent control. Lindane is still used as a human health pharmaceutical as a second-line treatment for control of head lice and scabies (mites) ; it is available in 1% preparations as a lotion, cream, or shampoo (ATSDR, 2005; HSDB, 2009; UNEP/WHO, 2015).

1.3 Measurement and analysis

Methods for the analysis of lindane and other organochlorine pesticides have been developed during the past few decades. Historically, lindane and other HCH isomers have been analysed using gas chromatography and electron capture detection (Prapamontol & Stevenson, 1991; López et al., 2001). In most of the methods currently available, lindane is part of multiple component analytical methods for the measurement of organochlorines and other pesticides in ambient air (Borrás et al., 2011), dust (Regueiro et al., 2007), water (McManus et al., 2013; Regueiro et al., 2008), sediments (Concha-Graña et al., 2010), crops (Walorczyk et al., 2013), human serum (López et al., 2001; Moreno Frías et al., 2001), and urine (Cazorla-Reyes et al., 2011). The analysis of lindane and other HCH isomers involves extraction, clean-up, and gas chromatography or gas chromatography-mass spectrometry-based instrumental analysis (representative analytical methods for lindane in various matrices are listed in Table 1.2).

Extraction methods for organochlorine compounds including lindane vary widely according to the matrix of interest and the sampling method. For example, water samples can be extracted on a rotating disk sorptive extraction technique (Giordano et al., 2011). For air samples collected with a polyurethane foam sampler, various sorbents have been used for solid-phase extraction (Martínez Vidal et al., 1997). Gaseous and particulate phases of lindane in the atmosphere can be extracted on XAD-2 and XAD-4 cartridges and glass fibre filters, respectively (Borrás et al., 2011). In vegetables, fruits, and other plant samples, lindane can be extracted by matrix solid-phase dispersion (Abhilash et al., 2007). Lindane in human serum samples can be extracted with organic solvents, clean-up of the organic extract using acid treatment with sulfuric acid, and elution of the cleaned-up extract by liquid column chromatography (Moreno Frías et al., 2001).

A concern with gas chromatography and electron-capture detection methods is the potential for interference from non-target chemicals, leading to misidentification or incorrect quantitation. More recently, gas chromatography-mass spectrometry methods are being used, which include single quadruple mass-spectrometry detectors running in electron ionization mode with target analyses monitored by selective ion monitoring and gas chromatography coupled with high-resolution mass spectrometry (Barr et al., 2003). These detection methods increase confidence in confirmative analysis by decreasing matrix interferences, improving selectivity.

Table 1.2 Representative methods for the analysis of lindane

Sample matrix	Assay procedure	Limit of detection	Reference
Ambient air	GC-MS		Borrás et al. (2011)
- Gas phase		25.79 pg/m^3	
- Particulate		0.052 pg/m^3	
Indoor dust	GC-μECD	0.22 ng/g	Regueiro et al. (2007)
Water	GC-MS	15 ng/L (LOQ)	McManus et al. (2013)
	GC-MS	21 ng/L	Regueiro et al. (2008)
Sediments	GC-MS	6.10 ng/g	Concha-Graña et al. (2010)
Crops	GC-QqQ-MS/MS	10 ng/g	Walorczyk et al. (2013)
Human serum	GC-ECD	3 ng/mL	López et al. (2001)
		10 ng/mL (β-HCH)	
	GC-ECD	0.006 ng/mL	Moreno Frías et al. (2001)
Urine	GC-IT-MS/MS	0.136 ng/mL	Cazorla-Reyes et al. (2011)

ECD, electron-capture detection; GC, gas chromatography; HCH, hexachlorocyclohexane; IT-MS/MS, ion trap mass spectrometry; LOQ, limit of quantitation; MS, mass spectrometry; QqQ-MS/MS, tandem quadrupole mass spectrometry

1.4 Occurrence and exposure

See Table 1.3, Table 1.4, and Table 1.5

Exposure to lindane is predominantly an exposure to the γ-HCH isomer, which has a very short half-life. Pure and technical forms of lindane exist, with almost pure lindane being γ-HCH, while technical-grade HCH consists of 10–40% γ-HCH plus various other isomers, including β-HCH.

In the present monograph, the terms given to lindane and its isomers are reported as specified by the authors of the referenced paper (e.g. authors may refer to "total HCH" when reporting the summed concentrations of various HCH isomers, or simply to "HCH").

1.4.1 Occupational exposure

Occupational exposure can occur during the manufacture and formulation of lindane, as well as in the treatment of wood and wooden structures, seed grains and in the agricultural application of lindane as a pesticide on livestock and crops (ATSDR, 2005). Exposure in occupational settings is principally through inhalation or dermal contact, although ingestion of lindane due to poor hygiene practices can occur. Hygiene measurement of lindane in air and hand wipes, together with biological measurement of lindane in serum and hair in workers from a range of occupations in the USA, Europe, and Asia have been reported (Table 1.3).

Studies of occupational exposure during the manufacture and formulation of lindane have reported detectable serum concentrations of γ-HCH and β-HCH (Baumann et al., 1980; Kashyap, 1986; Nigam et al., 1986). Baumann et al. reported mean concentrations of γ-HCH and β-HCH of 0.037 mg/L and 0.190 mg/L respectively among workers producing lindane in Germany (Baumann et al., 1980). Mean concentrations of γ-HCH and β-HCH in exposed workers involved in pesticide formulation in India were 0.06 mg/L and 0.413 mg/L respectively (Kashyap, 1986). The mean concentration of lindane in workers directly involved in handling the product in a manufacturing plant in India was 0.057 ppm (Nigam et al., 1986). Farmers in Nigeria were reported to have mean serum concentrations of lindane of 0.08 mg/kg (Sosan et al., 2008).

In commercial seed-conditioning plants in Montana, USA, in 1981–82, lindane levels in hand-wash samples and respiratory pads were

Table 1.3 Occupational exposure to lindane: environmental and biological measurements

Industry Location, year	Job/process	Sampling matrix	Exposure		Comments	References
			Mean	Range		
Lindane production Country and year, NR	NR	Serum	0.37 mg/L (arithmetic mean, γ-HCH)	0.005–0.19 mg/L	α-HCH: mean, 0.07; range, 0.01–0.27 mg/L β-HCH: mean, 0.19; range, 0.02–0.76 mg/L	Baumann et al. (1980)
Seed conditioning Montana, USA, 1981–1982	NR	Handshake sample; respiratory pads	NR	NR	Dermal exposure: site 9: 81.42 mg/hour; site 10: 54.80 mg/hour Respiratory exposure: site 9: 0.36 mg/hour; site 10: 0.54 mg/hour	Grey et al. (1983)
Pesticide manufacture Country and year, NR	Insecticide handlers	Serum	0.06 ppm (arithmetic mean, γ-HCH)	0.01–0.17 ppm	α-HCH: mean, 0.10; range, 0.02–0.18 ppm β-HCH: mean, 0.41; range, 0.16–0.72 ppm	Nigam et al. (1986)
Pesticide manufacture and formulation Country and year, NR	Employees involved in pesticide manufacture of organophosphates, HCH/BHC	Serum	Arithmetic mean (γ-HCH): Formulators: 0.06 mg/L; manufacturers: 0.02 mg/L; controls: 0.001 mg/L	Range (γ-HCH): Formulators: 0.01–0.17 mg/L; manufacturers: 0.0–0.04 mg/L; controls: 0.0–0.01 mg/L	Formulators mean; range (mg/L) α-HCH: mean, 0.10; range, 0.02–0.18 mg/L; β-HCH; mean, 0.41; range, 0.16–0.72 mg/L; Total HCH: mean, 0.60; range, 0.19–1.15 mg/L Biological levels also reported for manufacturing staff, and controls for other isomers and total HCH	Kashyap (1986)
Forestry workers Country NR, 1986		Plasma	NR	NR	Workers monitored for 20 weeks. Detected group mean of γ-HCH (nmol/L): 0 (April–June); 40 (mid July); 16 (August)	Drummond et al. (1988)
Agricultural spraymen and controls Allahabad, India, year NR	NR	Serum	Arithmetic mean (mg/L): Sprayers: γ-HCH: 0.03; β-HCH: 0.22; total HCH: 0.29; Controls: γ-HCH: 0.02; β-HCH: 0.11; total HCH: 0.15	Sprayers (mg/L) γ-HCH: 0.00–0.09; β-HCH: 0.02–0.95; total-HCH: 0.04–1.04 Controls (mg/L) γ-HCH: 0.00–0.71; β-HCH: 0.01–0.69; total HCH: 0.03–0.74	125 exposed sprayers and 47 controls	Joshi et al. (1996)

Table 1.3 (continued)

Industry Location, year	Job/process	Sampling matrix	Exposure		Comments	References
			Mean	Range		
Greenhouses, florists, veterinary departments Paris and suburbs, France, 2002		Air	14.32 ng/m^3 (arithmetic mean, lindane)	0.2–75 ng/m^3	Mean and range calculated from 10 measurements of indoor air	Bouvier et al. (2006)
		Hand wipes	22.76 ng/hand (arithmetic mean, lindane)	0–156.7 ng/hand	Mean and range calculated from 15 measurements	
Greenhouse workers, animal breeders, open cultivation workers Messara and Sitia districts, Crete, Greece, year NR		Hair	70.2 pg/mg (median, lindane)	48.2–95.0 pg/mg	Maximum level was 174.7 pg/mg	Tsatsakis et al. (2008)
Farmers Osun and Ondo states of south-western Nigeria, year NR	Cacao farmers; pesticide application	Serum	0.08 mg/kg (arithmetic mean, lindane)	NR	44 out of 76 farmers had lindane residue measurable in serum samples	Sosan et al. (2008)

HCH, hexachlorocyclohexane; NR, not reported

measured as 81.42 or 54.80 mg/hour and 0.36 or 0.54 mg/hour, respectively (Grey et al., 1983).

In France in 2002, mean lindane levels in indoor-air and hand-wipe samples from greenhouse workers, florists and veterinary-department workers were calculated as 14.32 ng/m^3 and 22.76 ng/hand, respectively (Bouvier et al., 2006). Hair samples from greenhouse workers and farmers in Greece contained lindane at concentrations in the range of 48.2–95.0 pg/mg (Tsatsakis et al., 2008).

Biological levels of lindane have been shown to decrease with reduced occupational exposure. Plasma concentrations of lindane in forestry workers monitored for 20 weeks starting in April 1986 rose from a group mean of zero to 40 nmol/L after 8 weeks, and dropped to 16 nmol/L after 16 weeks (Drummond et al., 1988). The difference in mean serum concentrations between non-exposed and exposed Indian agricultural sprayers was 0.01 mg/L for γ-HCH and 0.12 mg/L for β-HCH (Joshi et al., 1996).

1.4.2 Environmental occurrence

See Table 1.4

Lindane does not occur naturally in the environment. Occurrence may be due to pesticide application processes, release from manufacturing sites or landfills, or to precipitation. Biodegradation is the dominant degradative process for γ-HCH in aquatic systems and soil (ATSDR, 2005).

(a) Air

Historically, air contamination with lindane would have resulted from pesticide application and release from production plants (ATSDR, 2005). Weekly air samples in 1972, 1973, and 1974 taken in Stoneville, Mississippi, USA, contained a maximum lindane concentration of 9.3 ng/m^3 (Arthur et al., 1976). Around 1990, background levels of lindane in the range of 0.01–0.7 ng/m^3 were found in "unpolluted" remote areas, whereas levels in urban and agricultural areas range from 0.1 to 2 ng/m^3 (WHO, 2004). Air monitoring in Ontario, Canada, between 1988 and 1989 showed annual mean levels of β-HCH and γ-HCH of 1.8 and 60 pg/m^3, respectively (Hoff et al., 1992a).

Measurement of background levels of persistent organic pollutants at 71 sites in Europe in 2006 reported mean concentrations of γ-HCH and β-HCH of 35 and 2 pg/m^3, respectively. The presence of γ-HCH was attributed to either technical-grade HCH or lindane (Halse et al., 2011). Passive air sampling in 22 European countries in 2002 reported γ-HCH at concentrations in the range of 1.1–65 pg/m^3 with thehighest concentrations recorded in southern and eastern Europe, in particular, Spain, parts of France, Italy, and the Balkans region (Jaward et al., 2004).

Average annual concentrations in air for γ-HCH, β-HCH, α-HCH, and δ-HCH were reported between 1999 and 2001 in Niigata, Japan, as 32, 23, 92, and 3 × 10^{-3} ng/m^3, respectively (Murayama et al., 2003). A review of various studies on persistent organic pollutants in South China reported mean HCH concentrations of 666 × 10^{-3} ng/m^3 in 2003–2004, decreasing to a mean of 75 × 10^{-3} ng/m^3 in 2006–2007 (Zhang et al., 2013). In Shanghai, China, in 2008–2009, the mean concentration of HCH in air samples was measured as 6.93 × 10^{-3} ng/m^3 (Yu et al., 2012).

The Global Atmospheric Passive Sampling (GAPS) study report that between 2005 and 2008, distinct spatial and temporal patterns show that pesticides such as γ-HCH tend to be more prevalent in developing countries, especially in Asia. Samples taken over Delhi, India, had the highest levels of γ-HCH. In Europe, the levels of γ-HCH are not uniformly distributed, with samples from Paris having the highest levels. Levels of γ-HCH are not very high in North America and South Ameria, which may reflect decreased usage (Fig. 1.1; Shunthirasingham et al., 2010).

Table 1.4 Environmental exposure to lindane

Region, country, city Year	Sampling matrix	Exposure		Comments	Reference
		Mean	Range		
USA Mississippi, 1972–74	Air (weekly sampling)	NR	NR	Maximum level: lindane, 9.3 ng/m³ β-HCH, 49.4 ng/m³	Arthur et al. (1976)
Canada Ontario, 1988–1989	Air	Annual mean: γ-HCH, 60 pg/m³ Arithmetic mean: γ-HCH, 0.47 pg/m³	γ-HCH, 4.0–820 pg/m³	Annual mean (pg/m³): α-HCH, 145 β-HCH, 1.8 Arithmetic mean (pg/m³): α-HCH, 1.0 β-HCH, 0.34 Range (pg/m³): α-HCH, 10–540 β-HCH, MDC–28	Hoff et al. (1992a)
Japan Nigata, 1999–2001	Air	Annual mean (pg/m³): γ-HCH, 32	Annual ranges reported for five sampling points	All POPs decreased 41–80% during 2000 to 2001 except α-HCH and γ-HCH Annual mean (pg/m³): α-HCH, 92 β-HCH, 23 δ-HCH, 3	Murayama et al. (2003)
Europe 2006	Air	Average (pg/m³): γ-HCH, 35 Total HCH, 64	SD: γ-HCH, 38 Total HCH, 59	Average (pg/m³): α-HCH, 26 β-HCH, 2 SD: α-HCH, 24 β-HCH, 7	Halse et al. (2011)
China South China, [review paper]	Air	Mean range, HCH: 75–666 pg/m³	NR	Mean HCH levels from various studies, 2004–2007	Zhang et al. (2013)
Germany 1970–71	Water	238.14 ng/L (unfiltered water)	0–7100 ng/L (unfiltered water)	25 sites sampled in May 1971; 7 sites sampled monthly from April 1970 to June 1971	Herzel (1972)
Israel 1973	Water	NR	γ-HCH, ND–14.9 ng/L	Range: α-HCH, ND–4.1 ng/L	Lahav & Kahanovitch (1974)
USA Georgetown, South Carolina, Year, NR	Water	1.19 ppt	ND–2.21 ppt		Achari et al. (1975)

Table 1.4 (continued)

Region, country, city Year	Sampling matrix	Exposure		Comments	Reference
		Mean	Range		
USA New Orleans, 1970	Water	NR	Lindane, 1.3–2.9 ng/L	Estimated from graph	Brodtmann (1976)
Egypt Nile Delta, 1995–1997	Water	NR	Lindane, 0.286–0.352 µg/L		Abbassy et al. (1999)
Islamic Republic of Iran Karun River, Khuzestan, August 2008–March 2009	Water	Arithmetic mean (µg/L): γ-HCH, 1.58 Total HCH, 4.93	Range (µg/L): γ-HCH, 0.22–4.25 Total HCH, 0.73–11.12	Arithmetic mean (µg/L): α-HCH, 0.08 β-HCH, 1.81 δ-HCH, 1.45 Range (µg/L): α-HCH, 0.01–0.23 β-HCH, 0.08–6.07 δ-HCH, 0.29–3.26	Behfar et al. (2013)
China South China, [review paper]	Water	Mean range: 1.43–285 pg/m^3	NR	Mean HCH levels in water for various studies in 1999–2009	Zhang et al. (2013)
Turkey Konya Basin, 2012	Surface water	NR	March (µg/L): γ-HCH, 0.005–0.010 Total HCH, 0.015–0.065 August (µg/L): γ-HCH, ND–0.005 Total HCH, ND–0.025	March (µg/L): α-HCH, 0.005–0.010 β-HCH, 0.005–0.020 δ-HCH, ND–0.015 August (µg/L): α-HCH, ND–0.005 β-HCH, ND–0.005 δ-HCH, ND–0.025	Aydin et al. (2013)
Pakistan River Chenab, Punjab, January–March 2013	Water	3.3 ng/L (arithmetic mean)	0.33–11.9 ng/L		Mahmood et al. (2014)
Jordan Humrat Al-Sahn, 1998	Soil	NR	NR	Arithmetic mean, α-HCH (ppm): Ghor: 0.14; Wadi Um-Rishrash: 0.02; Wadi Al-Dafali: 0.02 Mean was of five replicates	Al-Mughrabi & Qrunfleh (2002)

Table 1.4 (continued)

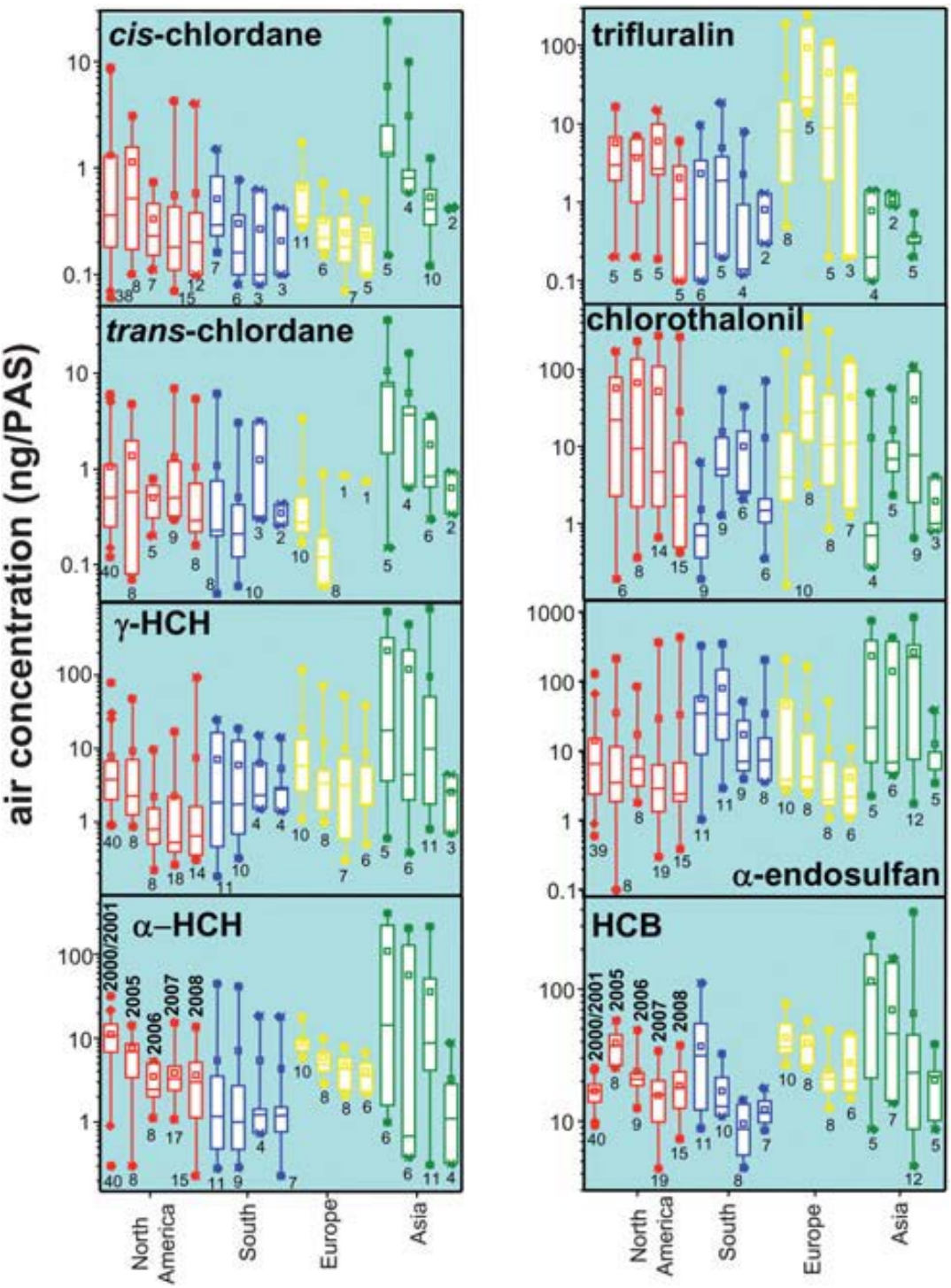
Region, country, city Year	Sampling matrix	Exposure		Comments	Reference
		Mean	Range		
China Hong Kong Special Administrative Region Year, NR	Soil	Arithmetic mean (μg/kg): Organic farm, 3.65 Agricultural, 10.50 Abandoned agricultural, 6.01 E-waste storage, 9.71 Container storage, 3.76 Metal recycling workshop, 1.39 Constructions waste, 3.81 Petrol station, 7.94 Open burning site, 2.89 E-waste dismantling workshop, 9.88 E-waste open burning site: 1.14 Car dismantling, 26.80	SD (μg/kg): Organic farm, 2.75 Agricultural, 36.90 Abandoned agricultural, 5.42 E-waste storage, 2.00 Container storage, 1.76 Metal recycling workshop, 0.89 Constructions waste, 2.39 Petrol station, 8.71 Open burning site, 3.43 E-waste dismantling workshop, 28.40 E-waste open burning site, 0.11 Car dismantling, 31.40		Man et al. (2011)
USA 1986–1991	Food	Arithmetic mean (μg/kg bw per day): Age, 6–11 months: γ-HCH, 0.0008; Age, 60–65 yrs: γ-HCH, 0.0006	NR	Mean levels for β-HCH; γ-HCH and α-HCH reported for age groups from 6–11 months to 60–65 yrs by sex Age, 6–11 months: β-HCH, < 0.0001 Age, 60–65 yrs: β-HCH, < 0.0001	Gunderson (1995)
China Beijing and Shenyang, 1970–2007	Food	Arithmetic mean, HCH (μg/kg bw per day): Age, 41–65 yrs: Beijing: 1970: 549; 1992: 26.8; 2005/2007: 1.66	Age 41–65 years: 1.66–549 μg/kg bw per day	Mean levels were reported for Beijing and Shenyang by time period and for five age groups	Yu et al. (2013)

Table 1.4 (continued)

Region, country, city Year	Sampling matrix	Exposure		Comments	Reference
		Mean	Range		
Sweden 2005	Food	Arithmetic mean, total HCH (ng/day): 2005, 70.5 1999, 81.0	NR	Levels reported for each of the five food groups in the article	Törnkvist et al. (2011)
Singapore City and year, NR	Ambient indoor air	Arithmetic mean (ng/g dust): γ-HCH, 2.9 Total HCH, 11	Range (ng/g dust): γ-HCH, < LOD–74 Total HCH, < LOD–240	α-HCH levels were highly correlated with γ-HCH Arithmetic mean (ng/g dust): α-HCH, 0.7 β-HCH, 2.2 δ-HCH, 5.5 Range (ng/g dust): α-HCH, < LOD–8.7 β-HCH, < LOD–57 δ-HCH, < LOD–170	Tan et al. (2007)

HCH, hexachlorocyclohexane; LOD, limit of detection; MDC, minimum detectable concentration; ND, not detected; NR, not reported; POPs, persistent organic pollutants

Fig. 1.1 Air concentrations of organochlorine pesticides (left) and current use pesticides (right) worldwide



Reproduced from Shunthirasingham et al. (2010). Spatial and temporal pattern of pesticides in the global atmosphere. J Environ Monit. 12(9):1650–7, with permission of The Royal Society of Chemistry
HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; PAS, passive air sampler

(b) Water

Lindane enters water from use in agriculture and forestry, from precipitation and, to a lesser extent, from occasional contamination of wastewater from manufacturing plants (WHO, 2004).

Early studies in the USA reported lindane levels in water. In Georgetown County, South Carolina, a mean lindane concentration of 1.19 ppt was reported in ground water (Achari et al., 1975). In 1970, potable water in Mississippi, USA, contained lindane at levels ranging between 1.3 and 2.9 ng/L (Brodtmann, 1976). In 1982, γ-HCH was detected in urban stormwater samples from Denver, Colorado, and Washington, DC, at 0.0027–0.1 µg/L and 0.052–0.1 µg/L in 20% and 11%, respectively, of the 86 samples collected (Cole et al., 1984; ATSDR, 2005). In the USA, α-, β-, γ-, and δ-HCH have been detected in surface water at 34, 18, 33, and 12, respectively, of the 1662 current or former National Priority Lists sites of the United States Environmental Protection Agency (EPA) (ATSDR, 2005). In the USA in 2001, γ-HCH was detectable in 1.6% and 4.4% of the samples from 83 sites in agricultural areas and from 30 urban sites, respectively (USGS, 2006).

Detectable γ-HCH levels in water have also been reported in the Middle East. In Israel, Lahav & Kahanovitch (1974) reported that γ-HCH levels ranged from non-detectable to 14.9 ng/L in well-water samples collected between 1972 and 1973. Lindane levels in water from the Nile Delta ranged from 0.286 to 0.352 µg/L between 1995 and 1997 (Abbassy et al., 1999). Surface water sampled in 2012 from the Konya Basin in Turkey contained total HCH at levels ranging from non-detectable to 0.065 µg/L, and γ-HCH at levels ranging from non-detectable to 0.010 µg/L (Aydin et al., 2013). Water samples taken monthly between 2009 and 2011 from the Karun river in Khuzestan Province, in the Islamic Republic of Iran, contained total HCH and γ-HCH at mean concentrations of 4.93 µg/L and 1.59 µg/L, respectively (Behfar et al., 2013).

In India, a review of historical and recent data indicated that surface water concentrations decreased three- to fourfold after the banning of production of technical HCH in 1997 (Sharma et al., 2014). In neighbouring Pakistan, the mean concentration of total HCH was 3.31 ng/L for water collected from the Chenab river between January and March 2013 (Mahmood et al., 2014). In southern China, mean HCH levels in surface water decreased from 285 to 1.43 ng/L between 1999 and 2009 (Zhang et al., 2013).

(c) Soil and dust

Lindane can be released into the soil from direct pesticide application, formulation processing, or release from hazardous landfill sites (ATSDR, 2005). In soil, lindane can be degraded under aerobic conditions; the half-life ranges from 88 to 1146 days. In the USA α-, β-, γ-, and δ-HCH have been detected in soil at 63, 78, 90, and 58, respectively, of the 1662 current or former National Priority List sites of the EPA (ATSDR, 2005).

Soil sampled in 1998 from Humrat Al-Sahn in Jordan contained α-HCH at mean levels ranging from 0.02 to 0.14 ppm (Al-Mughrabi & Qrunfleh, 2002). In Hong Kong Special Administrative Region, China, mean HCH levels ranged from 1.14 to 26.8 µg/kg in samples of soil from twelve different types of land use (Man et al., 2011). Elsewhere in China, mean levels of HCH in soil reported between 1999 and 2005 ranged from 3.65 to 5.92 ng/g dry weight (Zhang et al., 2013).

The presence of γ-HCH in household dust may contribute to human exposure; in a study in a household in the USA where γ-HCH in dust was measured at 5.85 ppb, a pesticide formulator and his wife had elevated serum concentrations of γ-HCH (ATSDR, 2005). In Singapore, indoor ambient dust samples from 31 homes contained γ-HCH and β-HCH at mean levels of 2.9 ng/g and 2.23 ng/g, respectively (Tan et al., 2007).

1.4.3 Exposure in the general population

(a) Diet

See Table 1.4

Isomers of HCH are found in dairy products, meat, fish, poultry, garden fruits, oils and fats, leafy and root vegetables, and sugar.

In adult diets in the USA in 1981–1982, γ-HCH was reported to be 8 ng/kg body weight (bw) (ATSDR, 1989). Data on the daily dietary intake of γ-HCH and β-HCH between 1986 and 1991 obtained through the Total Diet Study of the Food and Drug Administration (FDA) in the USA indicated very low levels. Mean intake of γ-HCH ranged from 0.8 to 0.6 ng/kg bw per day for the age groups 6–11 months and 60–65 years, respectively. Mean β-HCH levels were less than 0.1 ng/kg bw per day in all age groups (Gunderson, 1995).

A market basket survey in Sweden reported a dietary estimate of total HCH of 70.5 ng/day in 2005, a slight decrease from 81.0 ng/day in 1999 (Törnkvist et al., 2011).

Temporal trends suggest that dietary intake of HCH appears to be decreasing in China, where dietary intake of HCH has been reported from the 1970s until 2005/2007 across five age groups. The mean levels have shown a decrease for example in those aged 41–65 years in Beijing, from 549 μg/kg per day in the 1970s to 1.66 μg/kg per day in 2005/2007 (Yu et al., 2013).

(b) Biological measurements

See Table 1.5

Biological measurements of lindane in serum, human milk, adipose tissue, placental cord blood, and hair have been reported. In countries such as the USA, the percentage of samples with levels in the low detectable range has been increasing. Globally, the World Health Organization (WHO) has reported low mean levels of γ-HCH in breast milk samples from certain regions in Europe (WHO, 2015; Fig. 1.2).

(i) Europe

The detection of γ-HCH in samples from Europe has been decreasing since the 1970s. The median serum β-HCH concentration for a population of women participating in the Copenhagen City Heart Study, Denmark, decreased from 119.0 to 60.0 ng/g lipid between 1976–1978 and 1981–1983 (Høyer et al., 2000). In Norway, mean serum concentrations of β-HCH measured in women progressively decreased from 81.3 to 19.3 ng/g lipid from 1973–1975 to 1985–1990 (Fig. 1.3; Ward et al., 2000). The German Environmental Health Survey of environmental pollutants in blood quantified γ-HCH and β-HCH in 5.2% and 34% of blood samples in 1998 (Becker et al., 2002). In south-western Germany, the concentration of γ-HCH in whole blood samples from children was 0.07 μg/L in 1996/1997, while mean levels of β-HCH were 0.2, 0.07, and 0.04 μg/L in 1996/1997, 1998/1999, and 2000/2001 respectively. Reporting of γ-HCH and β-HCH was stopped in 1998/199 and 2000/2001, respectively, because levels were predominantly below the limit of detection (Link et al., 2005). In southern Spain, mean lindane concentrations in serum among women and young male volunteers were 1.53 ng/mL and 1.84 ng/mL, respectively (Botella et al., 2004; Carreño et al., 2007). Mean β-HCH concentrations were reported as 167.4 ng/g lipid (range, 155.8–179.9 ng/g lipid) from the European Prospective Investigation into Cancer and Nutrition (EPIC) Spanish cohort between 1992 and 1996 (Jakszyn et al., 2009). In the French National Nutrition and Health Study 2006–2007, γ-HCH was below detectable levels in serum, while the mean serum concentration of β-HCH was 27.0 ng/g lipid (Saoudi et al., 2014).

In Germany, two studies have shown a steady decrease in median β-HCH levels in human milk samples. Between 1986 and 1996, median β-HCH levels decreased from 0.19 to 0.03 mg/kg, while between 1999 and 2006 median β-HCH levels decreased by 0.04 to 0.012 mg/kg (Schade &

Table 1.5 Biological measurements of exposure to lindane (and other HCH isomers) in humans

Region, country, city Year	Sampling matrix	Mean	Range	Comments/ additional data	Reference
USA Wisconsin, Ohio and Michigan, 1993	Serum	Arithmetic mean: γ-HCH, ND β-HCH, 0.05 ppb	γ-HCH, ND β-HCH, 0.04–1.2 ppb		Anderson et al. (1998)
Mexico Mexico City, March 1994 and April 1996	Serum	Median β-HCH: Cases, 104.16 ng/g Controls, 92.98 ng/g	Cases, 53.29–418.54 ng/g Controls, 53.29–270.77 ng/g	95 cases of breast cancer and 95 controls	López-Carrillo et al. (2002)
USA Maryland, 1975–1994	Serum	Median β-HCH: Cases (NHL), 139 ng/g of lipid Controls, 138 ng/g of lipid	Cases, 71.1–286.5 ng/g lipid Controls, 56.9–219.3 ng/g lipid		Cantor et al. (2003)
New Zealand 1996–1997	Serum	Arithmetic mean: γ-HCH: NR β-HCH: 19.7 μg/kg lipid weight	γ-HCH: < 5–91.1 μg/kg lipid weight β-HCH: < 7–73.1	The mean value for γ-HCH was not calculated	Bates et al. (2004)
India Ahmedabad, year NR	Serum	Arithmetic mean (μg/L) γ-HCH: 1.69; α-HCH: 4.49; β-HCH: 35.06;	γ-HCH: 0.72–3.09 μg/L; α-HCH: 1.0–9.16; β-HCH: 20.11–82.09	Median: γ-HCH: 1.54; α-HCH: 3.62; β-HCH: 30.25	Bhatnagar et al. (2004)
Spain, southern, year NR	Serum	Arithmetic mean, lindane: 1.84 μg/L	SD: 2.27 μg/L	Median: 1.47 μg/L; maximum: 17.72 μg/L	Carreño et al. (2007)
Spain 1992–1996	Serum	Geometric mean, β-HCH (ng/g lipid) 167	155.8–179.9 ng/g lipid		Jakszyn et al. (2009)
Gran Canaria Island, Spain 1999–2001	Serum	Arithmetic mean, lindane (ng/g lipid): breast cancer women: 53.2; healthy women: 24.7	Breast cancer: 0.0–111.4; healthy: 0.0–220.0 ng/g lipid		Boada et al. (2012)
Slovakia, eastern, 2002–2004	Serum	Arithmetic mean (ng/mL) Maternal: β-HCH: 0.012; γ-HCH: 0.02; Infant cord blood: β-HCH:0.03; γ-HCH:0.01	SD (ng/mL) Maternal: β-HCH: 10.5; γ-HCH: 1.87; Infant cord blood: β-HCH: 10.4; γ-HCH: 4.67	The concentrations for most samples were higher than the detection limit except for γ-HCH	Patayová et al. (2013)
Benin Borgou, 2011	Serum	Arithmetic mean β-HCH (ng/g): 10.0	SD (ng/g): 20.4		Azandjeme et al. (2014)
USA 1999–2000	Serum	Arithmetic mean, γ-HCH (ng/g lipid): 0.06	< LOD–0.07 ng/g lipids	In subsequent studies of NHANES the levels of γ-HCH were undetectable	CDC (2009)

Table 1.5 (continued)

Region, country, city Year	Sampling matrix	Mean	Range	Comments/ additional data	Reference
France NR, 2006–2007	Serum	Geometric mean (ng/g lipid): γ-HCH: ND; α-HCH: 0.66; β-HCH: 30.4;	P50–P95: α-HCH: 0.74–1.77; β-HCH: 27.0–193.6; γ-HCH: < LOD–3.6 ng/g of lipid		Saoudi et al. (2014)
China Four cities (Beijing, Lanzhou, Taiyun, Xiamne), June–August 2010	Maternal and infant serum	Geometric mean β-HCH (ng/g lipid): Maternal, 67.67 Infant, 33.39	β-HCH (ng/g lipid): Maternal: < LOD–348.03 Infant; < LOD–261.29	Maternal: range, α-HCH: < LOD–8.83; γ-HCH, < LOD–4.24 Levels in infants cord blood and for other isomers were not measurable	Guo et al. (2014)
China Beijing, June 2006-July 2007	Placental and cord sera	Arithmetic mean (ng/g fat): Placenta: α-HCH, 0.85; β-HCH, 71.8; γ-HCH, 5.75; δ-HCH, 2.07; Umbilical cord blood: β-HCH, 97.0	Placenta: α-HCH: 031–1.57; β-HCH: 6.71–193; γ-HCH: ND–15.8; δ-HCH: ND–7.93; Umbilical cord blood: β–HCH: 9.12–336.0 ng/g fat	α-HCH, γ-HCH, and δ-HCH were not detectable in umbilical cord blood samples	Yu et al. (2013)
Spain Granada and Almeria Provinces, year NR	Serum and adipose tissue	Arithmetic mean, lindane serum: 1.56 (ng/mL) adipose tissue: 17.44 (ng/g lipid)	SD: serum, 17.84 ng/mL; adipose tissue, 2.26 ng/g lipid	Maximum levels reported for serum and adipose tissue were 12.77 ng/ mL and 113.31 ng/g lipid respectively	Botella et al. (2004)
South Africa year NR	Plasma	Geometric mean range (ng/g lipid): β-HCH: 2.4–10.6; γ-HCH: 1.4–1081	β-HCH: 1.6–44.3; γ-HCH: 150–896 ng/g lipid		Röllin et al. (2009)
South Africa KwaZulu-Natal, year NR	Plasma	Geometric mean, γ-HCH (ng/g lipid): 956	13–164 ng/g lipid	Mean, median, range values reported for three sites for γ-HCH; α -HCH, β-HCH	Channa et al. (2012)
Germany Baden-Wuerttemberg, 1996–2001	Whole blood	Arithmetic mean (μg/L): 1996/1997: β-HCH: 0.2; γ-HCH: 0.07; 1998/1999: β-HCH: 0.07; 2000/2001: β-HCH: 0.04	1996/1997: β-HCH: < 0.02–4.75; γ-HCH: < 0.02–1.38; 1998/1999: β-HCH: 0.02–0.51; 2000/2001: β-HCH: < 0.02–0.62 μg/L	Concentrations of γ-HCH were predominantly less than the detection limit of 0.02 μg/L and stopped in 1998/1999 Concentrations of β-HCH dropped to the detection limit in 2000/2001	Link et al. (2005)

Table 1.5 (continued)

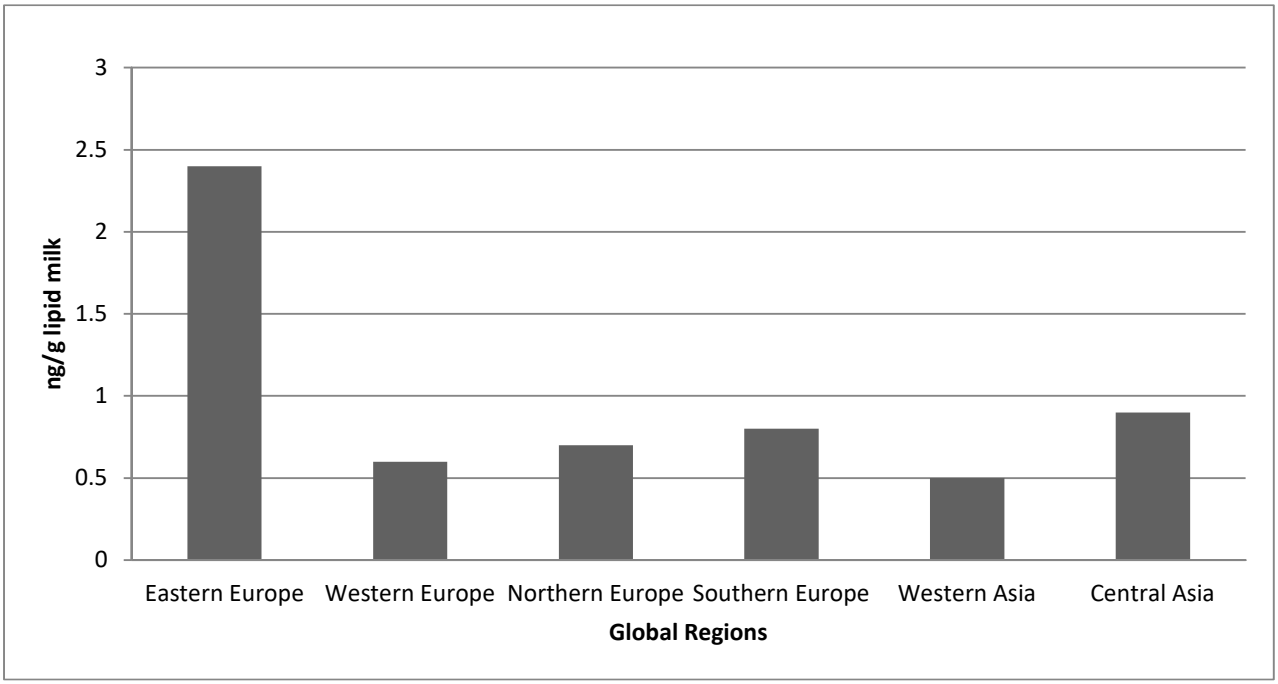
Region, country, city Year	Sampling matrix	Mean	Range	Comments/ additional data	Reference
Germany 1998	Whole blood	Arithmetic mean (μg/L) α-HCH: < 0.1; β-HCH: 0.16; γ-HCH: < 0.1	P50–Max: α-HCH: < 0.1–0.4; β-HCH: < 0.1–7.8; γ-HCH: < 0.1–4.7 μg/L	The percentage of β-HCH concentrations above the limit of quantification (0.1 μg/L) increased with age from 8.6% to 72%	Becker et al. (2002)
China year, NR	Placenta	Median (ng/g lipid): Cases: α-HCH: 1.5, β-HCH: 39, γ-HCH: 1.6, total HCH: 44; Controls: α-HCH: 0.96, β-HCH: 33, γ-HCH 0.99, total HCH: 36	Cases (ng/g lipid): α-HCH: 0.99–2.2, β-HCH: 13–65, γ-HCH: 0.7–2.7, total HCH: 18–71; Controls (ng/g lipid): α-HCH: 0.57–1.4, β-HCH: 22–52, γ-HCH: 0.55–1.7, total HCH: 24–56		Ren et al. (2011)
USA Connecticut, year NR	Breast adipose tissue	Median, β-HCH: Cases: 27.1 ppm; controls: 25.2 ppm	Cases: 16.1–41.6 ppm; controls: 16.3–41.2 ppm	Age-adjusted geometric mean: cases, 27.1; controls, 26.3	Zheng et al. (1999)
USA Connecticut, 1994–1997	Breast adipose tissue	Geometric mean, β-HCH: Cases: 27.1 ppm; controls: 26.3 ppm	NR	Median: Cases: 27.1 (16.1–41.6) ppm; controls, 25.2 (16.3–41.2) ppm	Zheng et al. (1999)
Germany Schleswig-Holstein, 1986–1997	Breast milk	Median, β-HCH: 1986: 0.19 mg/kg; 1997: 0.03 mg/kg	NR	NR	Schade & Heinzow (1998)
Tunisia 2003–2005	Breast milk	Arithmetic mean, γ-HCH: 31 ng/g lipid	SD (ng/g lipid): 17.5; range (ng/g lipid): ND–125.7		Ennaceur et al. (2008)
Germany Lower Saxony, January 1999-December 2006	Breast milk	Arithmetic mean (mg/kg lipid): γ-HCH: 0.001 β-HCH: 0.02	SD (mg/kg lipid): γ-HCH: 0.003 β-HCH: 0.05	Median β-HCH levels decreased 47.1% from 1999 to 2006	Zietz et al. (2008)
Japan Kyushu Island, May 2007-March 2008	Breast milk	Median lindane: 28.3 ng/g lipid	4.5–253 ng/g lipid		Miyake et al. (2011)
Islamic Republic of Iran November 2007-January 2008	Hair	Arithmetic mean, HCH: 14 ng/g	ND–67 ng/g	α-HCH, β-HCH, γ-HCH levels reported for three different sites	Dahmardeh Behrooz et al. (2012)
Tunisia Bizerte, 2010	Breast milk	Arithmetic mean, lindane: 36.5 ng/g lipid wt	ND–125.7 ng/g lipid wt	Median, 27.2 ng/g lipid wt	Ben Hassine et al. (2012)

Table 1.5 (continued)

Region, country, city Year	Sampling matrix	Mean	Range	Comments/ additional data	Reference
Turkey Ankara, year NR	Breast milk	Arithmetic mean (ng/g lipid wt): γ-HCH: 3.1; α-HCH: 7.3; β-HCH: 76.2	γ-HCH: < LOD–42.3 ng/g lipid wt; α-HCH: < LOD–88.7; β-HCH: < LOD–427.6	SD: γ-HCH, 9.0; α-HCH, 16.7; β-HCH, 96.7	Yalçin et al. (2014)
Denmark Copenhagen, 1976–1983	Serum	Median, β-HCH (ng/g lipid): 1976–1978: 119.0; 1981–1983: 60.0	NR	In 353 women, concentrations of β-HCH decreased between 1976–1978 and 1981–1983; in 61 women the β-HCH concentration increased for this period	Høyer et al. (2000)
Norway 1973–1990	Serum	Arithmetic mean, β-HCH (ng/g lipid) Cases, 63.4; controls: 60.0	NR	300 study subjects recruited, but 144 samples had > 90 pesticide compounds above the LOD and were used for analysis	Ward et al. (2000)
Guinea-Bissau 1990–2007	Serum	NR	γ-HCH: 240–< LOD; β-HCH: 320–< LOD ng/g fat	Samples were divided into five age groups and β-HCH; γ-HCH concentrations were reported for each group per time period	Linderholm et al. (2010)

HCH, hexachlorocyclohexane; LOD, limit of detection; NR, not reported

Fig. 1.2 Concentrations of γ-HCH in human milk, by region



Arithmetic mean concentrations (ng/g lipid) of γ-HCH in human milk in the following regions: eastern Europe: Bulgaria, Czech Republic, Hungary, Republic of Moldova, Russian Federation, Slovakia, Ukraine; western Europe: Belgium, Germany, Luxembourg, Switzerland; northern Europe: Ireland, Lithuania, Norway, Sweden; southern Europe: Italy, Spain; western Asia: Cyprus, Georgia, Israel; central Asia: Tajikistan
HCH, hexachlorocyclohexane
Compiled by the Working Group with data from WHO (2015)

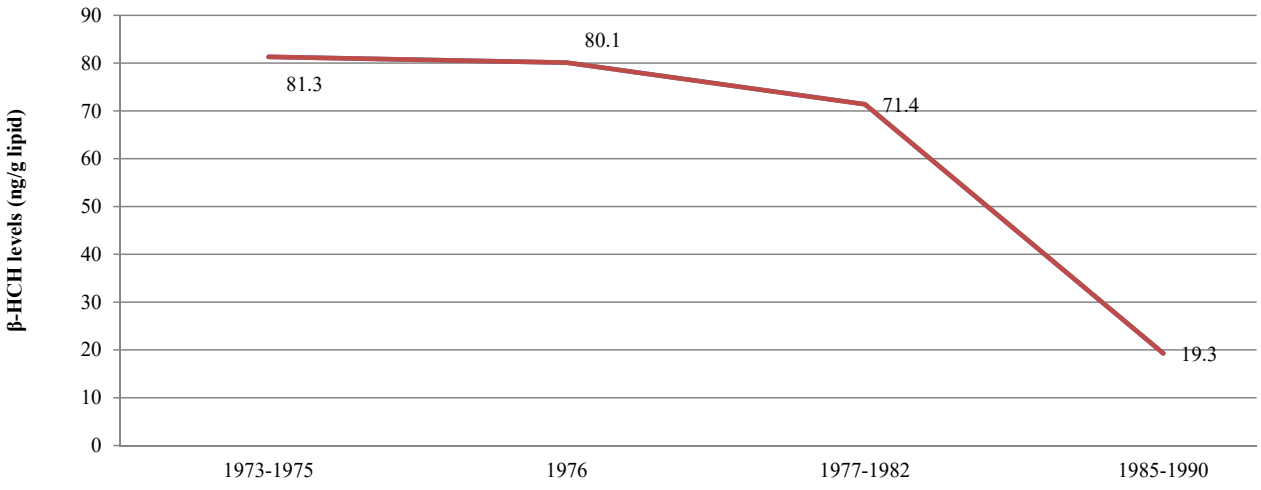
Heinzow, 1998; Zietz et al., 2008). In breast milk samples from 75 mothers in Ankara, Turkey [year not reported], α-HCH, β-HCH, and γ-HCH were reported at mean concentrations of 7.3, 76.2, and 3.1 ng/g lipid weight, respectively (Yalçin et al., 2014).

In Slovakia, between 2002 and 2004, mean levels of β-HCH and γ-HCH in maternal serum and cord-blood samples from infants were 0.12, 0.03, and 0.02, 0.01, respectively. In most samples, γ-HCH was below the limit of detection (LOD) (Patayová et al., 2013).

(ii) The Americas

In Mexico City, Mexico, between March 1994 and April 1996, serum levels of β-HCH levels ranged from 53.3 to 418.5 ng/g (López-Carrillo et al., 2002). In the USA, levels of γ-HCH in the general population have decreased since the 1970s. In a cohort started in 1974 in Maryland, USA, the levels of serum β-HCH among participants in the CLUE I study ranged from 56.9 ng/g lipid in controls to 286.5 ng/g lipid in cases (Cantor et al., 2003). In 1993, a study of the profiles of the Great Lakes critical pollutants reported non-detectable levels of γ-HCH and a median level of 0.05 ppb (range, 0.04–1.2 ppb) for β-HCH in serum from a convenience sample of 32 participants (Anderson et al., 1998). Between 1994 and 1996 in Long Island, New York, the mean concentrations of β-HCH in adipose tissue and serum were reported as 22.21 ng/g lipid and 0.824 ng/mL, respectively (Stellman et al., 1998). Between 1999 and 2000, the mean β-HCH serum level reported from the NHANES study in the USA was 0.058 ng/g, while γ-HCH was below detection limits from 1999 onwards (CDC, 2009).

Fig. 1.3 Temporal trends in organochlorine levels (as reflected in β-HCH concentrations) in serum samples from Norwegian women, 1973–1990



HCH, hexachlorocyclohexane
Compiled by the Working Group with data from Ward et al. (2000)

(iii) Asia and Oceania

Studies in Asia and Oceania have reported levels of lindane, γ-HCH, and β-HCH in samples of serum, human milk, and placental cord blood and tissue.

A mean serum γ-HCH level of 1.69 μg/L was reported among volunteers in Ahmedabad, India, in 2004 (Bhatnagar et al., 2004). Between December 1996 and January 1997, serum analysis from the National Nutrition Survey in New Zealand reported a weighted mean concentration of 19.7 μg/kg lipid weight basis for β-HCH in adults (Bates et al., 2004).

Levels of β-HCH in human milk in a population in Japan studied between 2007 and 2008 ranged from 18.3 ng/g to 45.3 ng/g (Miyake et al., 2011).

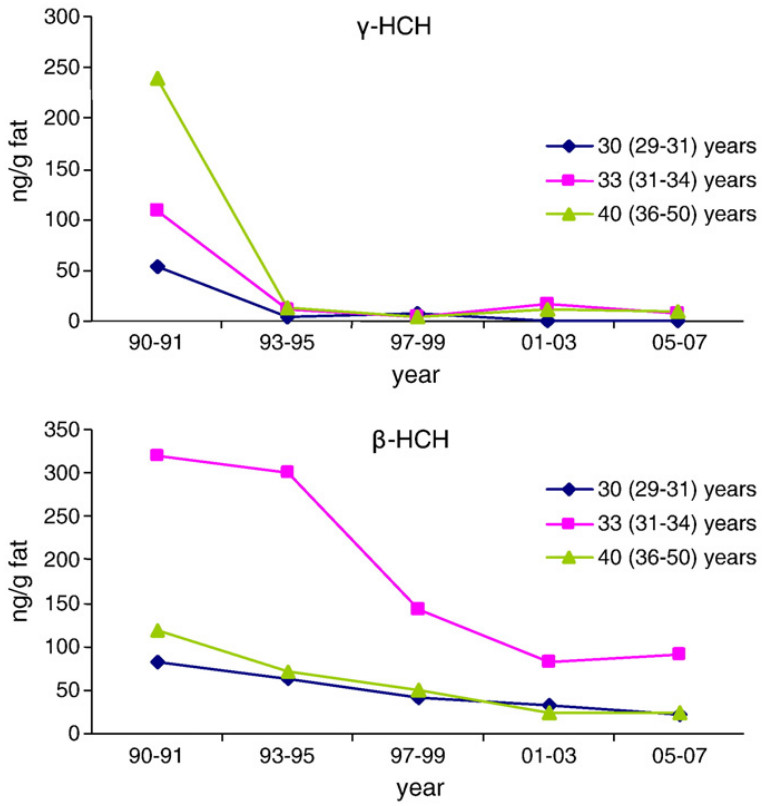
In samples of placental tissue in China, lindane levels ranged from 18 to 56 ng/g (Ren et al., 2011). In Beijing between June and July 2006, analysis of placental samples showed mean levels of α-HCH, β-HCH, and γ-HCH of 0.85, 71.8, and 5.75 ng/g fat, while in cord blood there was a mean β-HCH level of 97.0 ng/g fat and all other isomers were undetectable (Yu et al., 2013). Studies in four Chinese cities in 2010 reported levels of γ-HCH in most samples as below detectable limits in maternal blood and none in the cord blood samples while mean β-HCH levels in maternal and cord blood samples were 67.7 ng/g lipid and 33.4 ng/g lipid, respectively (Guo et al., 2014).

(iv) Africa and the Middle East

In various sites in South Africa, mean levels of γ-HCH in plasma ranged from 150 to 896 ng/g lipid (Röllin et al., 2009). In 2011 in north-eastern Benin, the mean serum level of β-HCH was reported as 10.0 ng/g total serum lipids (Azandjeme et al., 2014). In KwaZulu-Natal, South Africa, in 2008 the mean plasma level of γ-HCH was 956 ng/g (Channa et al., 2012).

In Guinea-Bissau, a cohort study conducted in 1990–2007 among men in the general population, with sampling at five different periods, showed a distinct decrease in concentrations of γ-HCH (240 ng/g fat to < LOD) and β-HCH

Fig. 1.4 Concentrations of γ-HCH and β-HCH in three pooled serum samples from Guinea-Bissau, sampled on five occasions between 1990 and 2007



The median and range of age corresponds to the first sampling occasion
HCH, hexachlorocyclohexane
Reprinted from *Environment International*, Volume 36, issue 7, Linderholm et al. (2010). Human exposure to persistent organic pollutants in West Africa — A temporal trend study from Guinea-Bissau, Pages No. 675–682, Copyright (2010), with permission from Elsevier

(320 ng/g fat to < LOD). There was a clear decrease between the first sampling period (1990–1991) and the second sampling period (1993–1995) (Fig. 1.4; Linderholm et al., 2010).

In breast milk samples from Tunisia, the mean concentration of γ-HCH was reported as 31 ng/g lipid in samples from 237 women between 2003 and 2005 (Ennaceur et al., 2008), while a mean lindane level of 36.5 ng/g lipid was reported in a study in 2010 (Ben Hassine et al., 2012).

In the Islamic Republic of Iran between November 2007 and January 2008, hair samples from women contained γ-HCH at a mean concentration of 14 ng/g (Dahmardeh Behrooz et al., 2012).

1.4.4 Exposure assessment in epidemiological studies on lindane

Eight epidemiological studies were evaluated as providing evidence for carcinogenicity of lindane to humans. These studies can be categorized as studies of occupational exposure involving farmers and/or commercial applicators, and studies based upon the general population with exposure assessed using questionnaires or biological assessments. Among

these studies, three were based on β-HCH as a marker for exposure to lindane, three on lindane exposure, and two were based on exposure to a commercial product that consisted of technical HCH or γ-HCH, depending on the time period. We here provide an assessment of the strengths and weaknesses of the exposure assessment and assignment methods used in these studies.

(a) Occupational exposure

One study of occupational exposure involved lindane specifically (Alavanja et al., 2014a), while the other two assessed exposure to a combination of technical HCH and γ-HCH over time (Rafnsson, 2006a, b).

The Agricultural Health Study (AHS) examined exposure to lindane among farmers and commercial applicators based on retrospective reporting of ever use and duration and frequency of use of 50 pesticides, including lindane. The exposure assessment methodology of the AHS is described in more detail in the *Monograph* on DDT in the present volume.

[The Working Group noted that the AHS has collected detailed information on pesticide use and practices and validation studies have shown this data to be appropriate for estimating historical exposure to pesticides. However, the validity studies are based on information reported at the time of the exposure surveys and would not necessarily reflect the recall of information reported for all aspects, in particular frequency and duration of use. The assessment of lindane exposure is based on the baseline questionnaire (1993–1997) and relies on recollection. The validity of such recall is unknown, but is not necessarily better or worse than that concerning other pesticides.]

In the other two studies of occupational exposure, exposure to technical-grade HCH and γ-HCH in sheep farmers in Iceland was estimated using records from the Icelandic Veterinary Services, in which the time of the sheep dipping using the pesticide, and the number of sheep owned by the farmer were recorded. The farmer was responsible for mixing the dip, dipping the sheep, and scrubbing the inside of the sheep shed. No advice was given to farmers on the use of personal protective equipment. The number of dipped sheep was used as a proxy of exposure. There was no assessment of additional sources of exposure in this study population (Rafnsson, 2006a, b). The authors indicated that parts of some records were incomplete for certain communities, and that farmers having small numbers of sheep may not have dipped the sheep themselves.

[The Working Group noted that due to the incompleteness of records, the fact that not all farmers were personally involved in dipping could result in exposure misclassification. The main assumption in the exposure assessment of lindane in this study was that the number of sheep dipped is directly related to lindane exposure. In the sheep-dipping process as described in other locations, three events involving exposure can be distinguished: mixing, dipping, and cleaning. Dipping consists of bodily grasping the sheep and plunging the animal in the dip. In an exposure study on organophosphate exposure during sheep dipping in the United Kingdom, Buchanan et al. (2001) identified contact with the pesticide concentrate that occurs during mixing as the most important exposure determinant. Furthermore, people involved in plunging the sheep were more highly exposed than those responsible for throwing or guiding the sheep into the dip. Such exposure to the concentrate is not directly related to the number of sheep, but more directly related to the number of dipping events. The papers did not indicate whether farmers had help in the dipping tasks or performed the dipping themselves. Consequently, the assumption that only the farmer was involved might be questioned.

The two papers under consideration indicated that dipping infested sheep required a longer time (3 minutes) than dipping non-infested sheep (1 minute), but the number of infested versus non-infested sheep per individual farmer

was not recorded. Reliance upon the number of sheep dipped as an indicator of exposure assumes an average similar infestation rate of sheep for all farmers and over calendar time. An additional complication is that technical-grade HCH was used for dipping between 1962 and 1970, and was substituted by lindane between 1970 and 1980. Taking these issues together, there is uncertainty regarding the level of lindane exposure, potentially leading to substantial exposure misclassification. Considering that the median of the exposure categories based on the number of sheep owned varied only by a factor of ~8, this could have resulted in substantial misclassification across the exposure categories.]

(b) General population

Among five studies assessing exposure among the general population, two were based on lindane and three were based on β-HCH.

(i) Questionnaire-based approaches

In a study by Blair et al. in the midwest USA, three different questionnaires were used, and these varied in terms of information collected on pesticide use (Blair et al., 1998). [The Working Group noted that studies based on self-reporting are prone to failures of recall and resulting exposure misclassification. Due to the absence of separate evaluations of recall and exposure assignment, the validity of the exposure determination used in this study is not known.]

(ii) Biomonitoring approaches

All of the biomonitoring studies relied upon measurement of β-HCH levels. In one of the studies (Ward et al., 2000), occupational category was also documented, but this did not provide any additional information on exposure. In the other studies, occupational information was not collected.

[The Working Group noted that the validity of using β-HCH as a proxy of lindane depends on the extent to which the two exposures are actually related and a simple equivalence cannot be assumed. In fact, apart from lindane, exposure to β-HCH can occur through the diet, through contact with other environment media, and through other products containing β-HCH (i.e. technical-grade HCH). Accordingly, the extent to which the β-HCH is indicative of lindane will depend on the specific exposure scenario and calendar time the biological sample was collected.]

1.5 Regulation

Most readily available information concerning the regulation of lindane was concerned with action to limit or eliminate usage of this pesticide in various jurisdictions (Weinhold, 2001). Current regulatory controls concerning lindane and other pesticides are briefly listed below.

1.5.1 International treaties and agreements

A summary of earlier international treaties and like measures concerning lindane has been prepared by the Commission for Environmental Cooperation (CEC, 2006), an authority based on collaboration between the countries of North America.

Lindane is listed in Annex III of the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade, adopted in February 2004 and legally-binding for Parties. Among the Parties to the Convention, 34 countries have banned all import of lindane, and 38 have restricted or severely restricted the conditions under which it may be imported (Rotterdam Convention, 2004).

Lindane is further regulated under the Stockholm Convention on Persistent Organic Pollutants (for further information about the Stockholm Convention, see Section 1.5 of the *Monograph* on DDT in this volume). As of December 2014, the Stockholm Convention

Secretariat had received three registrations of specific exemptions for allowable uses of lindane applicable in Canada, and Hong Kong and Macao, Special Administrative Regions, China, as described in Annexes A and B of the Convention (UNEP, 2002). Acceptable purposes for use of lindane are restricted to that of a human health pharmaceutical, adjuvant therapeutic drug, for control of head lice and scabies as second-line treatment (Vijgen et al., 2011).

WHO has specified a guideline value for water contamination by lindane of 2 µg/L (WHO, 2004).

1.5.2 Transnational and national regulations

Lindane is banned for use in 52 countries, restricted or severely restricted in 33 countries, not registered in 10 countries, and registered in 17 countries (CEC, 2006, 2015). In the USA, lindane was registered as an agricultural insecticide in the 1940s, and as a pharmaceutical in 1951. It was regulated as a pesticide by the EPA (EPA, 2015a, b), while lindane medications are regulated by the FDA (FDA, 2015). The EPA gradually began restricting its agricultural use in the 1970s. By 2002, use of lindane was limited to seed treatments for six crops, and finally banned in 2007. Under FDA regulation, a 1% γ-HCH lotion is available for the treatment of scabies, and a 1% shampoo is available for the treatment of head lice (CEC, 2006).

In Europe, the European Commission supported withdrawal of approval of lindane as an active substance (European Commission, 2000a, b) for plant protection products. In 2004, the European Parliament adopted Regulation 850/2004 that bans production and use of 13 persistent organic pollutants (European Commission, 2004). For lindane, the regulation allowed member states a phase-out period until December 2007. As assessed in 2006, several countries in Europe still allowed restricted use of lindane (CEC, 2006).

Maximum residue limits for lindane in various foods, particularly crops, are specified under many national and other authorities. As a persistent organic pollutant, lindane is recognized as a water contaminant and subject to regulation by transnational, national, and state or local authorities.

The United States Occupational Safety and Health Administration specifies permissible exposure limits for lindane of 0.5 mg/m^3 (time-weighted average) for general, construction and maritime industries (OSHA, 2017).

2. Cancer in Humans

This section reviews cohort and case–control studies that assessed exposure to lindane or β-HCH and cancer. Although lindane is the gamma isomer of hexachlorocyclohexane (γ-HCH), commercial lindane products may include other isomers, including the β form, which has a longer half-life; in addition, technical-grade HCH containing the γ-isomer and several other isomers has reportedly been used as an insecticide (see Section 1). Studies of cancer using biological measurements of β-HCH as an indicator of exposure to lindane are therefore included in this review, reflecting the Working Group's judgment that the level of exposure to β-HCH could be a proxy indicator of such exposure.

2.1 Cohort studies

See Table 2.1

Using the IARC International Register of Workers Exposed to Phenoxy Herbicides and Their Contaminants, Kogevinas et al. (1995) observed that exposure to lindane was associated with an excess risk of non-Hodgkin lymphoma (NHL), with an odds ratio (OR) of 1.6 (95% confidence interval [CI], 0.3–8.8).

Table 2.1 Cohort studies of cancer and exposure to lindane

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kogevinas et al. (1995) Australia, Canada, Europe, New Zealand, 1955 to 1991 Nested case–control study	Cases: 32 NHL, 11 sarcoma; cohort data linked to death certificates and cancer registration records Controls: 158 (NHL controls), 55 (sarcoma controls); selected from cohort, matched to each case by age, sex, and country of residence at time of employment Exposure assessment method: company records; exposure information on qualitative scale, based on departments worked	NHL	Lindane	NR	1.6 (0.3–8.8)	Age, sex, country of residence when employed	Strengths: examined cancer incidence Limitations: no quantitative exposure information
Cantor et al. (2003) Washington County, ML, USA; CLUE study 1974 enrolment/ follow-up to 1994 Nested case-control	Cases: 74 incident cases identified from Washington County Cancer Registry for participants from CLUE I or II cohort Controls: 147 controls, 2 per case matched on race, sex, date of birth (within 1 yr), participation in CLUE I or II or private census in 1963–75, date of blood sample (within 15 days), location of stored serum Exposure assessment method: total lipid corrected serum values	NHL (ICD-8, 200 202)	β-HCH (ng/g lipid): 0.0–84.9 85.6–138.0 138.7–177.3 179.4–302.0 Trend-test *P*-value, 0.96	 12 25 12 25	 1.0 3.0 (1.1–8.4) 1.0 (0.3–3.2) 1.5 (0.5–4.3)	Ever smoked or currently smoking cigarettes, years of education (< 12, ≥ 12), EBV-EA seropositivity, quartile of PCB concentration	Strengths: most cases pathologically confirmed; serum collected pre-diagnosis.; laboratory analysis blind to case-control status Limitations: evidence of possible exposure measurement error

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rafnsson (2006a) Iceland Follow-up, 1955–2003	7882 men (213 685 person-yrs), 429 women (10 439 person-yrs); sheep farmers in Iceland Exposure assessment method: records of sheep dipping is kept by the Icelandic Veterinary Services; population-based cancer registry	Lip	Men	41	1.50 (1.08–2.04)		Strengths: complete paper records for 1962–1980; population based cancer registry Limitations: comparison of cancer incidence among sheep farmers with the general population controlled for age only
			Women	2	9.09 (1.02–32.82)		
		Liver and gallbladder (155)	Men	26	0.71 (0.46–1.04)		
			Women	1	0.48 (0.01–2.66)		
		Trachea, bronchus and lung (162)	Men	137	0.54 (0.46–0.64)		
			Women	8	0.77 (0.33–1.52)		
		NHL (200–202)	Men	45	0.90 (0.66–1.21)		
			Women	2	1.04 (0.12–3.76)		
		All cancers combined	Men	1818	0.79 (0.76–0.83)		
			Women	77	0.72 (0.57–0.90)		
		Prostate (all cases)	Men	541	0.92 (0.85–1.00)		
Rafnsson (2006b) Iceland 1962–2003 Nested case–control	Cases: 45; Iceland population-based cancer registry Controls: 221; sample of registered sheep farmers in Iceland Exposure assessment method: paper records on sheep dipping from the Icelandic Veterinary Service	NHL	No. of sheep:			Age, period of birth (< 1910; 1910–1919; 1920 and later)	Strengths: longstanding programme of sheep dipping with lindane; precise estimates of numbers of sheep Limitations: occupational exposures other than lindane were not ascertained; personal habits and medical histories were not available
			3–99	8	1.00		
			> 100	37	3.86 (1.59–8.53)		
			100–199	22	3.83 (1.58–9.31)		
			200–683	15	3.44 (1.31–9.04)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Alavanja et al. (2014b) Iowa, North Carolina, USA 1993–2010	54 306 licensed pesticide applicators Exposure assessment method: questionnaire; population-based cancer registries	NHL	Lindane use: None Ever Total days of lindane exposure: None Low [≤ 8.75] Medium [> 8.75–56] High [> 56–457.25] Trend-test *P*-value, 0.004	 396 85 205 18 13 14	 1.0 1.0 (0.8–1.2) 1.0 1.2 (0.7–1.9) 1.0 (0.6–1.7) 2.5 (1.4–4.4)	Age, state, race, total days of herbicide use	Strengths: large prospective study, ascertainment of exposure before disease;, large number of lindane exposed participants
Mills & Yang (2003) California, USA 1988–1999 Nested case–control	Cases: 222 prostate cancers, resulting from a linkage between UFW union rosters and the population-based California cancer registry Controls: 1110 non-cancer members selected from the UFW union roster Exposure assessment method: California pesticide application records	Prostate	Lindane exposure 1 (low) High Level 2 Level 3 Level 4 (high) Trend-test *P*-value, 0.003	 93 129 49 47 33	 1.00 1.32 (0.88–1.96) 1.14 (0.45–1.77) 1.86 (1.10–3.17) 2.37 (1.12–4.61)	Age, date of first union membership, and duration of union affiliation	Strengths: workers with relatively high exposure to pesticides; cases and controls from the same population Limitations: econological exposure assessment method with potential for bias towards the null

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sawada et al. (2010) Japan enrolment, 1990-1994/follow up to 2005 Nested case–control	Cases: 201 incident cases identified from local hospitals, population-based cancer registries and death certificates, from the cohort of residents of public-health centre areas in Japan Controls: 402, matched by age, area of residence, date time of day, and duration of fasting before blood collection Exposure assessment method: personal monitoring; blood samples taken at baseline	Prostate	β-HCH (ng/g lipid) < 200 200–319 320–519 ≥ 520 Trend-test *P*-value, 0.05	 52 50 56 43	 1.00 0.89 (0.52–1.50) 0.85 (0.50–1.46) 0.56 (0.30–1.01)	Smoking status, alcohol consumption, marital status, BMI, intake of green tea, intake of green tea and miso soup	Strengths: pre-diagnosis blood samples Limitations: response rate not known
Koutros et al. (2013) Iowa and North Carolina, USA Enrolment, 1993–1997/ follow-up to 31 December 2007	54 412 male pesticide applicators Exposure assessment method: questionnaire	Prostate (all cases)	Lindane exposure: No exposure Q1 Q2 Q3 Q4 Trend-test *P*-value, 0.33	 840 43 36 39 39	 1.00 0.88 (0.63–1.23) 1.06 (0.76–1.49) 1.06 (0.76–1.48) 1.16 (0.84–1.60)	Age, state, race, family history of prostate cancer, smoking, fruit servings, and leisure-time physical activity in the winter	Agricultural Health Study Strengths: large cohort study, in agricultural population with high exposure prevalence; detailed exposure assessment

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
McGlynn et al. (2008) USA 1988–2003 Nested case–control	Cases: 739 cases identified among men who donated blood between 1 January 1987 and 31 December 2002 to the DoDSR Controls: 915 controls matched on birth year, race/ethnicity, and date of available serum sample (within 30 days) Exposure assessment method: personal monitoring	Testis (testicular germ cell tumours)	β-HCH (μg/g lipid) ≤ 0.00582 0.00583–0.00804 0.00805–0.0115 > 0.0115 Trend-test *P*-value, 0.4	 306 160 125 143	 1.00 1.05 (0.80–1.40) 0.82 (0.60–1.11) 0.90 (0.65–1.24)	Age at blood donation, ethnicity, date of serum draw, age at reference date, cryptorchidism, family history of testicular cancer, height, BMI	Strengths: large study size; analysis of pre-diagnostic serum samples; high response rate; histologically confirmed tumours Limitations: some participants could not be contacted due to military deployment; adjustment for self-reported BMI; multiple comparisons
Purdue et al. (2009) Norway Enrolment, 1972/follow up, 1978–1999 Nested case–control	Cases: 49 members of the Janus serum bank cohort identified through linkage with the Norwegian cancer registry Controls: 51 matched to by region, period of and age at blood draw Exposure assessment method: personal monitoring; median (range) among controls: β-HCH, 129.7 (59.7–295.9) ng/g lipid; γ-HCH, 6.4 (0.1–42.4) ng/g lipid	Testis Testis	β-HCH tertile 1 β-HCH tertile 2 β-HCH tertile 3 γ-HCH tertile 1 γ-HCH tertile 2 γ-HCH tertile 3	15 13 21 17 15 17	1.0 1.0 (0.4–2.7) 1.8 (0.5–6.1) 1.0 1.0 (0.3–3.1) 1.1 (0.2–5.0)	None (conditional logistic regression; matching criteria region/ age at blood draw/period of blood draw)	Strengths: use of serum samples collected before diagnosis; completeness of the Norway Cancer Registry Limitations: small study size

BMI, body mass index; CLUE, Campaign Against Cancer and Stroke; DoDSR, Department of Defense Serum Repository; DDT, dichlorodiphenyltrichloroethane; HCH, hexachlorocyclohexane; IQR, interquartile range; EBV-EA, Epstein-Barr virus early antigen; NHL, non-Hodgkin lymphoma; NR, not reported; PCB, polychlorinated biphenyl ; Q, quartile; UFW, United Farmer Workers

In the Clue I and II studies (Cantor et al., 2003), γ-HCH and β-HCH, were measured in serum samples for 74 cases of NHL and 147 matched controls. Data for γ-HCH were not reported as this isomer was detected in < 5% of samples. The concentration of β-HCH was significantly elevated among cases compared with controls. There was no clear pattern of risk with increasing quartile of lipid-corrected and recovery-adjusted level of exposure, with the highest odds ratio being in the second quartile for both unadjusted and adjusted (OR, 3.0; 95% CI, 1.1–8.4) analyses. [In this study most cases were confirmed from pathology information and serum was collected pre-diagnosis. The levels obtained for some compounds such as polychlorinated biphenyls and lindane were higher than expected, which may imply that there was some measurement error.]

A cohort (Rafnsson, 2006a) and nested case–control study (Rafnsson, 2006b) of sheep owners in Iceland provided additional, albeit indirect, evidence to evaluate the association between lindane and NHL. Sheep dipping with lindane formulations was compulsory in Iceland after 1959 to prevent ectoparasites, mainly sheep scab mites. Initially, technical-grade HCH (a mixture of isomers) was used. In the 1970s, technical-grade HCH was replaced by γ-HCH (lindane). A paper record of compliance with this law was available from 1962 to 1980 through the Icelandic Veterinary Services and was used as a surrogate measure of exposure to lindane.

The cohort (Rafnsson, 2006a) comprised 7882 men (213 685 person-years of follow-up) and 429 women (10 439 person-years). Observed and expected cancer cases were compared in an analysis of standardized incidence ratio (SIR), adjusted for age and calendar period. The standardized incidence ratio for all cancers was significantly less than expected for men (SIR, 0.79; 95% CI, 0.76–0.83) and women (SIR, 0.72; 95% CI, 0.57–0.90). Cancer of the lip was the only cancer found at a significantly greater rate than expected; the standardized incidence ratio was 1.5 (95% CI, 1.08–2.04) for men, and 9.09 (95% CI, 1.02–32.82) for women. All other standardized incidence ratios were not statistically significant. The standardized incidence ratio for NHL in men was 0.90 (95% CI, 0.66–1.21; 45 cases) and in women 1.92 (95% CI, 0.12–3.76; 2 cases).

In the nested case–control study (Rafnsson, 2006b), 45 histologically confirmed cases of NHL (International Classification of Disease seventh revision), in men diagnosed in 1962–2003 were recorded in the national cancer registry. A total of 221 cancer-free men sampled at random from the cohort served as controls. The age-adjusted odds ratio for NHL was 3.86 (95% CI, 1.59–8.53) for individuals who had 100 sheep or more compared with those who had less than 100 sheep. No analysis of risk in relation to the period of exposure was conducted. [The overall decreased cancer risk of sheep farmers in Iceland was consistent with findings reported previously among farmers in Iceland and in other countries. The excess risk of cancer of the lip found in this study has been observed in many previous studies of farmers and is usually attributed to long periods of unprotected occupational exposure to solar radiation. The disparity between the results of internal and external analysis may be attributed to more complete controlling for disparities in cancer determinants among farmers. The Working Group noted that the exposure metric used in this study, specifically the number of sheep, could lead to misclassification of the level of lindane exposure, but would likely not have materially affected the exposure rank order.]

In the USA, the AHS considered incident cases of NHL among more than 54 000 study participants who were free of cancer at the time of enrolment (Alavanja et al., 2014a). A history of lindane use was reported for 85 cases of NHL before onset of disease. Lindane was first registered for use in the USA in 1947, but its use was restricted to certified applicators in 1983,

and further restricted to specific crops in 2002. Pesticide exposure information was ascertained from two phases of questionnaire administration in this analysis. For participants who did not complete the follow-up questionnaire, a data-driven multiple imputation procedure with logistic regression and stratified sampling was used to impute specific pesticide exposure.

Relative risks were calculated for no, low, or high use of lindane according to histological subtype of NHL; relative risks were elevated for those with high exposure to lindane, although statistically significant increases in risk were seen only for follicular B-cell lymphoma (*P* for trend, 0.04). Statistically significant upward exposure–response trends for NHL were observed with total days of lindane use [1.0 (reference), 1.2 (95% CI, 0.7–1.9), 1.0 (95% CI, 0.6–1.7), 2.5 (95% CI, 1.4–4.4) (*P* for trend, 0.004)], and with intensity-weighted days of exposure [1.0 (reference), 1.3 (95% CI, 0.8–2.2), 1.1 (95% CI, 0.7–1.8), 1.8 (95% CI, 1.0–3.2) (*P* for trend, 0.04)] (Alavanja et al., 2014a). The risk estimates were adjusted for age, state of residence, race, and total days of pesticide use. Lindane was not associated with the use of other insecticides, fungicides, or fumigants. Smoking, other lifestyle factors, and other occupational exposures were not observed to confound the results reported. Similar results were observed in an earlier analysis by Purdue (Purdue et al., 2007).

2.2 Case–control studies nested within cohorts

Several case–control studies nested within cohorts assessed the association between exposure to lindane or γ-HCH and risk of cancer of the prostate or testis. Results for other isomeric forms (β-HCH) are also presented here. The major strength of most of these studies was the use of pre-diagnostic blood samples for measuring HCH.

2.2.1 Cancer of the prostate

A nested case–control study of cancer of the prostate was conducted within a large cohort of predominately Hispanic members of the United Farm Workers of America labour union in California, USA (Mills & Yang, 2007). Through electronic linkage between a roster of union members and the California cancer registry for the years 1988–1999, newly diagnosed cases of cancer of the prostate were identified from the union. Age-matched controls were randomly selected from the remained of the cancer-free cohort. Risk for cancer of the prostate was examined by the type of crops and commodities cultivated by the farm workers, as well as by the date of first union activity and duration of union membership. In addition, the risk of cancer of the prostate was evaluated in association with the use of several pesticides recorded by the California Department of Pesticide Regulation by place, time period and crop, rather than at the level of individual workers. Between 1988 and 1999, 222 newly diagnosed cases of cancer of the prostate were identified for analysis and 1110 age-matched controls were selected. The risk of prostate cancer was not associated with patterns of employment in any crop/commodity. However, risk was observed to increase monotonically with an increase in estimated use of lindane; the odds ratio was 2.37 (95% CI, 1.12–4.61) for the highest quartile of use compared with the lowest quartile, adjusted for age, date of first union membership, and duration of union membership. [The Working Group noted that the semi-ecological exposure assessment may have led to measurement error at the level of the individual, but had the advantage that it did not rely on self-report (eliminating the potential for recall bias) as exposure was obtained through record linkage. The Working Group also noted that these methods enabled estimation of whether a cohort member worked in an area with high use of pesticides; however,

level of exposure was based on the county, crop, and period when the person worked, and there was no information on job tasks collected from the participants, resulting in possible exposure misclassification.]

One nested case–control study reported results on risk of cancer of the prostate in relation to β-HCH (Sawada et al., 2010). This case–control study was nested within the Japan Public Health Center-based Prospective Study, a population-based cohort of 65 657 men aged 40–69 years at baseline in 1990–1993, of whom 14 203 provided blood samples. During follow up until December 2005, 201 cases of cancer of the prostate were identified from major hospitals, cancer registries, and death certificates. Two controls per case were matched by age, area of residence, date of blood sampling, time of day of blood sampling, and duration of fasting at blood collection. Organochlorine pesticides and polychlorinated biphenyls were measured in the blood samples taken before diagnosis. The incidence of cancer of the prostate tended to be inversely associated with exposure to β-HCH in this study (odds ratio for exposure in the highest exposure category as compared with the lowest: OR, 0.56; 95% CI, 0.30–1.01; *P* for trend, 0.05). [The Working Group noted that measurements of β-HCH in biological samples do not necessarily indicate exposure to lindane in the absence of information about the sources of exposure to HCH compounds.]

In the AHS, 1962 incident cases of cancer of the prostate among 54 412 licensed pesticide applicators were evaluated for exposure to 48 pesticides of widespread use in the cohort (Koutros et al., 2013). Increased use of lindane (lifetime days of use) was not associated with risk of total prostate cancer, nor was it associated with aggressive prostate cancer (i.e. Gleason score > 7). The rate ratio of total prostate cancer comparing the highest quartile of lindane use to those who did not use lindane was 1.16 (96% CI, 0.84–1.60; *P* for trend, 0.33) adjusted for age, state, race, family history of prostate cancer, smoking, fruit servings per day, and leisure-time physical activity in winter. [The Working Group noted that this was a large prospective study with controls for many potential confounders.]

2.2.2 Cancer of the testes

No studies of cancer of the testes and occupational exposure to lindane were available to the Working Group.

McGlynn et al. (2008) reported the results of a case–control study on testicular germ cell tumours among military servicemen in the USA, which included separate analyses for seminoma and non-seminoma, and data on β-HCH but not γ-HCH (lindane). The cases included in the analysis were 739 men who had donated blood to the Department of Defense Serum Repository (DoDSR) between 1987 and 2002, and who were subsequently diagnosed with testicular germ cell tumour. Controls were 915 men with a serum sample available in the DoDSR matched on birth year, ethnicity, and date of available serum sample (within 30 days). Each participant was given a computer-assisted telephone interview to obtain information on height, weight, medical conditions, and family history of cancer. Eleven organochlorine compounds were analysed in the serum. Total testicular germ cell tumours were not associated with β-HCH (highest versus lowest quartile: OR, 0.90; 95% CI, 0.65–1.24; *P* for trend, 0.40). Null results were reported for seminomas (OR, 0.97; 95% CI, 0.63–1.49; 78 exposed cases; *P* for trend, 0.83) and non-seminomas (OR, 0.85; 95% CI, 0.57–1.26; 65 exposed cases; *P* for trend, 0.24). [This was a well-conducted study with a large number of subjects, and high response rates. The use of pre-diagnostic serum samples in this study maybe an advantage; however, β-HCH measurements in biological samples do not necessarily indicate exposure to γ-HCH.]

Purdue et al. (2009) reported the findings of a case–control study on testicular germ cell

tumours that was nested within the Janus Serum Bank cohort of Norway. Cases were Janus cohort members with baseline blood collection between 1972 and 1978, who were identified with a diagnosis of testicular germ cell tumour between baseline and 31 December 1999 through linkage with the Norwegian cancer registry. One male control from the Janus cohort was matched to each case by region, time of blood draw, and age at blood draw. The analysis was conducted in 49 cases (80%) and 51 controls (81%) with adequate exposure data. Concentrations of 11 organochlorine pesticides, including β-HCH and γ-HCH (lindane), and of 34 polychlorinated biphenyls were measured in the serum samples. The odds ratios for highest versus lowest exposure tertile were 1.8 (95% CI, 0.5–6.1) and 1.1 (95% CI, 0.2–5.0) for β-HCH and γ-HCH, respectively. [This was a small but well-conducted study. An important strength was the use of serum samples collected before diagnosis; however, as noted previously, β-HCH measurements in biological samples do not necessarily indicate exposure to lindane.]

2.3 Case–control studies

2.3.1 Cancer of the breast

See Table 2.2

Exposure to lindane in relation to cancer of the breast has been assessed in three case–control studies, two in Spain and one in India.

A hospital-based case–control study was conducted in the three largest public hospitals in southern Spain (Ibarluzea et al., 2004). Cases were recruited from women aged 35-70 years undergoing surgery for newly diagnosed malignant carcinoma of the breast. Levels of lindane in adipose tissue samples were higher, but not statistically significantly, in 198 cases of cancer of the breast compared with 260 age-matched controls. After adjusting for potential confounders, a significant odds ratio of 1.76 (95% CI, 1.04–2.98) emerged for postmenopausal women with lindane concentrations greater than the LOD versus those with lindane concentrations less than or equal to the LOD. [More than half of the women had lindane values under the LOD.]

In the Canary Islands, Spain, Boada et al. (2012) found that serum levels of lindane were not associated with cancer of the breast in 121 cases compared with 103 healthy controls. [This study was not matched by age; cases were significantly older than controls, and few women were exposed.]

In a pilot study in India, Siddiqui et al. (2005) found significantly higher levels of lindane in blood samples from 25 cases of cancer of the breast compared with 25 controls with benign disease. No exposure–disease associations were reported. [The limitations of this study included the small sample size, the recruitment of cases from a single hospital, and the lack of controls for confounders.]

2.3.2 Lympho-haematopoietic cancers

See Table 2.3

This section describes case-control studies of risk of NHL or leukaemia and exposure to lindane. It should be noted that interpretation of the published literature was complicated by the change over time in the classification and coding systems for NHL and its subtypes (American Cancer Society, 2016).

Data from an in-person interview study of 622 white men with newly diagnosed NHL and 1245 population-based controls in Iowa and Minnesota, USA, were used to measure the risk associated with farming occupation and specific agricultural exposures (Cantor et al., 1992). Detailed information was collected on farming and pesticide use, including over 100 insecticides used on animals or crops, herbicides, and fungicides. Significantly elevated risks were found for ever handling lindane as a crop insecticide (OR, 2.0; 95% CI, 1.0–3.7) and for handling it before 1965 (OR, 2.2; 95% CI, 1.0–4.7) after adjusting for vital status, age, state, smoking,

Table 2.2 Case-control studies of cancer of the breast and exposure to lindane

Reference, location follow-up/enrolment period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Boada et al. (2012) Gran Canaria Island, Spain April 1999-June 2001	Cases: 121, from two university hospitals of Gran Canary Island Controls: 103, selected from representative population sample obtained in the Canary Islands Nutrition Survey Exposure assessment method: personal monitoring; serum, GC-ECD	Breast (ICD-O 2nd C50.0-C50.9)	Lindane (ng/g lipid) Trend-test *P*-value, 0.988	105	1.097 (0.420–28.412)	Age, BMI, menopausal status, lactation, and tobacco	Limitations: not matched by age; cases were significantly older than controls, and few women were exposed
Ibarluzea et al. (2004) Granada and Almeria, Spain April 1996-June 1998	Cases: 198 women aged 35-70 yrs undergoing surgery for newly diagnosed malignant breast carcinoma (invasive or in situ) without previous history of cancer Controls: 260, age-matched (± 3 yrs) and hospital; exclusion criteria for controls were the presence of gynaecological or endocrine disease, including diabetes, and history of cancer Exposure assessment method: personal monitoring; adipose tissue samples; GC-ECD	Breast (ICD-O 2nd C50.0-C50.9)	LOD (lindane ng/g lipid) < LOD > LOD (all) > LOD (premenopausal) > LOD (postmenopausal)	 67 54 33 53	 1.00 1.40 (0.92–2.13) 1.10 (0.50–2.37) 1.76 (1.04–2.98)	Age, reference hospital, BMI, number of children, age at first full-term pregnancy, family history of breast cancer, alcohol and tobacco	Strengths: control for confounders Limitations: many women had lindane values under the LOD

BMI, body mass index; GC-ECD, gas chromatography with electron-capture detection; LOD, limit of detection; yr, year

Table 2.3 Case-control studies of lympho-haematopoietic cancers and exposure to lindane

Reference, location follow-up/enrolment period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cantor et al. (1992) Iowa and Minnesota, USA Enrolment, 1980–1982	Cases: 622; Iowa Health Registry records and Minnesota hospital and pathology records Controls: 1245; population-based; no cancer of the lympho-haematopoietic system; frequency-matched to cases by age (5-yr group), vital status, state; random-digit dialling (age < 65 yrs); Medicare records (age ≥ 65 yrs); state death certificate files (deceased subjects) Exposure assessment method: questionnaire; in-person interview	NHL	Ever handled lindane:			Age, vital status, state, smoking status, family history of lympho-haematopoietic cancer, high-risk occupations, high-risk exposures	Data subsequently pooled in De Roos et al. (2003) Strengths: large population-based study in farming areas. Minimal evidence for confounding by exposure to other pesticides Limitations: not controlled for exposure to other pesticides; small numbers of cases in some analyses; multiple comparisons; use of proxy respondents; white men only
			As an animal insecticide	55	1.4 (1.0–2.1)		
			before 1965	40	1.7 (1.1–2.7)		
			without PPE	45	1.6 (1.0–2.4)		
			As a crop insecticide	21	2.0 (1.0–3.7)		
			before 1965	14	2.2 (1.0–4.7)		
			without PPE	16	2.6 (1.2–5.5)		
			before 1965 (Iowa residents)	9	1.4 (0.6–3.5)		
			before 1965 (Minnesota residents)	5	6.5 (1.2–35.0)		
Blair et al. (1998) Iowa, Minnesota, Nebraska, Kansas, USA 1980s	Cases: 987 white men Controls: 2895; frequency matched on age, race, state of residence; random-digit dialling for living cases aged < 65 yrs and from the Health Care Financing Administration for those aged ≥ 65 yrs; controls for deceased cases from deaths records in each state, matched for age and year of death Exposure assessment method: telephone interviews with subjects or next of kin in Kansas and Nebraska, and in person in Iowa and Minnesota	NHL	Lindane use:			Age, proxy/direct interview, state of residence	Strengths: pooled analysis with large numbers of cases and controls Limitations: use of proxy respondents
			Non-farmer	243	1.0		
			Farmer (used lindane, no adjustment for other pesticides)	93	1.5 (1.1–2.0)		
		NHL	First lindane use:				
			≥ 20 yrs ago	59	1.7 (1.1–2.5)		
			< 20 yrs ago	18	1.3 (0.7–2.3)		
			Days/year lindane use:				
			≤ 4	8	1.6 (0.6–4.0)		
			≤ 5	5	2.0 (0.6–6.4)		
			Protective equipment:				
			Used	25	1.4 (0.8–2.3)		
			Not used	63	1.5 (1.0–2.2)		

Table 2.3 (continued)

Reference, location follow-up/enrolment period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Blair et al. (1998) Iowa, Minnesota, Nebraska, Kansas, USA 1980s (cont.)			Histological type:				
			Follicular	36	1.6 (1.0–2.5)		
			Diffuse	28	1.5 (0.9–2.5)		
			Small lymphocytic	14	1.9 (0.9–4.0)		
			Other types	15	1.1 (0.6–2.1)		
Schroeder et al. (2001) Iowa and Minnesota, USA 1980–1983	Cases: 622; identified through the State Health Registry of Iowa and active surveillance of hospital and pathology laboratory records in Minnesota Controls: 1245 white males without lympho-haematopoietic cancer, frequency matched to cases on age (± 5 yrs), state, and vital status. identified using random-digit dialling (age < 65 yrs), Health Care Financing Administration Medicare files (age ≥ 65 yrs), and state death certificate files (deceased controls) Exposure assessment method: questionnaire	NHL	Ever exposed to lindane			Age, state	Same study population as Cantor et al. (1992) Limitations: 30% of the study participants were represented by next-of-kin respondents; some bias towards the null may have occurred due to t(14;18) breakpoints outside the range of PCR primers; unable to classify > 60% of NHL cases
			t(14;18)-positive NHL vs controls	14	2.3 (1.3–3.9)		
			t(14;18)-negative NHL vs controls	12	1.0 (0.5–1.7)		
			t(14;18)-positive vs -negative NHL	12	2.1 (0.9–5.1)		

Table 2.3 (continued)

Reference, location follow-up/enrolment period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
De Roos et al. (2003) Nebraska, Iowa, Minnesota, Kansas, USA 1979–1986	Cases: 650, from three previous case-control studies (Hoar et al., 1986; Zahm et al., 1990; Cantor et al., 1992) Controls: 1933, from three previous case-control studies (as for cases) Exposure assessment method: questionnaire; 47 pesticides in the pooled analysis (insecticides and herbicides), for which ≥ 20 persons were exposed; analysis restricted to "potentially carcinogenic pesticides"	NHL	Lindane ever use: Hierarchical regression Logistic regression	 59 59	 1.2 (0.8–1.9) 1.2 (0.7–2.0)	Other pesticides, age, location	Strengths: large number of exposed subjects; analysis of combined pesticide exposure and the number of pesticides used; evaluation of potential superadditivity of pesticides effects; use of hierarchical models Limitations: no quantification of exposure; no information on the timing of pesticide use; use of proxy respondents; many exclusions due to missing data
Lee et al. (2004) Iowa, Minnesota, Nebraska, USA 1980–83 for Iowa and Minnesota, 1983–86 for Nebraska	Cases: 872 from Iowa State Health Registry, surveillance system of Minnesota hospitals, Nebraska Lymphoma Study Group Controls: 2336, frequency-matched on age, race, state of residence; random-digit dialling for living cases (age < 65 yrs) and from the Health Care Financing Administration (age ≥ 65 yrs; controls for deceased cases from death records in each state, matched for age and year of death Exposure assessment method: questionnaire; telephone interviews with subjects or next-of-kin in Nebraska, and in person in Iowa and Minnesota	NHL	Lindane exposure: Non-farmers, non-asthmatics Nonasthmatics Asthmatics	 259 84 11	 1.0 1.3 (0.97–1.8) 2.4 (1.0–5.7)	Age, vital status, state of residence	Studies in midwest USA Strengths: pooled study so larger numbers Limitations: use of proxy respondents; no adjustment for co-exposures

Table 2.3 (continued)

Reference, location follow-up/enrolment period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
McDuffie et al. (2001) Alberta, Saskatchewan, Manitoba, Quebec, Ontario, British Columbia, Canada 1991–1994	Cases: 517 newly diagnosed men, age ≥ 19 yrs, enrolled from cancer registries Controls: 1506 (48%) men, age ≥ 19 yrs, enrolled from a random sample of health insurance and voting records; frequency-matched on province and age Exposure assessment method: postal questionnaire, followed by telephone interview for subjects with ≥ 10 h/yr of pesticide exposure and 15% random sample of the remainder; a list of chemical and brand names was mailed to these participants before interview; exposure defined as used at work, in home garden, or as hobby	NHL (200, 202)	Exposure to lindane Exposure to lindane	15 15	2.05 (1.01–4.16) 2.06 (1.01–4.22)	Age, province of residence Age, province of residence, medical variables	Strengths: large study; detailed exposure assessment through telephone interview; deceased were ineligible, reducing the number of surrogate responders; some modelling of multiple pesticide exposures Limitations: potential for recall bias; poor response rates; risk estimates were not adjusted for other pesticides
Miligi et al. (2003) Italy 1990–1993	Cases: 1145 NHL (ICD-9, 200, 202), 430 leukaemia (ICD-9, 204–208); all incident cases diagnosed in residents of the study area; age 20–74 yrs Controls: 1232 general-population controls, frequency-matched by sex and 5-yr age group, age 20–74 yrs Exposure assessment method: questionnaires reviewed by agronomists to assign pesticide-exposure histories	NHL (ICD-9, 200 & 202) and CLL (ICD-9, 204.1)	Ever occupationally exposed to lindane: Men	 9	 2.0 (0.6–7.7)	Age, area	NHL and CLL were analysed as a combined category due to biological similarities Strengths: expert assessment of exposure

Table 2.3 (continued)

Reference, location follow-up/enrolment period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
De Roos et al. (2005) Iowa, Los Angeles County, metropolitan areas of Detroit and Seattle, USA July 1998-June 2000	Cases: 100 with blood sample; 1321 incident cases of NHL without HIV infection; age 20–74 yrs; identified from four SEER registry areas Controls: 100 with blood sample; 1057 population controls identified by random-digit dialling (age < 65 yrs) and from Medicare eligibility files ≥ 65 yrs); frequency-matched to cases by age, sex, and race Exposure assessment method: blood sample	NHL	β-HCH (quartiles ng/g lipid)			Sex, study site, birth date, date of blood draw	1% samples had γ-HCH of > LOD, and 82% had β-HCH of > LOD
			≤ 9.1	23	1.00		
			> 9.1–15.0	26	1.19 (0.49–2.89)		
			> 15.0–26.0	28	1.21 (0.50–2.90)		
			> 26.0	23	1.05 (0.42–2.64)		
			All (continuous variable)	100	1.08 (0.94–1.25)		
			Trend-test *P*-value, 0.94				
Cocco et al. (2008) France, Germany, Spain (Epilymph multicentre study) Study period, NR	Cases: 174 incident cases recruited at hospital Controls: 203 from population and hospital Exposure assessment method: lipid-adjusted concentrations	NHL	β-HCH (ppb)			Age, sex, education, centre	Strengths: designed to give sufficient sample size Limitations: biological exposure assessed at diagnosis
			≤ 15	19	1.0		
			15.1–130.73	46	0.7 (0.3–1.6)		
			130.74–338.96	57	0.9 (0.4–1.9)		
			≥ 338.97	52	0.7 (0.3–1.5)		
			Trend-test *P*-value, 0.52				
		DLBCL	β-HCH (ppb)				
			≤ 15	5	1.0		
			15.1–130.73	14	0.8 (0.2–2.5)		
			130.74–338.96	13	0.8 (0.2–2.6)		
			≥ 338.97	12	0.7 (0.3–2.4)		
			Trend-test *P*-value, 0.66				
		SLL/CLL	β-HCH (ppb)				
			≤ 15	8	1.0		
			15.1–130.73	9	0.3 (0.1–1.1)		
			130.74–338.96	20	0.7 (0.2–1.9)		
			≥ 338.97	18	0.5 (0.2–1.5)		
			Trend-test *P*-value, 0.52				

Table 2.3 (continued)

Reference, location follow-up/enrolment period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Viel et al. (2011) Three electoral wards containing or surrounding a municipal solid waste incinerator, Besancon, France 1 January 2003-31 December 2005	Cases: 34 newly diagnosed at the department of haematology of the university hospital Controls: 34 randomly selected from donor registry of regional blood bank living in the area, matched on sex, age (± 5 yrs), blood draw (± 1 yr) Exposure assessment method: serum from a fasting blood sample; total lipid-adjusted concentration	NHL	ng/g lipid β-HCH γ-HCH	 NR NR	 1.05 (1.00–1.12) 1.16 (0.93–1.49)	NR	Strengths: exposure assessment does not rely on participant recall; detailed information on lifestyle factors, diet, occupation Limitations: substantial correlation between several classes of pesticides; the disease process or chemotherapy may have distorted the results
Leukaemia							
Brown et al. (1990) Iowa and Minnesota, USA 1980–1983	Cases: 578 from tumour registry (Iowa) and hospital records (Minnesota) ; review by pathologists Controls: 1245 population-based (random-digit dialling, Medicare records, state death certificates); frequency-matched by 5-yr age group, vital status and state of residence Exposure assessment method: detailed questionnaires: number of animals and crops, use of 24 animal insecticides, 34 crop insecticides, 38 herbicides, 16 fungicides; first and last year of use; tasks (mixing, applying);. days per year for each pesticide	Leukaemia (including myelodys-plasias)	Lindane use on animals: Ever Handled > 20 yrs ago 1–4 days/yr 5–9 days/yr > 10 days/yr	 38 28 15 3 10	 1.1 (0.7–1.7) 1.4 (0.8–2.3) 1.1 (0.5–2.0) 1.1 (0.3–4.1) 1.6 (0.7–3.7)	Vital status, age, state, tobacco use, family history lymphopoietic cancer, high risk occupations, high risk exposures	Studies in midwest USA Strengths: in-person interviews; detailed questionnaires including quantification; information on other potential risk factors; reviewed diagnosis Limitations: self-report of pesticide use
		Leukaemia (including myelodys-plasias)	Lindane use on crops: Ever 1–4 days/yr 5–9 days/yr > 10 days/yr	 14 6 2 3	 1.6 (0.8–3.2) 3.5 (0.9–12.6) 1.2 (0.2–6.9) 1.3 (0.3–5.3)	Vital status, age, state, tobacco use, family history lymphopoietic cancer, high-risk occupations, high-risk exposures	

CLL, chronic lymphocytic leukaemia; DLBCL, Diffuse large B-cell lymphoma; HCH, hexachlorocyclohexane; HD, Hodgkin disease; LOD, limit of detection; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NR, not reported; PCR, polymerase chain reaction; PPE, personal protective equipment; SEER, Surveillance, Epidemiology and End Results Program; SLL, small lymphocytic leukaemia; STS, soft tissue sarcoma; vs, versus; yr, year

family history, high-risk occupations, high-risk exposures). [Although exposure to one or more other substances was associated with NHL in this study, information on a large number of exposures was collected presenting potential problems of interpreting risk associated with a particular chemical as multiple comparisons increase the chances of false-positive findings.]

Data from the study by Cantor et al. (1992) were pooled with data from two other population-based case–control studies of NHL and exposure to pesticides in Kansas (Hoar et al., 1986) and Nebraska (Zahm et al., 1990), USA, in which exposure to lindane had not been analysed previously, to evaluate the risk associated with exposure to lindane (Blair et al., 1998). There were 987 cases and 2895 population-based controls. Information was obtained by telephone or in-person interviews, which included detailed questions on farm practices and agricultural use of chemicals. The risk of NHL (adjusted for age, state of residence, type of respondent - index or proxy) was significantly elevated among subjects reporting agricultural use of lindane (OR, 1.5; 95% CI, 1.1–2.0), and was greater among persons who first used the pesticide 20 years before diagnosis, among those who reported more frequent use of ≥ 5 days per year versus < 5 days per year, and from use on crops (OR, 1.9 95% CI, 1.1–1.3), rather than from use on animals (OR, 1.3; 95% CI, 0.9–1.8). However, odds ratios were lower for direct interviews (OR, 1.3; 95% CI, 0.9–1.8) than for proxy respondents (OR, 2.1; 95% CI, 1.0–4.4). Adjustments by use of chemical class of pesticides did not result in large changes in the odds ratios, with slight increases after adjusting for phenoxyacetic acids, triazines, amides, and benzoics, and slight decreases for organophosphates and natural products. Adjustment for reported use of two individual pesticides (dichlorodiphenyltrichloroethane, DDT; and fonofos) had no impact on the odds ratio for use of lindane, while adjustment for use of 2,4-D and diazinon reduced the odds ratios associated with use of lindane from 1.5 to 1.2 (95% CI, 0.5–3.2) and 1.3 (95% CI, 0.9–1.9), respectively.

The data from the study by Cantor et al. (1992) were also used to investigate the hypothesis that some risk factors might act specifically along t(14;18)-dependent pathways - the t(14;18) translocation is a common somatic mutation in NHL - leading to stronger associations with t(14;18)-positive than t(14;18)-negative non-Hodgkin lymphoma (Schroeder et al., 2001). Of 182 cases of NHL, 68 (37%) were t(14;18)-positive. Cases with t(14;18)-positive NHL were associated with several individual pesticides, including lindane (OR, 2.3; 95% CI, 1.3–3.9) in contrast to null or negative associations for the same self-reported exposures and t(14;18)-negative NHL. [No adjustment was made for shared agricultural exposures. This study had several limitations: 30% of the study participants were represented by next-of-kin respondents with consequent increased likelihood of inaccurate or missing data; some bias towards the null may have occurred due to t(14;18) breakpoints outside the range of the polymerase chain reaction (PCR) primers; the authors were unable to classify more than 60% of cases of NHL.]

In a further analysis of the a subset of the data from the same group of studies in the pooled analysis by Blair et al. (1998), De Roos et al. (2003) evaluated multiple exposures, including ever-use of 47 insecticides and herbicides, including lindane. The larger sample size provided adequate numbers of exposed subjects to analyse the set of pesticide exposures simultaneously, using hierarchical regression to adjust estimates based on prior distributions for the pesticide effects. The risk associated with exposures to several pesticides combined, defined as two pesticides used by the same person, but not necessarily at the same time, was also explored. Subjects with any missing information on exposure were omitted, and adjustments were made for the most frequently used pesticides. Ever exposure to lindane was not associated with an

increase in risk of NHL (OR, 1.2; 95% CI, 0.8–1.9). In a further analysis of a subset of 100 cases of NHL and 100 matched controls from this pooled data, De Roos et al. (2005) investigated plasma organochlorine levels and risk of NHL. No association was observed for increasing quartiles of β-HCH concentration (*P* for trend, 0.94).

A study of leukaemia in Iowa and Minnesota, USA, which included 578 cases and 1245 population controls, reported a weak non-significant association with ever use of lindane as an insecticide on crops (OR, 1.6; 95% CI, 0.8–3.2, based on 14 cases) or on animals 20 years before the study (OR, 1.4; 95% CI, 0.8–2.3), after adjusting by risk factors including high-risk occupations, and high-risk exposures. Risk associated with exposure to lindane used as a crop insecticide was highest in the lowest category of days per year of use, while a linear, though non-significant, increase in risk was observed for use as an animal insecticide (Brown et al., 1990). [No tests for trend were reported in this paper.]

NHL is known to be associated with a compromised immune status. Asthma is a condition that is also associated with moderate alterations in immune function. For this reason, the data from Iowa, Minnesota, and Nebraska were pooled to investigate whether asthma modified the risk of NHL associated with pesticide exposures; 872 cases and 2336 frequency-matched controls were included (Lee et al., 2004). History of asthma was collected during the interviews. 177 (45 cases, 132 controls) reported having been told by their doctor that they had asthma. Subjects with an asthma history had a lower risk of NHL than non-asthmatics (OR, 0.6; 95% CI, 0.3–1.4). However, asthmatics tended to have larger odds ratios associated with exposure to lindane than did non-asthmatics (OR, 2.4; 95% CI, 1.0–5.7 and 1.3; 95% CI, 0.97–1.8, respectively). The reference category was non-asthmatic farmers. Similar patterns of association were found for many other pesticides. [The use of proxy respondents in this study may have led to misclassification. In addition exposure to a large number of pesticides was assessed but there was no attempt to account for co-exposure in the analyses. The study had limited power to investigate effect modification.]

Concentrations of 17 organochlorine pesticides, including four lindane isomers (α-, β-, γ-, and δ-HCH), were measured in plasma samples from 174 cases of NHL and 203 controls from France, Germany, and Spain, who participated in the Epilymph multicentre European population-based case–control study (Cocco et al., 2008). There was no increased risk of NHL associated with increasing quartiles of β-HCH, the only isomer present at detectable levels in enough subjects to permit analysis, nor for the NHL subtypes investigated (diffuse large B-cell lymphoma and chronic/small lymphocytic leukaemia). [Although about half of the Spanish patients underwent blood withdrawal after initiating chemotherapy, results did not change after these patients were excluded. As noted previously, measurements of β-HCH in biological samples do not necessarily reflect exposure to lindane.]

A large, Canadian multicentre population-based incident case–control study (517 cases, 1506 controls) was carried out among men in a range of occupations using a postal questionnaire followed by a telephone interview for those reporting pesticide exposure of 10 hours/year or more, and a 15% random sample of the remainder (McDuffie et al., 2001). Exposure to lindane was significantly associated with an increased risk of NHL (OR, 2.05; 95% CI, 1.01–4.16), calculated with stratification by age and province, and was similar when additionally adjusted for significant medical variables such as measles, mumps, previous cancer, allergy desensitization shots, and a positive family history of cancer. [Although this was a large study, the response rate was relatively poor, especially in the controls, for whom it was less than 50%; however, a comparison of non-respondents with respondents using postal code as an indicator

of rural residence did not find any indication of rural bias among respondents.]

In an investigation of exposure to organochlorines and the risk of NHL in the neighbourhood of a municipal solid-waste incinerator with high levels of dioxin emissions in Besançon, France, serum concentrations of pesticides, dioxins, furans, and polychlorinated biphenyls (PCBs) were measured for 34 cases of NHL (newly diagnosed in 2003–2005) and 34 controls randomly selected from the donor registry of the regional blood bank (matched for age, sex, and date of blood draw) (Viel et al., 2011). The mean serum concentration of β-HCH was 98.61 ng/g lipid for cases and 48.08 ng/g lipid for controls. An increased risk of NHL was found for β-HCH (OR, 1.05; 95% CI, 1.00–1.12, per 10 ng/g lipid). There was a high correlation with these isomers with several other exposures, including PCBs and lindane. The study excluded eight cases with rapid death or poor prognosis (who were not well enough to be interviewed). [The serum concentrations in this study may have been influenced by the disease process as serum samples were taken after diagnosis. In addition, measurements of β-HCH in biological samples do not necessarily reflect exposure to lindane.]

Miligi et al. (2003) assessed exposure to lindane in a case-control study of NHL and leukaemia that was carried out in Italy in 1990–1993. The analyses included 1145 cases of NHL, 430 cases of leukaemia, and 1232 age- and sex-matched controls from the general population. In-person interviews were conducted by trained interviewers and a questionnaire recorded information on many variables, including lifetime occupational history for all jobs held for more than 6 months and occupational exposure to solvents and pesticides. More specific and detailed data on specific jobs were collected through a job-specific questionnaire developed by industrial hygenists and agronomists. For agricultural exposures, expert agronomists reviewed the data collected and translated it into pesticide-exposure histories that included use of specific active ingredients (including lindane). Cases of NHL (ICD-10, 200, 202) and chronic lymphocytic leukaemia (ICD-10, 204.1) were analysed as a combined category due to biological similarities. Men exposed to lindane had an odds ratio of 2.0 (95% CI, 0.6–7.7; 9 exposed cases) for NHL and chronic lymphocytic leukaemia after adjustment for area and age.

2.3.3 Other cancers

See Table 2.4

(a) Cancer of the prostate

In a case–control study of urology patients in Ontario, Canada, β-HCH was measured in serum from 79 men with incident cancer of the prostate and from 329 age-matched controls (Aronson et al., 2010). No association was observed between concentration of β-HCH and risk of cancer of the prostate (*P* for trend, 0.81). [As cases and controls underwent the same diagnostic procedures and were screened by prostate-specific antigen (PSA) test and digital rectal examination, selection bias was unlikely in this study.]

In a case-control study of cancer of the prostate in British Columbia, Canada, Band et al. (2011) found an elevated risk of cancer of the prostate associated with ever being exposed to lindane (OR, 1.47; 95% CI, 0.94–2.29) and high exposure to lindane (OR, 2.02; 95% CI, 1.15–3.55), with a significant trend in the exposure-response relationship (*P* for trend, 0.03).

(b) Cancer of the testis

Biggs et al. (2008) conducted a population-based case-control study of testicular germ cell carcinoma in three counties of Washington state, USA, in 1999–2003. Generally, concentration of β-HCH was not associated with testicular germ cell carcinoma; however, an odds ratio of 5.54 (95% CI, 1.65–18.56) was associated with an increase of 10 pg/g serum in concentrations of γ-HCH.

Table 2.4 Case-control studies of cancers of the prostate or testis and exposure to lindane

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Biggs et al. (2008) Washington state, USA January 1999-December 2008	Cases: 246 men (age, 18–44 yrs) diagnosed with invasive TGCT and resident of King, Pierce, Snohomish counties, Washington State, identified from SEER Controls: 630 men with no history of TGCT, frequency-matched to cases on age (± 5 yrs) and residing in the same three counties as the cases; identified using random-digit dialling Exposure assessment method: personal monitoring; median β-HCH, 4.32 ng/g lipid; median γ-HCH, 1.37 ng/g lipid	Testis (TGCT)	β-HCH (pg/g)			Age, ethnicity, change in BMI between reference date and blood draw, assay run number, serum lipids	Strengths: relatively large study size Limitations: poor between-run reliability of the analytic method for several of the analytes; use of post-diagnostic blood samples; low response rates of cases and controls
			≤ 29	113	1.00		
			> 29–65	83	1.26 (0.86–1.85)		
			> 65	25	0.92 (0.51–1.64)		
			Per 10 pg/g	221	0.97 (0.82–1.13)		
			Trend-test *P*-value, 0.83				
		Testis (TGCT)	γ-HCH (pg/g)				
			≤ 9	130	1.00		
			9–20	73	0.80 (0.53–1.20)		
			> 20	38	1.36 (0.75–2.46)		
			Per 10 pg/g	241	5.54 (1.65–18.56)		
			Trend-test *P*-value, 0.69				
Aronson et al. (2010) Kingston, Ontario, Canada 1997–1999	Cases: 79 cases identified from 1288 men who visited a group of five urologists Controls: 329 controls identified from 1288 men who visited a group of five urologists (same source as the cases); subdivided into 194 urology controls (non-cancerous prostate lesions) and 135 biopsy controls (no prostate cancer detected at biopsy) Exposure assessment method: personal monitoring	Prostate	β-HCH (μg/g lipid)			Age, teenage physical activity, alcohol consumption, smoking pack-years	Strengths: PSA and DRE screening in cases and controls Limitations: very small number of cases; total response rates, NR; controls with urological diseases possibly related to exposure
			< 13.5	22	1.00		
			13.5–21.8	27	1.03 (0.54–1.99)		
			> 21.8 to 230.9	29	1.08 (0.57–2.06)		
			Trend-test *P*-value, 0.81				

Table 2.4 (continued)

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Band et al. (2011) British Columbia, Canada, 1983–1990	Cases: 1153 histologically confirmed cases from British Columbia cancer registry Controls: 3999 age-matched cancer patients from the same registry: other sites, excluding lung and cancer of unknown primary site Exposure assessment method: lifetime occupational history obtained through a self-administered questionnaire plus JEM to estimate the participants' lifetime cumulative exposure to approximately 180 active compounds in pesticides	Prostate	Lindane exposure: Not exposed Ever Low High Trend-test *P*-value, 0.03	 1120 33 10 23	 1.00 1.47 (0.94–2.29) 0.91 (0.44–1.89) 2.02 (1.15–3.55)	Alcohol consumption, cigarette yrs, education level, pipe years, respondent type (proxy/direct)	Correlation between specific pesticides as assessed through JEM is reported (e.g. r = 0.72 between lindane and DDT) Strengths: large study size; histological confirmation; high response rates; use of JEM limiting differential exposure misclassification; lifetime cumulative exposure assessment Limitations: multiple comparisons (142 active chemicals evaluated); high correlations between specific pesticides; no mutual adjustment

BMI, body mass index; CI, confidence interval; DRE, digital rectal examination; HCH, hexachlorocyclohexane; JEM, job-exposure matrix; NR, not reported; PSA, prostate-specific antigen; SEER, Surveillance, Epidemiology and End Results Program; TGCT, testicular germ cell tumours; yr, year

2.4 Meta-analysis

In a meta-analysis of NHL and occupational exposures to agricultural pesticides (described in section 2.3.2 of the *Monograph* on DDT in the present volume), the meta relative risk (meta-RR) estimate for NHL and exposure to lindane was significant and relatively precise (meta RR, 1.6; 95% CI, 1.2–2.2; $I^2 = 26\%$) (Schinasi & Leon, 2014). An evaluation of risk for NHL overall and NHL subtype associated with occupational exposure to lindane in the Agricultural Health Study (Alavanja et al., 2014b) was not available at the time at which the meta-analysis by Schinasi & Leon (2014) was accepted for publication. [Inclusion of the paper by Alavanja et al. (2014b) (relative risk [RR] for ever-exposure to lindane, 1.0; 95% CI, 0.8–1.2) would not have changed the meta-estimate substantially, as the results were similar to those of Purdue (RR for lindane exposure, 1.3; 95% CI, 0.8–2.1).] The authors explained that a formal meta-analysis of the exposure-response relationship could not be conducted for lindane because of several limitations of the literature, including variability in the definition of NHL among studies, the small numbers of exposed cases, and because of the differences in cut-off points in the several published studies.

3. Cancer in Experimental Animals

The Working Group has previously reviewed and evaluated the carcinogenicity of hexachlorocyclohexane (HCH) and some of its isomers, including lindane (γ-HCH), in experimental animals (IARC, 1979b; 1987). The α-isomer and technical-grade HCH were classified as having *sufficient evidence* of carcinogenicity in experimental animals, and the β- and γ- (lindane) isomers as having *limited evidence* of carcinogenicity in experimental animals. None of the studies performed and reviewed in the early and mid-seventies followed the current widely accepted study designs for carcinogenicity evaluations in experimental animals.

This *Monograph* revisits the studies that were evaluated previously by the Working Group, describes any updates, and provides details on new studies published subsequently (see also Table 3.1).

3.1 Mouse

Oral administration

Groups of 20 male ICR-JCL mice (age, 5 weeks) were fed diets containing lindane at a concentration of 0 (control), 300, or 600 ppm for 26 weeks. Early mortality was noted in the group at 600 ppm, with five animals dying during the course of the study. This group also displayed lower body weight increases than the controls. At the end of the study, 10 animals per group were killed for histological examination of the liver, kidney, and heart. The incidence of tumours in the liver was 5/10 in the group at 600 ppm (5/10 versus 0/10, [$P < 0.02$]). The tumours were defined as benign hepatomas. No tumours were reported in mice at the lowest dose or in the control group (Goto et al. 1972) [The Working Group noted the short duration of the study, the small number of animals, and that the maximum tolerated dose may have been exceeded (overt toxicity in the group at the highest dose).]

Groups of 10–11 male and female dd strain mice (age, 6 weeks), were fed diets containing lindane [purity not reported] at a concentration of 100, 300, or 600 ppm for 32 weeks, and the surviving animals were killed between week 37 and 38 of the experiment. The control group contained 21 males and 20 females (Hanada et al., 1973). The incidence of hepatoma [not otherwise specified] was 0/14 (controls), 0/10, 0/9, 3/4 [$P < 0.005$] in males; and 0/15 (controls), 0/8, 0/7, and 1/3 in females. [The Working Group noted the short duration of the study, the small number of animals, and that the maximum tolerated dose

Table 3.1 Studies of carcinogenicity in experimental animals fed diets containing lindane

Species, strain (sex); age at start Duration Reference	Dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, ICR-JCL (M) ; age, 5 wk 26 wk Goto et al. (1972)	Lindane (purity, NR) at a dietary concentration of 0, 300, or 600 ppm 20/group	*Liver* Benign hepatomas: 0/10, 0/10, 5/10*	*[$P < 0.02$, Fisher 1-tail]	Limitations: small number of animals; short duration; one sex only; MTD may have been exceeded. At the end of the study, 10 animals per group were killed for histological examination of the liver, kidney, and heart Survival, 20, 20, 15
Mouse, CF-1 (M); age, 4 wk 110 wk Thorpe & Walker (1973)	Lindane (purity, 99.5%) at a dietary concentration of 0, or 400 ppm 45, 29/group	*Liver* Liver cell tumours (benign or malignant, combined): 11/45 (24%), 27/29 (93%)*	*$P < 0.01$, Finney 2 × 2 tables	Strengths: covered most of the lifespan Limitations: excessive mortality early in the study; single dose; MTD may have been exceeded Survival, 20, 5 (10% of mice died in first 3 mo of the study)
Mouse, CF-1 (F); age, 4 wk 110 wk Thorpe & Walker (1973)	Lindane (purity, 99.5%) at a dietary concentration of 0, or 400 ppm 45, 30/group	*Liver* Liver cell tumours (benign or malignant, combined): 10/44 (23%), 20/29 (69%)*	*$P < 0.01$, Finney 2 × 2 tables	Strengths: covered most of the lifespan Limitations: excessive mortality early in the study; single dose; MTD may have been exceeded Survival, 14, 1 (20% of female animals died in first 3 mo of the study)
Mouse, dd (M); age, 6 wk 37–38 wk Hanada et al. (1973)	Lindane (purity, NR) at a dietary concentration of 0, 100, 300, or 600 ppm for 32 wk followed by with basal diet for 5–6 wk 21 (control), 10–11 (treated)	*Liver* Hepatoma [NOS]: 0/14, 0/10, 0/9, 3/4*	[$P < 0.005$, Fisher 1-tail]	Limitations: short duration; small number of animals; MTD may have been exceeded Survival, 14, 10, 9, 4 (high mortality in the group at the highest dose)
Mouse, dd (F); age, 6 wk 37–38 wk Hanada et al. (1973)	Lindane (purity, NR) at a dietary concentration of 0, 100, 300, or 600 ppm for 32 wk followed by with basal diet for 5–6 wk 20 (control), 10–11 (treated)	*Liver* Hepatoma [NOS]: 0/15, 0/8, 0/7, 1/3	[NS]	Limitations: short duration; small number of animals; MTD may have been exceeded Survival, 15, 8, 7, 3 (high mortality in the group at the highest dose)
Mouse, NMRI (M); age, 5 wk 80 wk Herbst et al. (1975), Weisse & Herbst (1977)	Pulverized diet containing lindane (purity, NR) at a dietary concentration of 0, 12.5, 25, or 50 ppm 100, 50, 50, 50/group	*Liver* Adenoma: 4/97, 1/49, 0/48, 2/49	NS	Strengths: strain with 2% background incidence of liver tumours Limitations: dose-selection criteria not given; the high dose was below the MTD The studies looked at six sites for tumours: liver, lung, skin, ovary, lympho-haematopoietic system, and uterus; none of the sites had increased incidences of tumours compared with controls Survival, NR

Table 3.1 (continued)

Species, strain (sex); age at start Duration Reference	Dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, NMRI (F); age, 5 wk 80 wk Herbst et al. (1975), Weisse & Herbst (1977)	Pulverized diet containing lindane (purity, NR) at a dietary concentration of 0, 12.5, 25, or 50 ppm 100, 50, 50, 50/group	*Liver* Adenoma: 1/98, 1/49, 0/49, 0/48	NS	Strengths: used animal strain with 2% background incidence of liver tumours Limitations: dose selection criteria not given; the high dose was below the MTD The studies looked at six sites for tumours: liver, lung, skin, ovary, lympho-haematopoietic system, and uterus; none of the sites had increased incidences of tumours compared with controls Survival, NR
Mouse, B6C3F$_1$ (M); age, 5 wk 90–91 wk NTP (1977)	Lindane (purity, > 99.9%) at a dietary concentration of 0 (matched controls), 0 (pooled controls), 80, or 160 ppm for 80 wk, followed by basal diet for 10 wk 10, 50, 50, 50/group	*Liver* Hepatocellular carcinoma: 2/10, 5/49, 19/49*, 9/46 *Liver* Neoplastic nodules or hepatocellular carcinoma (combined): 3/10, 8/49, 19/49*, 10/46	*P = 0.001, Fisher exact test vs pooled controls *P = 0.010, Fisher exact test vs pooled controls	Strengths: covered most of the lifespan Limitations: number of matched controls was small Other comments: survival for treated and control groups within each sex was similar. Controls were pooled from four other contemporary studies to a total of 50 mice for statistical analysis of the data; the study was judged inadequate for the evaluation No. of survivors, NR
Mouse, B6C3F$_1$ (F); age, 5 wk 90–91 wk NTP (1977)	Lindane (purity, > 99.9%) at a dietary concentration of 0 (matched controls), 0 (pooled controls), 80, or 160 ppm for 80 wk, followed by basal diet for 10–11 wk 10, 50, 50, 50/group	*Liver* Hepatocellular carcinoma: 0/10, 2/47, 2/47, 3/46 *Liver* Neoplastic nodules or hepatocellular carcinoma (combined): 1/10, 3/47, 4/47, 3/46	NS compared with matched or pooled controls NS compared with matched or pooled controls	Strengths: covered most of the lifespan Limitations: number of matched controls was small Other comments: survival for treated and control groups within each sex was similar. Controls were pooled from other four contemporary studies to a total of 50 mice for statistical analysis of the data; the study was judged inadequate for the evaluation No. of survivors, NR

Table 3.1 (continued)

Species, strain (sex); age at start Duration Reference	Dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, Obese mottled yellow A^{vy}/a (YS × VY) F_1 hybrid (F); age, 4 wk 24 mo Wolff et al. (1987)	Lindane (purity, NR) at a dietary concentration of 0, or 160 ppm 96/group	*Liver* Hepatocellular adenoma or carcinoma (combined): 20/93, 49/94* Hepatocellular adenoma: 8/93, 33/94* Hepatocellular carcinoma 12/93, 16/94 *Lung* Bronchiolo-alveolar tumours: 4/95, 18/95*	 *[$P < 0.0001$, Fisher exact test] *[$P < 0.0001$, Fisher exact test] [NS] *[$P < 0.002$, Fisher exact test]	Strengths: covered most of the lifespan Limitations: use of a single dose and one sex only In a concurrent 18 mo-experiment with 36 mice per group, hepatocellular adenomas developed in 12/36 treated mice vs 0/34 controls [$P < 0.0001$, Fisher exact test] Survival, NR
Mouse, Lean pseudoagouti A^{vy}/a (YS × VY) F_1 hybrid (F); age, 4 wk 24 mo Wolff et al. (1987)	Lindane (purity, NR) at a dietary concentration 0, or 160 ppm 96/group	*Liver* Hepatocellular adenoma or carcinoma (combined): 7/95, 16/95* Hepatocellular adenoma: 5/95, 11/95 Hepatocellular carcinoma: 2/95, 5/95 *Lung* Bronchiolo-alveolar tumours: 6/95, 13/94	 *[$P < 0.05$, Fisher exact test] [NS] [NS] [NS]	Strengths: covered most of the lifespan Limitations: use of a single dose and one sex only Survival, NR
Mouse, Lean black a/a (YS × VY) F_1 hybrid mice (F); age, 4 wk 24 mo Wolff et al. (1987)	Lindane (purity, NR) at a dietary concentration of 0, or 160 ppm 96/group	*Liver* Hepatocellular adenoma or carcinoma (combined): 9/96, 4/96 Hepatocellular adenoma: 6/96, 3/96	 [NS] [NS]	Strengths: covered most of the lifespan Limitations: use of a single dose, and one sex only Survival, NR

Table 3.1 (continued)

Species, strain (sex); age at start Duration Reference	Dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, Lean black *a/a* (YS × VY) F_1 hybrid mice (F); age, 4 wk 24 mo Wolff et al. (1987) (cont.)		Hepatocellular carcinoma: 3/96, 1/96 *Lung* Bronchiolo-alveolar tumours: 2/96, 3/96	[NS] [NS]	
Mouse, Crl:CD-1(ICR) BR (M); age, 38–44 days 78 wk EPA (2001a, b)	Lindane (purity, 99.78%) at a dietary concentration of 0 (control), 10, 40, or 160 ppm 50/group	*Lung* Bronchiolo-alveolar adenoma: 16/49, 15/48, 11/49, 8/48 Bronchiolo-alveolar carcinoma: 0/49, 1/48, 3/49, 0/48 Bronchiolo-alveolar adenoma or carcinoma:(combined): 16/49, 16/48, 14/49, 8/48	 Significant negative trend NS (Significant negative trend)	Strengths: adequate duration, GLP study Incidences' denominator excluded mice that died before wk 44 Survival, 41, 34, 35, 38
Mouse, Crl:CD-1(ICR) BR (F); age, 38–44 days 78 wk EPA (2001a, b)	Lindane (purity, 99.78%) at a dietary concentration of 0 (control), 10, 40, or 160 ppm 50/group	*Lung* Bronchiolo-alveolar adenoma: 3/48, 7/46, 7/47, 11/48* Bronchiolo-alveolar carcinoma: 1/48, 2/46, 2/47, 1/48 Bronchiolo-alveolar adenoma or carcinoma (combined): 4/48, 8/46, 9/47, 12/48*	 $P = 0.0274$, exact trend test; *$P = 0.0200$, Fisher exact test NS $P = 0.0389$, exact trend test; *$P = 0.0264$, Fisher exact test	Strengths: adequate duration; GLP study Incidences' denominator excludes mice that died before wk 44; results of resectioning of lungs did not significantly change initial findings and conclusion Survival, 37, 31, 33, 40

Table 3.1 (continued)

Species, strain (sex); age at start Duration Reference	Dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, Osborne-Mendel (M); age, 5 wk 108–110 wk NTP (1977)	Lindane (purity,100%) at a dietary concentration of 0 (matched controls), 0 (pooled controls), 236, or 472 ppm TWA for 80 wk, and followed by basal diet for 28–30 wk 10, 55, 50, 50/group	*Spleen* Haemangioma: 0/8, 0/52, 0/44, 3/44 *Thyroid* C-cell adenoma: 1/6, 2/42, 3/37, 1/37 *Liver* Liver neoplastic nodules: 0/10, 0/49, 3/45, 2/45	$P = 0.030$, Cochran-Armitage trend test vs pooled controls NS NS	Strengths: covered most of the lifespan Limitations: reduction in dose levels during the course of studies due to death among treated rats; small number of matched controls Other comments: controls were pooled from four other contemporary cancer studies to a total of 55 rats for statistical analysis; the study was judged inadequate for the evaluation Survival, NR
Rat, Osborne-Mendel (F); age, 5 wk 108–110 wk NTP (1977)	Lindane (purity, 100%) at a dietary concentration of 0 (matched controls), 0 (pooled controls), 135, or 270 ppm TWA for 80 wk, and followed by basal diet for 28–30 wk 10, 55, 50, 50/group	*Thyroid* C-cell adenoma: 0/8, 0/48, 4/44*, 3/42 *Pituitary gland* Chromophobe adenoma: 3/7, 6/46, 14/45*, 8/45 *Liver* Neoplastic nodules: 0/10, 1/49, 4/48, 2/45	*$P = 0.049$, Fisher exact test vs pooled controls *$P = 0.033$, Fisher exact test vs pooled controls NS	Strengths: covered most of the lifespan Limitations: reduction in dose levels during the course of studies due to death among treated rats; small number of matched controls Other comments: controls were pooled from four other contemporary carcinogenicity studies to a total of 55 rats for statistical analysis; the study was judged inadequate for the evaluation Survival, NR

Table 3.1 (continued)

Species, strain (sex); age at start Duration Reference	Dosing regimen No. of animals/group at start	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, Wistar (M); age, NR 24 mo EPA (2001b)	Lindane (purity, 99.78%) at a dietary concentration of 0 (control), 1, 10, 100, or 400 ppm 50/group	*Adrenal gland* Pheochromocytoma, benign: 14%, 16%, 16%, 6%, 24% Pheochromocytoma, malignant: 0%, 0%, 6%, 8%, 2% Pheochromocytoma, benign or malignant (combined): 14%, 16%, 18%, 14%, 26%	NS (statistical tests, NR) NS (statistical tests, NR) NS (statistical tests, NR)	Strengths: adequate duration Limitations: limited study details No significant increase in tumour incidence in treated groups in the experiment with female rats with the same study design (EPA, 2001b) Survival, NR

F, female; GLP, good laboratory practice; M, male; mo, month; MTD, maximum tolerated dose; NR, not reported; NS, not significant; ppm, parts per million; TWA, time-weighted average; vs, versus; wk, week

may have been exceeded (overt toxicity and high mortality in the group at the highest dose).]

In a 2-year comparative study of oral toxicity and carcinogenicity, groups of 29 male and 30 female CF1 mice (age, 4 weeks) were fed diets containing lindane (purity, 99.5%) at 400 ppm for 110 weeks (Thorpe & Walker, 1973). The control group of 45 males and 45 females received basal diet only. During the first 3 months of the experiment, 10% of males and 20% of females died in the treated group. At necropsy, the incidences of benign or malignant (combined) tumours of the liver were 93% in treated males ($P < 0.01$) and 69% in treated females ($P < 0.01$), compared with 24% and 23% in controls, respectively. Metastasis of liver tumours to the lungs was observed in some of the treated animals. [The Working Group noted that the single dose tested may have exceeded the maximum tolerated dose.]

Groups of 50 male and 50 female NMRI mice (age, 5 weeks) were fed diets containing lindane at a concentration of 12.5, 25, or 50 ppm for 80 weeks. The control group contained 100 males and 100 females. No changes in body weight, feed consumption, or mortality were observed in the treated animals. There was no increase in the incidence of neoplasms of the liver, lung, skin, ovary, uterus, or lympho-haematopoietic system in the treated groups (Herbst et al., 1975; Weisse & Herbst, 1977). [The Working Group noted that lindane was tested below the maximum tolerated dose.]

Groups of 50 male and 50 female B6C3F_1 mice (age, 5 weeks) were fed diets containing lindane (purity, 100%) at a concentration of 80 or 160 ppm for 80 weeks, followed by an observation period of 10–11 weeks (NTP, 1977). The respective control groups had only 10 matching animals. For the statistical analysis, 10 control animals each were used from four other contemporaneous studies conducted over a period of 1 year at the same laboratory; this "pooled" control group consisted of a total of 50 animals. Survival of males and females in the treated and control groups was similar. Hepatocellular carcinomas and neoplastic nodules of the liver were the most frequent lesions observed in the controls and in the treated groups. The incidence of hepatocellular carcinoma in males at the higher dose (9/46) was not significantly different from that of the pooled control group (5/49). However, the incidence of hepatocellular carcinoma in males at the lower dose was significantly higher than that in the pooled controls (19/49, $P = 0.001$). There was no significant increase in the incidence of any tumour type in females. [The Working Group noted that, because of the small number of matched controls, pooled controls were used for statistical analyses which limited the interpretation of the study. The study was judged inadequate for evaluation.]

Lindane was studied in obese mottled yellow A^{vy}/a, lean pseudoagouti A^{vy}/a and lean black a/a (YS × VY) F_1 hybrid female mice (Wolff et al., 1987). F_1 hybrid mice were produced by mating a/a YS females with A^{vy}/a VY male mice. The dominant mutation at the A^{vy} locus in mice results in two phenotypic groups, obese mottled yellow and lean pseudoagouti, that are genetically identical but physiologically different. The hypothesis of the study was that these two phenotypes represent different degrees of expression of this mutation. To prove this hypothesis, the tumourigenic response to lindane of obese mottled yellow A^{vy}/a, lean pseudoagouti A^{vy}/a, and the relatively neoplasia-resistant black a/a (YS × VY) F_1 hybrid female mice were studied. The mice were given diets containing lindane [purity unspecified] at a concentration of 0 (control) or 160 ppm for 18 or 24 months before termination of the experiment. Each of the three phenotypes had their respective controls and treated groups. The 18-month and 24-month groups had 36 and 96 mice (age, 4 weeks) per group, respectively. At 18 months, only treated obese yellow mice had a significant increase [$P < 0.0001$] in the incidence of hepatocellular adenoma (controls, 0/34; treated, 12/36). At 24 months, the incidences of hepatocellular

tumours and lung bronchiolo-alveolar tumours differed quantitatively among the three phenotypes. The incidences of hepatocellular adenoma or carcinoma (combined) in the controls and treated groups were, respectively: 20/93, 49/94 [$P < 0.0001$] in the obese yellow mice; and 7/95, 16/95 [$P < 0.05$] in the lean pseudoagouti mice. In addition, lindane increased the incidence of bronchiolo-alveolar tumours in obese yellow (4/95, 18/95 [$P < 0.002$]) and lean pseudoagouti (6/95, 13/94 [not significant]) mice. Bronchiolo-alveolar tumours observed in this study were classified as either papillary or solid [and not further classified]. The black mouse was resistant to the induction of both hepatocellular and bronchiolo-alveolar tumours. [The Working Group noted the use of a single dose in a study on females only.]

In a study submitted to the EPA (2001a, b), which was carried out according to good laboratory practice, groups of 50 male and 50 female CD-1 mice (age, 38–44 days) were fed diets containing lindane (purity, 99.78%) at a concentration of 0, 10, 40, or 160 ppm for 78 weeks before termination of the experiment. There were no significant differences in body weights and survival between treated animals and controls. In females at the highest dose, there were significant decreases in weights of the uterus plus cervix. In female mice, there was a significant positive trend in the incidence of bronchiolo-alveolar adenoma ($P = 0.0274$), and a significant increase in incidence in the group at the highest dose ($P = 0.0200$) compared with controls. There was also a significant positive trend in the incidence ($P = 0.0389$), and a significant increase in the incidence of bronchiolo-alveolar adenoma or carcinoma (combined) at the highest dose group ($P = 0.0264$) compared with controls. Results of resectioning of lungs did not significantly change the initial findings and conclusion. Lindane did not increase the incidence of any tumour type in treated males.

3.2 Rat

Oral administration

Groups of 50 male and 50 female Osborne-Mendel rats (age, 5 weeks) were fed diets containing lindane (purity, 100%) at time-weighted average doses of 236 ppm (lower dose) or 472 ppm (higher dose) in males, and 135 ppm (lower dose) or 270 ppm (higher dose) in females for 80 weeks (NTP, 1977). The matched controls comprised 10 males and 10 females. The data from 45 untreated males and 45 untreated females from four other similar ongoing cancer bioassays in the same laboratory were pooled for the statistical analysis. Throughout the study, doses were lowered for all groups of treated animals due to mortality. All surviving animals were killed at 108–110 weeks. The incidences of thyroid C-cell adenoma in males were 1/6 (matched controls), 2/42 (pooled controls), 3/37 (lower dose), and 1/37 (higher dose); and in females were 0/8, 0/48, 4/44 ($P = 0.049$, versus pooled controls) and 3/42. The incidences of spleen haemangioma in males were 0/8, 0/52, 0/44, and 3/44, with a significant positive trend ($P = 0.030$, compared with pooled controls). The incidence of chromophobe adenoma of the pituitary gland in females was 3/7, 6/46, 14/45 ($P = 0.033$, versus pooled controls), and 8/45. The incidence of neoplastic nodules of the liver was 0/10, 0/49, 3/45, and 2/45 in males, and 0/10, 1/49, 4/48, and 2/45 in females. [The Working Group noted that dose levels were changed during the course of the study, and that because of the small number of matched controls, pooled controls were used for statistical analyses, which limited the interpretation of the study. The study was judged inadequate for evaluation.]

In a study submitted to the EPA (2001b), groups of 50 male and 50 female Wistar rats [age not reported] were fed diets containing lindane (purity, 99.78%) at a concentration of 0 (control), 1, 10, 100, or 400 ppm for 2 years. Final body weights of males at the highest dose were

significantly ($P < 0.05$) less than those of the controls. Body weights and body-weight gains for treated females were similar to those of the controls throughout the study. The percentages of males with tumours of the adrenal gland were: 14%, 16%, 16%, 6%, and 24% for benign tumours; and 0%, 0%, 6%, 8%, and 2% for malignant tumours, respectively. These incidences were not significantly increased compared with controls [statistical tests not reported]. There was no significant increase in tumour incidence in any group of treated females compared with controls. [The Working Group noted the limited reporting.]

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetics

4.1.1 Humans

(a) Absorption, distribution, and excretion

Lindane is a lipophilic compound that is expected to be readily absorbed after exposure. Absorption after inhalation has not been directly measured experimentally in humans, but has been inferred from body-burden measurements of lindane from occupational exposures (e.g. Baumann et al., 1980). While no experimental studies of oral intake of lindane in humans were available to the Working Group, uptake via ingestion has been inferred from accidental or intentional poisoning cases (e.g. Paul et al., 2013; Ramabhatta et al., 2014). Dermal absorption has also been demonstrated, but is dependent on the vehicle in which the chemical is administered. About 9% of the radiolabel was excreted in the urine after administration of lindane dissolved in acetone onto the forearm of healthy adult volunteers (Feldmann & Maibach, 1974). In a separate study, absorption into the systemic circulation after 6 hours was reported to be about 5% when using acetone as the vehicle, and about 60% when using white spirit (Dick et al., 1997). Dermal absorption of lindane from contaminated soil was measured to be in the range of 0.45–2.35% after 24 hours, depending on organic carbon content and soil loading (Duff & Kissel, 1996).

Lindane readily distributes throughout the body via the systemic circulation, with a preference for lipid-rich tissues such as adipose, or the brain (Baumann et al., 1980; Davies et al., 1983). Lindane has also been found in breast milk and umbilical cord blood, indicating lactational and placental transport (Siddiqui et al., 1981). Blood peak concentrations of lindane occurred approximately 4–6 hours after dermal administration (Ginsburg et al., 1977; Lange et al., 1981). Lindane is excreted mainly as metabolites in the urine, with very little excreted unchanged. Excretion terminal half-lives of 18–26 hours have been reported in several studies in adults and/or children (Feldmann & Maibach, 1974; Ginsburg et al., 1977; Aks et al., 1995). A more recent study of an ingestion overdose case estimated a longer half-life of 163 hours (Wiles et al., 2015). One study found that the elimination half-life, like the absorption rate, depended on the vehicle, with a shorter half-life of 25–58 hours with white spirit as vehicle, and a longer half-life of 50–111 hours with acetone (Dick et al., 1997). [The Working Group noted that the half-life of β-HCH is much longer, in the order of 7 years.]

(b) Metabolism

No studies on the metabolism of lindane in vivo in exposed humans were available to the Working Group. Based on biomonitoring of occupational exposures, numerous chlorophenols were identified in the urine of workers exposed to lindane and other HCH isomers (Engst et al., 1976a, b; Angerer et al., 1983). Specifically, 2-monochlorophenol, 3-monochlorophenol, and 4-monochlorophenol; 2,3-dichlorophenol, 2,4-dichlorophenol, 2,6-dichlorophenol, and

3,4-dichlorophenol; 2,4,6-trichlorophenol, 2,4,5-trichlorophenol, 2,3,4-trichlorophenol, 2,3,6-trichlorophenol, and 2,3,5-trichlorophenol; and 2,3,4,6-tetrachlorophenol and 2,3,4,5-tetrachlorophenol were identified. The metabolites 2,4-dichlorophenol and 2,4,6-trichlorophenol, 2,3,5-trichlorophenol, and 2,4,5-trichlorophenol were the most abundant metabolites in the urine, accounting for > 70% of urinary chlorophenols (Angerer et al., 1983). However, co-exposure to dichlorobenzene may have contributed to some of the dichlorophenol metabolites. One study in workers exposed to HCH isomers reported that several of the urinary metabolites were glucuronidated (Engst et al., 1976b). In a study in children given lindane for the treatment of lice, concentrations of 2,4,5- and 2,4,6-trichlorophenol and pentachlorophenol in the urine were elevated, but not statistically significantly so, in comparison to unexposed children, suggesting significant background exposures (Naeher et al., 2009).

In an experiment assessing the metabolism of lindane with human liver microsomes in vitro, six metabolites were reported: γ-1,2,3,4,5,6-hexachlorocyclohex-1-ene (3,6/4,5-HCCH), γ-1,3,4,5,6-pentachlorocyclohex-1-ene (3,6/4,5-PCCH), β-1,3,4,5,6-pentachlorocyclohex-1-ene (3,4,6/5-PCCH), 2,4,6-trichlorophenol 2,3,4,6-tetrachlorophenol, and pentachlorobenzene, the latter two of which were secondary metabolites of 3,6/4,5-HCCH (Fitzloff et al., 1982). The major pathways were through hexachlorocyclohex-1-ene and pentachlorocyclohex-1-ene, with trichlorophenol accounting for a smaller pathway. A separate experiment in human liver microsomes reported 3,4,6/5-PCCH oxide as the major product of 3,4,6/5-PCCH, with 17% of the original 3,4,6/5-PCCH converted to 3,4,6/5-PCCH oxide in 30 minutes (Fitzloff & Pan, 1984). However, this epoxide was found to be stable and not a substrate of epoxide hydrolase (Fitzloff & Pan, 1984). Pentachlorophenol was reported as one of the metabolites of lindane in some studies (Engst et al., 1976a, b), but not others (Angerer et al., 1983).

4.1.2 Experimental systems

(a) Absorption, distribution, and excretion

Lindane is readily absorbed by all species of experimental animal tested. Although no studies were available on the measurement of systemic absorption of lindane after inhalation, based on its lipophilicity, lindane would be expected to be absorbed by this route. Radiolabel studies in vivo with lindane in rats, rhesus monkeys, guinea-pigs, mice, pigs, and dogs have demonstrated dermal absorption (Reifenrath et al., 1984; Moody & Ritter, 1989; Franz et al., 1996), as have studies in vitro (Chang et al., 1994). Lindane is rapidly absorbed after ingestion, with between 30% and 62% reported to be absorbed after 30 minutes in mice and rats (Turner & Shanks, 1980; Ahdaya et al., 1981). In rats, the main route of entry into systemic circulation was blood, with only a small amount entering via the lymphatic system (Turner & Shanks, 1980). In a mouse model, cholestyramine reduced absorption of a single oral dose of lindane that was otherwise acutely toxic (Kassner et al., 1993).

After absorption, lindane and its metabolites are readily distributed to tissues via blood circulation. Due to its lipophilicity, lindane is preferentially stored in lipid-rich tissues such as adipose, but has been detected in a wide range of tissues, including the liver, brain, kidney, adrenals, heart, lungs, spleen, and testis (Eichler et al., 1983; Dalsenter et al., 1996; Siddiqui et al., 1996; Khanna et al., 2002). In all cases, tissues concentrations were higher than in the blood. In one study in the brain, it was reported that lindane preferentially concentrated in white matter as opposed to grey matter, with higher concentrations in the thalamus, mid-brain, and pons-medulla (Sanfeliu et al., 1988). When administered during or after pregnancy in rabbits and rats, lindane transfer via the placenta to the fetus and

via lactation to the neonate has been reported (Khanna et al., 1991; Pompa et al., 1994; Seiler et al., 1994; Dalsenter et al., 1997a).

Excretion of lindane occurs mainly through metabolites in the urine, with very little excreted unchanged or in the faeces (Chadwick et al., 1977, 1985; Ahdaya et al., 1981). Excretion appears to be limited by metabolic transformation, as increased body burden and reduced excretion occurred in mice exposed to higher doses that saturated biotransformation (Chadwick et al., 1987).

(b) Metabolism

The metabolism of lindane is complex and involves multiple intermediates and metabolites. Initial metabolism appears to be catalysed by cytochrome P450 (CYP), as shown by activity with rat liver microsomes (Fitzloff et al., 1982; Yamamoto et al., 1983). More than 70 metabolites have been identified in mammalian systems (Macholz & Kujawa, 1985). The ultimate fate of these metabolites is formation of mercapturic acid, glucuronide, or sulfate conjugates excreted in the urine (ATSDR, 2005).

[The Working Group noted that many of the metabolites of lindane, including trichlorophenols, may be biologically active (e.g. exhibit genotoxicity). However, there is a lack of adequate quantitative data to be able to attribute any of the observed effects of lindane to specific metabolites. Therefore, subsequent sections of the present monograph did not include evaluation of any data on metabolites of lindane.]

As with human liver microsomes, rat liver microsomes converted the lindane metabolite 3,4,6/5-PCCH to an epoxide, but this compound was found to be stable, with minimal further metabolism by rat liver microsomes or by purified epoxide hydrolase (Fitzloff & Pan, 1984).

[The Working Group noted that the formation of an epoxide, both in human and experimental systems (albeit in vitro), provides evidence that lindane may be metabolically activated to an electrophile. Additionally, the stability of the epoxide suggests the possibility that it may be systemically available beyond the site of formation (presumably the liver).]

4.1.3 Modulation of metabolic enzymes

(a) Humans

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

In a study in vitro, lindane (concentration, 25, 50, and 75 µM; exposure, 10 minutes to 18 hours) aromatase activity was increased after 10 minutes to 6 hours, but inhibited after 18 hours in human placental JEG-3 and transfected kidney E293 cells. There were no effects on *CYP19* mRNA, the gene transcript coding for aromatase (Nativelle-Serpentini et al., 2003). Lindane induced the mRNA expression of CYP2B6 (sevenfold), but inhibited that of CYP2D6 (0.5-fold) and CYP2E1 (0.2-fold) in freshly isolated human hepatocytes (Ellero et al., 2010).

(b) Experimental systems

In CD-1 mice exposed to lindane in utero (dams were dosed with 25 mg/kg bw on days 9–16 of gestation), CYP-dependent steroid hormone metabolism was impaired in male offspring (Di Consiglio et al., 2009). In the adult F_1 mice, CYP-mediated testosterone metabolism was dramatically affected at postnatal days 65–69, in the absence of systemic toxicity. During this period, testosterone 6β- and 2α-hydroxylation and dehydrogenation activities were strongly reduced, suggesting the CYP3A and CYP2C families as the major target of lindane-induced effects. Most changes had almost reversed by postnatal day 100. No effects on aromatase (CYP19) activity were seen. [These findings suggested an impairment of steroid hormone homeostasis, due to CYP-mediated disruption of testosterone catabolism (Di Consiglio et al., 2009).]

Oral administration of lindane (2.5, 5, 10, or 15 mg/kg bw) for 5 days caused a dose-dependent

increase in the activity of CYP-dependent 7-ethoxyresorufin-*O*-deethylase (EROD), 7-pentoxyresorufin-*O*-dealkylase (PROD), and *N*-nitrosodimethylamine demethylase (NDMA-*d*) in rat brain and liver (Parmar et al., 2003). Hepatic and brain CYP activity was also increased when the lowest dose (2.5 mg/kg) of lindane was given for a longer duration (15 or 21 days). CYP induction was greater in liver than in brain. Expression of CYP 1A1/1A2, 2B1/2B2 and 2E1 isoenzymes was increased by lindane. [The Working Group noted that each of these enzymes could affect the metabolism of other chemicals.]

Gastrointestinal nitroreductase activity was increased in the small intestine in weanling F344 rats given lindane at a dose of 20 mg/kg bw daily by gavage for 5 weeks (Chadwick et al., 1990). Lindane had no effect on either nitroreductase or dechlorinase enzyme activity in the caecum. [The Working Group noted that increased nitroreductase may account for the previously reported interaction between lindane and parathion.]

4.2 Mechanisms of carcinogenesis

4.2.1 Immunosuppression

(a) Humans

(i) Exposed humans

In comparison to an external control group of 20 clerks, 60 male workers in a factory producing lindane had significantly elevated levels of polymorphonuclear leukocytes and reticulocytes (Brassow et al., 1981). Significantly lower lymphocyte counts, prothrombin (Quick) test, and blood creatinine and uric acid concentrations were also seen in the factory workers. No other significant differences were identified, including in total erythrocytes and leukocytes, platelets, or haemoglobin content, or from case history, physical examination, neurological status, or electrocardiography. [The Working Group noted that the design of this study was weak because of the size and choice of control group.]

Nigam et al. studied 365 individuals exposed to HCH (80% β-HCH) during its manufacture and compared them with 146 controls (Nigam et al., 1993). Beta-globulins significantly increased as total HCH increased. In representative samples, circulating immune complexes were also detected. High concentrations of HCH were reported in the serum of all exposed workers. [The Working Group noted an apparent effect on antibody production in exposed humans.]

Aplastic anaemia was reported in multiple cases of lindane exposure, confirmed through serum blood measurements (Rauch et al., 1990; Rugman & Cosstick, 1990).

In addition to the studies suggesting modest effects of HCH on the immune system of exposed humans, two additional studies reported on mixed exposures to HCHs and other polychlorinated compounds. A study of 146 workers exposed primarily to PCBs for more than 6 months reported only weak associations between immunological abnormalities and concentrations of [α]-HCH, β-HCH, and [γ]-HCH (Daniel et al., 2001). In a separate study, pyruvate metabolism in peripheral blood lymphocytes was different relative to controls for 36 workers occupationally exposed to polychlorinated pesticides (Gammexane, DDT) (Hrycek et al., 1984). [The Working Group noted that these changes were of limited importance.]

Regarding related compounds, Dar et al. reported significantly higher blood β-HCH levels in patients with systemic lupus erythematosus than in healthy controls (Dar et al., 2012). In the patients, HCH concentrations correlated with marked increases in CD3(+)CD4(+) T-lymphocytes and decreases in CD4(+)CD25(+) T-lymphocytes.

(ii) Human cells in vitro

In early studies, Fisher and Mueller reported that γ-HCH inhibited the stimulation of lymphocyte growth by phytohaemagglutinin (Fisher & Mueller, 1971). Roux et al. confirmed the finding that lindane inhibits lymphocyte activation in studies in human peripheral blood mononuclear cells (Roux et al., 1979). Lindane (10^{-4} M) inhibited macromolecular biosynthesis in unstimulated lymphocytes, phytohaemagglutinin-activated lymphocytes, and dividing blast cells (Roux et al., 1979). Dar et al. (2012) corroborated this finding, reporting an inhibitory effect of HCH after treatment in vitro of peripheral blood mononuclear cells from patients with systemic lupus erythematosus. Interleukin-2 (IL-2) and interferon gamma (IFNγ) levels were decreased by HCH, while no effect was seen on IL-4 levels in the patients (Dar et al., 2012).

[The Working Group noted that together these studies show that lindane blocks lymphocyte activation in vitro, which is an immunosuppressive effect.]

Lindane was cytotoxic to human haematopoietic progenitor cells in vitro at concentrations similar to serum concentrations in acute poisonings (Parent-Massin et al., 1994).

(b) Experimental systems

Studies in multiple species show immunosuppressive effects with lindane and HCHs generally, and accumulation of HCHs in lymphoid organs.

(i) Non-human mammals in vivo

Mouse

Dose-dependent immunesuppressive effects with lindane and HCHs were seen in mice. In exposed albino mice, lindane suppressed both primary and secondary humoral immune responses in a time- and dose-dependent manner (Banerjee et al., 1996). With shorter durations of exposure, the secondary antibody response to sheep erythrocytes was more markedly suppressed than the primary response. A biphasic effect on cell-mediated and humoral immune responses was seen in mice exposed for 24 weeks to subtoxic doses of γ-HCH (0.012, 0.12, and 1.2 mg/kg) and evaluated 1 month later (Meera et al., 1992). Initial stimulation was followed by dose-dependent immunosuppression, accompanied by histological changes in lymphoid organs. No effect was seen on peritoneal macrophage function. A second study showed that uptake of ^{45}Ca increased during the initial immunostimulation, and then decreased concomitantly with immunosuppression in mice exposed to γ-HCH (0.012, 0.12, and 1.2 mg/kg) for 4, 12, and 24 weeks (Meera et al., 1993). Verapamil (a calcium-channel blocker) and trifluoperazine (a calmodulin inhibitor) inhibited lymphocyte proliferation during both phases of immunomodulation. Das et al. (1990) showed that HCH (10 and 100 mg/kg bw) can modulate the developing immune system in Swiss albino mice. HCH (α, β, and γ isomers) residues in pups were higher in the lymphoid organs than in the liver, and increased with dose. The delayed hypersensitivity response to sheep erythrocytes was significantly higher at the lower dose, but significantly impaired at the higher dose, compared with controls. The lower dose elevated both the mitogenic responsiveness of the spleen cells and the antibody response to sheep erythrocytes, while no effect on either measure was seen at the higher dose.

Rat

In rats, lindane and technical HCH suppressed the humoral immune response and were haematotoxic. Koner et al. demonstrated that subchronic lindane exposure in rats suppressed the humoral immune response, increased lipid peroxidation, and decreased antioxidant enzymes (Koner et al., 1998). Lindane (40 and 80 ppm in the diet, for 8 weeks) markedly reduced anti-sheep erythrocyte antibody titres, an effect attenuated by daily treatment with ascorbic acid (100 mg/kg, intragastric). A

suppressive effect of lindane on humoral immune responses was also seen in weanling rats exposed for 5 weeks (Dewan et al., 1980). The antibody titres attained in response to typhoid vaccine in untreated controls were significantly higher than those in treated animals. Administration of γ-HCH (20 mg/kg per day) for 30 days to ovariectomized rats significant changed the numbers of erythrocytes, neutrophils, and lymphocytes, as well as level of haemoglobin (see also Section 4.2.4) (Raizada et al., 1980). Joseph et al. (1992) showed that the haematotoxicity of dietary HCH (1000 ppm) in male albino rats is enhanced by vitamin A (2000 or 10^5 international units/kg). When vitamin A was absent from the diet, HCH induced severe haematotoxicity, as demonstrated by significantly reduced total leukocyte count, clotting time, and prothrombin time. On the other hand, the only indication of HCH-induced haematotoxicity in rats that received vitamin A supplements was a slight, significant decrease in total leukocyte count.

Rabbit

Kopeć-Szlezak et al. (1990) reported functional changes in granulocytes and structural changes in lymphocytes in the peripheral blood of rabbits exposed for 30 days to lindane (daily doses of 0.1 LD_{50}, or 7 mg/kg). Lindane significantly decreased phagocytic activity, and increased the number of non-phagocytizing granulocytes. Quantitative and qualitative changes were evident in the nucleoli and lysosomes of lymphocytes (Kopeć-Szlezak et al., 1990). Grabarczyk et al. (1990) reported reduced phagocytic activity of neutrophils, and increased number of lymphocytes with inactive nucleoli.

(ii) Non-human mammalian cells in vitro

Lindane caused concentration- and time-dependent cytotoxicity in C57BL/6 mouse splenocytes (Battaglia et al., 2010), and induced apoptotic and necrotic cell death in C57BL/6 mouse thymocytes (Olgun et al., 2004). Mixtures of lindane with either malathion or permethrin demonstrated a significantly greater than additive interaction in apoptotic and necrotic cells. Lindane was cytotoxic to rat haematopoietic progenitor cells, but at concentrations 1000-fold those in human progenitors (Parent-Massin et al., 1994).

(iii) Non-mammalian systems

Fish

At sublethal concentrations, lindane altered haematological parameters in the fish *Etroplus maculatus* (Bijoy Nandan & Nimila, 2012). Significant reductions were seen in erythrocyte count, haemoglobin, and haematocrit (erythrocyte volume fraction) with corresponding changes in mean corpuscular haemoglobin, mean corpuscular volume, and mean corpuscular haemoglobin concentration. In contrast, the leukocyte count) was significantly increased (Bijoy Nandan & Nimila, 2012).

In tilapia, lindane (20 or 40 mg/kg, intraperitoneal administration, for five consecutive days) decreased spleen and pronephros total leukocyte counts (Hart et al., 1997). Hypocellularity of lymphoid regions in the spleen and pronephros was also evident in fish exposed to lindane.

In rainbow trout, lindane (10, 50, or 100 mg/kg, intraperitoneal administration, for 5 days) affected antibody-secreting cells in a dose-dependent fashion. As a result, antibody production in sera, as demonstrated by agglutination, was suppressed (Dunier & Siwicki, 1994). A second study reported effects on immune function in rainbow trout exposed to lindane by oral (daily body dose of 1 mg/kg for 30 days) or intraperitoneal (10, 50, or 100 mg/kg) routes (Dunier et al., 1994).

In a study in leukocytes of gilthead seabream in vitro, lindane had no effect on cell viability, and only slightly altered immunological parameters (e.g. phagocytosis); however, lindane

upregulated genes related to the immune system (Cuesta et al., 2008).

Birds

Haematological changes were induced by lindane (5 mg/kg bw, twice in 1 week) in six bird species: house sparrow, baya weaver bird, common myna, rose-ringed parakeet, blue rock pigeon, and domestic duck (Mandal et al., 1986). Lindane induced anaemia, as demonstrated by reductions in erythrocyte count, haematocrit (erythrocyte volume fraction), and haemoglobin content, and in mean corpuscular volume, mean corpuscular haemoglobin, and mean corpuscular haemoglobin concentration. Prolonged bleeding and clotting times were observed. In most exposed birds, lindane also decreased splenic cell counts with minimal increases in splenic weight. Total leukocyte counts were increased. The differential leukocyte count revealed pronounced heterophilia and eosinophilia, with a decline in monocyte, lymphocyte and basophil numbers.

4.2.2 Oxidative stress

(a) Humans

(i) Exposed humans

Markers of oxidative stress were increased in human blood samples obtained from lindane poisoning cases admitted to the Guru Teg Bahadur Hospital, Delhi, India. Lipid peroxidation (thiobarbituric acid-reactive substances) and the activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione-*S*-transferase and γ-glutamyltransferase were increased, while glutathione levels decreased (Banerjee et al., 1999).

In 30 cases of lindane poisoning, γ-glutamyltransferase activity in plasma and glutathione levels in blood were significantly different from controls, but neither was altered in lymphocytes (Seth et al., 2001).

Maternal and cord blood levels of lindane correlated with both intrauterine growth retardation and oxidative stress (Pathak et al., 2011). Specifically, significant correlations were seen with oxidized DNA (8-hydroxy-2′-deoxyguanosine), malondialehyde, and glutathione, as well as protein carbonyl and the ferric reducing ability of plasma. However, as total HCH levels were also correlated with these effects, and considering that the HCH levels are also inter-correlated, the association could not be assigned specifically to lindane. [The Working Group noted the limitations of this study for evaluating these effects.]

(ii) Human cells in vitro

In human peripheral blood lymphocytes, lindane increased the formation of reactive oxygen species and decreased the mitochondrial transmembrane potential, effects that are likely to be responsible for caspase-3 activation (Michałowicz et al., 2013).

At non-cytotoxic concentrations, lindane synergistically increased hydrogen peroxide-induced DNA damage in human fibroblasts (Lueken et al., 2004). In contrast, antagonism was found when measuring DNA breakage in isolated PM2 DNA.

In human HaCaT keratinocytes, lindane increased the production of reactive oxygen species as assessed with dichlorodihydrofluorescein diacetate. Pre-treatment with *N*-acetyl cysteine markedly decreased lindane-induced ERK1/2 phosphorylation, but did not affect Raf or MEK1/2 activation by lindane (Ledirac et al., 2005).

(b) Experimental systems

Hepatic oxidative stress was induced by lindane (30 mg/kg, oral administration) in female Sprague-Dawley rats (Hassoun et al., 1993). Lindane (300 mg/kg, intraperitoneal) also induced oxidative stress in the liver of male Wistar rats as assessed by assay for malondialdehyde, glutathione peroxidase, glutathione

reductase, glucose-6-phosphate dehydrogenase, glutathione-*S*-transferase, γ-glutamyltransferase, catalase, and superoxide dismutase (Anilakumar et al., 2009). In the rat heart, oral administration of lindane (1.5 and 7 mg/kg per day for 21 days) induced lipid peroxidation (as measured by thiobarbituric acid-reactive substances), increased superoxide dismutase and catalase activities, and decreased glutathione levels (Ananya et al., 2005).

4.2.3 Receptor-mediated effects

(a) Humans

(i) Exposed humans

In 54 men exposed occupationally to HCH isomers during lindane production, testosterone levels were lower than in 20 unexposed control subjects (clerks of approximately the same age, not otherwise specified), but this was not statistically significant at the $P < 0.05$ level (6.8 ± 2.2 versus 8.0 ± 2.9 ng/mL, mean ± standard deviation) (Tomczak et al., 1981). Luteinizing hormone (LH) levels were significantly higher ($P < 0.01$) in exposed men than in controls (9.6 ± 4.2 versus 6.1 ± 2.1 mIU/mL), consistent with reduced circulating testosterone levels. Follicle-stimulating hormone levels were not different. Hormone levels were measured by a radioimmunoassay with excellent inter-assay variation values. Levels of HCH isomers in the serum measured using an unspecified method were 63.5 ± 45.1, 185 ± 150, and 36.6 ± 40.6 μg/L for α-, β-, and γ-HCH, respectively.

In a study of 304 men and 300 women from an area in Brazil that was heavily polluted with organochlorine pesticides, linear regression analysis found a borderline significant inverse association between testosterone and α-HCH and β-HCH in the serum of the men; there was no such association for γ-HCH (Freire et al., 2014). When β-HCH levels were divided into quartiles, a highly significant inverse association with testosterone levels was found with a *P* for trend of < 0.001. No significant associations were found between serum sex hormone and HCH levels in premenopausal women ($n = 210$). In peri-/postmenopausal women ($n = 77$), there was a borderline significant association between levels of LH and β-HCH, and a highly significant inverse association between levels of LH and β-HCH across β-HCH quartiles ($P = 0.008$). There were no significant associations between levels of serum γ-HCH and LH.

(ii) Human cells in vitro

Estrogen receptor-mediated effects

γ-HCH does not bind to the estrogen receptor (ER) in cytosolic binding assays (Danzo, 1997) or to ERα and ERβ in cells transfected with reporter vectors (Lemaire et al., 2006). Yeast-based assays yielded mixed results (Lee et al., 2002; Dhooge et al., 2006), while no binding was seen with recombinant ERs (Scippo et al., 2004). Consistent with these observations, γ-HCH does not have estrogenic effects on ER-positive human MCF-7 breast cancer cells (Soto et al., 1995; Briz et al., 2011). [In vivo, the effects of γ-HCH may be complex and display non-linear dose–response relationships based on studies in rats, but no data were available for humans or human cells.]

Estrogen is formed in humans and other mammals by the enzyme aromatase. γ-HCH at concentrations of 25–75 μM inhibited aromatase enzyme activity, but not mRNA expression in human placental JEG-3 cells and human embryonal kidney E293 cells stably transfected with the aromatase gene; proliferation of these cells in the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was not affected by γ-HCH (Nativelle-Serpentini et al., 2003).

Androgen receptor-mediated effects

γ-HCH (and δ-HCH) inhibited binding of radiolabelled 5α-dihydrotestosterone (DHT) to the androgen receptor and human sex hormone-binding globulin in vitro (Danzo, 1997).

Consistent with this finding, γ-HCH inhibited the growth of LNCaP human prostate cancer cells expressing androgen receptor by 20–30% over 72 hours at concentrations of 1 μM and higher, which may be associated with the presence of ERβ (Maranghi et al., 2007). However, γ-HCH did not activate or inhibit human androgen receptor transfected into PC-3 human prostate cancer cells or Chinese hamster ovarian cells with a reporter construct under transcriptional control of an androgen-responsive promoter (Schrader & Cooke, 2000; Roy et al., 2004). β-HCH did not have effects in this system, but α-HCH had clear anti-androgenic effects (Roy et al., 2004; Pavlíková et al., 2012).

Other receptor-mediated effects

γ-HCH has negligible binding affinity to the human progesterone receptor (Scippo et al., 2004), but inhibited progesterone-receptor transactivation by progesterone in a yeast system in a dose-dependent fashion, being significant at a concentration of 1 μM and above (Jin et al., 1997). γ-HCH at a concentration of 10 μM transactivated the human pregnane X receptor (PXR) and induced the protein expression of CYP3A4 and CAYP2B6, both of which are regulated by PXR (Lemaire et al., 2004).

To examine human adrenocortical NCI-H295R cells as a possible system in vitro for the assessment of adrenal disruption using molecular end-points, lindane was used as positive control. γ-HCH reduced the secretion of cortisol, in addition to downregulating the expression of several steroidogenic enzymes, and blocking the activation of the steroidogenic acute regulatory protein (StAR) gene promoter (Oskarsson et al., 2006).

(b) Experimental systems

(i) Non-human mammals in vivo

Estrogen receptor-mediated effects

Several rodent experiments using substantial γ-HCH doses reported effects in vivo on ER-related end-points, such as the development of the mouse female genital tract. Differences in outcome were evident across species, and other aspects of experimental design. A daily gavage dose of γ-HCH (10 mg/kg) increased circulating 17β-estradiol (E2) in young adult female F344 rats, whereas there was no such effect was seen at 20 mg/kg, and E2 was decreased at 40 mg/kg. LH levels as well as uterine weight were decreased at both higher doses (Cooper et al., 1989). In prepubertal Sprague-Dawley rats given seven daily intraperitoneal injections of γ-HCH at a dose of 15 mg/kg, the uterine-weight response to estrone treatment was decreased, and uptake of radiolabelled estrone was reduced (Welch et al., 1971). Treatment of prepubertal female F344 rats with γ-HCH at 30 mg/kg per day for 7 days also decreased the uterine-weight response to E2 and sharply reduced the E2-induced increase in serum LH (Cooper et al., 1989). Administration of γ-HCH (20 mg/kg per day) for 30 days to ovariectomized rats slightly reduced the estrogen-induced weight increase in tissues of the female genital tract, and caused significant changes in numbers of erythrocytes, neutrophils, and lymphocytes, as well as levels of haemoglobin (see also Section 4.2.4) (Raizada et al., 1980). Blunting of the uterine-weight response to E2 was also found in prepubertal Long Evans rats treated with γ-HCH at a daily dose of 40 mg/kg, but induction of the uterine progesterone receptor and nuclear redistribution of ER induced by E2 were not affected by γ-HCH (Laws et al., 1994). Similarly, in ovariectomized young adult Long Evans rats, progesterone-receptor induction in the uterus and pituitary gland was not affected

by γ-HCH at doses up to 40 mg/kg per day (Laws et al., 1994).

In contrast, prenatal treatment of pregnant CD-1 mice with γ-HCH at a daily oral dose of 15 mg/kg given on days 9–16 of gestation, age at vaginal opening of the female offspring was reduced by 2 days and uterine weight at postnatal day 22 was increased by about 15%, an effect that was no longer present at postnatal day 22 (Maranghi et al., 2007).

Aromatase activity in hepatic microsomes of female mice that had been exposed to γ-HCH (15 mg/kg per day) during pregnancy or in utero was not altered 22 days after parturition or birth (Maranghi et al., 2007).

Androgen receptor-mediated effects

In males, lindane caused an impairment of steroid hormone homeostasis, due to CYP-mediated disruption of testosterone catabolism. In particular, γ-HCH inhibited cytosolic 5α-dihydrotestosterone-androgen receptor (DHT-AR) complex formation in the prostate of F344 rats treated for 7 days at a dose of 60 mg/kg (Simić et al., 1991). There are also reports of inhibition in vivo by lindane (4–8 mg/kg per day by gavage for 30–45 days) of the activity of the androgen biosynthetic enzymes 3-hydroxysteroid dehydrogenase and 17-hydroxysteroid dehydrogenase in adult rat testes, and reduction of weights of testes, ventral prostate, and seminal vesicles, and of serum testosterone (by 29–44%) (Chowdhury & Gautam, 1994; Sujatha et al., 2001). Prenatal exposure of pregnant female Wistar rats to γ-HCH (30 mg/kg on day 15 of gestation) resulted in a 43% reduction in serum testosterone in male offspring aged 7 months (Dalsenter et al., 1997b). Prenatal exposure of pregnant female CD-1 mice to γ-HCH (25 mg/kg per day on days 9–16 of gestation) resulted in the impairment of androgen catabolism in pubertal and young adult male offspring (Di Consiglio et al., 2009). The impact of treatment with γ-HCH on the activity of hepatic CYP-mediated testosterone hydroxylase, aromatase, and other testicular parameters was tested at multiple time-points considered critical for the sexual maturation of CD-1 mice (postnatal days 50, 65–69, and 100). On postnatal days 65–69, significant changes to testis weight and spermatid number as well as CYP-mediated changes in testosterone metabolism were observed in the adult F_1 mice without evidence of systemic toxicity. Activities of testosterone 6β- and 2α-hydroxylation and dehydrogenation were most strongly reduced during this period, suggesting the CYP3A and CYP2C families as the major target of lindane-induced effects. Most changes had almost recovered by postnatal day 100. No effects on aromatase activity were seen.

(ii) Non-human mammalian cells in vitro

In rat pituitary tumour cells (MtT/E-2) that are estrogen responsive, estrogenic effects of lindane (γ-HCH) (growth stimulation and ER binding and transcriptional activation) have been reported, but only at concentrations of 100 μM, not at 10 μM and below (Maruyama et al., 1999). Anti-estrogenic effects of γ-HCH (10–30 μM) have been reported for several molecular end-points (activation of Akt and ERK 1/2) and downregulation of ERα, but not ERβ, in primary neuronal cells derived from NMRI mice (Briz et al., 2011).

Using endothelial cell proliferation and thymidine incorporation, wound healing, ascites formation and secretion, chorio-allantoic membrane formation, and an assay for neovascularization in vivo in male mice, lindane was shown to be a potent angiogenesis stimulator (Clere et al., 2012; Bharathi et al., 2013), and neovascularization in male Swiss mice was prevented by silencing of ERα expression (Clere et al., 2012).

γ-HCH (δ-HCH) inhibited binding of radiolabelled DHT in vitro to the rat prostate androgen receptor, but not to rat epididymal androgen binding protein (Danzo, 1997). γ-HCH

stimulated testosterone production and proliferation of rat Leydig cells in vitro at concentrations up to 10 µg/mL, effects that disappeared at higher concentrations (Ronco et al., 2001). It strongly counteracted the stimulatory effect of human chorionic gonadotropin on testosterone production by these cells at concentrations of 10 µg/mL and higher, probably via a decrease in cAMP production (Ronco et al., 2001). Inhibition of progesterone biosynthesis by α-, δ-, and γ-HCH at high (50 µM) concentrations was found in a mouse Leydig tumour cell line (Walsh & Stocco, 2000).

4.2.4 Genotoxicity and related effects

Lindane has been studied in a variety of assays for genotoxic and related potential. Tables 4.1–4.4 summarize the studies carried out in humans in vivo and in vitro, in experimental animals in vivo, in mammals in vitro, and in non-mammalian systems both in vitro and in vivo, respectively.

(a) Humans

(i) Exposed humans

No data in exposed humans were available to the Working Group. The relationship between Yq microdeletion in patients with normal karyotype and level of total HCH and its isomers α-HCH, β-HCH and γ-HCH in semen was studied (Khan et al., 2010). No effect was observed with lindane.

(ii) Human cells in vitro

See Table 4.1

No induction of DNA damage measured by DNA-adduct detection was observed after treatment of HepG2 hepatocarcinoma cells line with γ-HCH in vitro (Dubois et al., 1997). Effects were seen in rat cells, as described below. Similarly, negative results were found by the unscheduled DNA synthesis (UDS) assay in the VA-4 cell line after exposure to γ-HCH (Ahmed et al., 1977).

Regarding DNA strand breaks and other types of DNA damage, positive results were found in many but not all cell types. Induction of DNA strand breaks was detected by radioactive labelling of the 5′ broken ends of exposed total leukocytes to lindane (analytical grade) (Sreekumaran Nair et al., 2002). Induction of DNA damage as measured by the comet assay was observed after treatment with γ-HCH in MCL-5 metabolically competent cell line (Martin et al., 1999). Furthermore, a higher level of DNA damage was achieved in the presence of inhibitors of DNA repair. Results indicate that γ-HCH-induced DNA lesions are repaired by nucleotide excision repair (Martin et al., 1999). An increase in the frequency of DNA breaks as determined by the comet assay after lindane treatment was observed in nasal mucosal cells (Pool-Zobel et al., 1994); however, negative results were found in isolated lymphocytes (Pool-Zobel et al., 1993) and in gastric mucosa cells (Pool-Zobel et al., 1994).

Induction of chromosomal damage estimated by the frequency of micronucleus formation was observed after treatment with γ-HCH in MCF-7 cells (Kalantzi et al., 2004; Hewitt et al., 2007).

An increase in the frequency of chromosomal aberration (gap not included) and sister-chromatid exchange was observed after 72 hours of treatment with γ-HCH in human lymphocytes cultured without S9 microsomal fraction (Rupa et al., 1989).

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.2

In HPB black mice analysed after a single intraperitoneal treatment, binding of γ-HCH to DNA occurred only at very low levels (Iverson et al., 1984). An increase in the frequency of micronucleus formation was observed in the bone marrow of Park male mice treated with an intraperitoneal dose of γ-HCH (Yaduvanshi et al., 2012). On the other hand, no induction of micronucleus formation was observed in bone marrow

Table 4.1 Genetic and related effects of lindane (γ-HCH) in human cells in vitro

Tissue, cell line	End-point	Test	Results[a]		Concentration (LED or HID)	Comments	Reference
			Without metabolic activation	With metabolic activation			
HepG2 hepatocarcinoma cell line	DNA damage	DNA-adduct ^{32}P-postlabelling	–	NT	50 µM		Dubois et al. (1997)
Leukocytes	DNA damage	DNA strand breaks radioactive labelling assay	+	NT	20 µg/mL	Analytical grade lindane	Sreekumaran Nair et al. (2002)
MCL-5 metabolically competent lymphoblastoid cell line	DNA damage	DNA strand break Comet assay	+	NT	1.56 mM		Martin et al. (1999)
Nasal mucosa cells	DNA damage	DNA strand break Comet assay	+	NT	0.03 mM		Pool-Zobel et al. (1994)
Isolated lymphocytes	DNA damage	DNA strand break Comet assay	–	NT	0.1 mM		Pool-Zobel et al. (1993)
Gastric mucosa cells	DNA damage	DNA strand break Comet assay	–	NT	1 mM		Pool-Zobel et al. (1994)
VA-4 cell line	DNA damage	UDS assay	–	–	1000 µM		Ahmed et al. (1977)
Lymphocytes	Chromosomal damage	Chromosomal aberrations	+	NT	0.05 µg/mL		Rupa et al. (1989)
MCF-7 mammary carcinoma cell line	Chromosomal damage	Micronucleus induction	+	NT	1×10^{-12} M		Hewitt et al. (2007)
MCF-7 mammary carcinoma cell line	Chromosomal damage	Micronucleus induction	+	NT	1×10^{-12} M		Kalantzi et al. (2004)
Lymphocytes	Chromosomal damage	Sister-chromatid exchanges	+	NT	0.1 µg/mL		Rupa et al. (1989)

[a] +, positive result; –, negative result

HID, highest ineffective dose; LED, lowest effective dose; NT, not tested; UDS, unscheduled DNA synthesis

Table 4.2 Genetic and related effects of lindane (γ-HCH) in non-human mammals in vivo

Species, strain, sex	Tissue	End-point	Test	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mouse, HPB black	Hepatic cells	DNA damage	DNA binding	+	25 mg/kg	i.p. × 1		Iverson et al. (1984)
Mouse, Swiss albino, male	Germ cells	Chromosomal damage	Dominant lethal mutation	+	500 ppm	p.o. continuously × 4–8 mo	Formulation (not specified)	Lakkad et al. (1982)
Mouse, Swiss albino	Bone marrow	Chromosomal damage	Chromosomal aberration	+	1.6 mg/kg	gastric × 1 × 7 days	Formulation (not specified; 20% γ-HCH)	Kumar et al. (1995)
Mouse, Park, male	Bone marrow	Chromosomal damage	Micronucleus induction	+	35 mg/kg	i.p. × 1		Yaduvanshi et al. (2012)
Mouse, NMRI	Bone marrow	Chromosomal damage	Micronucleus induction	–	70 mg/kg	p.o. × 1		Pool-Zobel et al. (1993)
Mouse, CD-1	Testicle cells	Fertility	Chromatin abnormalities DNA content	+	25 mg/kg	p.o. × 1 on days 9–16 of gestation	Exposure in utero	Traina et al. (2003)
Rat, Sprague-Dawley	Hepatic cells	DNA damage	DNA strand break Alkaline elution	+	30 mg/kg	p.o. × 1		Hassoun et al. (1993)
Rat, Sprague-Dawley	Nasal mucosa cells	DNA damage	DNA strand break Comet assay	+	200 µg/kg	p.o. × 1		Pool-Zobel et al. (1993)
Rat, Sprague-Dawley	Gastric cells	DNA damage	DNA strand break Comet assay	(–)	60 mg/kg	p.o. × 1	[two animals not clearly reported]	Pool-Zobel et al. (1993)
Rat, Sprague-Dawley	Colonic mucous membrane cells	DNA damage	DNA strand break Comet assay	(+)	60 mg/kg	p.o. × 1	[two animals not clearly reported]	Pool-Zobel et al. (1993)
Rat , Sprague-Dawley	Isolated lymphocytes	DNA damage	DNA strand break Comet assay	(–)	60 mg/kg	p.o. × 1	[two animals not clearly reported]	Pool-Zobel et al. (1993)
Rat	Bone marrow	Chromosomal damage	Chromosomal aberration	–	15 mg/kg	p.o. × 12 wk		Gencik (1977)

Table 4.2 (continued)

Species, strain, sex	Tissue	End-point	Test	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Rat , Sprague-Dawley	Bone marrow	Chromosomal damage	Micronucleus induction	–	60 mg/kg	p.o. × 1		Pool-Zobel et al. (1993)
Rat, Wistar male	Bone marrow	Chromosomal damage	Micronucleus induction	–	100 mg/kg	p.o. × 4 wk		Etim et al. (2006)
Rat, Wistar male	Bone marrow	Chromosomal damage	Micronucleus induction	+	300 mg/kg	i.p. × 1		Anilakumar et al. (2009)
Hamster, Chinese	Bone marrow	Chromosomal damage	Micronucleus induction	–	120 mg/kg	p.o. × 1		Pool-Zobel et al. (1993)
Hamster, Chinese	Bone marrow	Chromosomal damage	Sister-chromatid exchange	–	120 mg/kg	p.o. × 1		Pool-Zobel et al. (1993)

[a] +, positive result; –, negative result; +/–, equivocal (variable response in several experiments within an adequate study); (+) or (–), positive/negative in a study of limited quality
HCH, hexachlorocyclohexane; HID, highest ineffective dose; i.p., intraperitoneal; LED, lowest effective dose; mo, month; NT, not tested; p.o., oral administration; wk, week

cells of NMRI mice after a single oral treatment with γ-HCH (Pool-Zobel et al., 1993). In the male offspring of female CD-1 mice treated in utero with γ-HCH from day 9 to day 16 of gestation, alterations in the DNA content (possibly attributable to DNA strand breaks) of testicle cells was observed (Traina et al., 2003).

In Sprague-Dawley rats treated orally with γ-HCH, DNA damage evaluated by the alkaline elution assay gave positive results in hepatocytes (Hassoun et al., 1993). When DNA damage was evaluated by comet assay, positive results were found in the nasal mucosa of Sprague-Dawley rats treated orally (Pool-Zobel et al., 1993), while results were inconclusive for gastric and colonic mucous membrane cells as well in isolated lymphocytes in the same treated animals (Pool-Zobel et al., 1993). No induction of chromosomal aberration was observed in the bone marrow cells of rats exposed orally to γ-HCH for 12 weeks (Gencik, 1977). While induction of micronucleus formation was reported in bone marrow cells of Wistar male rats after a single intraperitoneal treatment with γ-HCH (Anilakumar et al., 2009), no such effect was reported after oral exposure to γ-HCH, regardless of the treatment period (Pool-Zobel et al., 1993; Etim et al., 2006).

Neither induction of micronucleus formation nor sister-chromatid exchange was observed in bone marrow cells from Chinese hamsters treated orally with γ-HCH (Pool-Zobel et al., 1993).

In several studies, a causative effect of lindane alone could not be demonstrated because the exposure was to a mixture. Induction of DNA damage estimated by the increased frequency of chromosomal aberration was observed in the bone marrow cells of Swiss albino mice after gastric treatment with technical-grade HCH (γ-HCH, 20%) for up to 7 days (Kumar et al., 1995). The dominant-lethal assay gave positive results for DNA damage in the germ cells of Swiss albino males continuously exposed orally to technical-grade HCH for 4–8 months (Lakkad et al., 1982).

(ii) Non-human mammalian cells in vitro

See Table 4.3

γ-HCH gave negative results in two studies in Chinese hamster ovary and V79 cells. In the hypoxanthine-guanine phosphoribosyl-transferase (Hgprt) or sister-chromatid exchange assays, negative results were reported for γ-HCH either in the presence or absence of a S9 microsomal fraction (Pool-Zobel et al., 1993). Interaction of lindane with the DNA of hepatic cells in HPB black mice was analysed in vitro after treatment with γ-HCH. Positive results were observed for γ-HCH either in the presence or in the absence of S9 metabolic fraction (Iverson et al., 1984).

In fetal rat hepatocytes, an increase in the frequency of DNA adducts was observed using ^{32}P post-labelling after treatment in vitro with γ-HCH (Dubois et al., 1997). The comet assay also gave positive results in gastric mucosa and nasal mucosa cells of Sprague-Dawley rats exposed to γ-HCH in vitro (Pool-Zobel et al., 1994). On the other hand, negative results were previously reported for the same end-point and by the same research group for γ-HCH-exposed cells (Pool-Zobel et al., 1993). The comet assay gave negative results in Sprague-Dawley rat primary hepatocytes exposed to γ-HCH (Pool-Zobel et al., 1993).

(iii) Non-mammalian systems

See Table 4.4

The frequency of DNA adduct formation was increased by treatment with γ-HCH in embryonic cells from the quail *Coturnix coturnix* (Dubois et al., 1997).

Treatment with γ-HCH caused DNA damage in the haemocytes of Pacific oyster *Crassostrea gigas*, as determined by the comet assay (Anguiano et al., 2007). Lindane did not induce micronucleus formation in haemocytes from the Mediterranean mussel *Mytilus galloprovincialis* after 15 days of exposure (Raftopoulou et al., 2006).

Table 4.3 Genetic and related effects of lindane (γHCH) in non-human mammalian cells in vitro

Species, strain	Tissue, cell line	End-point	Test	Results[a]		Concentration (LEC or HIC)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Mouse, HPB black	Hepatic cells	DNA damage	DNA binding	+	+	1 µM		Iverson et al. (1984)
Rat	Fetal hepatocytes	DNA damage	DNA adduct-^{32}P-postlabelling	+	NT	50 µM		Dubois et al. (1997)
Rat, Sprague-Dawley	Gastric mucosa cells	DNA damage	DNA strand breaks, comet assay	+	NT	0.125 mM	Positive results for 3 out of the 4 rats tested	Pool-Zobel et al. (1994)
Rat, Sprague-Dawley	Nasal mucosa cells	DNA damage	DNA strand breaks, comet assay	+	NT	0.5 mM		Pool-Zobel et al. (1994)
Rat, Sprague-Dawley	Gastric mucosa cells	DNA damage	DNA strand breaks, comet assay	–	NT	0.1 mM		Pool-Zobel et al. (1993)
Rat, Sprague-Dawley	Primary hepatocytes	DNA damage	DNA strand breaks, comet assay	–	NT	0.1 mM		Pool-Zobel et al. (1993)
Hamster, Chinese	CHO cells	Mutation	*Hprt* assay	–	–	300 mM		Pool-Zobel et al. (1993)
Hamster, Chinese	CHO cells	Chromosomal damage	Sister-chromatid exchange	–	–	300 mM		Pool-Zobel et al. (1993)

[a] +, positive result; –, negative result; ±, equivocal (variable response in several experiments within an adequate study); (+) or (–), positive/negative result in a study of limited quality
CHO, Chinese hamster ovary; HCH, HCH, hexachlorocyclohexane; HIC, highest ineffective concentration; LEC, lowest effective concentration, NT, not tested

Table 4.4 Genetic and related effects of lindane (γ-HCH) in non-mammalian systems

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]		Concentration (LEC or HIC)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Bird	Quail, *Coturnix coturnix japonica*, embryonic cells	DNA damage	DNA-adduct ^{32}P-postlabelling	+	NA	50 µM		Dubois et al. (1997)
Mollusc	Pacific oyster, *Crassostrea gigas*	DNA damage	Comet assay	+	NA	0.7 mg/L	Haemocytes exposed to γ-HCH	Anguiano et al. (2007)
	Mediterranean mussel, *Mytilus galloprovincialis*	Chromosomal damage	Micronucleus induction	–	NA	0.03 mg/L	Exposure for 15 days with change of xenobiotic every 2 days	Raftopoulou et al. (2006)
Insect	*Drosophila melanogaster*, Oregon-R strain	Mutation	X-chromosome-linked recessive lethal	+	NA	5.0 µg/L in feeding solution	Formulation (not specified; 20% γ-HCH)	Kumar et al. (1995)
	Drosophila melanogaster, Oregon-R strain	Mutation	Lethal mutation expressed as larval hatchability	+	NA	20.0 µg/L in feeding solution	Formulation (not specified; 20% γ-HCH)	Kumar et al. (1995)
Plant systems	Onion, *Allium cepa*	Chromosomal damage	Chromosomal aberrations	+	NA	Saturated water solution		Hervás (1976)
	Onion, *Allium cepa*	Chromosomal damage	Chromosomal aberrations	+	NA	9.0 mg/L	Formulation (not specified; 20% γ-HCH)	Kumar et al. (1995)
Lower eukaryote (yeast)	*Saccharomyces cerevisiae*	Mutation	Mitotic gene conversion	–	NT	NR		Fahrig (1974)
	Saccharomyces cerevisiae, D61.M	Mutation	Mitotic recombination and mutation	–	NT	0.170 mM		Albertini et al. (1988)
	Saccharomyces cerevisiae, D61.M	Chromosomal damage	Aneuploidy, chromosomal loss assay	–	NT	0.170 mM		Albertini et al. (1988)

Table 4.4 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]		Concentration (LEC or HIC)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Prokaryote (bacteria)	*Salmonella typhimurium*, TA98, TA100, and TA102,	Mutation	Reverse mutation	+	+	5 µg/plate		Yaduvanshi et al. (2012)
	Salmonella typhimurium, TA98	Mutation	Reverse mutation	–	(+)	50 µg/plate	Positive results in two out of three experiments	Gopalaswamy & Aiyar (1986)
	Bacillus subtilis, M45 Rec^-, H17 Rec^+	Mutation	Rec assay, differential toxicity	–	NT	NR	Mixture of α-, β-, γ-HCH	Shirasu et al. (1976)

[a] +, positive result; –, negative result; ±, equivocal (variable response in several experiments within an adequate study); (+) or (–), positive/negative result in a study of limited quality
HCH, hexachlorocyclohexane; HIC, highest ineffective concentration; LEC, lowest effective concentration; NA, not applicable; NR, not reported; NT, not tested

In *Drosophila melanogaster*, mutagenicity was observed using the X-chromosome-linked recessive-lethal assay after exposure to a formulation containing 20% γ-HCH (Kumar et al., 1995).

γ-HCH was not mutagenic in *Saccharomyces cerevisiae* (strain not specified) using a mitotic gene-conversion assay in the absence of a microsomal S9 fraction (Fahrig, 1974) as well as in *S. cerevisiae* D61.M in the presence and in the absence of metabolic activation (Albertini et al., 1988). Negative results were also demonstrated for *S. cerevisiae* D61.M exposed to γ-HCH in the chromosomal loss assay, both in the presence and in the absence of metabolic activation (Albertini et al., 1988).

In plants, an increase in the frequency of chromosomal aberration was reported in root meristematic cells of *Allium cepa* after treatment with γ-HCH, with an induction of viable multinucleate cells with aneuploid nuclei after cytokinesis inhibition by caffeine (Hervás, 1976) and by a non-specified formulation containing 20% γ-HCH (Kumar et al., 1995).

In *Salmonella typhimurium*, γ-HCH produced statistically significant mutagenic effects in strains TA98, TA100, and TA102 with or without S9 microsomal fraction (Yaduvanshi et al., 2012). [Although the authors reported a positive finding, the Working Group noted that the reported effect sizes were minimal to achieve statistical significance, i.e. the mutagenic rate was not doubled.] Negative or inconclusive results were reported when *S. typhimurium* strain TA98 was exposed to γ-HCH in the absence or presence of metabolic activation, respectively (Gopalaswamy & Aiyar, 1986).

4.2.5 Altered cell proliferation or death

(a) Humans

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

In studies in vitro, lindane demonstrated cell type-specific induction of cell proliferation or effects on cell proliferation through receptor-mediated mechanisms in ERα-positive cells, such as MCF-7 human breast cancer cells (Briz et al., 2011). However, lindane may inhibit cell proliferation, in a dose-dependent manner (1–100 μM) through receptor-mediated mechanisms in ERβ- and androgen receptor-positive LNCaP cells (Maranghi et al., 2007). [In comparison with 17β-estradiol, these effects were not marked.]

Through the intracellular release of Ca^{2+}, lindane induces apoptosis in HL-60 cells (Kang et al., 1998), an effect that may contribute to immunotoxicity (Betoulle et al., 2000). While other studies have not observed marked decreases in cell viability, altered levels of apoptosis-related factors such as Bcl-2 (increases in MCF-7 cells after exposure at up to 0.1 nM) or Bax (increases in MCF-7 cells after exposure at 100 μM; increases in PC-3 cells after exposure at 0.01 nM) have been noted (Kalantzi et al., 2004). A consistent observation with lindane is the presence of a biphasic dose–response relationship with distinct effects at low (< 1 μM) and high (> 1 μM to < 100 μM) doses (Llabjani et al., 2011). Kalantzi et al. (2004) reported a distinction between lindane-induced alterations in the Bcl-2:Bax ratio at low concentrations (nM) and cytotoxicity at high doses (μM). Cell type may be critical; for instance, biologically relevant levels of lindane induce apoptosis in human lymphocytes, together with an associated increase in reactive oxygen species and a reduction in mitochondrial transmembrane potential (Michałowicz et al., 2013). Whether lindane-induced modulation of Bcl-2:Bax ratios promotes apoptosis or facilitates cell survival remains to be established, and may depend on a range of other confounding factors (Hewitt et al., 2007).

(b) Experimental systems

Exposure of pregnant mice to lindane in vivo increased apoptosis in primordial germ cells, an effect associated with Akt modulation (La Sala et al., 2009). In male Wistar rats, a single dose of

lindane induced testicular apoptosis associated with the nuclear translocation of nuclear factor kappa β (NF-κβ) and the increased expression of a range of pro-apoptotic factors (e.g. cytochrome *c*, caspase-3 and -9, Fas, and FasL) (Saradha et al., 2009). Lindane also increased oxidative stress, triggering NF-κβ translocation and upregulation of target genes such as TNF-α and IL-1α (Videla et al., 2004). Sentinel organisms such as Pacific oysters, *Crassostrea gigas*, exhibit an in-vivo susceptibility to the cytotoxic effects of lindane, with genotoxicity being induced in isolated haemocytes (Anguiano et al., 2007). Finally, in the male offspring of CD-1 females treated in utero with γ-HCH from day 9 to day 16 of gestation, alterations in the DNA content of testicle cells, possibly attributable to DNA strand breaks, were observed (Traina et al., 2003) (see Section 4.2.4).

The results above are consistent with lindane causing a slight elevation in levels of apoptosis in murine splenocytes in vitro (Battaglia et al., 2010). An immunotoxic effect associated with apoptotic and necrotic cell death in murine thymocytes in vitro is linked with the induction of drug metabolizing mixed function oxidase enzymes (Olgun et al., 2004). Despite the generation of reactive oxygen species and the depletion of glutathione, lindane primarily induces apoptosis as opposed to necrosis in exposed Madin-Darby canine kidney cells (Piskac-Collier & Smith, 2009). Its transforming activity in BALB/c 3T3 cells is also associated with cell proliferation (Perocco et al., 1995). This is in contrast to lindane-induced toxicity in primary rat hepatocytes, which could be jointly attributed to the disruption of the autophagic process, the inhibition of apoptotic cell death, and the induction of necrosis (Zucchini-Pascal et al., 2009). Slight increases in levels of Bad mRNA after exposure were noted in PC12 rat pheochromocytoma cells (Aoki et al., 2008). The observation of cytotoxicity at high doses (μM) is consistent with the observation that lindane inhibits phytohaemagglutinin-P-induced stimulation of the mitogenic response in bovine lymphocytes (Kensler & Mueller, 1978).

4.2.6 Inflammation

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

Meade et al. first reported in 1984 that lindane (γ-HCH) induced arachidonic acid release from mouse macrophage phospholipids and also strongly stimulated leukotriene C4 production (Meade et al., 1984). However, in comparison with zymosan, lindane exerts only a modest effect on prostaglandin production. Lindane may therefore affect phosphatidylinositol metabolism (Meade et al., 1984).

The similarity between lindane and inositol 1,4,5-triphosphate (IP3) may explain why lindane releases Ca^{++} from IP3-sensitive intracellular stores in macrophages, myometrial cells as well as cat kidney cells (reviewed in Sauviat & Pages, 2002). Furthermore, lindane was found to influence the metabolic function of hepatic mitochondria, as well as affect the synthesis of inositol phosphate in neuronal cells. Lindane is not a competitive agonist of the IP3 receptor. In mouse peritoneal macrophage cells, lindane can mobilize Ca2+ stores. Lindane also decreases the concentration of phosphatidylinositol (PI), phosphatidylinositol 4-phosphate (PIP), and phosphatidylinositol 4,5-bisphosphate (PIP2) in the membrane of erythrocytes and cerebral cells of rats exposed for 3 or 6 months. Lindane can also promote oxidative stress by modifying the activity of scavenger enzymes, an effect that may also be involved in the inhibition of intercellular gap junctions. [Thus, lindane produces multiple effects on many cell types, rather than being a sole inducer of inflammation.]

In a study in vitro, the influence of γ-HCH (lindane) on the metabolism of arachidonic acid and production of oxygen metabolites was

investigated in mouse peritoneal macrophages by Forgue et al. (1990). Lindane stimulated production of prostacyclins (6KPGF1α), prostaglandin E2 (PGE2), leukotriene C4 (LTC4), leukotriene B4 (LTB4), and hydroxyeicosatetraenoic acids (HETEs), and increased luminol-dependent chemiluminescence. Lindane produced a synergistic effect on prostaglandin-leukotriene (PG-LT) and chemiluminescence production when combined with phorbol ester. The calcium ionophore A23187 similarly stimulated chemiluminescence and PG-LT production, suggesting that lindane acts through mobilization of calcium stores (Forgue et al., 1990).

In perfused rat liver, low (5–20 mg/kg), but not high (60 mg/kg) doses of lindane stimulated Kupffer cell activity and led to enhanced liver injury (Videla et al., 1997). At lower exposures, lindane caused an elevation in carbon uptake and in carbon-induced oxygen consumption that was abrogated by the Kupffer cell-inactivator, gadolinium chloride ($GdCl_3$). $GdCl_3$ had no effect in animals given a higher dose of lindane (60 mg/kg), which significantly increased both the rate of oxygen consumption, as well as the sinusoidal efflux of lactate dehydrogenase. Thus, toxicity at higher doses (60 mg/kg) appears to be independent of Kupffer cell activity, and instead related to oxidative stress mechanisms at the parenchymal cell level (Videla et al., 1997).

Paracrine mechanisms leading to enhanced production of prostaglandins (which have been implicated in tumour promotion) were investigated by Kroll et al. (1999). In male Wistar rats, phenobarbital (0.75 g/L in drinking-water) or lindane (350 mg/kg diet) significantly increased the levels of *COX-2* mRNA and protein from isolated Kupffer cells evaluated after 2, 5, or 56 days of exposure. Additionally, treatment in vitro of primary Kupffer cell cultures with lindane (for 1 hour) increased COX-2 protein expression, markedly increased levels of PGE2 and prostaglandin D2 (PGD2) (by 50-fold), and also elevated prostaglandin F2α (PGF2α) (by more than threefold). Lee and Edwards, however, in 2001 challenged the idea that prostaglandins were responsible for the tumour-promoting effects of lindane and phenobarbital in rat liver (Lee & Edwards, 2001). They demonstrated a concentration-dependent increase by PGE2, PGF2α, and PGD2 in the level of DNA synthesis by hepatocytes. Arachidonic acid alone, however, had no effect on DNA synthesis. PGE2 and PGF2α required dexamethasone to mediate their effects and did not further enhance the stimulatory effect of epidermal growth factor (EGF). On the other hand, PGD2 was capable of stimulating DNA synthesis regardless of whether insulin, dexamethasone, or EGF were present or absent. The phorbol ester 12-O-tetradecanoyl phorbol-13-acetate (TPA) significantly increased [(3)*H*]arachidonic acid release, as well as PGE2 formation in hepatocytes, in contrast to α-HCH and other compounds tested, including phenobarbital and DDT. Inhibitors of arachidonic acid metabolism did not selectively block the ability of lindane (or other compounds tested) to stimulate DNA synthesis (Lee & Edwards, 2001).

4.3 Data relevant to comparisons across agents and end-points

4.3.1 General description of the database

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

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

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

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

1. *Is electrophilic or can undergo metabolic activation (31 end-points)*: no assays directly measure electrophilicity or metabolic activation. However, assay end-points measuring CYP inhibition (29 end-points) and aromatase inhibition (2 end-points) were mapped to this characteristic.
2. *Is genotoxic (0 end-points):* no assay end-points were mapped to this characteristic.
3. *Alters DNA repair or causes genomic instability (0 end-points):* no assay end-points were mapped to this characteristic.
4. *Induces epigenetic alterations (11 end-points):* the assay end-points mapped to this characteristic measure targets associated with DNA binding (e.g. transcription factors) (4 end-points) and transformation catalysts (e.g. histone deacetylase) (7 end-points).
5. *Induces oxidative stress (18 end-points):* the assay end-points mapped to this characteristic measure oxidative stress via cell imaging (7 end-points), markers of oxidative stress (e.g. nuclear factor erythroid 2-related factor, NRF2) (6 end-points), and metalloproteinase (5 end-points).
6. *Induces chronic inflammation (45 end-points):* the assay end-points mapped to this characteristic measure cellular adhesion (14 end-points), cytokines (e.g. IL8) (29 end-points), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity (2 end-points).
7. *Is immunosuppressive (0 end-points):* no assay end-points were mapped to this characteristic.
8. *Modulates receptor-mediated effects (92 end-points):* a large and diverse collection of cell-free and cell-based assay end-points measuring nuclear and other receptor bioactivity, specifically aryl hydrocarbon receptor (AhR) (2 end-points), androgen receptor (11 end-points), ER (18 end-points), farnesoid X receptor (FXR) (7 end-points), peroxisome proliferator-activated receptor (PPAR) (12 end-points), pregnane X receptor_vitamin D receptor (PXR_VDR) (7 end-points), retinoic acid receptor (RAR) (6 end-points), and

others (29 end-points), were mapped to this characteristic.

9. *Causes immortalization (0 end-points):* no assay end-points were mapped to this characteristic.
10. *Alters cell proliferation/death or nutrient supply (68 end-points):* the assay end-points mapped to this characteristic measure cytotoxicity (41 end-points), mitochondrial toxicity (7 end-points), cell cycle (16 end-points), and cell proliferation (4 end-points).

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

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

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

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

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

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

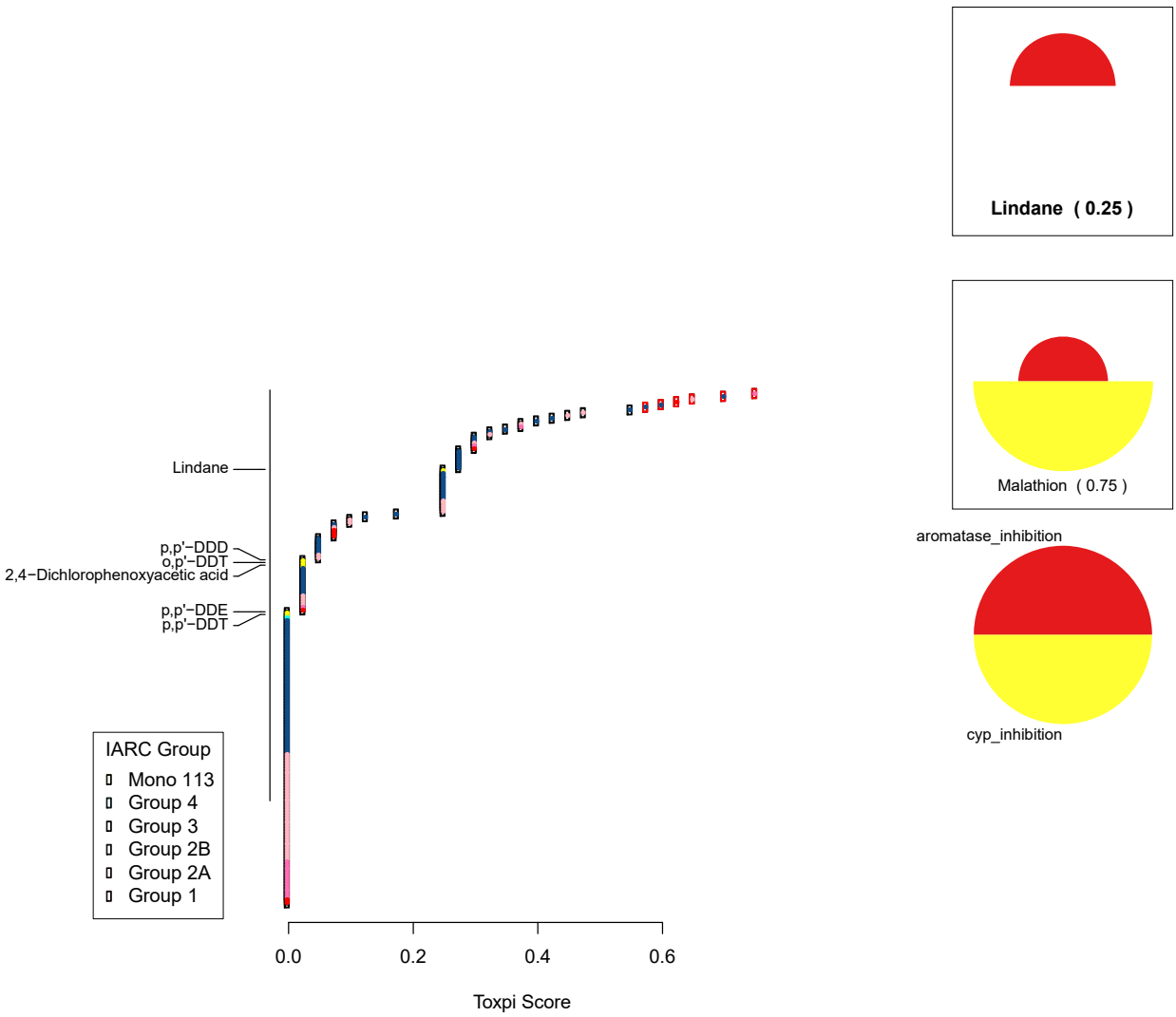
Characteristic (1) *Is electrophilic or can undergo metabolic activation*: Lindane was tested for all 31 assay end-points mapped to this key characteristic. Lindane was active in none of the 29 assay end-points related to CYP inhibition, and in 1 of the 2 assay end-points related to aromatase inhibition. In comparison, the highest-ranked chemical, malathion (IARC Group 2A; IARC, 2017a), was active in 20 out of 29 assay end-points related to CYP inhibition and in 1 out of 2 related to aromatase inhibition (Fig. 4.1).

Characteristic (4) *Induces epigenetic alterations:* Lindane was tested for all 11 assay end-points mapped to this characteristic. Lindane was active in none of the assays. In comparison, the highest-ranked chemical, captan (IARC Group 3; IARC, 1983) was active for 0 out of 4 DNA-binding assay end-points, and 5 out of 7 transformation-catalyst (e.g. histone modification) assay end-points (Fig. 4.2).

Characteristic (5) *Induces oxidative stress*: lindane was tested for all 18 assay end-points mapped to this characteristic. The 18 assay end-points that were mapped to this characteristic are in subcategories of metalloproteinase (5 end-points), oxidative stress (7 end-points), and oxidative stress marker (6 end-points). Lindane was active for 2 of the assay end-points measuring oxidative-stress markers, but none of the other assay end-points. In comparison, the highest-ranked chemical, carbaryl (IARC Group 3; IARC, 1976) was active for 2 out of 5 metalloproteinase assay end-points, 3 out of 7 oxidative stress assay end-points, and 3 out of 6 oxidative-stress marker assay end-points (Fig. 4.3).

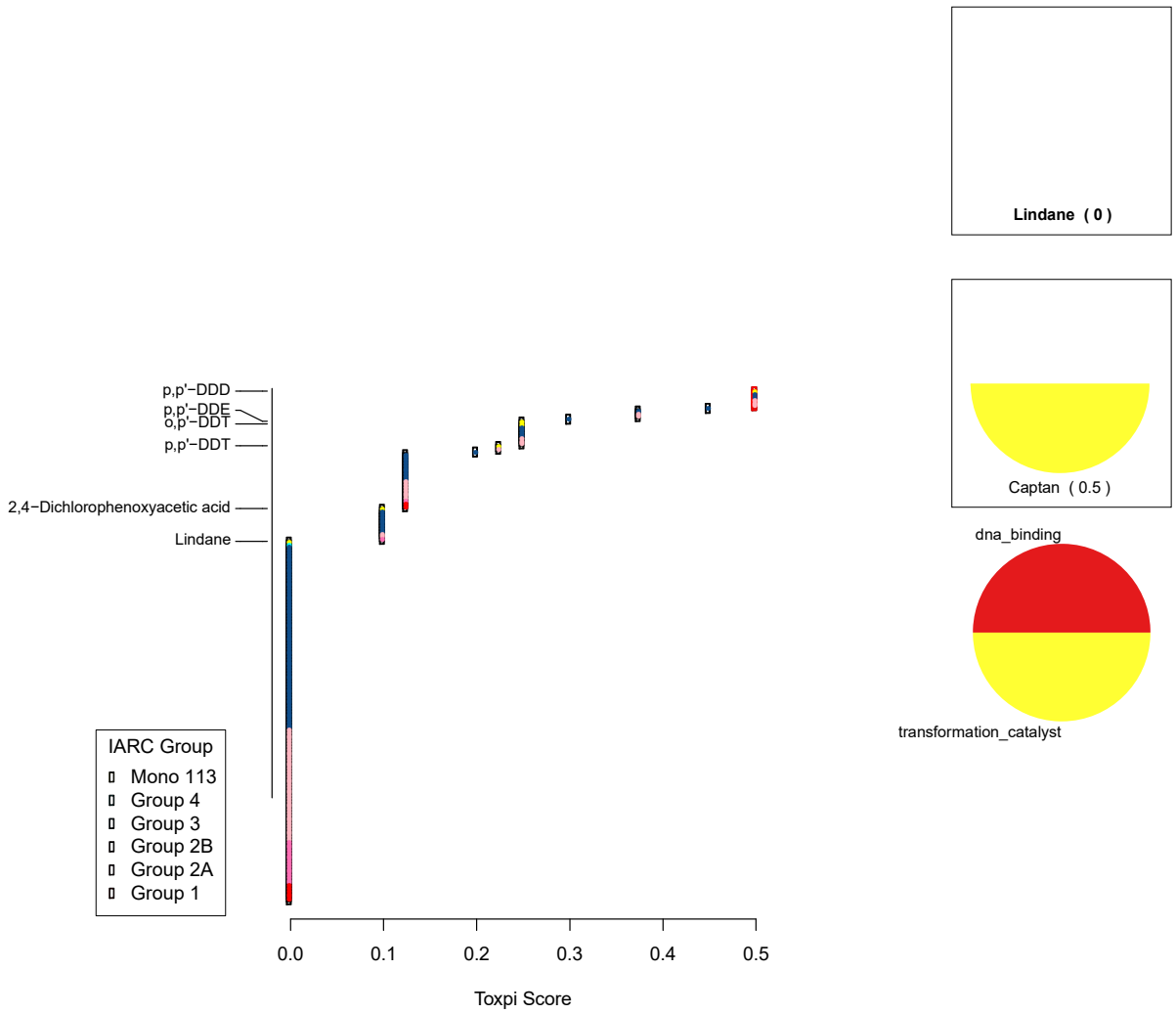
Characteristic (6) *Induces chronic inflammation*: lindane was tested for all 45 assay end-points mapped to this characteristic, and was active for 1 assay end-point related to cytokine levels. In comparison, the highest-ranked chemical, 4,4′-methylenedianiline (IARC Group 2B; IARC, 1986) was active for 2 out of 14 cellular-adhesion assay end-points, and 2 out of 29 cytokine-assay end-points (Fig. 4.4).

Fig. 4.1 ToxPi ranking for lindane using ToxCast assay end-points mapped to metabolic activation



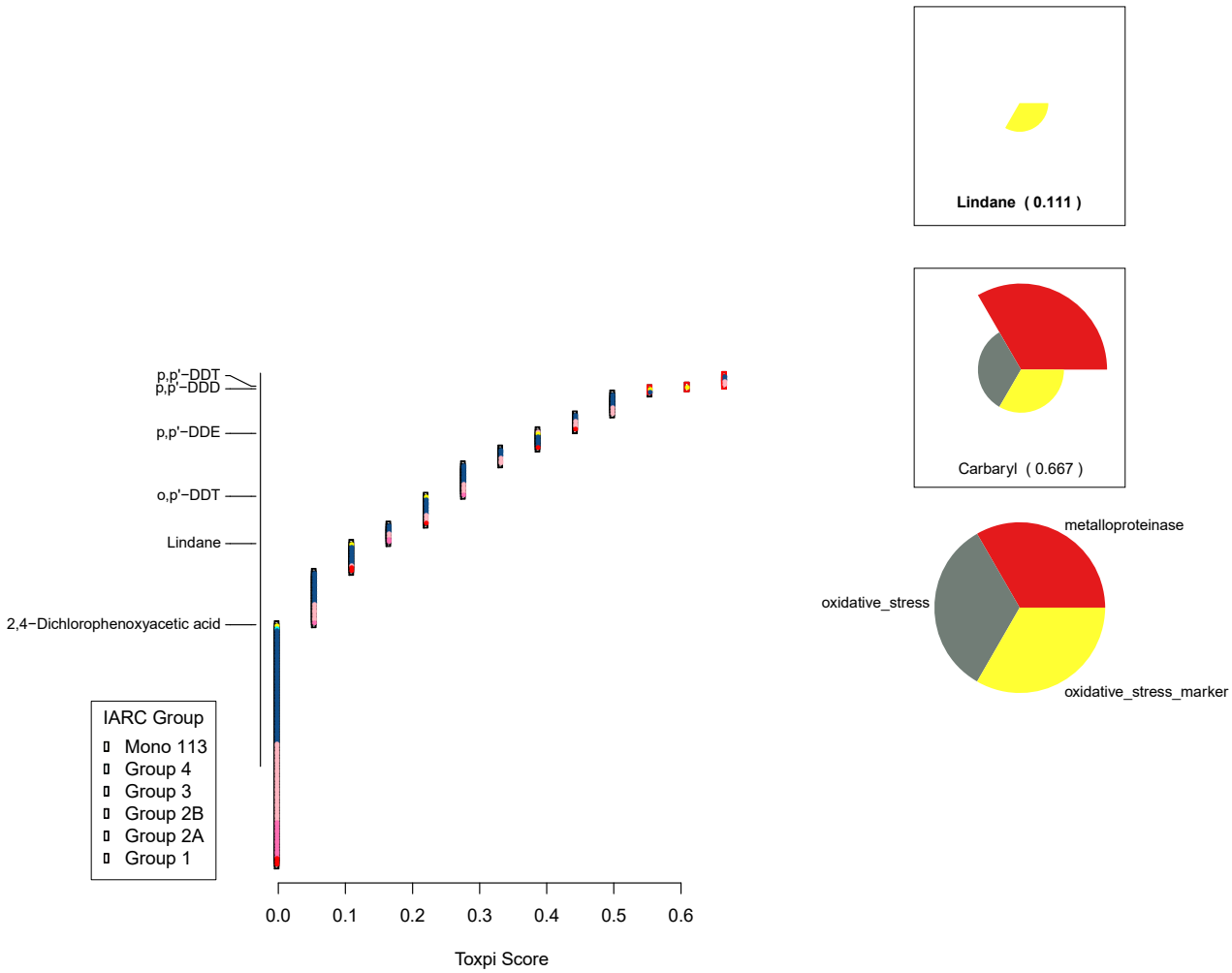
On the left-hand side, the relative rank of lindane is shown (*y*-axis) with respect to its ToxPi score (*x*-axis) as compared with the other chemicals evaluated in the present volume (Volume 113) and the 181 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of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

Fig. 4.2 ToxPi ranking for lindane using ToxCast assay end-points mapped to epigenetic alterations



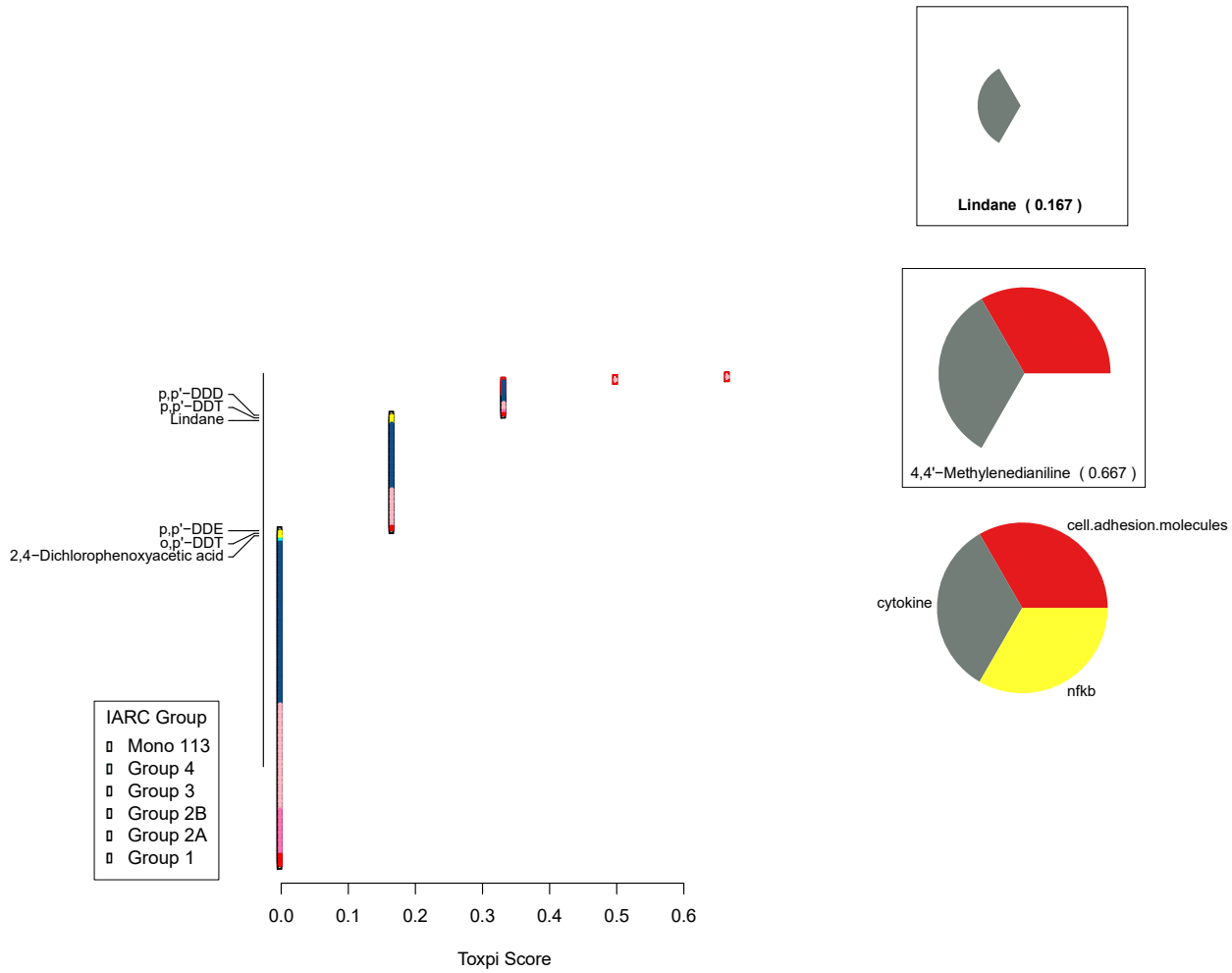
On the left-hand side, the relative rank of lindane is shown (*y*-axis) with respect to its ToxPi score (*x*-axis) as compared with the other chemicals evaluated in the present volume (Volume 113) and the 178 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the top-ranked chemical (in this case, captan) and the target chemical(s) (lindane) are shown with their respective ToxPi score in parentheses.

Fig. 4.3 ToxPi ranking for lindane using ToxCast assay end-points mapped to oxidative stress markers



On the left-hand side, the relative rank of lindane is shown (*y*-axis) with respect to its ToxPi score (*x*-axis) as compared with the other chemicals evaluated in the present volume (Volume 113) and the 178 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the top-ranked chemical (in this case, carbaryl) and the target chemical(s) (lindane) are shown with their respective ToxPi score in parentheses.

Fig. 4.4 ToxPi ranking for lindane using ToxCast assay end-points mapped to induction of chronic inflammation



On the left-hand side, the relative rank of lindane is shown (*y*-axis) with respect to its ToxPi score (*x*-axis) as compared with the other chemicals evaluated in the present volume (Volume 113) and the 178 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the top-ranked chemical (in this case, 4,4′-methylenedianiline) and the target chemical(s) (lindane) are shown with their respective ToxPi score in parentheses.

Characteristic (8) *Modulates receptor-mediated effects:* lindane was tested for all 92 assay end-points mapped to this characteristic, and was active in 3 out of 18 ER assay end-points, 1 out of 7 FXR assay end-points, 1 out of 29 other nuclear-receptor assay end-points, 1 out of 12 PPAR assay end-points, 3 out of 7 PXR_VDR assay end-points, and 2 out of 6 RAR assay end-points. In comparison, the highest-ranked chemical, clomiphene citrate (IARC Group 3; IARC, 1979a) was active for 5 out of 11 androgen-receptor assay end-points, 13 out of 18 ER assay end-points, 3 out of 7 FXR assay end-points, 6 out of 29 other nuclear-receptor assay end-points, 2 out of 12 PPAR assay end-points, 5 out of 7 PXR_VDR assay end-points, and 1 out of 6 RAR assay end-points (Fig. 4.5).

Characteristic (10) *Alters cell proliferation, cell death, or nutrient supply:* lindane was tested for 67 out of 68 assay end-points mapped to this characteristic and was active for 2 of the 41 assay end-points related to cytotoxicity. In comparison, the highest-ranked chemical, ziram (IARC Group 3; IARC, 1991) was active for 2 out of 16 cell-cycle assay end-points, 33 out of 41 cytotoxicity end-points, and 2 out of 7 mitochondrial-toxicity assay end-points (Fig. 4.6).

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

As a high-level summary of activity, data were recombined into six ToxPi slices, where each slice represents activity across all component assays mapped to a given characteristic. In the figure (Fig. 4.7), slices are labelled "metabolism" (*Is electrophilic or can undergo metabolic activation*), "epigenetic" (*Induces epigenetic alterations*), "stress" (*Induces oxidative stress*), "inflammation" (*Induces chronic inflammation*), "receptor" (*Modulates receptor-mediated effects*), and "cellular" (*Alters cell proliferation, cell death, or nutrient supply*). Lindane was tested for 264 of 265 assay end-points mapped to any characteristic. Overall, lindane was active for 17 of the assay end-points mapped to any characteristic. In comparison, the highest-ranked chemical, clomiphene citrate (IARC Group 3; IARC, 1979a) was active for 97 assay end-points.

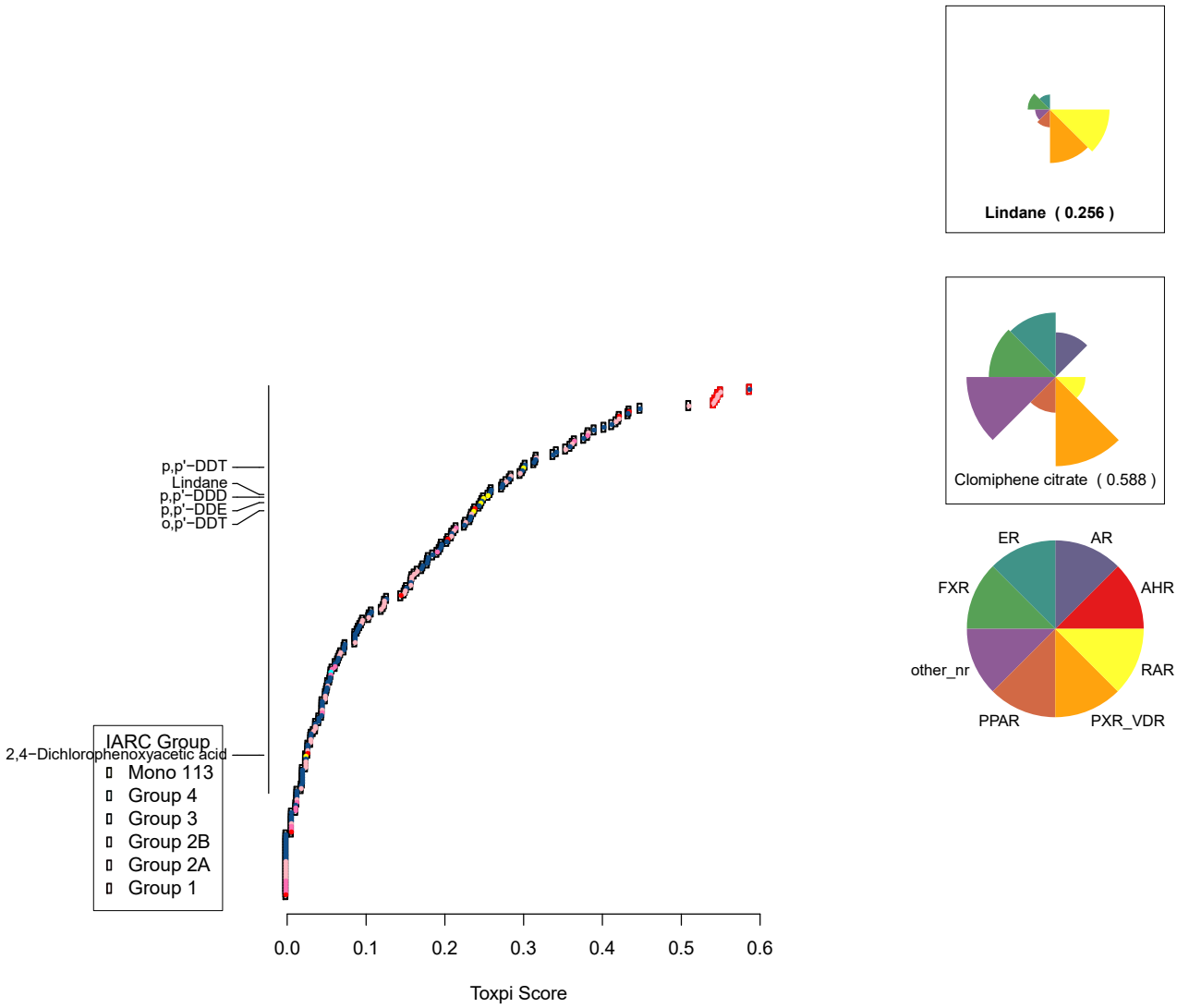
4.4 Cancer susceptibility data

There is a paucity of studies that examine susceptibility to cancer associated with exposure to lindane in humans. Two case–control studies of similar size found opposing evidence for postmenopausal status as a susceptibility factor for cancer of the breast (Zheng et al., 1999; Ibarluzea et al., 2004). A history of asthma did not modify a non-significant association between non-Hodgkin lymphoma and exposure to lindane (Lee et al., 2004). No studies of carcinogenicity with lindane in experimental animals have examined susceptibility. [The Working Group noted that few studies evaluated life-stage, and genetic and disease susceptibility. There is no compelling evidence for factors enhancing susceptibility to cancer in association with exposure to lindane.]

4.5 Other adverse effects

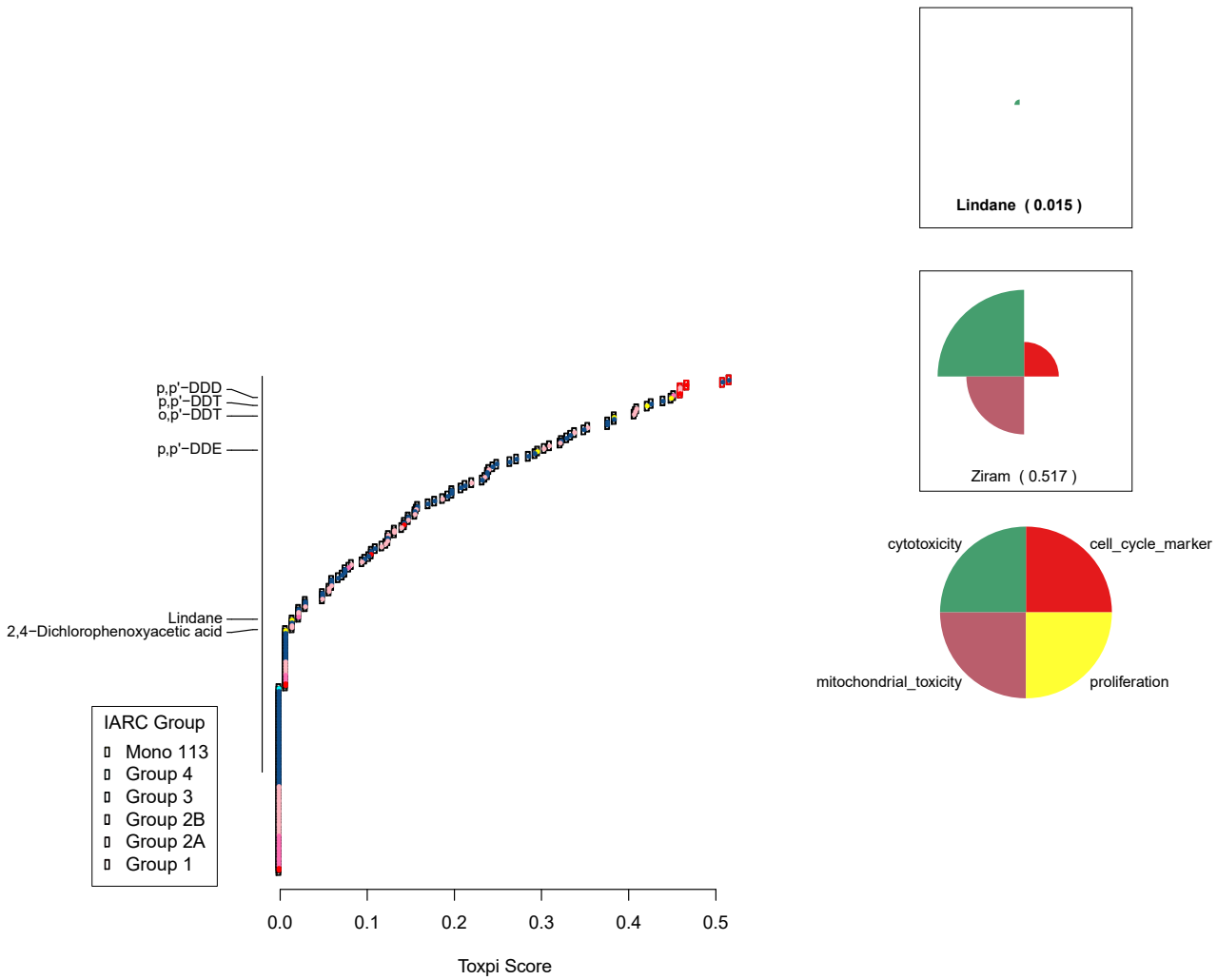
Other adverse effects not addressed in Sections 4.1–4.4 that may be relevant to cancer hazard identification for lindane include toxicity in the liver, kidney, haematopoietic system, and testis. These effects have also been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2005).

Fig. 4.5 ToxPi ranking for lindane using ToxCast assay end-points mapped to modulation of receptor-mediated effects



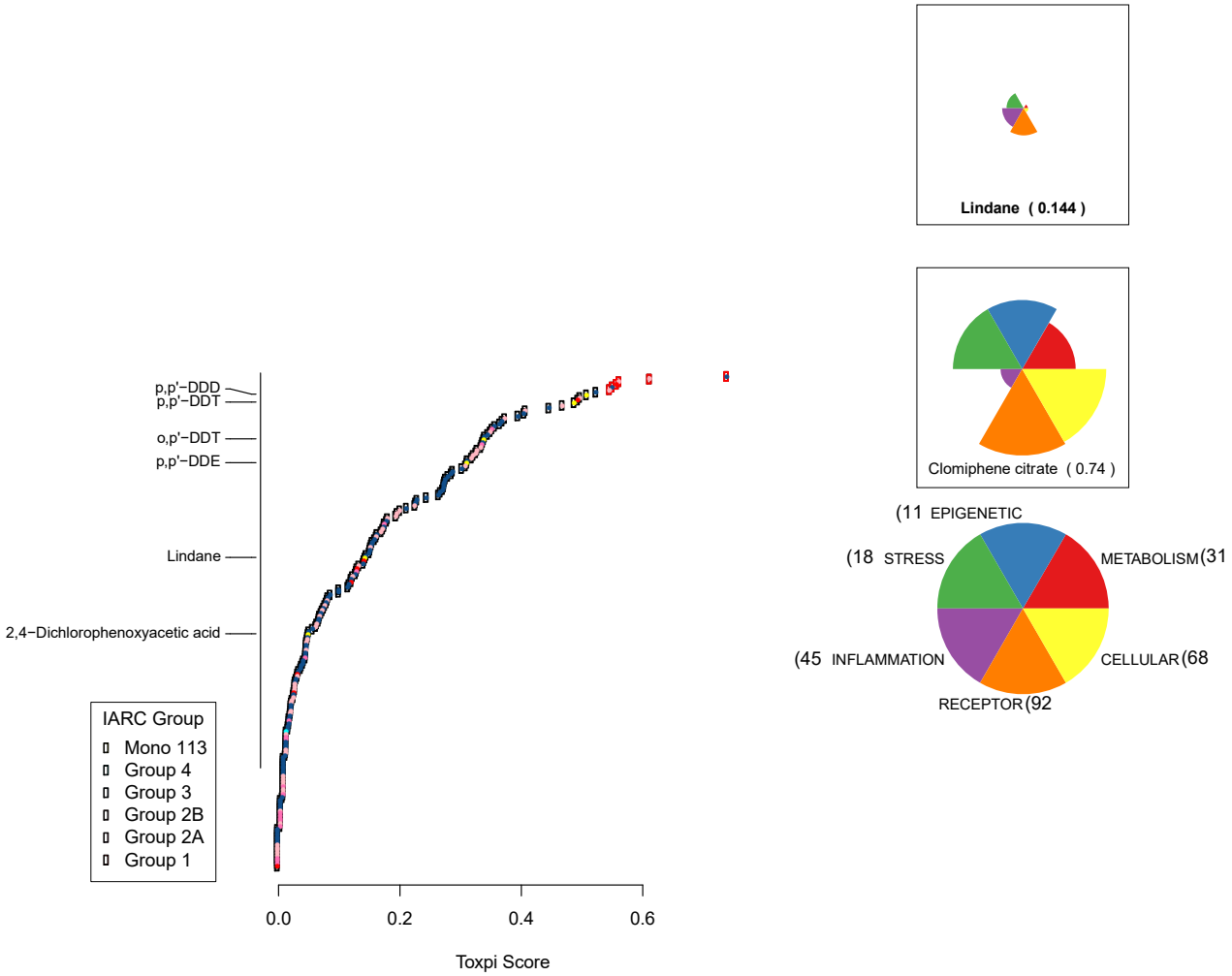
On the left-hand side, the relative rank of lindane is shown (*y*-axis) with respect to its ToxPi score (*x*-axis) as compared with the other chemicals evaluated in the present volume (Volume 113) and the 178 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the top-ranked chemical (in this case, clomiphene citrate) and the target chemical(s) (lindane) are shown with their respective ToxPi score in parentheses.

Fig. 4.6 ToxPi ranking for lindane using ToxCast assay end-points mapped to alteration of cell proliferation, cell death, and nutrient supply



On the left-hand side, the relative rank of lindane is shown (*y*-axis) with respect to its ToxPi score (*x*-axis) as compared with the other chemicals evaluated in the present volume (Volume 113) and the 178 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the top-ranked chemical (in this case, ziram) and the target chemical(s) (lindane) are shown with their respective ToxPi score in parentheses.

Fig. 4.7 ToxPi ranking for lindane using ToxCast assay end-points: summary of key characteristics



On the left-hand side, the relative rank of lindane is shown (*y*-axis) with respect to its ToxPi score (*x*-axis) as compared with the other chemicals evaluated in the present volume (Volume 113) and the 178 chemicals previously evaluated by IARC. The inset in the scatter plot shows subcategories of the ToxPi chart, as well as their respective colour coding. On the right-hand side, the ToxPi charts of the top-ranked chemical (in this case, clomiphene citrate) and the target chemical(s) (lindane) are shown with their respective ToxPi score in parentheses.

4.5.1 Humans

Several studies have reported increases in liver enzyme levels associated with occupational exposure to technical-grade HCH (Kashyap, 1986; Nigam et al., 1993). Renal failure was reported in multiple cases of acute poisoning with lindane (Munk & Nantel, 1977; Sunder Ram Rao et al., 1988). In one case, simultaneous renal and hepatic injury was reported (Paul et al., 2013).

No studies of associations between exposure to lindane and testicular toxicity in humans were available to the Working Group.

4.5.2 Experimental systems

Experimental studies in rats and rabbits have reported liver toxicity after administration of lindane, as demonstrated by alterations in clinical markers, such as serum aspartate transaminase, alanine transaminase, and lactate dehydrogenase, and by histopathological lesions, such as cytotoxicity, necrosis, and focal degeneration (Schulte Hermann et al., 1971; Grabarczyk et al., 1990; Junqueira et al., 1991; Raizada et al., 2001; Videla et al., 2004; Matsuura et al., 2005; Anilakumar et al., 2007; Vijaya Padma et al., 2011).

Experimental studies in rats and rabbits have reported kidney toxicity after administration of lindane, as demonstrated by clinical markers, such as elevated serum urea, creatinine, and uric acid, and by histopathological lesions, such as focal degeneration (Grabarczyk et al., 1990; Vijaya Padma et al., 2011).

Haematological effects, including reduced phagocytic activity of neutrophils, increased number of lymphocytes with inactive nucleoli, and reduced total leukocyte count have also been reported in rats and rabbits (Grabarczyk et al., 1990; Joseph et al., 1992).

Histological and functional changes in the testes have been reported after administration of lindane in rats. Reported effects include organ-weight changes, alterations in steroidogenesis, decreased spermatogenesis, reduction in antioxidant defence, alterations in testicular morphology, and degeneration of Leydig cells (Samanta et al., 1999a, b; Suwalsky et al., 2000; Pagès et al., 2002; Saradha et al., 2008). Effects in the male reproductive tract in adulthood have also been reported when rats are exposed during lactation (Dalsenter et al., 1997a). In a two-generation study of reproductive toxicity in rats, there were no changes in the testes in the F_0 generation, and decreases in absolute, but not relative, testicular weights in the F_1 and F_2 generations only at the highest dietary concentration of 300 ppm (Matsuura et al., 2005). Srinivasan et al. (1991) did not report any effects on the testes in pups exposed in utero or via lactation through the maternal diet.

5. Summary of data reported

5.1 Exposure data

Lindane is the γ-isomer of hexachlorocyclohexane (HCH). While there are several isomers of HCH, among which the β-, γ-, δ-, and ε-isomers are relatively stable, only γ-HCH has insecticidal properties. Technical-grade lindane containing 90% γ-HCH, and technical-grade HCH containing 10–40% γ-HCH, have both been used worldwide as pesticides.

Lindane has been extensively manufactured and used in the past, primarily as an insecticide to treat wood and wooden structures, seed, crops, and livestock. Occupational exposure to lindane can occur, or has occurred, in the course of its manufacture and formulation, and during agricultural application. Use of lindane decreased significantly from the 1970s to the 1990s due to restrictions and bans on its use in agriculture. Lindane continues to be used for public health purposes, although with decreasing numbers of

prescriptions, for the second-line treatment of scabies (mites) and lice in humans (as a specific exemption under the Stockholm Convention on Persistent Organic Pollutants).

Lindane is mobile in the environment and, as a result of long-range atmospheric transport, has been deposited worldwide. Lindane has been measured in food, air, surface water, groundwater, sediment, soil, fish, wildlife, and humans. Current exposure of the general population in countries worldwide occurs mainly through the diet. In most regions of the world, the proportion of human biological samples containing lindane at detectable levels is decreasing.

5.2 Human carcinogenicity data

Cancer risks associated with exposure to lindane have been evaluated in cohort and case–control studies in several countries. The largest body of data concerns non-Hodgkin lymphoma (NHL).

Cohort and case–control studies of mostly occupational exposure to pesticides provide consistent evidence of an association between NHL and lindane. A large prospective cohort study of farmers in the USA estimated exposure through a detailed assessment, and observed significant upward trends in risk of NHL in relation to several indicators of occupational exposure to lindane, while controlling for other risk factors. Another cohort study investigating the mortality of Icelandic sheep farmers reported that the risk of NHL increased with the number of sheep owned. The number of sheep owned is an indirect measure of exposure to lindane because treatment of sheep to control ectoparasites was a legal requirement, with a technical-grade HCH mixture used for this purpose before the 1970s, and lindane alone used afterwards; however, this metric could lead to misclassification of the level of exposure.

A pooled analysis of three population-based case–control studies in the midwestern USA reported a 50% increase in the risk of NHL associated with any use of lindane. The association was stronger with several indicators of higher exposure and remained positive after individual adjustments for other pesticides and pesticide classes. The association between NHL and exposure to lindane was reduced to a 20% excess in a subsequent analysis of a subset of the population with simultaneous adjustment for multiple pesticides. A population-based case–control study in Canada, in which pesticide exposures were assessed using questionnaires, also found moderately increased risks for NHL associated with exposure to lindane. A meta-analysis of four studies examining ever-exposure to lindane in agricultural settings, including the original pooled analysis described above, found a 60% increased risk of NHL with exposure to lindane.

A cohort study in the USA and three case-control studies in Europe investigated the association between NHL and β-HCH in the general population using measurements in serum. The cohort study and two case–control studies reported some positive associations between β-HCH and risk, while the other case–control study did not. However, the interpretation of general-population studies using levels of other HCH isomers measured in biological samples is uncertain since such measurements do not necessarily reflect exposure to lindane.

Associations between cancers of the breast, prostate, or testis with lindane or HCH isomers measured in serum have been evaluated in several studies, but the results were not consistent and the findings for HCH isomers may not reflect exposure to lindane, as noted above.

5.3 Animal carcinogenicity data

Lindane was tested for carcinogenicity by oral administration (feeding) in seven studies in mice and two studies in rats. These studies had several limitations, such as short duration of exposure, use of one sex only, inadequate dose selection,

lack of rationale for dose selection, and limited reporting.

In treated mice, lindane consistently increased the incidence of benign and/or malignant tumours of the liver, which were classified across the various studies as benign or malignant liver cell tumours, hepatomas (not further classified), benign or malignant hepatomas, or hepatocellular adenoma or carcinoma. In one study in males, there was an increase in the incidence of benign hepatomas. In a second study in males and females, there was an increase in the incidence of benign or malignant (combined) liver cell tumours in both sexes. In a third study in males and females, there was an increase in the incidence of liver hepatoma (not further classified) in males. In a fourth study in females of three different strains of mice, there was an increase in the incidence of hepatocellular adenoma or carcinoma (combined) in two strains, and of bronchiolo-alveolar tumours of the lung (not further classified) in one of these two strains. In a fifth study in males and females, there was a positive trend in the incidence of bronchiolo-alveolar adenoma or carcinoma (combined) in females. One study in males and females gave negative results, and another one study in males and females was inadequate for the evaluation.

In rats, one study in males and females gave negative results, and another study was inadequate for the evaluation.

5.4 Mechanistic and other relevant data

Lindane is highly lipophilic, readily absorbed via all routes of exposure, and distributes widely in the body, with a preference for adipose and other lipid-rich tissues. It is extensively metabolized via cytochrome P450s to a multitude of metabolites and excreted as various conjugates, including mercapturic acids. Terminal half-lives in humans have been estimated to be around 1 day, with a few studies reporting half-lives of up to approximately 1 week. Lindane induces several cytochrome P450 enzymes in rats, and induces CYP2B6 and inhibits CYP2D6 and CYP2E1 in human hepatocytes.

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

The evidence is *strong* that lindane is immunosuppressive, and this characteristic can operate in humans. Lindane causes dose-dependent immunosuppressive effects in vivo in several species, including mice, rats, birds and fish. Lindane suppresses the humoral immune response in mice and rats. In vitro, lindane suppresses the activation of human lymphocytes and is toxic to murine lymphocytes. Immunological studies in exposed humans are inconclusive with respect to immunosuppression, but haematotoxic effects have been observed in humans and rodents.

The evidence is *strong* that lindane induces oxidative stress. Markers of oxidative stress in blood lymphocytes were increased in cases of acute poisoning with lindane in humans. Additional data in experimental systems, including in human lymphocytes in vitro and rats in vivo, provide consistent evidence of increases in reactive oxygen species or markers of oxidative stress.

The evidence is *moderate* that lindane modulates receptor-mediated effects. No consistent associations between lindane and serum hormone levels were found in a few studies in humans. Lindane binds and blocks the androgen receptor in human cells and experimental systems. It did not activate transfected human androgen receptor in vitro. Studies in experimental systems indicate that lindane has anti-estrogenic and anti-androgenic activity.

The evidence is *moderate* that lindane is genotoxic. In human cells in vitro, chromosomal aberration, sister-chromatid exchange, and increased micronucleus formation were reported after treatment with lindane. Negative or mixed results were reported in assays for DNA-adduct formation and other types of DNA damage. In rats, mice, and Chinese hamsters, findings were mixed across experimental systems, including chromosomal and other DNA damage end-points. Negative or statistically significant but very small effects were reported in bacteria and lower eukaryotes. No reliable genotoxicity data were available in exposed humans.

The evidence is *weak* that lindane alters cell proliferation or death, or induces chronic inflammation. No data were available in exposed humans. Studies of apoptosis and proliferation in human cancer cells gave mixed results. Induction of apoptosis was reported in mice in vivo and in several mouse cell types in vitro, but inhibition of apoptosis was reported in rat hepatocytes. A few studies in rats in vivo and in vitro have reported Kupffer cell activation in the liver.

In high-throughput testing in the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the government of the USA, lindane gave positive results for 17 assay end-points, mostly related to receptor-mediated effects, among the 265 assay end-points relevant to the key characteristics of human carcinogens.

No cancer susceptibility factors have been identified in humans.

Adverse effects of lindane in the liver, kidney, and haematopoietic systems have been reported in exposed humans, as well as in experimental systems. Additionally, testicular toxicity has been reported in rats exposed to lindane.

Overall, the mechanistic data provide strong support for the carcinogenicity of lindane. This includes strong evidence that lindane is immunosuppressive and induces oxidative stress, and that effects can operate in humans.

6. Evaluation

6.1 Cancer in humans

There is *sufficient evidence* in humans for the carcinogenicity of lindane. Lindane causes non-Hodgkin lymphoma.

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

Lindane is *carcinogenic to humans* (*Group 1*).

References

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